

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN PATENTE NACIONAL

09-3499

21. EXPEDIENTE No.

54. TITULO

COMPOSICIÓN DE REBAUDIOSIDA A Y MÉTODO PARA PURIFICAR

REBAUDIOSIDA A

51. CLASIFICACION INTERNACIONAL

71. SOLICITANTE

THE COCA-COLA COMPANY

DOMICILIO

ATLANTA, GA, ESTADOS UNIDOS DE AMÉRICA

74. APODERADO

JUAN PABLO CADENA SARMIENTO

22. SANTAFE DE BOGOTA, D.C.

PETITORIO

AS: 109.230



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-003499- -00000-0000

Fecha: 2009-01-16 16:48:08 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 392FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

14 de 2009

1

SOLICITUD DE:



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

SOLICITANTE

Nombre: THE COCA-COLA COMPANY

Dirección: One Coca-cola Plaza, NW, Atlanta, GA 30313, Estados Unidos de América

Nacionalidad o Domicilio: Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

Teléfono:

Fax:

E-mail

IDENTIFICACIÓN

C.C. ☐NIT ☐C.E. ☐Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: JUAN PABLO CADENA SARMIENTO

Dirección: Cra. 7 No. 71-21 Torre B – Piso 4, Bogotá, Colombia.

Teléfono: 744-2200

Fax: 742-2200

E-mail:

IDENTIFICACIÓN

C.C. ☒NIT ☐C.E. ☐Otro ☐

Cual _____

Número 80.410.337 TP 57492

4

INVENTOR (ES)
(72)

Nombre: Indra PRAKASH, Grant E. DUBOIS, George A. KING, Mani UPRETI,

Dirección: 9750 Talisman Drive, Alpharetta, GA 30022, US; 215 Quincy Lane, Roswell, GA 30076, US; 1755 Wildwood Road, Atlanta, GA 30306, US; 1943 Rotherham Way, Dunwoody, GA 30338, US (Respectivamente).

Nacionalidad o Domicilio: Estados Unidos de América

5 PCT (86)

Solicitud Internacional No. PCT/US2007/069548

Fecha 23-05-2007

Publicación Internacional No. WO 2007/149672 A3

Fecha 27-12-2007

6 Título (54): COMPOSICIÓN DE REBAUDIOSIDA A Y MÉTODO PARA PURIFICAR REBAUDIOSIDA A

7 Clasificación Internacional (51):

8 Prioridad

SI ☒NO ☐

(33) País de Origen

(32) Fecha

(31) Número de Solicitud

US

19-06-2006

60/805,216

US

12-02-2007

60/889,318

9 Comprobante de pago No. 08-96,476; 08-96,477; 09-1,109; 09-1,110; 08-87,538; 09-1,220; 08-98,232

Fecha 16-01-2009

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

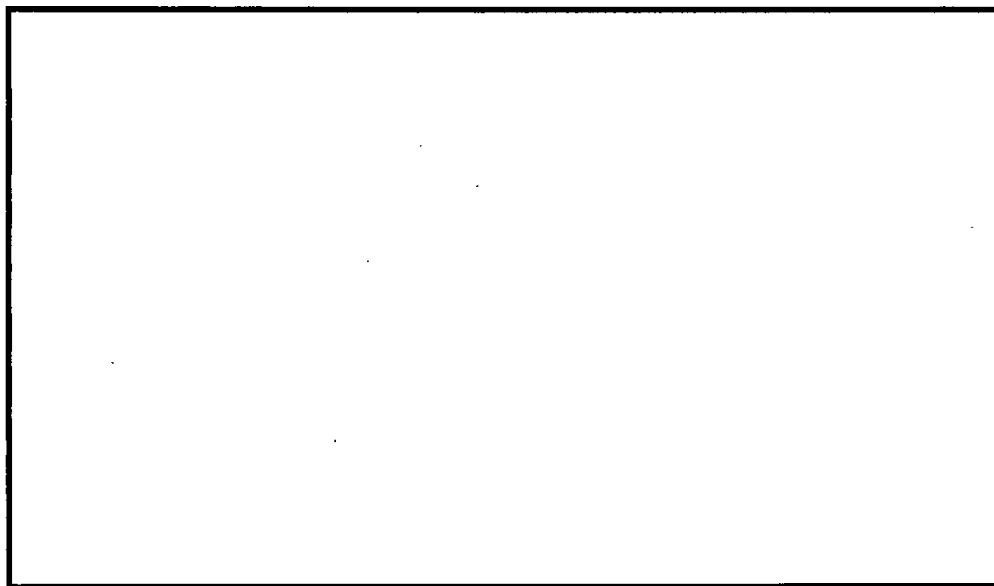
10

ANEXOS

2

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$ 540.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA), y anexos.
- ☒ Traducción de examen preliminar internacional efectuado por la IPEA, y anexos.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Tarjeta de Propietarios
Documentos PCT
Comprobante(s) de pago de la tasa por concepto de Reivindicaciones Modificadas adicionales (IPRP). \$575.000 (23*\$25.000)
Extracto para Publicación y Tarjeta de Archivo Temático

11 FIGURA CARACTERÍSTICA:



12

Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén TP. 57492 del C.S.J.

M

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-003499- -00000-0000

Fecha: 2009-01-16 16:48:08 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 392

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 96,476
FECHA : DICIEMBRE 12 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3249923	12/12/2008	25,011,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
		TOTAL :	\$ 501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

109 230

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 1,109
FECHA : ENERO 6 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-003499- -00000-0000

Fecha: 2009-01-16 16:48:08 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 392

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	RECIBO DE CAJA			1039	06/01/2009	5,012,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I 998 VALOR COMPLEMENTO TARIFA A#0 ANTR	39,000.00
TOTAL :			\$ 39,000.00

SON: TREINTA Y NUEVE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-003499-00000-0000

Fecha: 2009-01-16 16:48:08 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 392

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 96,477
FECHA : DICIEMBRE 12 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3249923	12/12/2008	25,011,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
		TOTAL :	\$ 501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

109230

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 1,110
FECHA : ENERO 6 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-003499-00000-0000

Fecha: 2009-01-16 16:48:08

Tra. 11 PATENTEIYII

Act. 411 PRESENTACION

Dep. 2020 NUECREACIONI

Eve: 379 FASENACIONALI

Folios: 392

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	RECIBO DE CAJA			1039	06/01/2009	5,012,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO	
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	998 VALOR COMPLEMENTO TARIFA AÑO ANTR	39,000.00
TOTAL :			\$ 39,000.00	

SON: TREINTA Y NUEVE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 87,538
FECHA : NOVIEMBRE 6 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-003499- -00000-0000

Fecha: 2009-01-16 16:48:08 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 392

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	79585914	06/11/2008	31,842,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI
			TOTAL : \$ 23,000.00

SON: VEINTITRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

8

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 1,220
FECHA : ENERO 6 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-003499- -00000-0000

Fecha: 2009-01-16 16:48:08 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 411 PRESENTACION Folios: 392

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	RECIBO DE CAJA			1039	06/01/2009	5,012,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	998 VALOR COMPLEMENTO TARIFA A#0 ANTR
		TOTAL :	\$ 2,000.00

SON: DOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 98,232
 FECHA : DICIEMBRE 17 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-003499-00000-0000

Fecha: 2009-01-16 16:48:08 Dep. 2020 NUECREACION
 Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
 Act. 411 PRESENTACION Folios: 392

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	80854012	17/12/2008	30,330,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	10,000.00
		TOTAL :	\$ 10,000.00

SON: DIEZ MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
 COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
 SUSTITUIDA POR NINGUN RECIBO.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

21

PATENTE ☒ PCT/US2007/069548 ☐
MODELO DE UTILIDAD

DISEÑO INDUSTRIAL ☐

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES THE COCA-COLA COMPANY

DOMICILIO ATLANTA, GA, ESTADOS UNIDOS DE AMERICA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO COMPOSICION DE REBAUDIOSIDA A Y METODO PARA PURIFICAR
REBAUDIOSIDA A CLASIFICACION

EXPEDIENTE No. _____ FECHA DE SOLICITUD _____ ROLLO MICROFILM _____

CERTIFICADO No. _____ FECHA DE CONCESION _____ VIGENCIA DESDE _____ HASTA _____

PRORROGA _____ CAMBIO DE NOMBRE _____

TRASPASO A _____

INVENTOR (ES) INDRA PRAKASH, GRANT E. DUBOIS, GEORGE A. KING, MANI UPRETI.

OTROS _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

TARJETA ARCHIVO TEMÁTICO

PATENTE DE INVENCION ☒ PCT ☒ MODELO DE UTILIDAD

DISEÑO INDUSTRIAL

(21) No. de solicitud:		(22) Fecha de solicitud:	
(51) Clasificación Internacional:			
(71) Solicitante (s): THE COCA-COLA COMPANY			
(72) Inventor (es): Indra PRAKASH, Grant E. DUBOIS, George A. KING, Mani UPRETI.			
(74) Agente: JUAN PABLO CADENA SARMIENTO			
(30) Prioridad	(31) No. Prioridad	(32) Fecha	(33) Pais
	60/805,216	19-06-2006	US
	60/889,318	12-02-2007	US
(85) Fecha inicio fase nacional: 19-01-2009		(87) Publicación internacional:	
(86) Datos relativos a la presentación de la solíc. PCT		Fecha: 27-12-2007	
Fecha de presentación de la solicitud: 23-05-2007		No. Publicación: WO 2007/149672 A3	
No. de solicitud: PCT/US2007/069548			

FIGURA CARACTERÍSTICA
6 x 6 cm

(54) Título: COMPOSICIÓN DE REBAUDIOSIDA A Y MÉTODO PARA PURIFICAR REBAUDIOSIDA A

(55) Reivindicaciones:

1.- Un método para purificar rebaudiosida A que comprende los pasos de:

combinar rebaudiosida A cruda y una solución orgánica acuosa para formar una solución de rebaudiosida A, la rebaudiosida A cruda comprendiendo rebaudiosida A en un pureza de alrededor de 40% a alrededor de 85% en peso sobre una base seca, y la solución orgánica acuosa comprendiendo agua en una cantidad de alrededor de 10% a alrededor de 25% en peso; y

CONTINUA AL RESPALDO ...

cristalizar la solución de rebaudiosida A en un solo paso una composición de rebaudiosida A que comprende rebaudiosida A en una pureza mayor de alrededor de 95% en peso sobre una base seca.

Y la composición substancialmente pura hecha de conformidad con dicho método.

21



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCION PCT

(21) No. de solicitud:					(51) Int Cl:				
(22) Fecha de solicitud:					(71) Solicitante(s): THE COCA-COLA COMPANY				
(30) Prioridad	(31) No. Prioridad	(32) Fecha	(33) Pais		(72) Inventor (es): Indra PRAKASH, Grant E. DUBOIS, George A. KING, Mani UPRETI.				
	60/805,216	19-06-2006	US		(74) Agente: JUAN PABLO CADENA SARMIENTO				
	60/889,318	12-02-2007	US		(87) Publicación internacional				
(85) Fecha inicio fase nacional: 19-01-2009					Fecha: 27-12-2007				
(86) Datos relativos a la presentación de la solíc. PCT					No. publicación: WO 2007/149672 A3				
Fecha de presentación de la solicitud: 23-05-2007									
No. de solicitud: PCT/US2007/069548									
(54) Título: COMPOSICIÓN DE REBAUDIOSIDA A Y MÉTODO PARA PURIFICAR REBAUDIOSIDA A									

(55) Reivindicaciones:

1.- Un método para purificar rebaudiosida A que comprende los pasos de:

combinar rebaudiosida A cruda y una solución orgánica acuosa para formar una solución de rebaudiosida A, la rebaudiosida A cruda comprendiendo rebaudiosida A en un pureza de alrededor de 40% a alrededor de 85% en peso sobre una base seca, y la solución orgánica acuosa comprendiendo agua en una cantidad de alrededor de 10% a alrededor de 25% en peso; y

crystalizar la solución de rebaudiosida A en un solo paso una composición de rebaudiosida A que comprende rebaudiosida A en una pureza mayor de alrededor de 95% en peso sobre una base seca.

Y la composición substancialmente pura hecha de conformidad con dicho método.

109230
1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 December 2007 (27.12.2007)

PCT

(10) International Publication Number
WO 2007/149672 A3

- (51) International Patent Classification:
A23L 1/236 (2006.01) C07H 1/08 (2006.01)
- (21) International Application Number:
PCT/US2007/069548
- (22) International Filing Date: 23 May 2007 (23.05.2007)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/805,216 19 June 2006 (19.06.2006) US
60/889,318 12 February 2007 (12.02.2007) US

(74) Agents: PAPPAS, Peter, G. et al.; Sutherland Asbill & Brennan LLP, 999 Peachtree Street, NE, Atlanta, GA 30309-3996 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(71) Applicant (for all designated States except US): THE COCA-COLA COMPANY [US/US]; Patents, One Coca-cola Plaza, NW, Atlanta, GA 30313 (US).

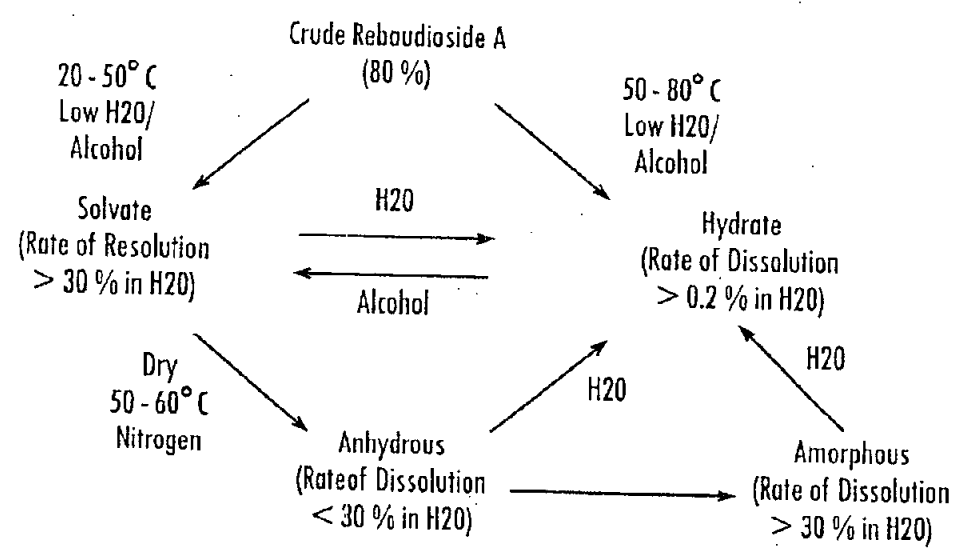
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors: PRAKASH, Indra; 9750 Talisman Drive, Alpharetta, Georgia 30022 (US). DUBOIS, Grant, E.; 215 Quincy Lane, Roswell, GA 30076 (US). KING, George, A.; 1755 Wildwood Road, Atlanta, Georgia 30306 (US). UPRETI, Mani; 1943 Rotherham Way, Dunwoody, Georgia 30338 (US).

Published:
— with international search report

[Continued on next page]

(54) Title: REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A



(57) Abstract: Exemplary embodiments of this invention encompass a method for purifying crude rebaudioside A. In particular, this invention relates to a method for purifying crude rebaudioside A compositions comprising purities from approximately 40 % to approximately 95 % rebaudioside A to obtain a substantially pure rebaudioside A product with a single crystallization step. Resulting polymorph and amorphous forms of rebaudioside A and methods for preparing polymorph and amorphous forms of rebaudioside A from crude rebaudioside A compositions and substantially pure rebaudioside A compositions also are disclosed.

WO 2007/149672 A3

WO 2007/149672 A3



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
10 April 2008

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/069548

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23L1/236 C07H1/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A23L C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/083838 A1 (JACKSON MEL C [US] ET AL) 20 April 2006 (2006-04-20) claims 1-20; tables 3,6	1-4, 6-13, 18-42
X	CA 2 278 083 A1 (ALBERTA RES COUNCIL [CA]) 20 January 2001 (2001-01-20) claim 1; example 5	1-4, 6-12, 14, 18-32, 34-42
X	DATABASE WPI Week 198145 Derwent Publications Ltd., London, GB; AN 1981-82360D XP002469089 & JP 56 121455 A (AJINOMOTO KK) 24 September 1981 (1981-09-24) abstract	1, 35-39, 42
-/--		

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *I* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

14 February 2008

Date of mailing of the international search report

25/02/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,

Authorized officer

Grah Riann

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/069548

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/038221 A (COUNCIL SCIENT IND RES [IN]; KUMAR JONNALA KOTESH [IN]; BABU GARIKAPAT) 13 April 2006 (2006-04-13) pages 4-7	35-39, 42
X	US 4 082 858 A (MORITA TOYOSHIGE ET AL) 4 April 1978 (1978-04-04) claim 1; example 1	35-39, 42
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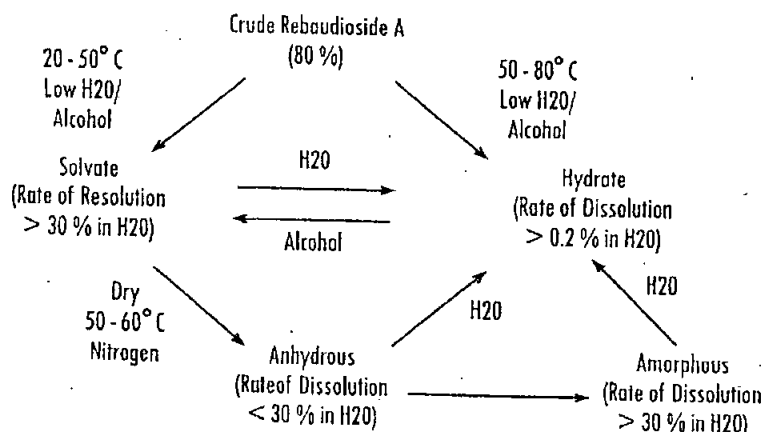
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(54) Title: REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A



(57) Abstract: Exemplary embodiments of this invention encompass a method for purifying crude rebaudioside A. In particular, this invention relates to a method for purifying crude rebaudioside A compositions comprising purities from approximately 40 % to approximately 95 % rebaudioside A to obtain a substantially pure rebaudioside A product with a single crystallization step. Resulting polymorph and amorphous forms of rebaudioside A and methods for preparing polymorph and amorphous forms of rebaudioside A from crude rebaudioside A compositions and substantially pure rebaudioside A compositions are also disclosed.

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REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A

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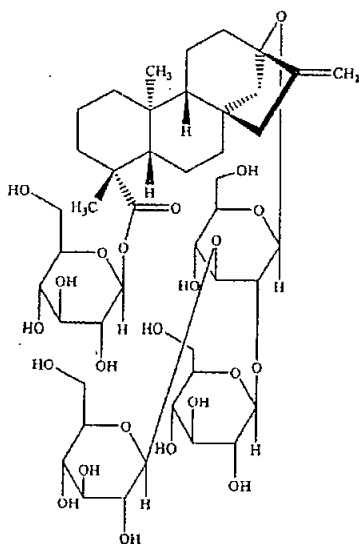
FIELD OF INVENTION

This invention relates generally to polymorphic and amorphous forms of rebaudioside A, methods for purifying rebaudioside A, and methods for preparing polymorphic and amorphous forms of rebaudioside A. More particularly, this invention relates to polymorphic and amorphous forms of rebaudioside A and methods
10 for the purification or crystallization of rebaudioside A with aqueous organic solvents or organic solvents to obtain a product in high yield and high purity.

BACKGROUND OF INVENTION

Rebaudioside A is a high-potency diterpenoid glycoside sweetener having the chemical structure:

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Rebaudioside A is isolated and extracted, along with other steviol glycosides, from the *Stevia rebaudiana* (Bertoni) plant ("Stevia"), which is commercially cultivated in
20 Japan, Singapore, Taiwan, Malaysia, South Korea, China, Israel, India, Brazil, Australia, and Paraguay. It is an alternative non-caloric sweetener with functional and

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sensory properties superior to those of many high-potency sweeteners. Processed forms of *Stevia* can be 70 to 400 times more potent than sugar; however, *Stevia* also has a bitter component. Of the four major diterpenoid glycoside sweeteners present in *Stevia*, rebaudioside A has been identified as the least bitter, and with the least persistent aftertaste. Bitterness often is significantly due to the impurities in extracts.

Rebaudioside A is generally available at ≤ 80 % pure. The primary impurities comprise stevioside, steviolbioside, rebaudioside B, rebaudioside C, rebaudioside D, dulcoside A, rebaudioside F, and other steviol glycosides. It is very difficult to obtain a high purity of rebaudioside A in high recovery because the rebaudioside A and the impurities have similar solubilities.

Previously reported efforts to purify rebaudioside A from mixtures of rebaudioside A and stevioside require numerous repeated purification steps. U.S. Patent No. 5,962,678 discloses the re-crystallization of rebaudioside A using an anhydrous methanol solution to obtain an 80 % pure rebaudioside A. By repeating the re-crystallization with anhydrous methanol numerous times, the purity of rebaudioside A may be increased to over 95 %. U.S. Patent Publication No. 2006/0083838 discloses purification of rebaudioside A through re-crystallization with a solvent comprising ethanol and between 4 and 15 % water. Japanese Patent Application No. 55-23756 discloses a method for purifying rebaudioside A and stevioside by crystallization from aqueous ethanol (> 70 %) to obtain an 80 % pure rebaudioside A. U.S. Patent Publication No. 2007/0082103 discloses a method for purifying rebaudioside A by recrystallization from aqueous ethanol, asserting a two-step recrystallization from crude rebaudioside (60 %) results in the formation of > 98 % pure rebaudioside at 97 % yield. These prior art methods, however, do not provide a substantially pure rebaudioside A composition using only a single recrystallization step.

Accordingly, there exists a need for a simple, efficient, and economical method for producing substantially pure rebaudioside A.

SUMMARY OF INVENTION

Exemplary embodiments of the invention address the above-identified need by providing a substantially pure rebaudioside A, polymorphic and amorphous forms of

rebaudioside A, methods for purifying rebaudioside A, and methods for making polymorphic and amorphous forms of rebaudioside A.

In a particular embodiment, the method for purifying rebaudioside A comprises a simple crystallization. In one embodiment, a method for purifying rebaudioside A comprises combining crude rebaudioside A and an aqueous organic solvent to form a rebaudioside A solution, the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight, and crystallizing from the crude rebaudioside A solution, in a single step, a substantially pure rebaudioside A in a purity greater than about 95% by weight on a dry basis.

In other particular embodiments, different polymorphic and amorphous forms of rebaudioside A and methods for preparing different polymorphic and amorphous forms of rebaudioside A are provided.

Other objects, features, and advantages of the invention will be apparent from the following detailed description, drawings, and claims. Unless otherwise defined, all technical and scientific terms and abbreviations used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and compositions similar or equivalent to those described herein can be used in the practice of the present invention, suitable methods and compositions are described without intending that any such methods and compositions limit the invention herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustrating a method for purifying rebaudioside A in accordance with an embodiment of this invention.

Fig. 2 is a schematic of the formation and conversion of rebaudioside A polymorphic and amorphous forms of rebaudioside A in accordance with an embodiment of this invention.

Fig. 3 is a powder x-ray diffraction scan comparing four rebaudioside A polymorphs, Forms 1, 2, 3A and 3B, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 4 is a powder x-ray diffraction scan comparing rebaudioside A polymorphs, Form 1 and Form 2, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 5 is a powder x-ray diffraction scan comparing rebaudioside A polymorphs, Form 3A and Form 3B, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 6 is a powder x-ray diffraction scan comparing rebaudioside A polymorphs, Forms 2, 3A and 3B, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 7 is a powder x-ray diffraction scan of rebaudioside A polymorph Form 1 on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 8 is a powder x-ray diffraction scan of rebaudioside A polymorph Form 2 on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 9 is a powder x-ray diffraction scan of rebaudioside A polymorph Form 3A on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 10 is a powder x-ray diffraction scan of rebaudioside A polymorph Form 3B on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 11 is a powder x-ray diffraction scan of rebaudioside A amorphous Form 4 on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

DETAILED DESCRIPTION OF INVENTION

Rebaudioside A is a natural high-potency sweetener that generally is available at moderate cost at $\leq 80\%$ purity and at $> 80\%$ purity only at high cost. Commercial samples of rebaudioside A often have a bitter taste that is believed to be due to impurities. Accordingly, there exists a need for a substantially pure rebaudioside A and

a simple and economic method for purifying rebaudioside A in order to obtain a substantially pure rebaudioside A suitable for use as a natural high-potency sweetener.

As used herein, the term "substantially" or "substantially pure" refers to a rebaudioside A composition that includes at least about 85 % by dry weight of the rebaudioside A, in another embodiment at least about 90 % by dry weight, in another embodiment from about 95 % to about 98 % by dry weight, and in yet another embodiment from about 99 % to about 100 % by dry weight.

Exemplary embodiments of this invention satisfy these needs by providing a method for purifying crude rebaudioside A to substantially pure rebaudioside A by crystallizing a crude rebaudioside A from an aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight and crystallizing in at least one step a substantially pure rebaudioside A. Other exemplary embodiments of this invention encompass a composition of a substantially pure rebaudioside A and compositions comprising one, or more than one, polymorph(s) of rebaudioside A. Still other exemplary embodiments of this invention encompass an amorphous form of rebaudioside A and methods of preparing amorphous forms of rebaudioside A. In yet another embodiment, a method for converting one form of polymorph into another form of polymorph or amorphous form is provided. Exemplary embodiments of this invention are described in detail below and illustrated in Figures 1-11.

Method of Purifying Crude Rebaudioside A Mixture

Crude rebaudioside A products are commercially available comprising rebaudioside A in purities from about 40 % to about 95 % by weight, about 60 % to about 85 % by weight, or about 70 % to about 85 % by weight. It is envisioned that crude rebaudioside A in its raw form as extracted from Stevia plants, may be purified by recrystallization. The primary impurities, identified by HPLC, are stevioside, rebaudioside B, rebaudioside C, and rebaudioside D. Rebaudioside D impurities can be removed by increasing the amount of water in an aqueous organic recrystallization solvent; however, excessive water content in the crystallization solvent will result in a lower recovery of rebaudioside A. Rebaudioside B impurity can be reduced significantly by slurring the crude rebaudioside A in an organic solvent or an aqueous organic solution or through treatment of the crude rebaudioside A solution with an

anion exchange resin. Accordingly, the method of purification depends on the impurities present in the crude rebaudioside A starting material.

In an exemplary embodiment of a method for purifying rebaudioside A 110, illustrated in Figure 1, crude rebaudioside A 112 may be combined 114 with an aqueous organic solution 116 to form a rebaudioside A solution 118. The aqueous organic solution 116 comprises water in an amount from about 10 % to about 25 % by weight and at least one organic solvent. Alternatively, the aqueous organic solution 116 may comprise water in an amount from about 15 % to about 20 % by weight and at least one organic solvent.

Aqueous organic solvents, as used herein, refer to mixtures of water and at least one organic solvent. Non-limiting examples of organic solvents include alcohol, acetone, and acetonitrile. Alcohol, as used herein, refers to any straight, branched, or cyclic; substituted or unsubstituted alkyl, alkenyl, or alkynyl group attached to at least one hydroxyl moiety. Non-limiting examples of alcohols include ethanol, methanol, isopropanol, 1-propanol, 1-butanol, 2-butanol, tert-butanol, and isobutanol.

In an exemplary embodiment, the aqueous organic solution 116 comprises a mixture of water and at least one organic solvent. In another exemplary embodiment, at least one organic solvent comprises an alcohol, the alcohol comprising ethanol, methanol, or mixtures thereof. In exemplary embodiments wherein the at least one organic solvent comprises a mixture of ethanol and methanol, the ethanol and methanol may be combined in the aqueous organic solvent in a weight ratio ranging from about 20 parts to about 1 part ethanol to about 1 part methanol. In another exemplary embodiment, the ethanol and methanol may be combined in the aqueous organic solvent in a weight ratio ranging from about 3 parts to about 1 part ethanol to about 1 part methanol.

In an exemplary embodiment, the rebaudioside A solution 118 comprises the aqueous organic solvent 116 and the crude rebaudioside A 112 in a weight ratio ranging from about 10 to about 4 parts aqueous organic solvent to about 1 part crude rebaudioside A. In another exemplary embodiment, the rebaudioside A solution 118 comprises the aqueous organic solution 116 and the crude rebaudioside A 112 in a

weight ratio ranging from about 5 to about 3 parts aqueous organic solvent to about 1 part crude rebaudioside A.

In an exemplary embodiment, the method 110 may be carried out at approximately room temperature. In another embodiment, the method 110 further comprises the step of heating 120 the rebaudioside A solution 118. In an embodiment, the step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution to a temperature in a range from about 20°C to about 70°C, from about 20°C to about 60°C, from about 20°C to about 40°C, or from about 40°C to about 60°C. In another embodiment, the step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution to about reflux temperature. The step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution for about 0.25 hours to about 8 hours. In another exemplary embodiment, wherein the method for purifying rebaudioside A 110 comprises the step of heating 120 the rebaudioside A solution 118, the method further comprises the step of cooling 122 the rebaudioside A solution. In an embodiment, the step of cooling 122 the rebaudioside A solution 118 comprises cooling the rebaudioside A solution to a temperature in the range from about 4°C to about 25°C. The step of cooling 122 the rebaudioside A solution 118 comprises cooling the rebaudioside A solution for about 0.5 hours to about 24 hours.

The method for purifying rebaudioside A 110 further comprises the step of crystallizing 124 from the rebaudioside A solution 118 in a single step a substantially pure rebaudioside A composition 126 comprising rebaudioside A in an amount greater than about 85 % by weight on a dry basis, greater than about 90 % by weight on a dry basis, greater than about 95 % by weight on a dry basis, greater than about 97 % by weight on a dry basis, greater than about 98 % by weight on a dry basis, or greater than about 99 % by weight on a dry basis. The rebaudioside A solution 118 during the single crystallization step may be stirred or unstirred.

In an exemplary embodiment, the method 110 may further comprise the optional step of seeding 128 the rebaudioside A solution 118 at an appropriate temperature with substantially pure crystals of rebaudioside A 130 sufficient to promote crystallization of the rebaudioside A to form pure rebaudioside A. An amount of rebaudioside A 130 sufficient to promote crystallization of substantially pure

rebaudioside A 126 comprises an amount of rebaudioside A from about 0.0001 % to about 1 % by weight of the rebaudioside A present in the solution. In another embodiment, an amount of rebaudioside A 130 sufficient to promote crystallization of the rebaudioside A to form a composition of a substantially pure rebaudioside A 126
5 comprises an amount of rebaudioside A from about 0.01 % to about 1 % by weight. An appropriate temperature for the step of seeding 128 comprises a temperature in a range from about 18°C to about 35°C.

In another exemplary embodiment, the method further comprises the steps of separating 132 and washing 134 the substantially pure rebaudioside A composition 126.
10 The substantially pure rebaudioside A composition 126 may be separated from the aqueous organic solution 118 by a variety of solid-liquid separation techniques that utilize centrifugal force, that include, without limitation, vertical and horizontal perforated basket centrifuge, solid bowl centrifuge, decanter centrifuge, peeler type centrifuge, pusher type centrifuge, Heinkel type centrifuge, disc stack centrifuge and
15 cyclone separation. Additionally, separation may be enhanced by any pressure, vacuum, or gravity filtration methods, that include without limitation, the use of belt, drum, nutsche type, leaf, plate, Rosenmund type, sparkler type, and bag filters and filter press. Operation of the rebaudioside A solid-liquid separation device may be continuous, semi-continuous or in batch mode. The substantially pure rebaudioside A
20 composition 126 also may be washed 134 on the separation device using various aqueous organic solvents 136 and mixtures thereof. The substantially pure rebaudioside A composition 126 can be partially or totally dried on the separation device using any number of gases, including, without limitation, nitrogen or argon, to evaporate residual liquid solvent 136. The substantially pure rebaudioside A
25 composition 126 may be automatically or manually removed from the separation device using liquids, gases or mechanical means by either dissolving the solid or maintaining the solid form.

In still another exemplary embodiment, the method 110 further comprises the step of drying 138 the substantially pure rebaudioside A composition 126. Such
30 methods are known to those skilled in the art and include, but are not limited to, the use of a rotary vacuum dryer, fluid bed dryer, rotary tunnel dryer, plate dryer, tray dryer, Nauta type dryer, spray dryer, flash dryer, micron dryer, pan dryer, high and low speed

paddle dryer and microwave dryer. In an exemplary embodiment, the step of drying 138 comprises drying the substantially pure rebaudioside A composition 126 using a nitrogen or argon purge to remove the residual solvent 120 at a temperature in a range from about 40°C to about 60°C for about 5 hours to about 100 hours.

5 In yet another exemplary embodiment, wherein the crude rebaudioside A mixture 112 comprises substantially no rebaudioside D impurity, the method 110 further comprises the step of slurrying 140 the composition of substantially pure rebaudioside A 126 with an organic solvent or an aqueous organic solvent 142 prior to the step of drying 138 the substantially pure rebaudioside A composition. The slurry
10 may be a mixture comprising a solid and an aqueous organic solvent or organic solvent, wherein the solid comprises the substantially pure rebaudioside A composition 126 and is only sparingly soluble in the aqueous organic solvent or organic solvent 142. In an embodiment, the substantially pure rebaudioside A composition 126 and aqueous organic solvent or organic solvent 142 may be present in the slurry in a weight ratio
15 ranging from about 15 parts to about 1 part aqueous organic solvent to about 1 part substantially pure rebaudioside A composition. In one embodiment, the slurry may be maintained at room temperature. In another embodiment, the step of slurrying 140 comprises heating the slurry to a temperature in a range from about 20°C to about 40°C. The substantially pure rebaudioside A composition 126 may be slurried for about 0.5
20 hours to about 24 hours.

In still yet another exemplary embodiment, the method further comprises the steps of separating 132 the substantially pure rebaudioside A composition 126 from the aqueous organic solvent 142 of the slurry and washing 134 the substantially pure rebaudioside A composition followed by the step of drying 138 the substantially pure rebaudioside A composition.
25

If further purification is desired, the method of purifying rebaudioside A 110 described herein may be repeated or the substantially pure rebaudioside A composition may be further purified using an alternative purification method, such as the column chromatography.

30 Purity, as used herein, represents the weight percentage of rebaudioside A present in a rebaudioside A composition in raw or purified form. In one embodiment, a

rebaudioside A composition comprises rebaudioside A in a particular purity, with the remainder of the composition comprising a mixture of other steviol glycosides or any component that is not rebaudioside A. The purity of the composition may be measured using methods known to those of ordinary skill in the art. One such method includes high performance liquid chromatography (HPLC). Those of ordinary skill in the art also should appreciate that the moisture in the sample may affect the accuracy of purity measurements. Accordingly, the composition should be substantially dry when measured for purity. As used herein, a substantially dry composition comprises up to about 10 % by weight of moisture.

10

Rebaudioside A Polymorphic and Amorphous Forms

The purification of rebaudioside A using the method described hereinabove results in the formation of at least three different polymorphs of rebaudioside A: Form 1: a rebaudioside A hydrate; Form 2: an anhydrous rebaudioside A, and Form 3: a rebaudioside A solvate. Those of ordinary skill in the art will appreciate that both the aqueous organic solution and the temperatures of the purification process described herein may influence the resulting polymorphs of a substantially pure rebaudioside A composition.

Polymorphism is defined as the ability of a substance to exist as two or more crystalline states that have different arrangements and/or conformations of the molecules in the crystal lattice. Approximately 30 % of organic compounds are believed to exhibit polymorphism (Zell, et al., *Tetrahedron* 56(36)6603-16 (2000)). Polymorphism is important in the formulation of pharmaceuticals, pigments and dyes, sweeteners, explosives, and agrochemicals. Polymorphism may cause physical properties such as density, melting point, and rate of dissolution to change.

The polymorphs of rebaudioside A were identified by analysis of samples with powder x-ray diffraction (XRPD), a technique well known to those skilled in the art. Figs. 3-11 are XRPD scans of substantially pure rebaudioside A compositions obtained from the purification process described herein. The XRPD scans of rebaudioside A polymorphs were created by plotting the scattering intensity versus the scattering angle 2θ . Samples were analyzed by XRPD using a Shimadzu XRD-6000 X-ray powder diffractometer using Cu K α radiation. The instrument was equipped with a long fine

focus X-ray tube. The tube voltage and amperage were set to 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1°, and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A θ -2 θ continuous scan at 3°/min (0.4 sec/0.02° step) from 2.5 to 40° 2 θ was used. A silicon standard was analyzed to check the instrument alignment. Data were collected and analyzed using XRD-60000 v. 4.1. The patterns exhibit resolution of reflections, indicating that the samples are comprised of crystalline material.

Fig. 3 shows representative patterns for Form 1, Form 2, and Forms 3A (methanol solvate) and 3B (ethanol solvate). The pattern for Form 2 (top pattern) is distinctively different from the other patterns. It should be noted that multiple polymorphs can exist within each classification of Forms 1, 2, and 3.

Fig. 4 highlights the differences between Forms 1 and 2. Additionally, the two patterns of Form 2 are shown to illustrate the reproducibility in generation of the different polymorphs under varying recrystallization conditions of the polymorphs.

Fig. 5 shows a significant similarity between the XRPD patterns of Forms 3A and 3B. Not wishing to be bound by any theory, it is possible that these polymorphs are isostructural solvates, wherein the only differences between the patterns are the shifting of certain peaks due to the variation of the solvent identity. This isostructural relationship between Forms 3A and 3B could be verified by indexing the patterns if necessary. The asterisks identify the peaks that are shifted to the right by about 0.2 degrees 2 θ in the pattern for Form 3A. In addition, several peaks in Form 3B are more intense than the corresponding peaks in Form 3A. For example, the peaks at 5.5, 11.0, 14.2, and 19.4 degrees are more intense for Form 3B than for Form 3A.

Fig. 6 compares Form 2 to Forms 3A and 3B from Fig. 5. Form 2 is more similar to Form 3A than to that of Form 3B. Although the peaks identified in Fig. 5 as being more intense in Form 3B than in Form 3A are not observed in the pattern of Form 2, there are at least three peaks (marked with a double-asterisks underneath the patterns) that show the reverse trend (i.e., the peaks are present in Form 2, small in Form 3A, and larger in Form 3B). Finally, a large peak in Form 3B at 17.6 degrees appears to be shifted slightly to the right in Form 3A (17.9 degrees) and shifted further to the right in Form 2 (18.0 degrees). Two other sets of peaks between 21 and 23

degrees show this shifting as well. Not wishing to be bound by any theory, the shifting of the peaks may be an indication that Form 3A is partially desolvated, thus containing a mixture of both the solvate and Form 2 crystals.

Figs. 7-10 are XRPD scans of the individual polymorphs Form 1, Form 2, Form 3A, and Form 3B, respectively, from a substantially pure rebaudioside A composition obtained from the purification process described hereinabove.

As illustrated in Fig. 2, the type of polymorph formed may be dependent on the factors such as the composition of the aqueous organic solution, the temperature of the crystallization step, and the temperature during the drying step. Not wishing to be bound by any theory, Form 1 and Form 3 are believed to be formed during the single crystallization step while Form 2 is believed to be formed during the drying step after conversion from Form 1 and Form 3.

Low temperatures during the crystallization step, in the range of about 20°C to about 50°C, and a low ratio of water to the organic solvent in the aqueous organic solvent results in the formation of Form 3. High temperatures during the crystallization step, in the range of about 50°C to about 80°C, and a high ratio of water to the organic solvent in the aqueous organic solvent results in the formation of the Form 1. Form 1 can be converted to Form 3 by slurring in an anhydrous solvent at about room temperature for about 2 to about 16 hours or by slurring in an anhydrous solvent at about reflux temperature for about 0.5 to about 3 hours. Form 3 can be converted to Form 1 by slurring the polymorph in water at about room temperature for approximately 16 hours or at about reflux temperature for about 2 to about 3 hours. Form 3 can be converted to the Form 2 during the drying process; however, increasing either the drying temperature above about 70°C or the drying time of a substantially pure rebaudioside A composition can result in decomposition of the rebaudioside A and increase the remaining rebaudioside B impurity in the substantially pure rebaudioside A composition. Form 2 can be converted to Form 1 with the addition of water.

In addition to the at least three polymorphic forms of rebaudioside A, the purification of rebaudioside A may result in the formation of an amorphous form of rebaudioside A, Form 4, as shown in Fig. 11. Form 4 has a broad amorphous halo that identifies the composition as being amorphous.

Amorphous, as used herein, describes a non-crystalline solid material. The amorphous form of rebaudioside A (Form 4) has an improved rate of dissolution as compared to the polymorphic forms of rebaudioside A (Forms 1, 2, or 3). Those of ordinary skill in the art should appreciate that the rate of dissolution of a sweetener composition may be important in the formulation of solid and liquid sweetenable compositions, non-limiting examples of which include chewing gum, baked goods, and beverages.

As described hereinabove, Form 4 may be obtained during the initial purification of rebaudioside A or directly from any individual polymorph or combination of polymorphs using methods well known to those of ordinary skill in the art. In addition, Form 4 may be obtained from a crude rebaudioside A composition or a substantially pure rebaudioside A composition obtained through purification means other than those described hereinabove. Non-limiting examples of methods for preparing amorphous forms of rebaudioside A include ball milling, precipitation, lyophilization, cryogrinding, and spray-drying of a rebaudioside A composition.

In a particular embodiment, the purification of rebaudioside A described hereinabove results in a composition comprising the amorphous rebaudioside A of Form 4. Those of ordinary skill in the art should appreciate that the parameters of the crystallization procedure may be modified to enhance the formation of Form 4.

In another particular embodiment, Form 4 can be prepared from a rebaudioside A composition by spray-drying a solution of the rebaudioside A composition. Briefly described, spray-drying generally requires the feed of a solution of rebaudioside A through a feed pump into a nozzle atomizer which atomizes the solution into a spray of droplets with the help of a constant flow of nitrogen/air. The moisture is evaporated from the droplets under controlled temperature conditions and airflow conditions in the drying chamber, resulting in the formation of dry particles of amorphous rebaudioside A. The purity of the amorphous rebaudioside A will depend upon the purity of the solution of rebaudioside A.

In another particular embodiment, Form 4 can be prepared from a rebaudioside A composition by milling non-amorphous forms of rebaudioside A. Milling is a mechanical process that is believed to produce localized areas of energy that convert

crystalline forms of rebaudioside A to the amorphous form. Exemplary milling techniques include ball milling or air jet milling, both techniques well known to those of ordinary skill in the art. Briefly described, non-amorphous forms of rebaudioside A are milled for a period of time and at a speed effective to form an amorphous rebaudioside A. These parameters may be determined by those of ordinary skill in the art. Typical milling time periods may range from about 15 minutes to about 2 hours, although other time periods also may be employed.

The material properties of the three rebaudioside A polymorphs and the rebaudioside A amorphous form are summarized in the following table:

Table 1: Rebaudioside A Polymorph and Amorphous Forms

	Form 1 Polymorph	Form 2 Polymorph	Form 3 Polymorph	Form 4 Amorphous
Rate of dissolution in H2O at 25°C	Very low (<0.2 % in 60 minutes)	Intermediate (<30 % in 5 minutes)	High (> 30 % in 5 minutes)	High (> 35 % in 5 minutes)
Alcohol content	< 0.5 %	< 1 %	1-3 %	< 0.05 %
Moisture content	> 5 %	< 1 %	< 3 %	< 6 %

The above-described material properties are only illustrative of particular embodiments of the polymorphic and amorphous forms of rebaudioside A. Those of ordinary skill in the art should appreciate that the anhydrous rebaudioside A polymorph (Form 2), rebaudioside A solvate polymorph, and amorphous rebaudioside A are hygroscopic and may absorb moisture to an amount up to about 10 % by weight on a dry basis.

Those of ordinary skill in the art should appreciate that the rebaudioside A composition may be modified to obtain a desired mixture of rebaudioside A polymorphic and amorphous forms depending on the desired qualities of the rebaudioside A composition (i.e., rate of dissolution, etc.). In one embodiment, a substantially pure rebaudioside A composition may comprise a particular polymorphic or amorphous form of rebaudioside A in an amount in the range of about 1 % to about 100 % by weight. For example, a substantially pure rebaudioside A composition may comprise a polymorphic or amorphous form of rebaudioside A in an amount greater than about 25 % by weight, more particularly in an amount greater than about 50 % by weight, still more particularly in an amount greater than about 75 % by weight, or still even more particularly in an amount greater than about 85 % by weight. Suitable amounts of rebaudioside A polymorphic or amorphous forms also may be used within

these ranges. In another embodiment, a substantially pure rebaudioside A composition may comprise a combination of particular polymorphic and/or amorphous form of rebaudioside A.

The present invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications, and equivalents thereof which, after reading the description therein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or the scope of the appended claims. Unless otherwise specified, percentages (%) are by weight.

EXAMPLES

The purity of the rebaudioside A compositions described in the examples hereinbelow was determined using HPLC. Methods of performing HPLC analysis are well known to those of ordinary skill in the art. Briefly described, the HPLC analysis was performed using a ZORBAX NH₂ column (150 x 4.6 mm, 5 μ m) at a temperature of 30°C. The mobile phase comprised a solution of 20 % buffer (0.0125 % acetic acid and 0.0125 % ammonium acetate) and 80 % acetonitrile at a flow rate of 1.5 mL/min. 12 μ L of each sample was injected in duplicate and the sample was analyzed using a UV detector at 210 nm (4 nm bandwidth) with a reference of 260 nm (100 nm bandwidth). The HPLC analysis required a run time ranging from 40 to 60 min.

A buffer solution of 0.0125 % acetic acid and 0.0125 % ammonium acetate was prepared by dissolving 0.125 g ammonium acetate and 125 μ L glacial acetic acid in one liter of water. The retention time of rebaudioside B was adjusted by varying the ratio of ammonium acetate to acetic acid while maintaining a total of 0.025 % of both combined. Increasing the amount of acetic acid decreased the retention time of rebaudioside B.

The mobile phase was prepared by mixing the buffer solution with acetonitrile to achieve a rebaudioside A retention time of 7.0 ± 0.5 min. Initially, this was approximately 20 % buffer (200 mL of buffer and 800 mL of acetonitrile). Increasing the amount of acetonitrile by 1 to 2 % increased the retention time of rebaudioside A by about one minute.

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A diluent solution was prepared by mixing 750 mL of acetonitrile and 250 mL of the buffer solution. Rebaudioside A standards were prepared by diluting 20.0 ± 0.5 mg (recorded to the nearest 0.1 mg) of the rebaudioside A standard with 4 mL of the diluent solution to make a standard solution of approximately 5000 mg/L. The rebaudioside A standard solution was injected at 10.8, 11.4, 12.6 and 13.2 μ L. The moisture content was measured by Karl Fischer analysis every time a standard was prepared and corrections were made based on the solvent purity according to the certificate of analysis. Alternatively, rebaudioside A standards were prepared by diluting individual samples of 18, 19, 21 and 22 (each ± 0.2) mg of rebaudioside A standard with 4 mL of the diluent solution (correcting for moisture and purity). The individually prepared samples were injected at the same level as the samples (12 μ L).

Stevioside standards were prepared by diluting 12.5 ± 0.5 mg (recorded to the nearest 0.1 mg) of the stevioside standard with 5 mL of the diluent solution to make a standard solution of approximately 2500 mg/L standard (stock A) (correcting for moisture and purity). The stevioside standard was then diluted using one mL of stock A to ten mL of diluent to produce a 250 mg/L standard (stock B), and stock standards were diluted to final concentrations ranging from 2.5 to 50 mg/L.

Samples of the rebaudioside A compositions were prepared by diluting 125 ± 2 mg (recorded to the nearest 0.1 mg) of the rebaudioside A composition with 25 mL of the diluent solution to make a sample solution of approximately 5000 mg/L (correcting for moisture). If the samples were not analyzed immediately, they were stored without headspace, under nitrogen, and desiccated.

The following table provides a guideline for retention times (RT) for rebaudioside A and other steviol glycosides. However, those of ordinary skill in the art should appreciate that the retention times may be modified as needed.

Table 2: HPLC Retention Guidelines

Compound	RT (min)
Stevioside	4.53
Rebaudioside C	5.21
Rebaudioside F	5.62
Rebaudioside A	7.07
Rebaudioside D	15.79
Steviolbioside	18.35
Rebaudioside B	35.83

EXAMPLE SET A

Table 3: Summary of Examples A1-3

	Crude Rebaudioside A (g)	Ethanol (95 %)(mL)	Solvent Methanol (99 %)(mL)	Water (mL)	Heating T (°C)	Drying T (°C)	Yield (g)	HPLC Purity (wt/wt %)
A1	400	1200	400	320	50	50	130	98.9
A2	100	320	120	50	30-40	60	72	98.3
A3	50	160	60	25	~ 30	60	27.3	98.2

EXAMPLE A1

Crude rebaudioside A (77.4 % purity) mixture was obtained from a commercial source. The impurities (6.2 % stevioside, 5.6 % rebaudioside C, 0.6 % rebaudioside F, 1.0 % other steviol glycosides, 3.0 % rebaudioside D, 4.9 % rebaudioside B, 0.3 % steviolbioside) were identified and quantified using HPLC on a dry basis (moisture content 4.7 %).

Crude rebaudioside A (400 g), ethanol (95 %, 1200 mL), methanol (99 %, 400 mL) and water (320 mL) were combined and heated to 50°C for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystals were filtered and washed twice with ethanol (2 x 200 mL, 95%) and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm).

The final composition of substantially pure rebaudioside A (130 g) comprised 98.91 % rebaudioside A, 0.06 % stevioside, 0.03 % rebaudioside C, 0.12 %

rebaudioside F, 0.13 % other steviol glycosides, 0.1 % rebaudioside D, 0.49 % rebaudioside B and 0.03 % steviolbioside, all by weight.

EXAMPLE A2

5 Crude rebaudioside A (80.37 %) was obtained from a commercial source. The impurities (6.22 % stevioside, 2.28 % rebaudioside C, 0.35 % dulcoside A, 0.78 % rebaudioside F, 0.72 % other steviol glycosides, 3.33 % rebaudioside B, 0.07 % steviolbioside) were identified and quantified by HPLC on a dry basis (moisture content 3.4 %).

10 Crude rebaudioside A (100 g), ethanol (95%, 320 mL), methanol (99%, 120 mL) and water (50 mL) were combined and heated to 30-40°C for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystals were filtered and washed twice with ethanol (2 x 50 mL, 95 %). The wet filter cake (88 g) was slurried in ethanol (95 %, 1320 mL) for 16 hours, filtered, washed with ethanol (95 %, 2 x 100 mL) and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm).

The final composition of substantially pure rebaudioside A (72 g) comprised 98.29 % rebaudioside A, 0.03 % stevioside, 0.02 % rebaudioside C, 0.17 % rebaudioside F, 0.06 % rebaudioside D and 1.09 % rebaudioside B. Steviolbioside was not detected by HPLC.

EXAMPLE A3

Crude rebaudioside A (80.37 %) was obtained from a commercial source. The impurities (6.22 % stevioside, 2.28 % rebaudioside C, 0.35% dulcoside A, 0.78 % rebaudioside F, 0.72 % other steviol glycosides, 3.33 % rebaudioside B, 0.07 % steviolbioside) were identified and quantified by HPLC on a dry basis (moisture content 3.4 %).

Crude rebaudioside A (50 g), ethanol (95 %, 160 mL), methanol (99 %, 60 mL) and water (25 mL) were combined and heated to approximately 30°C for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystals were filtered and washed twice with ethanol (2 x 25 mL, 95 %). The wet filter cake (40 g) was

slurried in methanol (99 %, 600 mL) for 16 hours, filtered, washed with methanol (99 %, 2 x 25 mL) and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm).

The final composition of substantially pure rebaudioside A (27.3g) comprised 98.22 % rebaudioside A, 0.04 % stevioside, 0.04 % rebaudioside C, 0.18 % rebaudioside F, 0.08 % rebaudioside D and 1.03 % rebaudioside B. Steviolbioside was not detected by HPLC.

EXAMPLE SET B

Table 4: Summary of Examples B1-19

	Crude Rebaudioside A (g)	Solvent			Wash Solvent	Yield (g)	HPLC Purity (%)
		Ethanol (95%)(mL)	Organic Co-solvent (mL)	Water (mL)			
B1	5	16	Methanol (6)	2	EtOH/MeOH (4:1.5 v/v)	3.2	>97
B2	5	16	Methanol (4)	2	EtOH/MeOH (4:1 v/v)	3.1	>97
B3	5	9.5	1-Butanol (9.5)	1	EtOH/1-Butanol (1:1 v/v)	3.2	>95
B4	5	9.5	1-Butanol (9)	1	EtOH/MeOH (1:1 v/v)	3.5	>96
B5	5	12.5	Methanol (6)	2	*EtOH/MeOH (4:1 v/v)	3.3	>97
B6	5	12.5	Acetonitrile (6)	1.5	*EtOH/Acetonitrile (6:3 v/v)	3.4	>95
B7	5	14.5	Ethyl acetate (4)	4	*EtOH/Ethyl Acetate (7:2 v/v)	3.4	>95
B8	5	16	Methanol (6)	2	EtOH/MeOH (4:1.5 v/v)	3.2	>97
B9	5	16	Methanol (4)	2	EtOH/MeOH (4:1 v/v)	3.1	>97
B10	5	14.5	Methanol (4)	1.5	EtOH/MeOH (7:2 v/v)	3.4	>97
B11	5	16	Methanol (6)	1.5	EtOH/MeOH (8:3 v/v)	3.2	>97
B12	5	16	Methanol (6)	2	*EtOH/MeOH (8:3 v/v)	3.2	>96
B13	5	16	Methanol (6)	2	*EtOH/MeOH (8:3 v/v)	3.4	>96
B14	5	15	Methanol (5)	2.5	EtOH/MeOH (3:1 v/v)	3.2	>97
B15	5	15	Methanol (5)	3	EtOH/MeOH (3:1 v/v)	2.7	>97
B16	5	15	Methanol (6)	3.5	EtOH/MeOH (3:1 v/v)	2.6	>99
B17	5	15	Methanol (5)	4	EtOH/MeOH (3:1 v/v)	2.3	>99
B18	5	16	Methanol (6)	2.5	*EtOH/MeOH (8:3 v/v)	3.0	>97
B19	5	16	Methanol (6)	2.5	*EtOH/MeOH (8:3 v/v)	3.2	>98

EXAMPLE B1

Crude rebaudioside A (77.4 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5 mL, 4:1.5, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 97 % by HPLC).

EXAMPLE B2

Crude rebaudioside A (77.4 % purity, 5 g), ethanol (95 %, 16 mL), methanol (4 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5 mL, 4:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.1 g of purified product (> 97 % by HPLC).

EXAMPLE B3

Crude rebaudioside A (77.4 % purity, 5 g), ethanol (95 %, 9.5 mL), 1-butanol (9.5 mL) and water (1 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:1-butanol (5 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 95 % by HPLC).

EXAMPLE B4

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 9.5 mL), methanol (9 mL) and water (1 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.5 g of purified product (> 96 % by HPLC).

EXAMPLE B5

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 12.5 mL), methanol (6 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C. The solution was seeded with 10 mg of 98 % pure rebaudioside A and the mixture was left at 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5 mL, 4:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.3 g of purified product (> 97 % by HPLC).

EXAMPLE B6

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 12.5 mL), acetonitrile (6 mL) and water (1.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C. The solution was seeded with 10 mg of 98 % pure rebaudioside A and the mixture was left at 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:acetonitrile (5 mL, 6:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.4 g of purified product (> 95 % by HPLC).

EXAMPLE B7

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 14.5 mL), ethyl acetate (4 mL) and water (1.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C. The solution was seeded with 10 mg of 98 % pure rebaudioside A and the mixture was left at 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:acetonitrile (5 mL, 7:2, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.4 g of purified product (> 95 % by HPLC).

EXAMPLE B8

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.5 mL, 4:1.5, v/v) mixture and dried in a

vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 97 % by HPLC).

EXAMPLE B9

5 Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (4 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 4:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.1 g of purified product (> 97 % by HPLC).

10 EXAMPLE B10

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 14.5 mL), methanol (4 mL) and water (1.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 7:2, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.4 g of purified product (> 97 % by HPLC).

EXAMPLE B11

20 Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (1.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 97 % by HPLC).

EXAMPLE B12

25 Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C and seeded with 10 mg of pure rebaudioside A (> 98 %). The mixture was kept at room temperature for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried

in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 98 % by HPLC).

EXAMPLE B13

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol
5 (6 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C and seeded with 10 mg of pure rebaudioside A (> 98 %). The mixture was kept at room temperature for 16 hours while stirring. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure
10 (20 mm) to yield 3.4 g of purified product (> 96 % by HPLC).

EXAMPLE B14

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 15 mL), methanol
(5 mL) and water (2.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours while stirring. The white crystalline
15 product was filtered, washed twice with ethanol:methanol (5.0 mL, 3:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 97 % by HPLC).

EXAMPLE B15

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 15 mL), methanol
20 (5 mL) and water (3.0 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours while stirring. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 3:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 2.7 g of purified product (> 97 % by HPLC).

25 EXAMPLE B16

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 15 mL), methanol
(5 mL) and water (3.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours while stirring. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 3:1, v/v) mixture

and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 2.6 g of purified product (> 99 % by HPLC).

EXAMPLE B17

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 15 mL), methanol
5 (5 mL) and water (4.0 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours while stirring. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 3:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 2.3 g of purified product (> 99 % by HPLC).

10 EXAMPLE B18

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol
(6 mL) and water (2.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C. This mixture was stirred at room temperature for 15-
30 minutes during which time crystals started to appear. The stirring was stopped and
15 the mixture was kept at room temperature for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.0 g of purified product (> 97 % by HPLC).

EXAMPLE B19

20 Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (2.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 2 hours. During this time crystals started to appear. The mixture was stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 8:3, v/v) mixture
25 and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 98 % by HPLC).

EXAMPLE SET C

Table 5: Summary of Examples C1-9

	Crude Rebaudioside A (g)	Solvent			Wash Solvent	Yield (g)	HPLC Purity (%)
		Organic Solvent (mL)	Organic Co-solvent (mL)	Water (mL)			
C1	5	Isopropanol (9.5)	Methanol (9.5)	1	Isopropanol/MeOH (1:1 v/v)	3.85	>91
C2	5	<i>sec</i> -Butanol (9.5)	Methanol (9.5)	1	MeOH/ <i>sec</i> -Butanol (1:1 v/v)	4.0	>91
C3	5	1-Propanol (9.5)	Methanol (9.5)	1	MeOH/1-Propanol (1:1 v/v)	3.55	>91.2
C4	5	Ethanol (9.5)	1-Propanol (9.5)	1	EtOH/1-Propanol (1:1 v/v)	2.5	>94
C5	5	1-Butanol (9.5)	Methanol (9.5)	1	MeOH/1-Butanol (1:1 v/v)	3.7	>91.5
C6	5	Ethanol (9.5)	2-Propanol (9.5)	1	EtOH/2-Propanol (1:1 v/v)	2.4	>93.5
C7	5	Ethanol (9.5)	<i>sec</i> - Butanol (9.5)	1	EtOH/ <i>sec</i> -Butanol (1:1 v/v)	2.9	>93
C8	5	<i>tert</i> -Butanol (9.5)	Methanol (9.5)	1	MeOH/ <i>tert</i> -Butanol (1:1 v/v)	3.9	>83
C9	5	Ethanol (9.5)	<i>tert</i> - Butanol (9.5)	1	EtOH/ <i>tert</i> -Butanol (1:1 v/v)	2.9	>88

EXAMPLE C1

Crude rebaudioside A (80.37 % purity, 5 g), methanol (99 %, 9.5 mL), isopropanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with an ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.85 g of purified product (> 91.0 % by HPLC).

EXAMPLE C2

Crude rebaudioside A (80.37 % purity, 5 g), methanol (99 %, 9.5 mL), *sec*-butanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with a methanol: *sec*-butanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 4.0 g of purified product (> 91.0 % by HPLC).

EXAMPLE C3

Crude rebaudioside A (80.37 % purity, 5 g), methanol (99 %, 9.5 mL), 1-propanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with a methanol: 1-propanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.55 g of purified product (> 91.21 % by HPLC).

EXAMPLE C4

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 9.5 mL), 1-propanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with an ethanol: 1-propanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 2.5 g of purified product (> 94.0 % by HPLC).

EXAMPLE C5

Crude rebaudioside A (80.37 % purity, 5 g), methanol (99 %, 9.5 mL), 1-butanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with a methanol: 1-butanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.7 g of purified product (> 91.5 % by HPLC).

EXAMPLE C6

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 9.5 mL), 2-propanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with an ethanol: 2-propanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24

hours under reduced pressure (20 mm) to yield 2.4 g of purified product (> 93.5 % by HPLC).

EXAMPLE C7

Crude rebaudioside A (77.4 % purity, 5 g), ethanol (95 %, 9.5 mL), *sec*-butanol
5 (9.5 mL) and water (1 mL) were combined and heated to reflux for 10 minutes. The
clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for
16 hours. The white crystalline product was filtered, washed twice with an ethanol: *sec*-
butanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24
hours under reduced pressure (20 mm) to yield 2.9 g of purified product (> 93.0 % by
10 HPLC).

EXAMPLE C8

Crude rebaudioside A (77.4 % purity, 5 g), methanol (99 %, 9.5 mL), *tert*-
butanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10
minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room
15 temperature for 16 hours. The white crystalline product was filtered, washed twice with
methanol (99 %, 7.0 mL) and dried in a vacuum oven at 50°C for 16-24 hours under
reduced pressure (20 mm) to yield 3.9 g of purified product (> 83.0 % by HPLC).

EXAMPLE C9

Crude rebaudioside A (77.4 % purity, 5 g), ethanol (95 %, 9.5 mL), *tert*-
20 butanol (9.5 mL) and water (1 mL) were combined and heated to reflux for 10 minutes.
The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature
for 16 hours. The white crystalline product was filtered, washed twice with ethanol (95
%, 7.0 mL) and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure
(20 mm) to yield 2.9 g of purified product (> 88.0 % by HPLC).

EXAMPLE SET D

Table 6: Summary of Examples D1-12

	Crude Rebaudioside A (g)	Solvent		Wash Solvent	Yield (g)	HPLC Purity (%)
		Organic Solvent (mL)	Water (mL)			
D1	50	MeOH (180)	20	MeOH	29.8	96.2
D2	50	MeOH (160)	40	MeOH	31.2	95.5
D3	50	EtOH (188)	12	EtOH	37.3	93.4
D4	50	EtOH (184)	16	EtOH	31.7	95.3
D5	50	EtOH (180)	10	EtOH	35.7	94.7
D6	50	EtOH (176)	24	EtOH	38.2	97.3
D7	50	EtOH (172)	28	EtOH	32	98.1
D8	50	EtOH (160)	40	EtOH	19.8	99.5
D9	50	1-Propanol (180)	20	1-Propanol	27	92.9
D10	50	2-Propanol (180)	20	2-Propanol	34.9	91.4
D11	50	1-Butanol (180)	20	1-Butanol	40.6	93.1
D12	50	2-Butanol (180)	20	2-Butanol	40.4	90.5

EXAMPLE D1

- 5 Crude rebaudioside A (77.4 % purity, 50 g), methanol (99 %, 180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with methanol (99 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 29.8 g
- 10 of purified product (96.2 % by HPLC).

EXAMPLE D2

- Crude rebaudioside A (80.37 % purity, 50 g), methanol (99 %, 160 mL) and water (40 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 1 week. The white crystalline product
- 15 was filtered, washed twice with methanol (99 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 31.2 g of purified product (95.5 % by HPLC).

EXAMPLE D3

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 188 mL) and water (12 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 37.3 g of purified product (93.4 % by HPLC).

EXAMPLE D4

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 184 mL) and water (16 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 31.7 g of purified product (95.3 % by HPLC).

EXAMPLE D5

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 35.7 g of purified product (94.7 % by HPLC).

EXAMPLE D6

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 176 mL) and water (24 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 38.2 g of purified product (97.3 % by HPLC).

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EXAMPLE D7

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 172 mL) and water (28 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product
5 was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 32.0 g of purified product (98.1 % by HPLC).

EXAMPLE D8

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 160 mL) and water
10 (40 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 19.8 g of purified product (99.5 % by HPLC).

15 EXAMPLE D9

Crude rebaudioside A (80.37 % purity, 50 g), 1-propanol (180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with 1-propanol (25 mL), and dried in a vacuum oven at
20 60°C for 16-24 hours under reduced pressure (20 mm) to yield 27.0 g of purified product (92.9 % by HPLC).

EXAMPLE D10

Crude rebaudioside A (80.37 % purity, 50 g), 2-propanol (180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then
25 allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with 2-propanol (25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 34.9 g of purified product (91.4 % by HPLC).

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EXAMPLE D11

Crude rebaudioside A (80.37 % purity, 50 g), 1-butanol (180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with 1-butanol (25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 40.6 g of purified product (93.1 % by HPLC).

EXAMPLE D12

Crude rebaudioside A (80.37 % purity, 50 g), 2-butanol (180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with 2-butanol (25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 40.4 g of purified product (90.5 % by HPLC).

EXAMPLE SET E

Table 7: Summary of Examples E1-E3

	Crude Rebaudioside A (g)	Ethanol (95%)(mL)	Organic Co-solvent (mL)	Water (mL)	Methanol Slurry (mL)	Yield (g)	HPLC Purity (%)
E1	50	160	Methanol (60)	25	200	12.7	>97
E2	50	160	Methanol (60)	25	300	18.6	>97
E3	50	160	Methanol (60)	25	350	22.2	>97

EXAMPLE E1

Crude rebaudioside A (41 % purity, 50 g), ethanol (95 %, 160 mL), methanol (99.8 %, 60 mL) and water (25 mL) were combined by stirring at 22°C. A white product crystallized out in 5-20 hours. The mixture was stirred for additional 48 hours. The white crystalline product was filtered and washed twice with ethanol (95 %, 25 mL). The wet cake of white crystalline product then was slurried in methanol (99.8 %, 200 mL) for 16 hours, filtered, washed twice with methanol (99.8 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 12.7 g of purified product (> 97 % by HPLC).

EXAMPLE E2

Crude rebaudioside A (48 % purity, 50 g), ethanol (95 %, 160 mL), methanol (99.8 %, 60 mL) and water (25 mL) was combined by stirring at 22°C. The white product crystallized out in 3-6 hours. The mixture was stirred for additional 48 hours.

- 5 The white crystalline product was filtered and washed twice with ethanol (95 %, 25 mL). The wet cake of white crystalline product then was slurried in methanol (99.8 %, 300 mL) for 16 hours, filtered, washed twice with methanol (99.8 %, 25 mL) and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 18.6 g of purified product (> 97 % by HPLC).

10 EXAMPLE E3

Crude rebaudioside A (55 % purity, 50 g), ethanol (95 %, 160 mL), methanol (99.8 %, 60 mL) and water (25 mL) was combined by stirring at 22°C. The white product crystallized out in 15-30 minutes. The mixture was stirred for an additional 48 hours. The white crystalline product was filtered and washed twice with ethanol (95 %, 25 mL). The wet cake of white crystalline product was slurried in methanol (99.8 %, 350 mL) for 16 hours, filtered, washed twice with methanol (99.8 %, 25 mL) and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 22.2 g of purified product (> 97 % by HPLC).

EXAMPLE F

- 20 A solution of substantially pure rebaudioside A obtained using the purification technique described hereinabove (>97 % pure by HPLC) was prepared in double distilled water (12.5 gm in 50 mL, 25 % concentration) by stirring the mixture at 40°C for 5 minutes. An amorphous form of rebaudioside A was formed by immediately using the clear solution for spray drying with the Lab-Plant spray drier SD-04 instrument (Lab-Plant Ltd., West Yorkshire, U.K.). The solution was fed through the feed pump into the nozzle atomizer, which atomized the rebaudioside A solution into a spray of droplets with the help of a constant flow of nitrogen / air. Moisture was evaporated from the droplets under controlled temperature conditions (about 90 to about 97°C) and airflow conditions in the drying chamber and resulted in the formation of dry particles.
- 25
- 30 This dry powder (11-12 g, H₂O 6.74 %) was discharged continuously from the drying

chamber and was collected in a bottle. The rate of dissolution in water at room temperature was determined to be > 35.0 %.

5 While the invention has been described in detail with respect to specific embodiments thereof, it will be appreciated that those skilled in the art, upon attaining an understanding of the foregoing, may readily conceive of alterations to, variations of, and equivalents to these embodiments. Accordingly, the scope of the present invention should be assessed as that of the appended claims and any equivalents thereof.

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We claim:

1. A method for purifying rebaudioside A comprising the steps of:
combining crude rebaudioside A and an aqueous organic solvent to form a rebaudioside A solution, the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight; and
crystallizing from the rebaudioside A solution in a single step a substantially pure rebaudioside A composition comprising rebaudioside A in a purity greater than about 95 % by weight on a dry basis.
2. The method of claim 1, further comprising the step of heating the rebaudioside A solution.
3. The method of claim 2, further comprising the step of cooling the rebaudioside A solution.
4. The method of claim 1, wherein rebaudioside A solution in the single crystallization step is stirred or unstirred.
5. The method of claim 1, further comprising the step of seeding (optional) the rebaudioside A solution at an appropriate temperature with an amount of rebaudioside A sufficient to promote crystallization of rebaudioside A.
6. The method of claim 1, further comprising the steps of separating and washing the substantially pure rebaudioside A composition.
7. The method of claim 6, further comprising the step of drying the substantially pure rebaudioside A composition.

8. The method of claim 1, wherein the crude rebaudioside A comprises substantially no rebaudioside D impurity, and the method further comprises slurrying the substantially pure rebaudioside A composition in an aqueous organic solvent or in an organic solvent.
9. The method of claim 8, further comprising the steps of separating and washing the substantially pure rebaudioside A composition.
10. The method of claim 9, further comprising the step of drying the composition of a substantially pure rebaudioside A.
11. The method of claim 1, wherein the aqueous organic solvent comprises a mixture of at least one organic solvent and water.
12. The method of claim 11, wherein at least one organic solvent comprises an alcohol.
13. The method of claim 12, wherein the alcohol comprises ethanol.
14. The method of claim 12, wherein the alcohol comprises methanol.
15. The method of claim 12, wherein the alcohol comprises a mixture of ethanol and methanol.
16. The method of claim 15, wherein the ethanol and methanol are present in the aqueous organic solution in a weight ratio from about 20 parts to about 1 parts ethanol to about 1 part methanol.
17. The method of claim 15, wherein the ethanol and methanol are present in the aqueous organic solution in a weight ratio from about 3 parts to about 1 part ethanol to about 1 part methanol.

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18. The method of claim 1, wherein the at least one aqueous organic solvent comprises an organic solvent selected from the group consisting of acetone, acetonitrile, methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, tert-butanol, and mixtures thereof.
19. The method of claim 1, wherein the aqueous organic solvent and the crude rebaudioside A are present in the rebaudioside A solution in a weight ratio from about 4 to about 10 parts aqueous organic solvent to about 1 part crude rebaudioside A.
20. The method of claim 1, wherein the aqueous organic solvent and the crude rebaudioside A are present in the rebaudioside A solution in a weight ratio from about 3 to about 5 parts aqueous organic solvent to about 1 part crude rebaudioside A.
21. The method of claim 1, wherein aqueous organic solvent comprises water in an amount from about 10 % to about 25 % by weight.
22. The method of claim 1, wherein the crude rebaudioside A mixture comprises rebaudioside A in a purity from about 40 % to about 95 % by weight.
23. The method of claim 1, wherein the crude rebaudioside A mixture comprises rebaudioside A in a purity from about 60 % to about 85 % by weight.
24. The method of claim 1, wherein the crude rebaudioside A mixture comprises rebaudioside A in a purity from about 70 % to about 85 % by weight.
25. The method of claim 1, wherein the method is carried out at approximately room temperature.

26. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to a temperature in a range from about 20°C to about 40°C.

27. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to a temperature in a range from about 40°C to about 60°C.

28. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to about a reflux temperature.

29. The method of claim 3, wherein the step of cooling the rebaudioside A solution comprises cooling the rebaudioside A solution to a temperature in a range from about 4°C to about 25°C.

30. The method of claim 3, wherein the step of cooling the rebaudioside A solution comprises cooling the rebaudioside A solution for about 0.5 hours to about 24 hours.

31. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 97 % rebaudioside A by weight on a dry basis.

32. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 98 % rebaudioside A by weight on a dry basis.

33. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 99 % rebaudioside A by weight on a dry basis.

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34. The method of claim 1, further comprising the steps of:
heating the rebaudioside A aqueous organic solvent mixture;
cooling the rebaudioside A solution;
separating and washing a substantially pure rebaudioside A composition;
and
drying the substantially pure rebaudioside A composition.
35. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 7.
36. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 8.
37. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 9.
38. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 10.
39. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises an amorphous form having an X-ray diffraction pattern substantially similar to Figure 11.
40. The method of claim 1, further comprising the step of forming an amorphous form of the substantially pure rebaudioside A composition.

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41. The method of claim 38, wherein the step of forming an amorphous form of the substantially pure rebaudioside A composition comprises a method selected from the group consisting of ball milling, precipitation, lyophilization, cryogrinding, and spray-drying.

42. A substantially pure rebaudioside A composition made according to the method of claim 1.

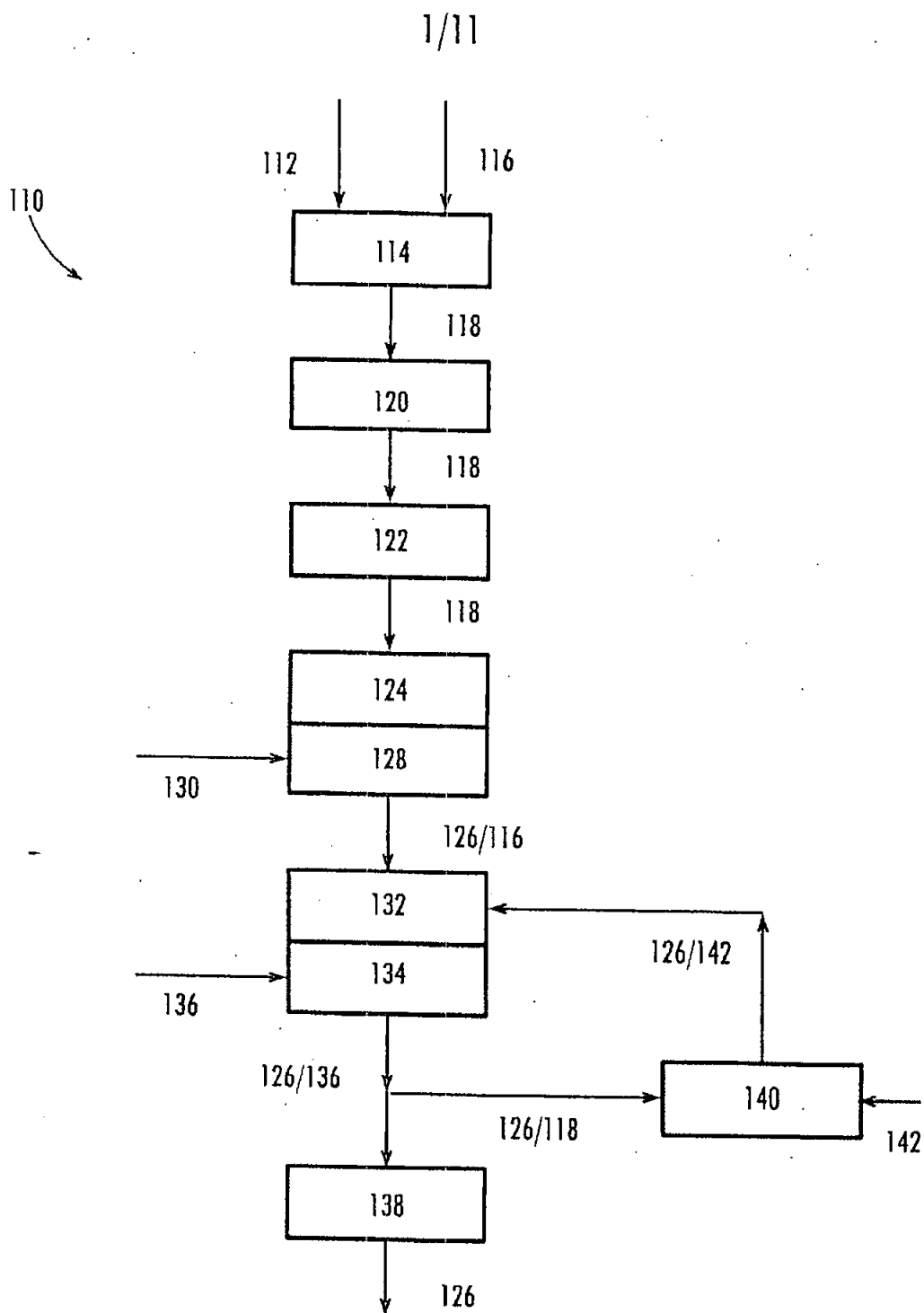


Fig. 1

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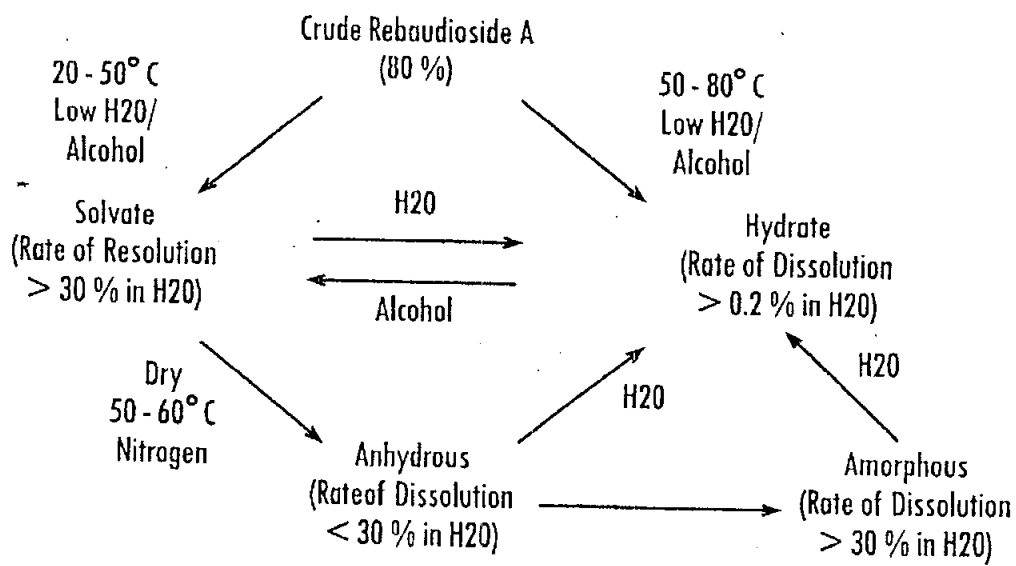


Fig. 2

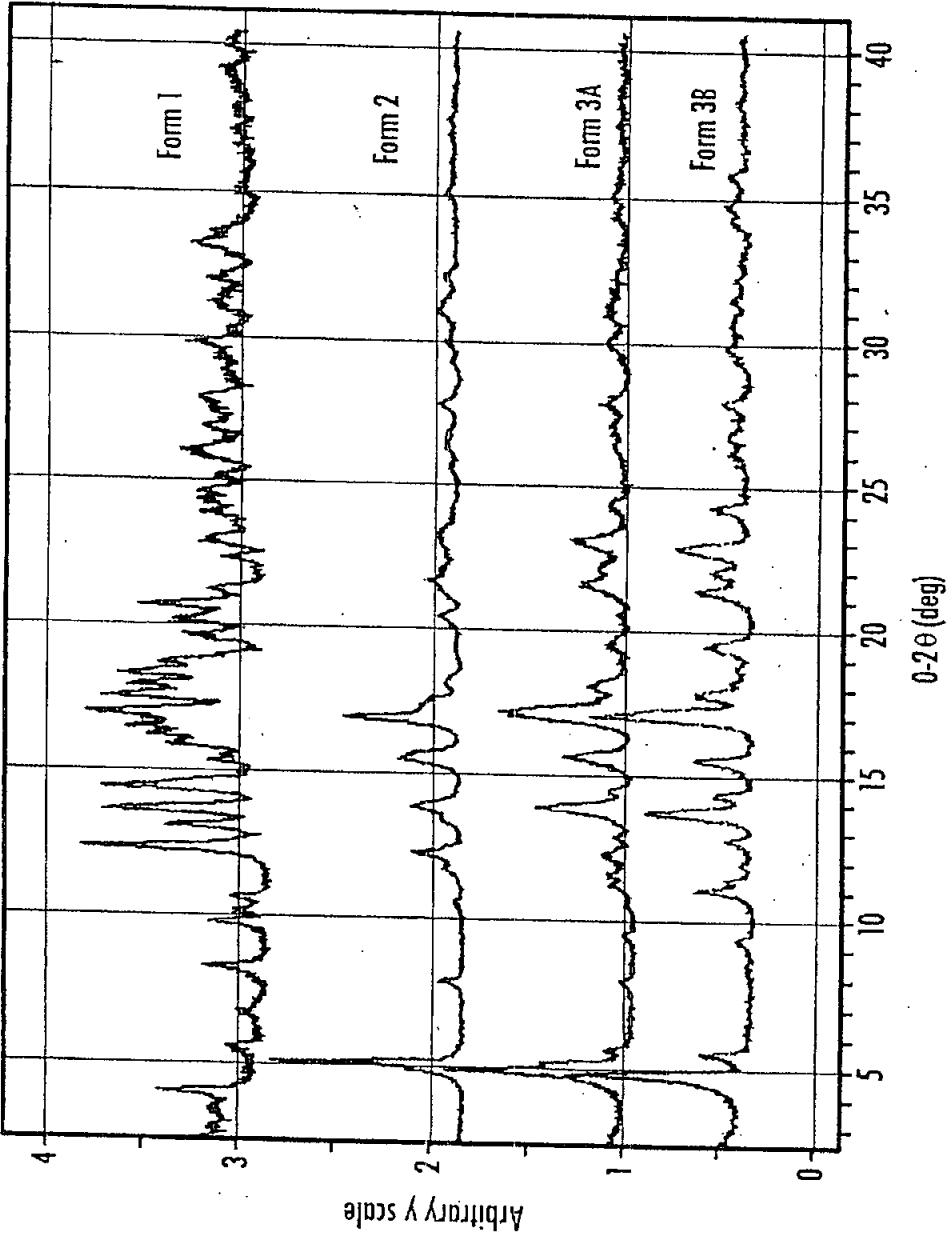


Fig. 3

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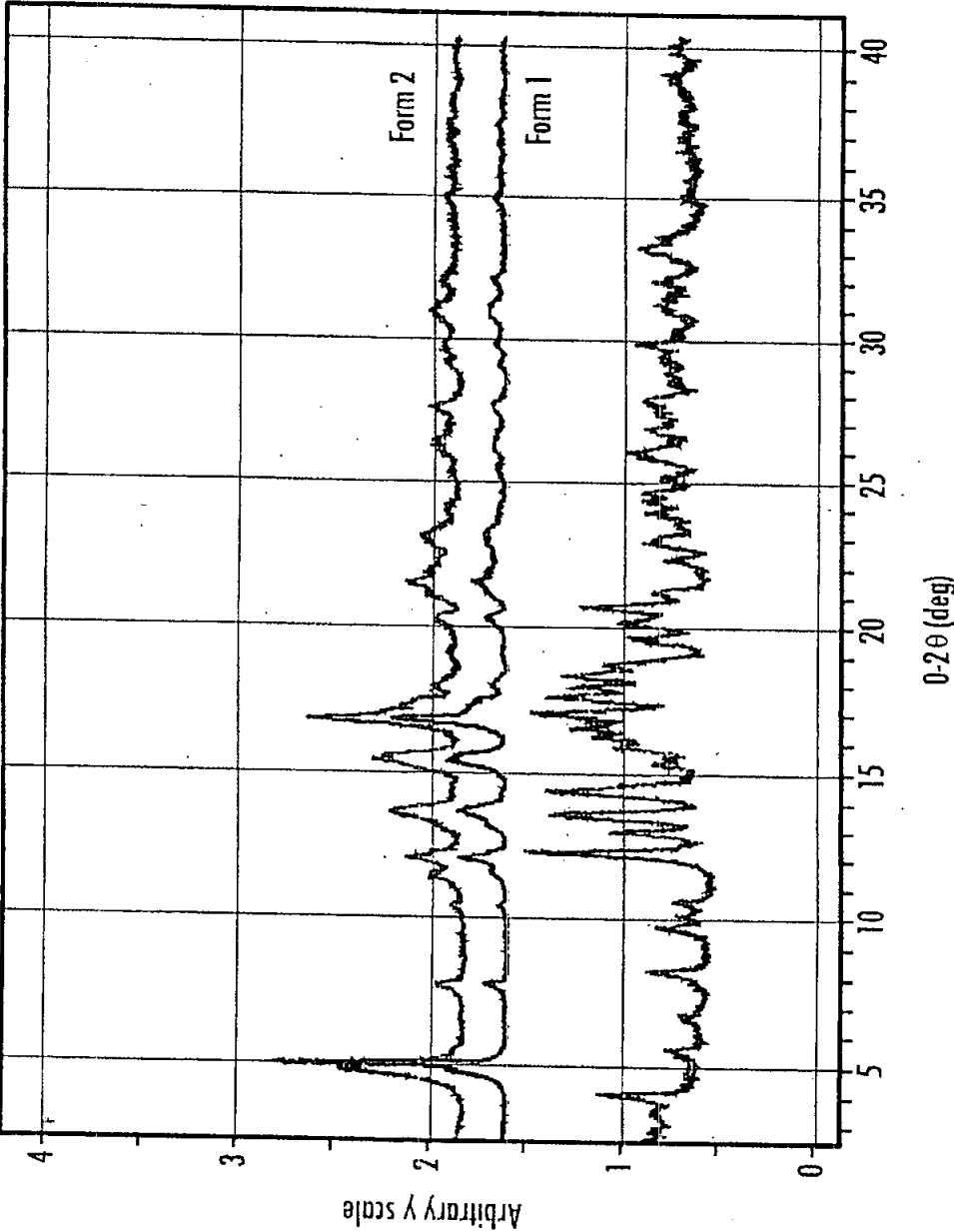


Fig. 4

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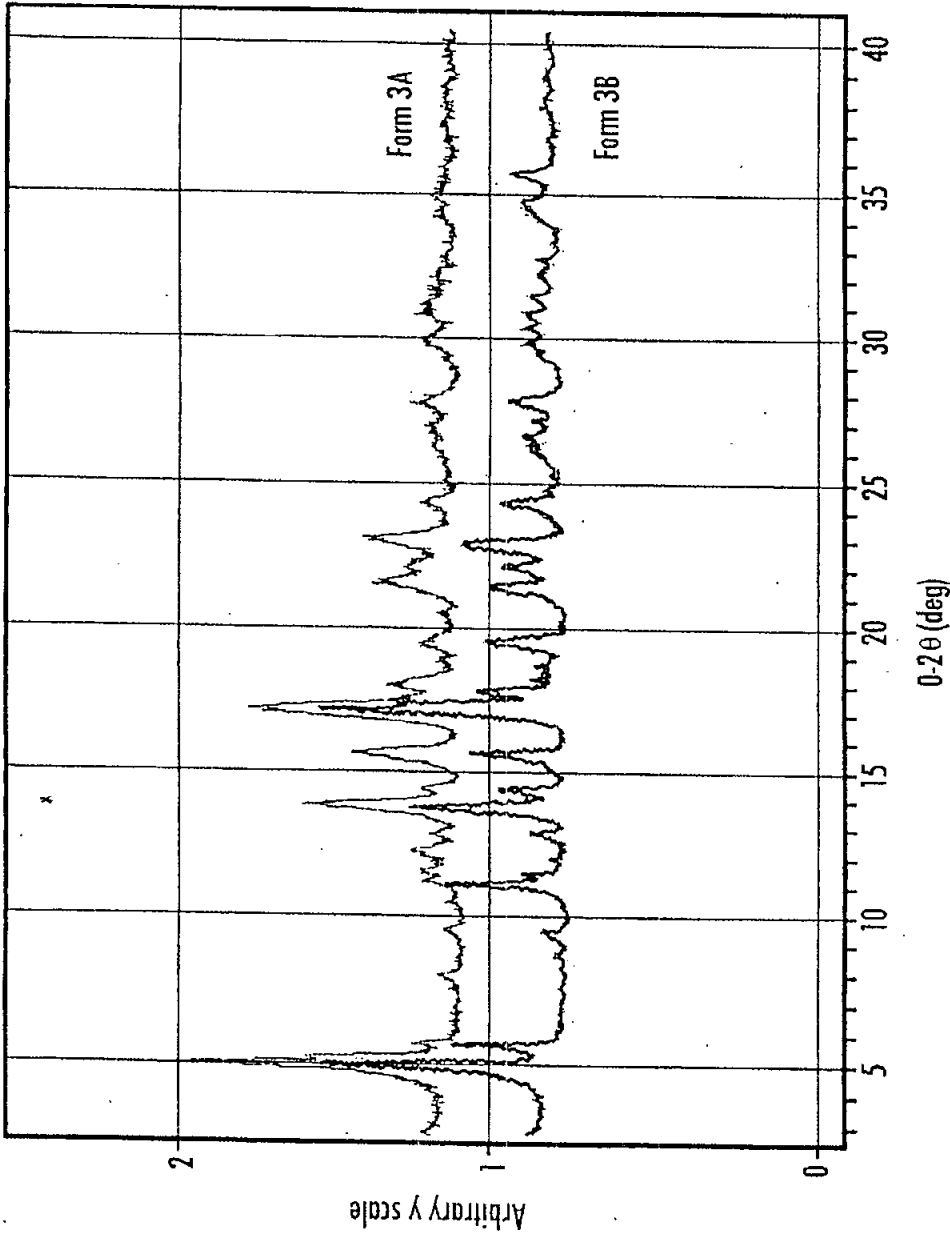


Fig. 5

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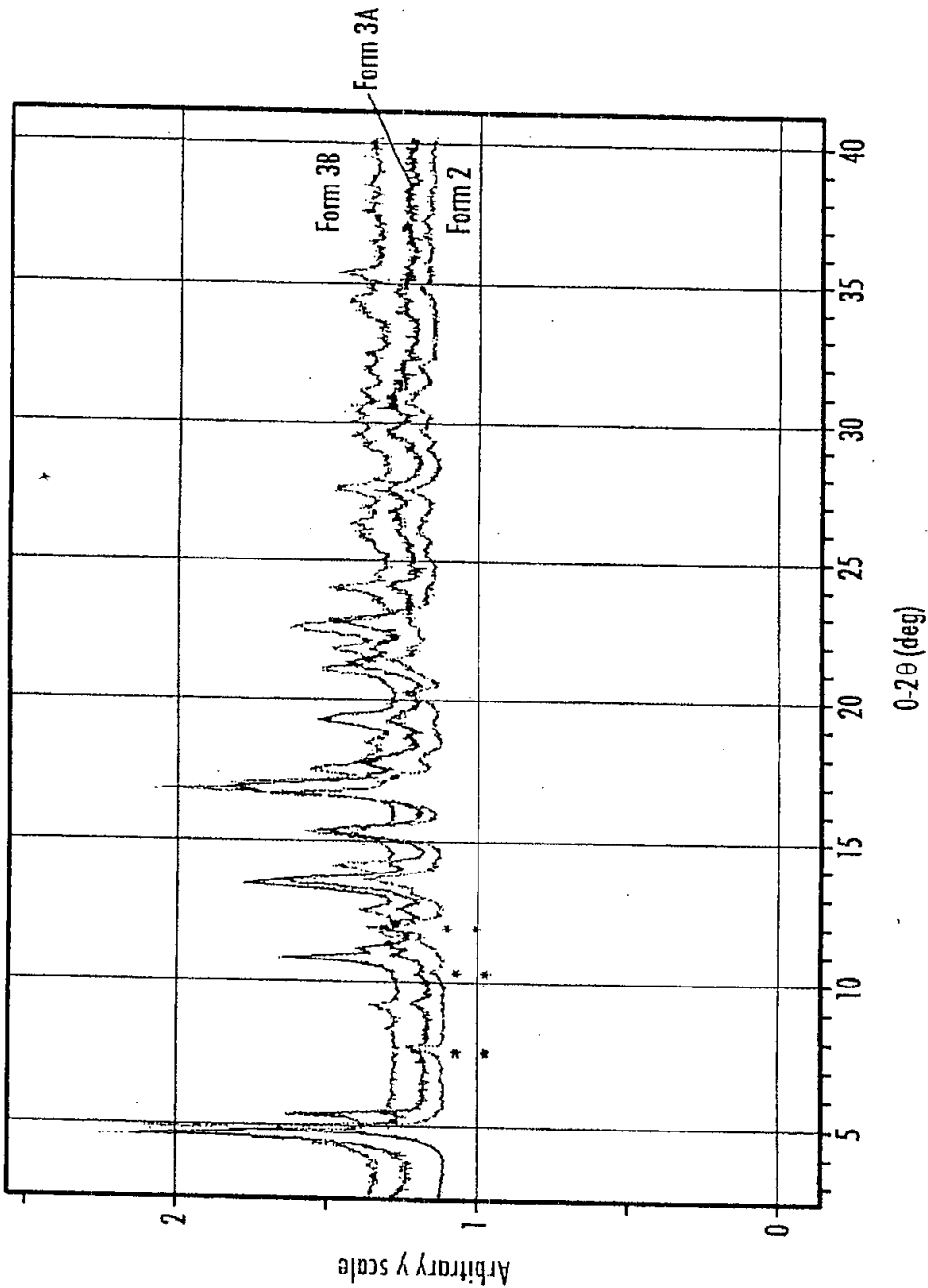


Fig. 6

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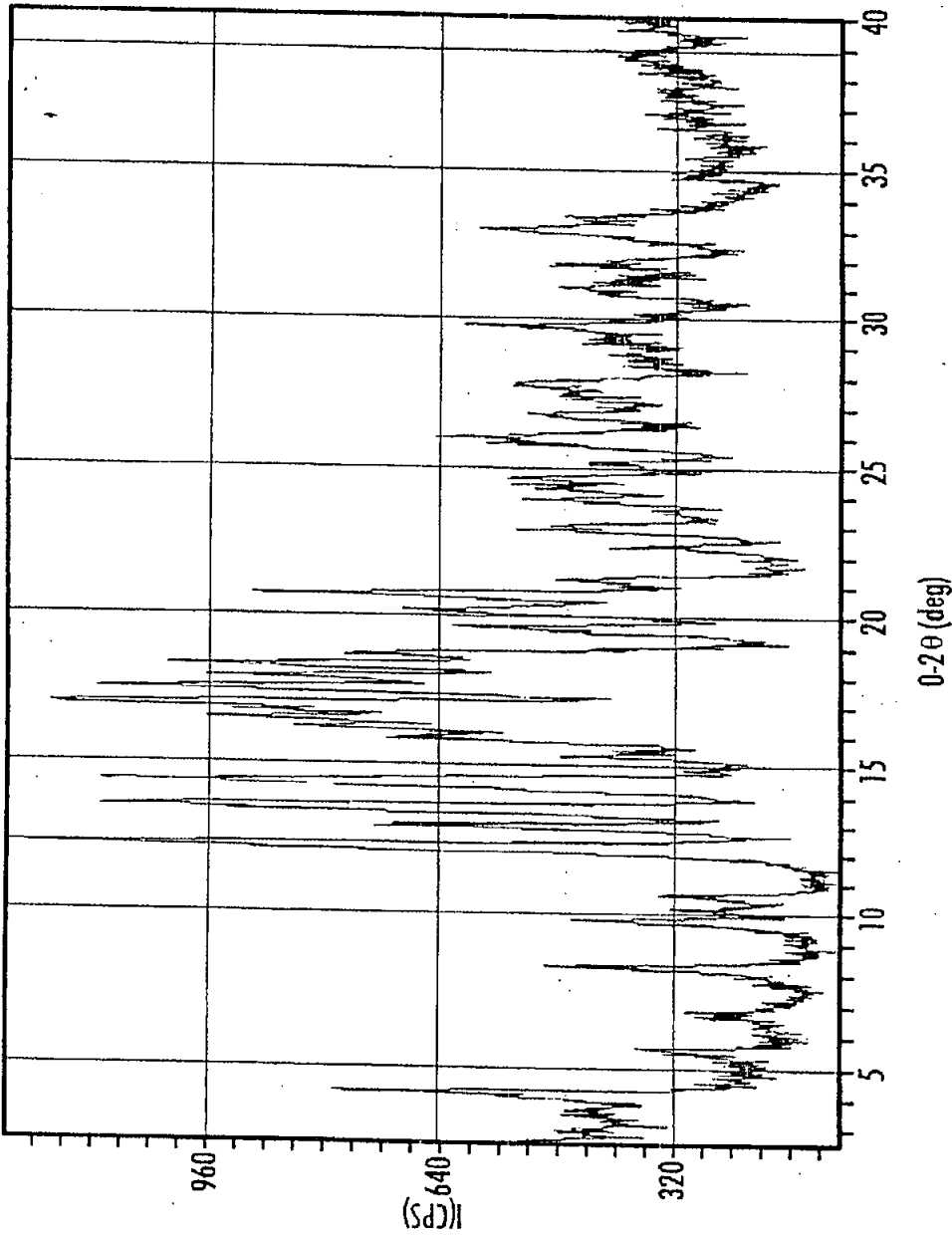


Fig. 7

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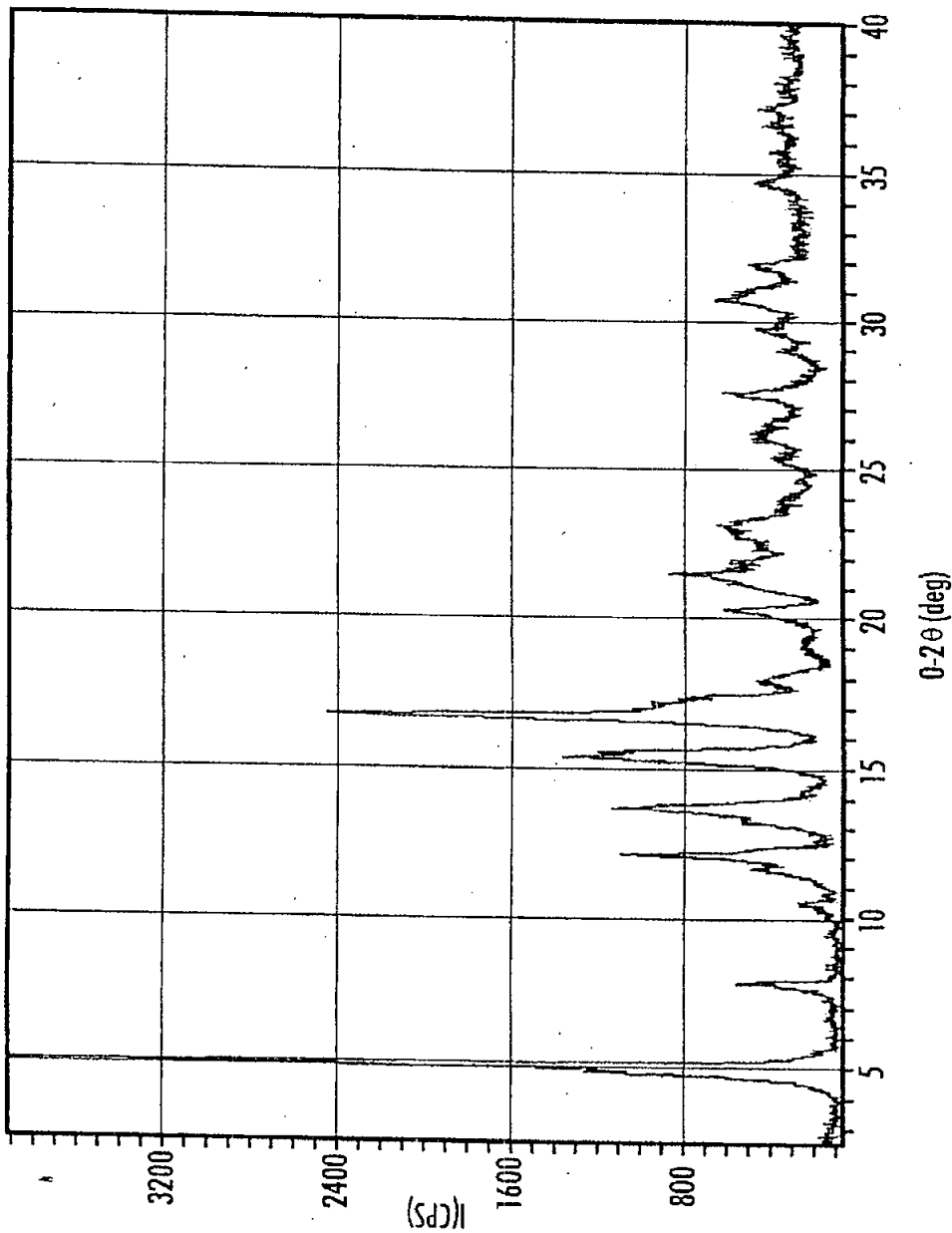


Fig. 8

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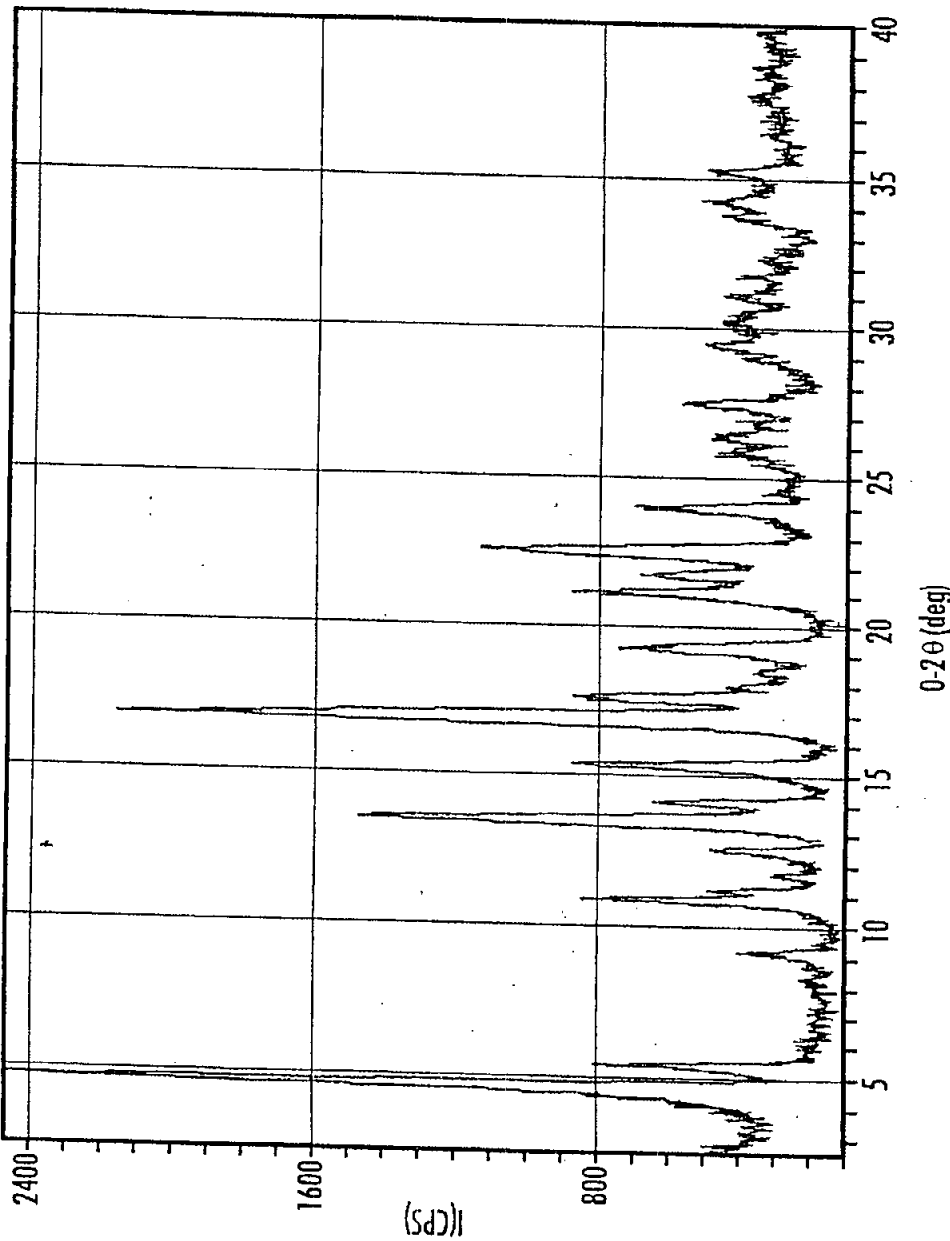


Fig. 9

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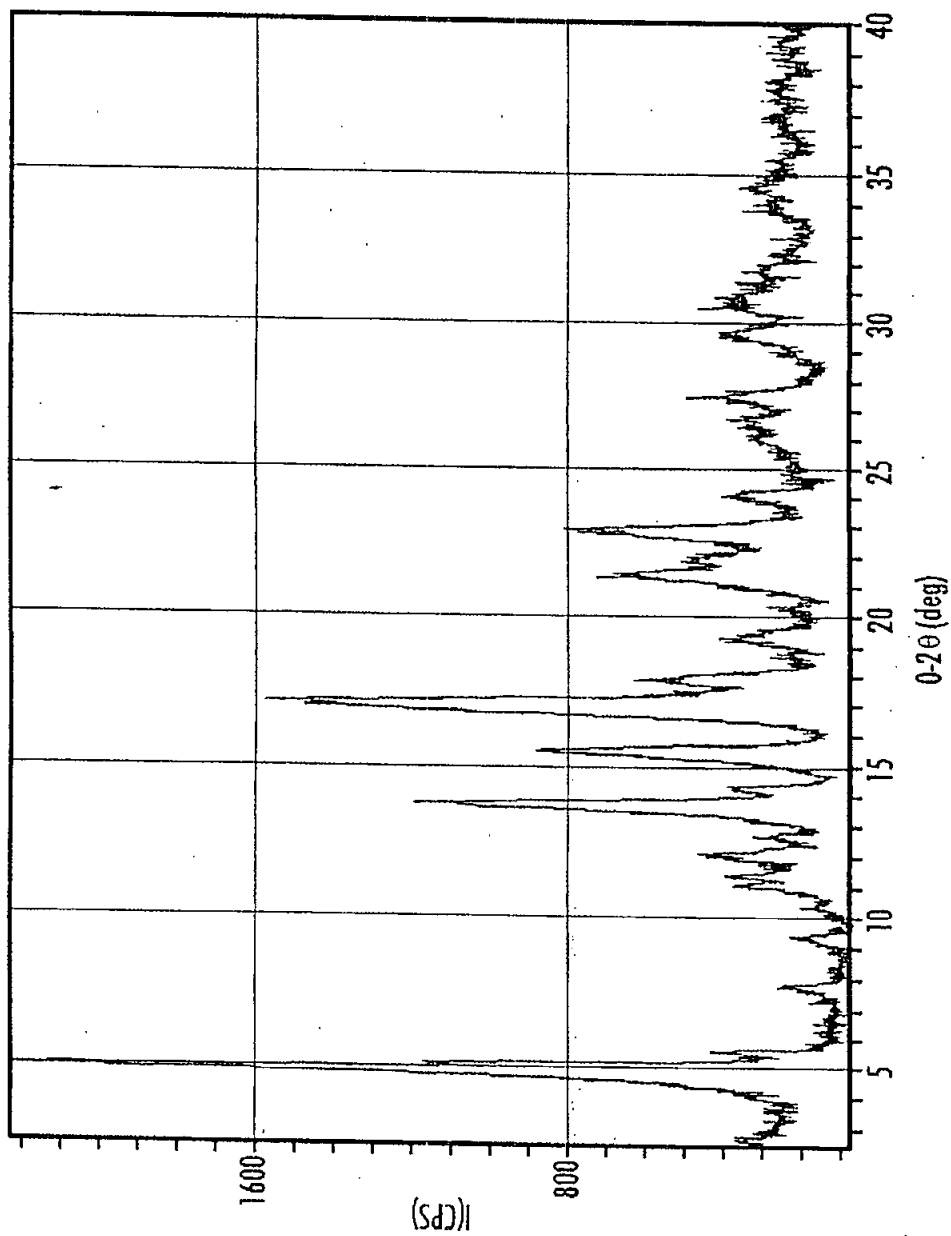


Fig. 10

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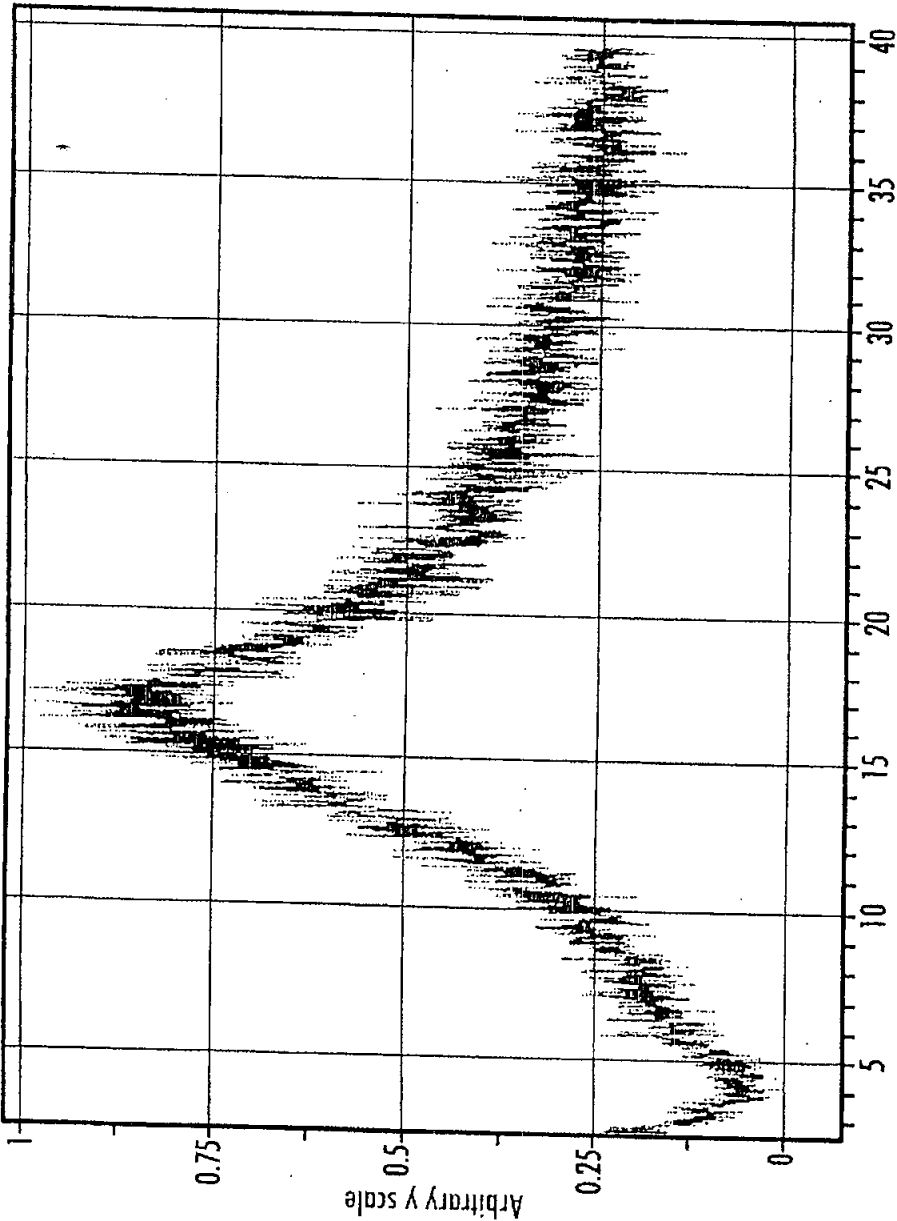


Fig. 11

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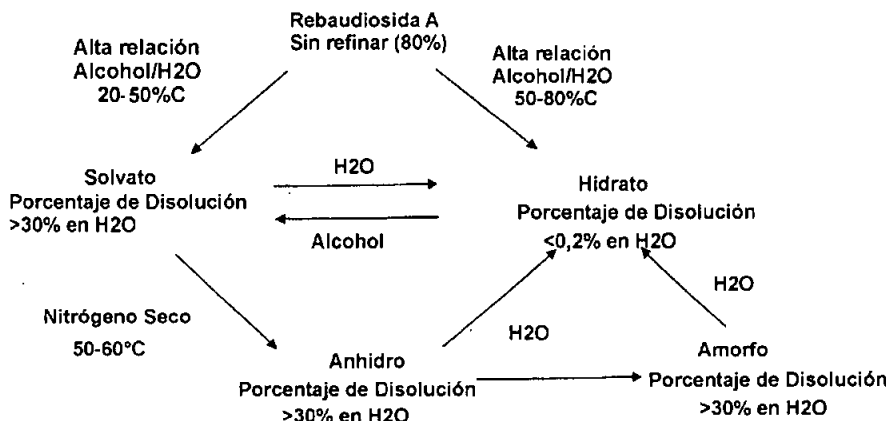
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(54) Título: COMPOSICIÓN DE REBAUDIOSIDA A Y MÉTODO PARA PURIFICAR REBAUDIOSIDA A



(57) Resumen: Realizaciones ilustrativas de este invento abarcan un método para purificar rebaudiosida A sin refinar. En particular, este invento se refiere a un método para purificar composiciones de rebaudiosida A sin refinar que comprenden purezas desde alrededor de 40% a alrededor de 95% de rebaudiosida A para obtener un producto de rebaudiosida A substancialmente puro con un solo paso de cristalización. Se publican también formas polimórficas y amorfas resultantes de rebaudiosida A y métodos para preparar formas polimórficas y amorfas de rebaudiosida A desde composiciones de rebaudiosida A sin refinar y composiciones de rebaudiosida A substancialmente pura.

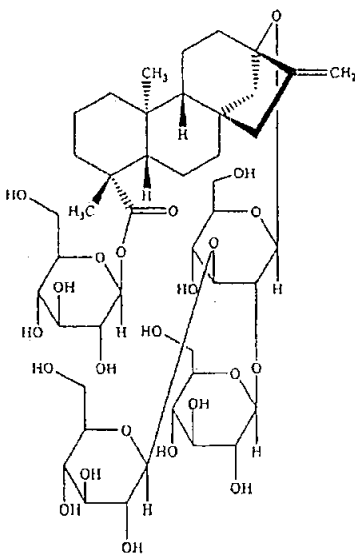
MEMORIA DESCRIPTIVA

CAMPO DEL INVENTO

Este invento se refiere en general a formas polimórficas y amorfas de rebaudiosida A, a métodos para purificar la rebaudiosida A y métodos para preparar formas polimórficas y amorfas de rebaudiosida A. Más específicamente, este invento se refiere a formas polimórficas y amorfas de rebaudiosida A, y a métodos para la purificación o cristalización de rebaudiosida A con solventes orgánicos acuosos o con solventes orgánicos para obtener un producto de alto rendimiento y alta pureza.

ANTECEDENTES DEL INVENTO

La rebaudiosida A es un endulzante glicósido diterpenoide de alto poder que tiene la estructura química:



La rebaudiosida A es aislada y extraída, junto con otros glicósidos de esteviol, de la planta *Stevia rebaudiana* (Bertoni) ("Stevia"), cultivada comercialmente en Japón, Singapur, Taiwán, Malasia, Corea del Sur, China, India, Brasil, Australia y Paraguay. Es un endulzante no-calórico alternativo con propiedades funcionales y sensoriales superiores a las de muchos endulzantes de alta potencia. Las formas procesadas de *Stevia* pueden ser de 70 a 400 veces más potentes que el azúcar;

sin embargo, *Stevia* tiene también un componente amargo. De los cuatro endulzantes glicósidos diterpenoides principales presentes en *Stevia*, rebaudiosida A ha sido identificada como la menos amarga y con el resabio menos persistente. Con frecuencia, el amargor se debe significativamente a las impurezas en los extractos.

Rebaudiosida A está habitualmente disponible con una pureza de $\leq 80\%$. Las principales impurezas comprenden esteviosida, esteviolbiosida, rebaudiosida B, rebaudiosida C, rebaudiosida D, dulcosida A, rebaudiosida F, y otros glicósidos de esteviol. Es muy difícil obtener una rebaudiosida A de alta pureza de recuperación intensa, porque la rebaudiosida A y las otras impurezas tienen solubilidades similares.

Los esfuerzos reportados con anterioridad para purificar la rebaudiosida A de mezclas de rebaudiosida A y esteviosida, requieren de numerosos pasos de purificación repetidos. La patente norteamericana N° 5.962.678 revela la recrystalización de rebaudiosida A usando una solución de metanol anhidro para obtener una rebaudiosida A 80% pura. Repitiendo numerosas veces la recrystalización con metanol anhidro, es posible aumentar la pureza de rebaudiosida A, a más de 95%. La publicación de la patente norteamericana N° 2006/0083838 revela la purificación de rebaudiosida A mediante recrystalización con un solvente que comprende etanol y entre 4 y 15% de agua. La solicitud de patente japonesa N° 55-23756 revela un método para purificar rebaudiosida A y esteviosida mediante cristalización de etanol acuoso ($>70\%$) para obtener una rebaudiosida A 80% pura. La publicación de patente norteamericana N° 2007/0082103 revela un método para purificar rebaudiosida A mediante recrystalización desde etanol acuoso, aseverando que una recrystalización en dos pasos desde rebaudiosida sin refinar (60%) da como resultado la formación de rebaudiosida A $>98\%$ pura con un rendimiento de 97%. Estos métodos de la especialidad anterior, sin embargo, no

proporcionan una composición de rebaudiosida A substancialmente pura usando un paso de recristalización único.

En consecuencia, se necesita un método sencillo, eficiente y económico para producir rebaudiosida A substancialmente pura.

RESEÑA DEL INVENTO

Realizaciones ejemplares del invento tratan la necesidad identificada anteriormente, proporcionando una rebaudiosida A substancialmente pura, formas polimórficas y amorfas de rebaudiosida A, métodos para purificar rebaudiosida A, y métodos para preparar formas polimórficas y amorfas de rebaudiosida A.

En una realización en particular, el método de purificación de rebaudiosida A comprende una cristalización simple. En una realización, un método para purificar rebaudiosida A comprende combinar rebaudiosida A sin refinar y un solvente orgánico acuoso para formar una solución de rebaudiosida A, en que la solución orgánica acuosa comprende agua en una cantidad desde alrededor de 10% hasta 25% en peso, aproximadamente, y cristalizar desde la solución de rebaudiosida A sin refinar, en un solo paso, una rebaudiosida A substancialmente pura con una pureza superior a 95% en peso en una base seca.

En otras realizaciones particulares, se proporcionan diferentes formas polimórficas y amorfas de rebaudiosida A y métodos para preparar diferentes formas polimórficas y amorfas de rebaudiosida A.

Otros objetos, propiedades y ventajas del invento serán evidentes a partir de la descripción detallada, dibujos y reivindicaciones expuestos a continuación. A menos que se defina de otro modo, todos los términos científicos y abreviaturas usados aquí tienen el mismo significado que sería comprendido habitualmente por una persona con experiencia común en la especialidad. Si bien es posible usar métodos y composiciones

similares o equivalentes a esos descritos aquí en la práctica de este invento, se describen métodos y composiciones apropiadas sin pretender que tales métodos y composiciones limiten el invento.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

La Figura 1 es un gráfico que ilustra un método para purificar rebaudiosida A según una realización de este invento.

La Figura 2 es un gráfico de la formación y conversión de formas polimórficas y amorfas de rebaudiosida A según una realización de este invento.

La Figura 3 es una exploración por difracción de rayos X que compara cuatro formas polimórficas de rebaudiosida A, las formas 1, 2, 3A y 3B, en un trazado de dispersión de intensidad versus el ángulo de dispersión 2θ (página 3) según una realización de este invento.

La Figura 4 es una exploración por difracción de rayos X en polvo, que compara polimorfos de rebaudiosida A, Forma 1 y Forma 2, en un trazado de dispersión de intensidad versus ángulo de dispersión 2θ según una realización de este invento.

La Figura 5 es una exploración por difracción de rayos X en polvo, que compara polimorfos de rebaudiosida A, Forma 3A y Forma 3B, en un trazado de dispersión de intensidad versus ángulo de dispersión 2θ según una realización de este invento.

La Figura 6 es una exploración por difracción de rayos X en polvo, que compara polimorfos de rebaudiosida A, Formas 2, 3A y 3B, en un trazado de dispersión de intensidad versus ángulo de dispersión 2θ según una realización de este invento.

La Figura 7 es una exploración por difracción de rayos X en polvo, de un polimorfo de rebaudiosida A, Forma 1 en un trazado de dispersión de intensidad versus ángulo de dispersión 2θ según una realización de este invento.

La Figura 8 es una exploración por difracción de rayos X en polvo, de un polimorfo de rebaudiosida A, Forma 2 en un

trazado de dispersión de intensidad versus ángulo de dispersión 2θ según una realización de este invento.

La Figura 9 es una exploración por difracción de rayos X en polvo, de un polimorfo de rebaudiosida A, Forma 3A en un trazado de dispersión de intensidad versus ángulo de dispersión 2θ según una realización de este invento.

La Figura 10 es una exploración por difracción de rayos X en polvo, de un polimorfo de rebaudiosida A, Forma 3B en un trazado de dispersión de intensidad versus ángulo de dispersión 2θ según una realización de este invento.

La Figura 11 es una exploración por difracción de rayos X en polvo, de Forma 4 amorfa de rebaudiosida A, en un trazado de dispersión de intensidad versus ángulo de dispersión 2θ según una realización de este invento.

DESCRIPCIÓN DETALLADA DEL INVENTO

La rebaudiosida A es un endulzante natural de alta potencia, disponible generalmente a un costo moderado con $\leq 80\%$ y $> 80\%$ pureza sólo a costos elevados. Las muestras comerciales de rebaudiosida A tienen, con frecuencia un sabor amargo que se cree que se debe a impurezas. Por consiguiente, existe una necesidad de rebaudiosida A substancialmente pura y un método simple y económico para purificar rebaudiosida A, a fin de obtener una rebaudiosida A substancialmente pura, apropiada para usar como endulzante natural de alta potencia.

En la forma usada aquí, el término "substancialmente" o "substancialmente pura" se refiere a una composición de rebaudiosida A que incluye por lo menos alrededor de 85% en peso seco de rebaudiosida A, en otra realización, por lo menos 90% en peso seco, en otra realización, desde alrededor de 95% hasta alrededor de 98% en peso seco, aproximadamente, y en otra realización más, desde alrededor de 99% hasta 100% en peso seco, aproximadamente.

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Las realizaciones ejemplares de este invento satisfacen estas necesidades al proporcionar un método para purificar rebaudiosida A sin refinar a rebaudiosida A substancialmente pura, por cristalización de una rebaudiosida A sin refinar desde una solución orgánica acuosa que comprende agua en una cantidad desde alrededor de 10% hasta alrededor de 25% en peso y cristalizar en por lo menos un paso una rebaudiosida A substancialmente pura. Otras realizaciones ejemplares de este invento abarcan una composición de una rebaudiosida A substancialmente pura y composiciones que comprenden uno, o más de un polimorfo(s) de rebaudiosida A. Otras realizaciones ejemplares de este invento abarcan una forma amorfa de rebaudiosida A y métodos para preparar formas amorfas de rebaudiosida A. En otra realización más, se proporciona un método para convertir una forma de polimorfo en otra forma de polimorfo o en una forma amorfa. A continuación se describen en detalle realizaciones ejemplares de este invento y son ilustradas en las Figuras 1-11.

Método de Purificación de una Mezcla de Rebaudiosida A

Hay productos de rebaudiosida A sin refinar, disponibles en el comercio, que comprenden rebaudiosida A en purezas desde alrededor de 40% hasta alrededor de 95% en peso. desde alrededor de 60% hasta alrededor de 85% en peso, o desde alrededor de 70% hasta alrededor de 85% en peso. Se prevee que la rebaudiosida A sin refinar, en su forma sin depurar tal como se extrae de plantas de *Stevia*, puede ser purificada por cristalización. Las impurezas principales, identificadas por HPLC, son esteviosida, rebaudiosida B, rebaudiosida C, y rebaudiosida D. Las impurezas de rebaudiosida D pueden ser eliminadas aumentando la cantidad de agua en un solvente de recristalización orgánico acuoso; sin embargo, un contenido excesivo de agua en el solvente de recristalización dará como resultado una menor recuperación de rebaudiosida A. La impureza

de rebaudiosida B puede ser reducida significativamente formando una lechada con la rebaudiosida A sin refinar en un solvente orgánico o en una solución orgánica acuosa, o mediante el tratamiento de la solución de rebaudiosida A sin refinar con una resina de intercambio de aniones. En consecuencia, el método de purificación depende de las impurezas presentes en el material iniciador de rebaudiosida A sin refinar. 96

En una realización ejemplar de un método para purificar rebaudiosida A 110, ilustrado en la Figura 1, se puede combinar 114 rebaudiosida A 112 con una solución orgánica acuosa 116 para formar una solución de rebaudiosida A 118. La solución orgánica acuosa 116 comprende agua en una cantidad desde alrededor de 10% hasta alrededor de 25% en peso y, por lo menos, un solvente orgánico. Alternativamente, la solución orgánica acuosa 116 puede comprender agua en una cantidad desde alrededor de 15% hasta alrededor de 20% en peso y por lo menos un solvente orgánico.

Solventes orgánico acuosos, en la forma usada aquí se refieren a mezclas de agua y por lo menos un solvente orgánico. Ejemplos no limitantes de solventes orgánicos incluyen alcohol, acetona, y acetonitrilo. Alcohol, como se usa aquí, se refiere, a cualquier grupo alquilo, alquenilo o alquinilo lineal, ramificado o cíclico, substituido o insubstituido, unido a, por lo menos, una porción hidroxilo. Ejemplos no limitantes de alcoholes incluyen etanol, metanol, isopropanol, 1-propanol, 1-butanol-2-butanol, ter-butanol e isobutanol.

En una realización ilustrativa, la solución orgánica acuosa 116 comprende una mezcla de agua y por lo menos un solvente orgánico. En otra realización ilustrativa, por lo menos un solvente orgánico comprende un alcohol, el alcohol comprende etanol, metanol, o mezclas suyas. En realizaciones ilustrativas en que el por lo menos un solvente orgánico comprende una mezcla de etanol y metanol, el etanol y metanol pueden ser combinados en el solvente orgánico con una proporción en peso que varía desde

alrededor de 20 partes por una parte de etanol hasta alrededor de una parte de metanol. En otra realización ilustrativa, el etanol y metanol pueden ser combinados en el solvente orgánico acuoso en una proporción en peso que varía desde alrededor de 3 partes a 1 parte de etanol, hasta alrededor de 1 parte de metanol.

En una realización ilustrativa, la solución de rebaudiosida A 118 comprende el solvente orgánico acuoso 116 y la rebaudiosida A sin refinar 112 en una relación en peso que varía desde alrededor de 10 hasta alrededor de 4 partes de solvente orgánico acuoso con alrededor de 1 parte de rebaudiosida A sin refinar. En otra realización ilustrativa, la solución de rebaudiosida A 118 comprende la solución orgánica acuosa 116 y la rebaudiosida A sin refinar 112 en una relación en peso que varía desde alrededor de 5 hasta 3 partes de solvente orgánico acuoso con alrededor de una parte de rebaudiosida A sin refinar.

En una realización ilustrativa, el método 110 puede ser llevado a cabo a una temperatura aproximada a la temperatura ambiente. En otra realización, el método 110 comprende adicionalmente el paso de calentar 120 de la solución de rebaudiosida A 118. En una realización, el paso de calentar 120 de la solución de rebaudiosida A 118, comprende calentar la solución de rebaudiosida A hasta una temperatura que varía desde alrededor desde 20°C hasta alrededor de 70°C, desde alrededor de 20°C hasta alrededor de 60°C, desde alrededor de 20°C hasta alrededor de 40°C, o desde alrededor de 40°C hasta alrededor de 60°C. En otra realización, el paso de calentar 120 de la solución de rebaudiosida A 118 comprende calentar la solución de rebaudiosida A hasta una temperatura aproximada a la temperatura de reflujo. El paso de calentar 120 de la solución de rebaudiosida A 118 comprende calentar la solución de rebaudiosida A durante aproximadamente 0,25 horas hasta alrededor de 8 horas. En otra realización ilustrativa, donde el método para purificar rebaudiosida A 110 comprende el paso de calentar 120 de la

solución de rebaudiosida A 118, en que el método comprende adicionalmente el paso de enfriar 122 la solución de rebaudiosida A. En una realización, el paso de enfriar 122 la solución de rebaudiosida A, comprende enfriar la solución de rebaudiosida A hasta una temperatura dentro del margen de variación desde alrededor de 4°C hasta alrededor de 25°C. El paso de enfriar 122 la solución de rebaudiosida A 118 comprende enfriar la solución de rebaudiosida A durante aproximadamente 0,5 hasta alrededor de 24 horas.

El método para purificar rebaudiosida A 110 comprende adicionalmente el paso de cristalizar 124 desde la solución de rebaudiosida A 118 en un paso único, una composición de rebaudiosida A substancialmente pura 126 que comprende rebaudiosida A en una cantidad superior a alrededor de 85% en peso en base seca, superior a 97% en peso en una base seca, superior a alrededor de 98% en una base seca, o superior a 99% en peso en una base seca. La solución de rebaudiosida A 118 durante el paso único de cristalización puede ser o no agitada.

En una realización ilustrativa, el método 110 puede incluir además el paso opcional de sembrar 128 la solución de rebaudiosida A 118 a una temperatura apropiada, con cristales de rebaudiosida A substancialmente puros 130 suficientes para promover la cristalización de la rebaudiosida A para formar rebaudiosida A pura. Una cantidad de rebaudiosida A 130 suficiente para promover la cristalización de rebaudiosida A substancialmente pura 126 comprende una cantidad de rebaudiosida A desde alrededor de 0,0001% hasta alrededor de 1% en peso de la rebaudiosida A presente en la solución. En otra realización, una cantidad de rebaudiosida A 130 suficiente para promover la cristalización de la rebaudiosida A para formar una composición de rebaudiosida A substancialmente pura 126, comprende una cantidad de rebaudiosida A desde alrededor de 0,01% hasta 1% en peso. Una temperatura apropiada para el paso de sembrar 128

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comprende una temperatura en un margen de variación de alrededor de 18° hasta alrededor de 35°C.

En otra realización ilustrativa el método comprende, adicionalmente, los pasos de separar 132 y lavar 134 la composición de rebaudiosida A substancialmente pura 126. La composición de rebaudiosida A substancialmente pura 126, puede ser separada de la solución orgánica acuosa 118 empleando una diversidad de técnicas de separación sólido-líquido que usan fuerza centrífuga, que incluye sin limitaciones, centrífuga de cesta perforada vertical y horizontal, centrífuga de campana tubular (*solid bowl*), centrífuga decantadora, centrífuga descascaradora (*peeler type*), centrífuga de empuje, centrífuga tipo Heinkel, centrífuga con separador de discos, y separador ciclónico. Además, se puede intensificar la separación mediante cualesquier métodos de filtración por presión, al vacío, o por gravedad que incluyen, sin limitación el uso de filtros de banda, de tambor, tipo Nutsche, de hoja, de placa, Rosenmund, tipo centelleo (*Sparkler*), y filtros de bolsa y filtros prensa. La operación del dispositivo de separación sólido-líquido de rebaudiosida A puede ser en modalidad continua, semi-continua o por lotes. La composición de rebaudiosida A substancialmente pura 126 puede ser lavada 134 también sobre el dispositivo de separación usando diversos solventes orgánicos acuosos 136 y mezclas de ellos. La composición de rebaudiosida A substancialmente pura 126 puede ser secada total o parcialmente sobre el dispositivo de separación usando muchos gases, incluyendo sin limitación, nitrógeno o argón, para evaporar el solvente líquido residual 136. La composición de rebaudiosida A substancialmente pura 126 puede ser retirada manual o automáticamente del dispositivo de separación usando medios mecánicos, gases o líquidos, ya sea disolviendo el sólido o manteniendo la forma sólida.

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En otra realización ilustrativa más, el método 110 comprende adicionalmente el paso de secar 138 la composición de rebaudiosida A substancialmente pura 126. Tales métodos son conocidos por los peritos en la especialidad e incluyen, pero no se limitan, al uso de un secador rotatorio al vacío, secador de lecho fluido, secador de túnel rotatorio, secador de placas, secador de bandejas, secador tipo Nauta, secador de rociado, secador instantáneo, secador de micrón, secador tipo recipiente, secador de paleta de baja y alta velocidad y secador por microondas. En una realización ilustrativa, el paso de secado 138 comprende secar la composición de rebaudiosida A substancialmente pura 126 usando una purga de nitrógeno o argón para eliminar el solvente residual 120 a una temperatura en un margen de variación de alrededor de 40°C hasta alrededor de 60°C durante 5 horas, aproximadamente, hasta alrededor de 100 horas.

En otra realización ilustrativa más, donde la mezcla de rebaudiosida A sin refinar 112 no comprende substancialmente ninguna impureza de rebaudiosida D, el método 110 comprende además el paso de formar una lechada 140 con la composición de rebaudiosida A substancialmente pura 126, con un solvente orgánico o con un solvente orgánico acuoso 142 previo al paso de secar 138 la composición de rebaudiosida A substancialmente pura. La lechada puede ser una mezcla que comprende un sólido y un solvente orgánico acuoso o un solvente orgánico donde el sólido comprende la composición de rebaudiosida A substancialmente pura 126 y es sólo escasamente soluble en el solvente orgánico acuoso o en el solvente orgánico 142. En una realización, una composición de rebaudiosida A substancialmente pura 126 y el solvente orgánico acuoso o el solvente orgánico 142 pueden estar presentes en la lechada en una relación en peso en un margen de variación desde aproximadamente 15 partes hasta aproximadamente 1 parte de solvente orgánico acuoso hasta alrededor de 1 parte de composición de rebaudiosida A substancialmente pura. En una

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realización, la lechada puede ser mantenida a la temperatura ambiente. En otra realización, el paso de formar una lechada 140 comprende calentar la lechada hasta una temperatura dentro de un margen de variación desde aproximadamente 20° C hasta alrededor de 40° C. La composición de rebaudiosida A substancialmente pura 126 puede ser suspendida durante 0,5 hasta 24 horas aproximadamente.

En otra realización ilustrativa más, el método comprende adicionalmente los pasos de separar 132 la composición de rebaudiosida A substancialmente pura 126 del solvente orgánico acuoso 142 de la lechada y lavar 134 la composición de rebaudiosida A substancialmente pura seguido por el paso de secado 138 de la composición de rebaudiosida A substancialmente pura.

Si se desea una purificación más amplia, puede repetirse el método para purificar la rebaudiosida A 110 descrito aquí, o se puede purificar adicionalmente la composición de rebaudiosida A substancialmente pura, usando un método de purificación alternativo, tal como la cromatografía en columna.

La pureza, en el sentido usado aquí, representa el porcentaje en peso de rebaudiosida A presente en una composición de rebaudiosida A sin refinar o purificada. En una realización la composición de rebaudiosida A comprende rebaudiosida A de una pureza específica, y el resto de la composición comprende una mezcla de otros glicósidos de esteviol o de cualquier componente que no sea rebaudiosida A. La pureza de la composición puede ser medida usando métodos conocidos por las personas con experiencia común en la especialidad. Uno de tales métodos incluye cromatografía líquida de alto rendimiento (HPLC). Las personas con experiencia común en la especialidad apreciarán también que la humedad de la muestra puede afectar la precisión de las medidas de pureza. En consecuencia, la composición debería estar substancialmente seca cuando se mide su pureza. En la forma usada

aquí, una composición substancialmente seca comprende hasta 10% en peso de humedad.

Formas Amorphas y Polimórficas de Rebaudiosida A

La purificación de rebaudiosida A usando el método descrito anteriormente, da como resultado la formación de por lo menos tres polimorfos diferentes de rebaudiosida A: Forma 1: un hidrato de rebaudiosida A; Forma 2: una rebaudiosida A anhidra, y Forma 3: un solvato de rebaudiosida A. Las personas con experiencia común en la especialidad apreciarán que, tanto la solución orgánica acuosa como las temperaturas del proceso de purificación descritas aquí, podrán influir sobre los polimorfos resultantes de una composición de rebaudiosida A substancialmente pura.

Se define polimorfismo como la capacidad de una sustancia de existir como dos o más estados cristalinos que tiene diferentes disposiciones y/o conformaciones de las moléculas en la red de cristales. Se cree que aproximadamente 30% de los compuestos orgánicos exhiben polimorfismo (Zell, y colaboradores, *Tetrahedron* 56(36)6603-16 (2000)). El polimorfismo es importante en la formulación de farmacéuticos, pigmentos y colorantes, endulzantes, explosivos y agroquímicos. El polimorfismo puede hacer variar las propiedades físicas tales como densidad, punto de fusión, y porcentaje de disolución.

Los polimorfos de rebaudiosida A fueron identificados por análisis de muestras con difracción de rayos X en polvo (XRPD), una técnica muy conocida por los peritos en la especialidad. Las Figuras 3-11 son exploraciones de XRPD de composiciones de rebaudiosida A substancialmente pura obtenidas del proceso de purificación descrito aquí. Las exploraciones de XRPD de polimorfos de rebaudiosida A fueron creadas trazando la intensidad de dispersión versus el ángulo de dispersión 2θ . Las muestras fueron analizadas por XRPD usando un difractómetro de

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rayos X en polvo Shimadzu XRD-6000, usando radiación Cu K α . El instrumento estaba equipado con un tubo enfocador de rayos X largo y fino. El voltaje y amperaje del tubo fueron ajustados a 40 kV y 40 mA, respectivamente. La divergencia y ranuras de dispersión fueron ajustadas a 1" y la ranura receptora fue ajustada a 0,15 mm. La radiación difractada fue detectada con un detector de centelleo NaI. Se usó una exploración continua θ -2 θ a 3"/min (paso de 0,4 seg/0,02") desde 2,5 a 40" 2 θ . Se analizó un estándar de silicio para revisar la alineación del instrumento. Los datos fueron recolectados y analizados usando XRD-60000 v. 4,1.- Los patrones muestran resolución de reflejos, que indican que las muestras están compuestas de material cristalino.

La Figura 3 muestra patrones representativos de las Forma 1, Forma 2, y Forma 3^a (solvato de metanol) y 3B (solvato de etanol). El patrón de la forma 2 (patrón superior) es distintivamente diferente de los otros patrones. Debería advertirse que pueden existir múltiples polimorfos dentro de cada clasificación de Formas 1, 2, y 3.

La Figura 4 destaca las diferencias entre las Formas 1 y 2. Adicionalmente se muestran los dos patrones de la Forma 2 para ilustrar la reproductividad en la generación de diferentes polimorfos bajo condiciones variables de cristalización de los polimorfos.

La Figura 5 muestra una similitud significativa entre los patrones XRPD de las Formas 3A y 3B. Sin que se desee ser forzado por ninguna teoría, es posible que estos polimorfos sean solvatos isoestructurales, donde las únicas diferencias entre los patrones son los desplazamientos de ciertos valores máximos debido a la variación de la identidad del solvente. Esta relación isoestructural entre las Formas 3A y 3B podría ser verificada de ser necesario indexar los patrones. Los asteriscos identifican los valores máximos que son desplazados a la derecha en alrededor

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de 0,2 grados 2θ en el patrón para la Forma 3A. Además, varios valores máximos en la Forma 3B son más intensos que los valores máximos correspondientes en la Forma 3A. Por ejemplo, los valores máximos a 5,5, 11,0, 14,2 y 19,4 grados son más intensos para la Forma 3B que para la Forma 3A.

* La Figura 6 compara la Forma 2 con las Formas 3A y 3B de la Figura 5. La Forma 2 se parece más a la Forma 3A que a la Forma 3B. Aunque no se observan en el patrón de la Forma 2, los valores máximos identificados en la Figura 5 como más intensos en la Forma 3B que en la Forma 3A, hay por lo menos tres valores máximos (marcados con un doble asterisco bajo los patrones) que muestran la tendencia inversa (es decir, los valores máximos están presentes en la Forma 2, pequeños en la forma 3A y más grandes en la Forma 3B). Finalmente, un valor máximo grande en la Forma 3B en 17,6 grados parece estar desplazado ligeramente a la derecha en la Forma 3A (17,9 grados) y desplazado más a la derecha en la Forma 2 (18,0 grados). Otras dos series de valores máximos entre 21 y 23 grados muestran también este desplazamiento. Sin que se desee ser forzado por ninguna teoría, el desplazamiento de los valores máximos puede ser una indicación de que la Forma A estar desolvatado parcialmente, conteniendo así una mezcla tanto del solvato como de los cristales de Forma 2.

Las Figuras 7-10 son exploraciones XRPD de los polimorfos individuales de Forma 1, Forma 2, Forma 3A, y Forma 3B, respectivamente, desde una composición de rebaudiosida A substancialmente pura obtenida del proceso de purificación descrito aquí anteriormente.

Como se ilustra en la Figura 2, el tipo de polimorfo formado puede ser dependiente de factores tales como la composición de la solución orgánica acuosa, la temperatura del paso de cristalización, y la temperatura durante el paso de secado. Sin que se desee ser forzado por ninguna teoría, se cree que la Forma 1 y la Forma 3 se forman durante el paso de

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cristalización único, en tanto que se cree que la Forma 2 se forma durante el paso de secado después de la conversión desde la Forma 1 y la Forma 3.

Las temperaturas bajas durante el paso de cristalización, entre alrededor de 20° C y alrededor de 50°C, y una baja relación de agua con el solvente orgánico en el solvente orgánico acuoso da como resultado en la formación de la Forma 3. Altas temperaturas durante el paso de cristalización, entre alrededor de 50°C hasta alrededor de 80°C, y la alta relación entre agua y solvente orgánico en el solvente orgánico acuoso dan como resultado la formación de la Forma 1. La Forma 1 puede ser convertida en la Forma 3 formando una lechada en un solvente anhidro a una temperatura próxima a la temperatura ambiente durante alrededor de 2 hasta alrededor de 16 horas, o formando una lechada en un solvente anhidro a una temperatura próxima al reflujo durante aproximadamente 0,5 hasta alrededor de 3 horas. La Forma 3 puede ser convertida en la Forma 1 formando una lechada del polimorfo en agua a una temperatura aproximada a la temperatura ambiente durante aproximadamente 16 horas o hasta alrededor de la temperatura de reflujo durante aproximadamente 2 a 3 horas. La Forma 3 puede ser convertida en la Forma 2 durante el proceso de secado; sin embargo, el aumento ya sea de la temperatura de secado sobre 70°C o el tiempo de secado de una composición de rebaudiosida A substancialmente pura, puede dar como resultado la descomposición de la rebaudiosida A y el aumento de la impureza de rebaudiosida B remanente en la composición de rebaudiosida A substancialmente pura. La Forma 2 puede ser convertida en la Forma 1 con la adición de agua.

Además de las, por lo menos tres, formas polimórficas de rebaudiosida A, la purificación de rebaudiosida A puede dar como resultado la formación de una forma amorfa de rebaudiosida A, la Forma 4, como se muestra en la Figura 11. La Forma 4 tiene un halo amorfo amplio que identifica la composición como amorfa.

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Amorfo, en la forma usada aquí, describe un material sólido no-cristalino. La forma amorfa de rebaudiosida A (Forma 4) tiene un porcentaje de disolución mejorado comparado con las formas polimórficas de rebaudiosida A (Formas 1, 2, o 3). Las personas con experiencia común en la especialidad apreciarán que el porcentaje de disolución de una composición endulzante puede ser importante en la formulación de composiciones endulzantes sólidas y líquidas, ejemplos no limitantes de las cuales incluyen goma de mascar, productos horneados y bebidas.

Como se describió aquí anteriormente, la Forma A puede ser obtenida durante la purificación inicial de rebaudiosida A, o directamente desde cualquier polimorfo individual o combinación de polimorfos usando métodos muy conocidos por las personas con experiencia común en la especialidad. Además, la Forma 4 puede ser obtenida desde una composición de rebaudiosida A sin refinar o desde una composición de rebaudiosida A substancialmente pura, obtenida a través de medios de purificación diferentes de los descritos aquí anteriormente. Ejemplos no limitantes de métodos para preparar formas amorfas de rebaudiosida A incluyen molienda con molinos de bolas, precipitación, liofilización, criomolienda, y secado por aspersion de una composición de rebaudiosida A.

En una realización en particular, la purificación de rebaudiosida A descrita aquí anteriormente, da como resultado una composición que comprende la rebaudiosida A amorfa de la Forma A. Las personas con experiencia común en la especialidad deberán apreciar que los parámetros del procedimiento de cristalización pueden ser modificados para intensificar la formación de la Forma 4.

En otra realización en particular, la Forma 4 puede ser preparada desde una composición de rebaudiosida A secando por aspersion una solución de la composición de rebaudiosida A. Dicho en pocas palabras, el secado por aspersion requiere en general la alimentación de una solución de rebaudiosida A, a través de una

bomba de alimentación en una boquilla atomizadora que atomiza la solución en un rocío de gotitas con la ayuda de un flujo constante de nitrógeno/aire. La humedad es evaporada desde las gotitas en condiciones de temperatura y condiciones de flujo de aire controladas en la cámara de secado, dando como resultado la formación de partículas secas de rebaudiosida A amorfa. La pureza de la rebaudiosida A amorfa dependerá de la pureza de la solución de rebaudiosida A.

En otra realización en particular, se puede preparar la Forma A desde una composición de rebaudiosida A moliendo las formas no-amorfas de rebaudiosida A. La molienda es un proceso mecánico que se cree que produce áreas de energía localizadas que convierten las formas cristalinas de rebaudiosida A en la forma amorfa. Las técnicas de molienda ilustrativas incluyen molienda con molino de bolas, o molienda por chorro de aire, ambas muy conocidas por las personas con experiencia común en la especialidad. Descrito en pocas palabras, las formas no amorfas de rebaudiosida A son molidas por un período de tiempo y a una velocidad eficaz para formar una rebaudiosida A amorfa. Estos parámetros pueden ser determinados por personas con experiencia común en la especialidad. Los períodos típicos de molienda pueden fluctuar desde alrededor de 15 minutos hasta alrededor de dos horas, aunque también se pueden emplear otros períodos de tiempo.

Las propiedades materiales de los tres polimorfos de rebaudiosida A y la forma amorfa de rebaudiosida A se resumen en la tabla siguiente:

Tabla 1: Formas de Rebaudiosida A Polimórficas y Amorfa

	Forma 1 Polimórfica	Forma 2 Polimórfica	Forma 3 Polimórfica	Forma 4 Amorfa
Porcentaje de disolución	Muy bajo ($<0,2\%$ en 60 minutos)	Intermedio ($<30\%$ en 5 minutos)	Alto ($>30\%$ en 5 minutos)	Alto ($>35\%$ en 5 minutos)

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en H ₂ O a 25°C				
Contenido de Alcohol	<0,5%	<1%	1-3%	<0,05%
Contenido de humedad	>5%	<1%	<3%	<6%

Las propiedades de los materiales descritas anteriormente son sólo ilustrativas de realizaciones particulares de las formas polimórficas y amorfas de rebaudiosida A. Las personas con experiencia común en la especialidad apreciarán que el polimorfo de rebaudiosida A anhidra (Forma 2), el polimorfo de solvato de rebaudiosida A, y la rebaudiosida A amorfa son higroscópicas y pueden absorber humedad hasta alrededor de 10% en peso en una base seca.

Las personas con experiencia común en la especialidad apreciarán que la composición de rebaudiosida A puede ser modificada para obtener una mezcla deseada de formas polimórficas y amorfas de rebaudiosida A que dependen de las cualidades deseadas de la composición de rebaudiosida A (es decir, porcentaje de disolución, etc.). En una realización, una composición de rebaudiosida A substancialmente pura puede comprender una forma polimórfica o amorfa particular de rebaudiosida A en una cantidad que varía entre alrededor de 1% hasta alrededor de 100% en peso. Por ejemplo, una composición de rebaudiosida A substancialmente pura puede comprender una cantidad polimórfica o amorfa de rebaudiosida A en una cantidad superior a alrededor de 50% en peso, aún más particularmente en una cantidad superior a 75% en peso, o aún más todavía en una cantidad superior a alrededor de 85% en peso. También pueden emplearse cantidades apropiadas de formas polimórficas o amorfas de rebaudiosida A dentro de estos márgenes de variación. En otra realización, una composición de rebaudiosida A substancialmente

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pura puede comprender una combinación de una forma polimórfica y/o amorfa en particular de rebaudiosida A.

Este invento es ilustrado adicionalmente por los ejemplos siguientes, que no deben ser considerados de ningún modo como limitantes de su campo de acción. Por el contrario, debe entenderse claramente que debe hacerse uso de otras diversas realizaciones, modificaciones y equivalentes suyos que, después de leer la descripción incluida aquí, puedan sugerirse por sí mismas a los peritos en la especialidad, sin alejarse del espíritu del presente invento y/o el campo de acción de las reivindicaciones anexas. A menos que se especifique algo diferente, los porcentajes (%) son expresados en peso.

EJEMPLOS

La pureza de las composiciones de rebaudiosida A descritas en los ejemplos citados aquí, a continuación, fue determinada usando HPLC. Los métodos para ejecutar análisis por HPLC son muy conocidos por aquellos con experiencia común en la especialidad. En pocas palabras, el análisis empleando HPLC fue ejecutado usando una columna ZORBAX NH₂ (150 x 4,6 mm, 5µm) a una temperatura de 30°C. La fase móvil comprendió una solución de solución amortiguadora 20% (0,0125% de ácido acético y 0,0125% de acetato de amonio) y acetonitrilo (80%) con una velocidad de flujo de 1,5 mL/min. Se inyectaron 12 µL de cada muestra en duplicado y la muestra fue analizada usando un detector UV a 210 nm (ancho de banda 4 nm) con una referencia de 260 nm (ancho de banda 100 nm). Los análisis empleando HPLC necesitaron un tiempo de recorrido fluctuó de 40 a 60 min.

Se preparó una solución amortiguadora de 0,0125 de ácido acético y 0,0125% de acetato de amonio disolviendo 0,125 g de acetato de amonio y 125 µl de ácido acético glacial en un litro de agua. El tiempo de retención (TR) de rebaudiosida B fue ajustado variando la relación de acetato de amonio a ácido

D
↓

acético mientras se mantenía un total de 0,025% de ambos combinado. El aumento de la cantidad de ácido acético disminuyó el tiempo de retención de rebaudiosida B.

La fase móvil fue preparada mezclando la solución amortiguadora con acetonitrilo para lograr un tiempo de retención de rebaudiosida A de $7,0 \pm 0,5$ min. Inicialmente, esto fue de aproximadamente 20% de solución amortiguadora (200 mL de solución amortiguadora y 800 mL de acetonitrilo)... El aumento de la cantidad de acetonitrilo en 1 a 2% aumentó el tiempo de retención de rebaudiosida A en alrededor de 1 minuto.

Se preparó una solución disolvente mezclando 750 mL de acetonitrilo y 250 mL de solución amortiguadora. Los patrones de rebaudiosida A fueron preparados diluyendo $20,0 \pm 0,5$ mg (registrado hasta el 0,1 mg más cercano) del patrón de rebaudiosida A con 4 mL de solución disolvente para elaborar una solución patrón de 5000 mg/L aproximadamente. La solución patrón de rebaudiosida A fue inyectada a 10,8, 11,4, 12,6 y 13,2 μ L. El contenido de humedad fue medido por análisis de Kart Fischer cada vez que se preparó un patrón, y se realizaron correcciones basados en la pureza del solvente según el certificado de análisis. En forma alternativa, se prepararon patrones de rebaudiosida A diluyendo muestras individuales de 18, 19, 21, y 22 (cada $\pm 0,2$) mg del patrón de rebaudiosida A con 4 mL de solución disolvente (corrigiendo por humedad y pureza. Las muestras preparadas individualmente fueron inyectadas al mismo nivel que las muestras (12 μ L.)

Se prepararon los patrones de esteviosida diluyendo $12,5 \pm 0,5$ mg (registrado hasta el 0,1 mg más cercano) del patrón de esteviosida con 5 mL de solución disolvente para preparar una solución patrón de aproximadamente 2500 mg/ patrón (disolución madre A) (corrigiendo por humedad y pureza). El patrón de esteviosida fue diluido después usando un mL de disolución madre

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A para diez mL de diluyente para producir 250 mg/L de patrón (disolución madre B) y los patrones de disolución madre fueron diluidos hasta concentraciones finales que fluctuaban desde 2,5 a 50 mg/L.

Se prepararon muestras de composiciones de rebaudiosida A diluyendo 125 ± 2 mg (registrado hasta el 0,1 mg más cercano) de la composición de rebaudiosida A con 25 mL de solución disolvente para elaborar una solución de muestra de 5000 mg/L aproximadamente (corrigiendo por humedad). Si las muestras no fueron analizadas inmediatamente, fueron almacenadas sin dejar espacio libre superior (*headspace*), bajo nitrógeno y desecadas.

La tabla siguiente proporciona una pauta para tiempos de retención (TR) para rebaudiosida A y otros glicósidos de esteviol. Sin embargo, las personas con experiencia común en la especialidad deberían apreciar que los tiempos de retención pueden ser modificados según se necesite.

Tabla 2: Pautas de retención de HPLC

Compuesto	TR (min)
Esteviosida	4,53
Rebaudiosida C	5,21
Rebaudiosida F	5,62
Rebaudiosida A	7,07
Rebaudiosida D	15,79
Esteviolbiosida	18,35
Rebaudiosida B	35,83

CONJUNTO DE EJEMPLOS A

Tabla 3: Resumen de los Ejemplo A1-3

	Rebaudiosida A sin refinar	Etanol (95%) (mL)	Metanol Solvente (99%) (mL)	Agua (mL)	Calentamiento T(°C)	Secado T(°C)	Rendimiento (g)	Pureza de HPLC %p/p)
A1	400	1200	400	320	50	50	130	98,9

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A2	100	320	120	50	30-40	60	72	98,3
A3	50	160	60	25	~30	60	27,3	98,2

EJEMPLO A1

Se obtuvo una mezcla de rebaudiosida sin refinar (77,4% de pureza) desde una fuente comercial. Las impurezas (6,2% de esteviosida, 5,6% de rebaudiosida C, 0,6% de rebaudiosida F, 1,00% de otros glicósidos de esteviol 3,0% de rebaudiosida D, 4,9% de rebaudiosida B, 0,3% de esteviolbiosida) fueron identificados y cuantificados usando HPLC en base seca (contenido de humedad 4,7%).

Rebaudiosida A sin refinar (400 g), etanol (95% 1200 mL), metanol (99% 40 mL), y agua (320 mL) fueron combinados y calentados a 50°C durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 16 horas. Los cristales blancos fueron filtrados y lavados dos veces con etanol (2x 200 mL, 95%) y secados en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm).

La composición final de la rebaudiosida A substancialmente pura (130 g) comprendió 98,91% de rebaudiosida A, 0,06% de esteviosida, 0,03% de rebaudiosida C, 0,12% de rebaudiosida F, 0,13% de glicósidos de esteviol, 0,1% de rebaudiosida D, 0,49% de rebaudiosida B y 0,03% de esteviolbiosida, todos en peso.

EJEMPLO A2

La rebaudiosida A sin refinar (80,37%) fue obtenida desde una fuente comercial. Las impurezas (6,22% de esteviosida, 2,28% de rebaudiosida C, 0,35% de dulcosida A, 0,78% de rebaudiosida F, 0,72% de otros glicósidos de esteviol, 3,33% de rebaudiosida B, 0,07% de esteviolbiosida, fueron identificadas y

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cuantificadas empleando HPLC en base seca (contenido de humedad 3,4%).

La rebaudiosida A sin refinar (100 g), etanol (95%, 320 mL), metanol (99%, 120 mL) y agua fueron combinados y calentados a 30-40°C durante 10 minutos. La solución transparente fue enfriada a 22°C durante 16 horas. Los cristales blancos fueron filtrados y lavados dos veces con etanol (2 x 50 mL, 95%). Se formó una lechada con la torta de filtrado húmeda (88 g) en etanol (95%, 1320 mL) durante 16 horas, y fue filtrada, lavada con etanol 95%, 2 x 100 mL) y secada en un horno de vacío durante 16-24 horas bajo presión reducida (20 mm).

La composición final de la rebaudiosida A substancialmente pura (72 g) comprendió 98,29% de rebaudiosida A, 0,03% de esteviosida, 0,02% de rebaudiosida C, 0,17% de rebaudiosida F, 0,06% de rebaudiosida D y 1,09% de rebaudiosida B. No se detectó esteviolbiosida empleando HPLC.

EJEMPLO A3

La rebaudiosida A sin refinar (80,37%) fue obtenida desde una fuente comercial. Las impurezas (6,22% de esteviosida, 2,28% de rebaudiosida C, 0,35% de dulcosida A, 0,78% de rebaudiosida F, 0,72% de otros glicósidos de esteviol, 3,33% de rebaudiosida B, 0,07% de esteviolbiosida) fueron identificados y cuantificados empleando HPLC en una base seca (contenido de humedad 3,4%)

La rebaudiosida A sin refinar (50 g), etanol (95%, 160 mL), metanol (99%, 60 mL) y agua (25 mL) fueron combinados y calentados hasta 30°C aproximadamente, durante 10 minutos. La solución transparente fue enfriada a 22°C durante 16 horas. Los cristales blancos fueron filtrados y lavados dos veces con etanol (2 x 25 mL, 95%). La torta de filtrado húmeda (40 g) formó una lechada en etanol (99%, 600 mL) durante 16 horas, fue filtrada, lavada con metanol 99%, 2 x 25 mL) y secada en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm).

La composición final de la rebaudiosida A substancialmente pura (27,3 g) comprendió 98,22% de rebaudiosida A, 0,04% de esteviosida, 0,04% de rebaudiosida C, 0,18% de rebaudiosida F, 0,08 de rebaudiosida D y 1,03% de rebaudiosida B. No se detectó esteviolbiosida empleando HPLC.

CONJUNTO DE EJEMPLOS

Tabla 4: Resumen de los Ejemplos B1-19

	Rebaudiosida A, sin refinar (g)	Solvente			Solvente de Lavado	Rendimiento (g)	Pureza HPLC (%)
		Etanol (95%) (mL)	Co-solvente orgánico (mL)	Agua (mL)			
B1	5	16	Metanol (6)	2	EtOH/MeOH (4:1,5 v/v)	3,2	>97
B2	5	16	Metanol (4)	2	EtOH/MeOH (4:1 v/v)	3,1	>97
B3	5	9,5	1-Butanol (9,5)	1	EtOH/1- Butanol (1:1 v/v)	3,2	>95
B4	5	9,5	1-Butanol (9)	1	EtOH/MeOH (1:1 v/v)	3,5	>96
B5	5	12,5	Metanol (6)	2	*EtOH/2- Butanol (4:1 v/v)	3,3	>97
B6	5	12,5	Acetonitrilo (6)	1,5	*EtOH/ Acetonitrilo (6:3 v/v)	3,4	>95
B7	5	14,5	Acetato de etilo (4)	4	*EtOH/ Acetato de etilo 7:2 v/v)	3,4	>95
B8	5	16	Metanol (6)	2	EtOH/MeOH (4:1,5 v/v)	3,2	>97
B9	5	16	Metanol (4)	2	EtOH/MeOH (4:1 v/v)	3,1	>97
B10	5	14,5	Metanol (4)	1,5	EtOH/MeOH (7:2 v/v)	3,4	>97
B11	5	16	Metanol (6)	1,5	EtOH/MeOH (8:3 v/v)	3,2	>97
B12	5	16	Metanol (6)	2	*EtOH/MeOH (8:3 v/v)	3,2	>96
B13	5	16	Metanol (6)	2	*EtOH/MeOH (8:3 v/v)	3,4	>96
B14	5	15	Metanol (5)	2,5	*EtOH/MeOH (3:1 v/v)	3,2	>97

	Rebaudiosida A, sin refinar (g)	Solvente					
		Etanol (95%) (mL)	Co-solvente orgánico (mL)	Agua (mL)	Solvente de Lavado	Rendimiento (g)	Pureza HPLC (%)
B15	5	15	Metanol (5)	3	*EtOH/MeOH (3:1 v/v)	2,7	>97
B16	5	15	Metanol (6)	3,5	*EtOH/MeOH (3:1 v/v)	2,6	>99
B17	5	15	Metanol (5)	4	*EtOH/MeOH (3:1 v/v)	2,3	>99
B18	5	16	Metanol (6)	2,5	*EtOH/MeOH (8:3 v/v)	3,0	>97
B19	5	16	Metanol (6)	2,5	*EtOH/MeOH (8:3 v/v)	3,2	>98

EJEMPLO B1

Rebaudiosida A sin refinar (pureza, 77,4%, 5g), etanol (95%, 16mL), metanol (6 mL), y agua (2 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 16 horas. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5 mL, 4:1,5, v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,2 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B2

Rebaudiosida A sin refinar (pureza 77,4%, 5g), etanol (95% 16 mL), metanol (4 mL) y agua (2 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada a 22°C durante 16 horas. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5 mL, 4:1, v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,1 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B3

Rebaudiosida A sin refinar (pureza 77,4%, 5 g), etanol (95%, 9,5 mL), 1-butanol (9,5 mL) y agua (1 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución

transparente fue enfriada hasta 22°C durante 16 horas. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:1-butanol (5 mL, 1:1, v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,2 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B4

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 9,5 mL), metanol (9 mL) y agua (1 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada a 22°C durante 16 horas. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5 mL, 1:1, v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,5 g del producto purificado (> 96% empleando HPLC).

EJEMPLO B5

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 12,5 mL), metanol (6 mL) y agua (2 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C. La solución fue sembrada con 10 mg de rebaudiosida A 98% pura, y la mezcla fue dejada a 22°C durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de etanol:metanol (5 mL, 4:1, v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,3 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B6

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 12,5 mL), acetonitrilo (6 mL) y agua (1,5 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada a 22°C. La solución fue sembrada con 10 mg de rebaudiosida A 98% pura, y la mezcla fue dejada a 22°C

durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de etanol:acetonitrilo (5 mL, 6:3, v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,4 g del producto purificado (> 95% empleando HPLC).

EJEMPLO B7

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 14,5 mL), acetato de etilo (4 mL) y agua (1,5 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada a 22°C. La solución fue sembrada con 10 mg de rebaudiosida A 98% pura y la mezcla fue dejada a 22°C durante 16 horas. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:acetonitrilo (5 mL, 7:2, v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,4 g del producto purificado (> 95% empleando HPLC).

EJEMPLO B8

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 16 mL), metanol (6 mL) y agua (2 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 16 horas. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5,5 mL, 4:1,5 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,2 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B9

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 16 mL), metanol (4 mL) y agua (2 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada a 22°C durante 16 horas. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 4:1 v/v) y fue secado en un horno de

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vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,1 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B10

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 14,5 mL), metanol (4 mL) y agua (1,5 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada a 22°C durante 16 horas. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 7:2 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,4 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B11

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 16 mL), metanol (6 mL) y agua (1,5 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 16 horas. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 8:3 v/v) mezclado y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,2 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B12

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 16 mL), metanol (6 mL) y agua (2 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C y sembrada con 10 mg de rebaudiosida A pura (>98%). La mezcla fue mantenida a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 8:3 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,2 g del producto purificado (> 98% empleando HPLC).

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EJEMPLO B13

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 16 mL), metanol (6 mL) y agua (2 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C y sembrada con 10 mg de rebaudiosida A pura (>98%). La mezcla fue mantenida a la temperatura ambiente durante 16 horas mientras se agitaba. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 8:3 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,4 g del producto purificado (> 96% empleando HPLC).

EJEMPLO B14

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 15 mL), metanol (5 mL) y agua (2,5 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada a 22°C durante 16 horas mientras se agitaba. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 3:1 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,2 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B15

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 15 mL), metanol (5 mL) y agua (3 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 16 horas mientras se agitaba. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 3:1 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm). para rendir 2,7 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B16

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Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 15 mL), metanol (5 mL) y agua (3 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 16 horas mientras se agitaba. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 3:1 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 2,6 g del producto purificado (> 99% empleando HPLC).

EJEMPLO B17

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 15 mL), metanol (5 mL) y agua (4 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 16 horas mientras se agitaba. El producto blanco cristalino fue filtrado y lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 3:1 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 2,3 g del producto purificado (> 99% empleando HPLC).

EJEMPLO B18

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 15 mL), metanol (6 mL) y agua (2,5 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C. Esta mezcla fue agitada a la temperatura ambiente durante 15-20 minutos, tiempo durante el cual empezaron a aparecer cristales. Se dejó de agitar y la mezcla fue mantenida a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 8:3 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,0 g del producto purificado (> 97% empleando HPLC).

EJEMPLO B19

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Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95%-16 mL), metanol (6 mL) y agua (2,5 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 2 horas. Durante este tiempo empezaron a aparecer cristales. La mezcla fue agitada a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 8:3 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,2 g del producto purificado (> 98% empleando HPLC).

CONJUNTO DE EJEMPLOS C

Tabla 5: Resumen de los Ejemplos C1-9

		Solvente					
	Rebaudiosida A, sin refinar (g)	Solvente Orgánico (mL)	Co- solvente orgánico (mL)	Agua (mL)	Solvente de Lavado	Rendimiento (g)	Pureza HPLC (%)
C1	5	Isopropanol (9,5)	Metanol (9,5)	1	Isopropanol/ MeOH (1:1 v/v)	3,85	>91
C2	5	sec-Butanol (9,5)	Metanol (9,5)	1	MeOH/sec- Butanol (1:1 v/v)	4,0	>91
C3	5	1-Propanol (9,5)	Metanol (9,5)	1	MeOH/1- Propanol (1:1 v/v)	3,55	>91,2
C4	5	Etanol (9,5)	1- Propanol (9,5)	1	EtOH/1- Propanol (1:1 v/v)	2,5	>94
C5	5	1-Butanol (9,5)	Metanol (9,5)	1	MeOH/1- Butanol (1:1 v/v)	3,7	>91,5
C6	5	Etanol (9,5)	2- Propanol (9,5)	1	EtOH/2- Propanol (1:1 v/v)	2,4	>93,5
C7	5	Etanol (9,5)	sec- Butanol (9,5)	1	EtOH/sec- Butanol (1:1 v/v)	2,9	>93
C8	5	ter-Butanol (9,5)	Metanol (9,5)	1	MeOH/ter Butanol (1:1 v/v)	3,9	>83

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		Solvente					
	Rebaudiosida A, sin refinar (g)	Solvente Orgánico (mL)	Co- solvente orgánico (mL)	Agua (mL)	Solvente de Lavado	Rendimiento (g)	Pureza HPLC (%)
C9	5	Etanol (9,5)	ter- Butanol (9,5)	1	EtOH/ter Butanol (1:1 v/v)	2,9	>88

EJEMPLO C1

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), metanol (99%, 9,5 mL), isopropanol (9,5 mL) y agua (1 mL) fueron combinados y calentados hasta alrededor de 40-50°C durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 2 horas y después agitada a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de etanol:metanol (5,0 mL, 8:3 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,85 g del producto purificado (> 91% empleando HPLC).

EJEMPLO C2

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), metanol (99% 9,5 mL), sec-butanol (9,5 mL) y agua (1 mL) fueron combinados y calentados hasta alrededor de 40-50 °C durante 10 minutos. La solución transparente fue enfriada a 22°C durante 2 horas y después agitada a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de metanol:sec-butanol (10,0 mL, 1:1 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 4,0 g del producto purificado (> 91% empleando HPLC).

EJEMPLO C3

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), metanol (99% 9,5 mL), 1-propanol (9,5 mL) y agua (1 mL) fueron combinados y calentados hasta alrededor de 40-50°C durante 10

minutos. La solución transparente fue enfriada a 22°C durante 2 horas y después agitada a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de metanol:1-propanol (10,0 mL, 1:1 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,55 g del producto purificado (> 91,21% empleando HPLC).

EJEMPLO C4

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 9,5 mL), 1-propanol (9,5 mL) y agua (1 mL) fueron combinados y calentados hasta alrededor de 40-50°C durante 10 minutos. La solución transparente fue enfriada a 22°C durante 2 horas y después agitada a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de etanol:1-propanol (10,0 mL, 1:1 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 2,5 g del producto purificado (> 94,0% empleando HPLC).

EJEMPLO C5

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), metanol (99% 9,5 mL), 1-butanol (9,5 mL) y agua (1 mL) fueron combinados y calentados hasta alrededor de 40-50°C durante 10 minutos. La solución transparente fue enfriada a 22°C durante 2 horas y después agitada hasta la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de metanol:1-butanol (10,0 mL, 1:1 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,7 g del producto purificado (> 91,5% empleando HPLC).

EJEMPLO C6

Rebaudiosida A sin refinar (pureza 80,37%, 5 g), etanol (95% 9,5 mL), 2-propanol (9,5 mL) y agua (1 mL) fueron combinados

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y calentados hasta alrededor de 40-50°C durante 10 minutos. La solución transparente fue enfriada a 22°C durante 2 horas y después agitada a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de etanol:2-propanol (10,0 mL, 1:1 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 2,4 g del producto purificado (> 93,5% empleando HPLC).

EJEMPLO C7

Rebaudiosida A sin refinar (pureza 77,4%, 5 g), etanol (95% 9,5 mL), sec-butanol (9,5 mL) y agua (1 mL) fueron combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 2 horas y después agitada a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con una mezcla de etanol:sec-butanol (10,0 mL, 1:1 v/v) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 2,9 g del producto purificado (> 93,0% empleando HPLC).

EJEMPLO C8

Rebaudiosida A sin refinar (pureza 77,4%, 5 g), metanol (99% 9,5 mL), ter-butanol (9,5 mL) y agua (1 mL) fueron combinados y calentados hasta alrededor de 40-50°C durante 10 minutos. La solución transparente fue enfriada a 22°C durante 2 horas y después agitada a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con metanol (99%, 7,0 mL) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 3,9 g del producto purificado (> 83,0% empleando HPLC).

EJEMPLO C9

Rebaudiosida A sin refinar (pureza 77,4%, 5 g), etanol (95% 9,5 mL), ter-butanol (9,5 mL) y agua (1 mL) fueron

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combinados y calentados a reflujo durante 10 minutos. La solución transparente fue enfriada hasta 22°C durante 2 horas y después agitada a la temperatura ambiente durante 16 horas. El producto blanco cristalino fue filtrado, lavado dos veces con etanol (95%, 7,0 mL) y fue secado en un horno de vacío a 50°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 2,9 g del producto purificado (> 88,0% empleando HPLC).

CONJUNTO DE EJEMPLOS D

Tabla 6: Resumen de los Ejemplos D1-D12

	Rebaudiosida A, sin refinar (g)	Solvente				
		Solvente Orgánico (mL)	Agua (mL)	Solvente de Lavado	Rendimiento (g)	Pureza HPLC (%)
D1	50	MeOH(180)	20	MeOH	29,8	96,2
D2	50	MeOH(160)	40	MeOH	31,2	95,5
D3	50	EtOH(188)	12	EtOH	37,3	93,4
D4	50	EtOH(184)	16	EtOH	31,7	95,3
D5	50	EtOH(180)	10	EtOH	35,7	94,7
D6	50	EtOH(176)	24	EtOH	38,2	97,3
D7	50	EtOH(172)	28	EtOH	32	98,1
D8	50	EtOH(160)	400	EtOH	19,8	99,5
D9	50	1-Propanol (180)	20	1-Propanol	27	92,9
D10	50	2-Propanol (180)	20	2-Propanol	24,9	91,4
D11	50	1-Butanol (180)	20	1-Butanol	40,6	93,1
D12	50	2-Butanol (180)	20	2-Butanol	40,4	90,5

EJEMPLO D1

Rebaudiosida A sin refinar (pureza 77,4%, 50 g), metanol (99% 180 mL) y agua (20 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado, lavado dos veces con metanol (99%, 25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 29,8 g del producto purificado (> 96,2% empleando HPLC).

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EJEMPLO D2

Rebaudiosida A sin refinar (pureza 80,37%, 50 g), metanol (99% 160 mL) y agua (40 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 1 semana. El producto blanco cristalino fue filtrado, lavado dos veces con metanol (99%, 25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 31,2 g del producto purificado (> 95,5% empleando HPLC).

EJEMPLO D3

Rebaudiosida A sin refinar (pureza 80,37%, 50 g), etanol (95% 188 mL) y agua (12 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado, lavado dos veces con etanol (95%, 25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 37,3 g del producto purificado (> 93,4% empleando HPLC).

EJEMPLO D4

Rebaudiosida A sin refinar (pureza 80,37%, 50 g), etanol (95% 184 mL) y agua (16 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado, lavado dos veces con etanol (95%, 25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 31,7 g del producto purificado (> 95,3% empleando HPLC).

EJEMPLO D5

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Rebaudiosida A sin refinar (pureza 80,37%, 50 g), etanol (95% 180 mL) y agua (20 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado, lavado dos veces con etanol (95%, 25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 35,7 g del producto purificado (> 94,7% empleando HPLC).

EJEMPLO D6

Rebaudiosida A sin refinar (pureza 80,37%, 50 g), etanol (95% 176 mL) y agua (24 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado, lavado dos veces con etanol (95%, 25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 38,2 g del producto purificado (> 97,3% empleando HPLC).

EJEMPLO D7

Rebaudiosida A sin refinar (pureza 80,37%, 50 g), etanol (95% 172 mL) y agua (28 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado, lavado dos veces con etanol (95%, 25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 32,0 g del producto purificado (> 98,1% empleando HPLC).

EJEMPLO D8

Rebaudiosida A sin refinar (pureza 80,37%, 50 g), etanol (95% 160 mL) y agua (40 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado, lavado dos veces con etanol (95%,

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25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 19,8 g del producto purificado (> 99,5% empleando HPLC).

EJEMPLO D9

Rebaudiosida A sin refinar (pureza 80,37%, 50 g), 1-propanol (180 mL) y agua (20 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado, lavado dos veces con 1-propanol (25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 27,0 g del producto purificado (> 92,9% empleando HPLC).

EJEMPLO D10

Rebaudiosida A sin refinar (pureza 80,37%, 50 g), 2-propanol (180 mL) y agua (20 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado, lavado dos veces con 2-propanol (25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 34,9 g del producto purificado (> 91,4% empleando HPLC).

EJEMPLO D11

Rebaudiosida A sin refinar (pureza 80,37%, 50 g), 1-butanol (180 mL) y agua (20 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado, lavado dos veces con 1-butanol (25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 40,6 g del producto purificado (> 93,1% empleando HPLC).

EJEMPLO D12

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Rebaudiosida A sin refinar (pureza 80,37%, 50 g), 2-butanol (180 mL) y agua (20 mL) fueron combinados y calentados a reflujo durante 30 minutos. La mezcla se dejó enfriar después hasta la temperatura ambiente durante 16-24 horas. El producto blanco cristalino fue filtrado y lavado dos veces con 2-butanol (25 mL) y fue secado en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 40,4 g del producto purificado (> 90,5% empleando HPLC).

CONJUNTO DE EJEMPLOS E

Tabla 7: Resumen de los Ejemplos E1-E3

	Rebaudiosida A, sin refinar (g)	Etanol (95%) (mL)	Co-Solvente Orgánico (mL)	Agua (mL)	Lechada de Metanol (mL)	Rendimiento (g)	Pureza HPLC (%)
E1	50	160	Metanol (60)	25	200	12,7	>97
E2	50	160	Metanol (60)	25	300	18,6	>97
E3	50	160	Metanol (60)	25	350	22,2	>97

EJEMPLO E1

Rebaudiosida A sin refinar (pureza 41%, 50 g), etanol (95%, 160 mL) metanol (99,8%, 60 mL) y agua (25 mL) fueron combinados por agitación a 22°C. El producto blanco cristalizó en 5-20 horas. La mezcla fue agitada por 48 horas más. El producto blanco cristalino fue filtrado y lavado dos veces con etanol (95%, 25 mL). Se formó después una lechada con la torta húmeda del producto cristalino blanco en metanol (99,8%, 20 mL) durante 16 horas, se filtró y lavó dos veces con metanol (99,8%, 25 mL) y fue secada en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 12,7 g del producto purificado (> 97% empleando HPLC).

EJEMPLO E2

Rebaudiosida A sin refinar (pureza 48%, 50 g), etanol (95%, 160 mL) metanol (99,8%, 60 mL) y agua (25 mL) fueron combinados por agitación a 22°C. El producto blanco cristalizó

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en 3-6 horas. La mezcla fue agitada por 48 horas más. El producto blanco cristalino fue filtrado y lavado dos veces con etanol (95%, 25 mL). Se formó después una lechada con la torta húmeda del producto cristalino blanco en metanol (99,8%, 300 mL) durante 16 horas, se filtró y lavó dos veces con metanol (99,8%, 25 mL) y fue secada en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 18,6 g del producto purificado (> 97% empleando HPLC).

EJEMPLO E3

Rebaudiosida A sin refinar (pureza 55%, 50 g), etanol (95%, 160 mL) metanol (99,8%, 60 mL) y agua (25 mL) fueron combinados por agitación a 22°C. El producto blanco cristalizó en 15-30 minutos. La mezcla fue agitada por 48 horas más. El producto blanco cristalino fue filtrado y lavado dos veces con etanol (95%, 25 mL). Se formó después una lechada con la torta húmeda del producto cristalino blanco en metanol (99,8%, 350 mL) durante 16 horas, se lavó y filtró dos veces con metanol (99,8%, 25 mL) y fue secada en un horno de vacío a 60°C durante 16-24 horas bajo presión reducida (20 mm) para rendir 22,2 g del producto purificado (> 97% empleando HPLC).

EJEMPLO F

Una solución de rebaudiosida A substancialmente pura, obtenida empleando la técnica de purificación descrita aquí anteriormente, (>97% pura empleando HPLC) fue preparada en agua destilada dos veces (12,5 gm en 50 mL, 25% de concentración) agitando la mezcla a 40°C durante 5 minutos. Se formó una forma amorfa de rebaudiosida A al usar inmediatamente la solución transparente para secado por aspersión con el secador por aspersión SD-04 de Lab Plant (Lab Plant Ltd., West Yorkshire, U.K.). La solución fue alimentada a través de una bomba de alimentación a una boquilla atomizadora, que pulverizó la solución de rebaudiosida A en un rocío de gotitas con la ayuda de

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un flujo de nitrógeno/aire constante. La humedad fue evaporada de las gotitas bajo condiciones de temperatura (alrededor de 90 a 97°C aproximadamente) y condiciones de flujo de aire controladas en la cámara de secado y dio como resultado la formación de partículas secas. Este polvo seco (11-12 g, H₂O 6,74%) fue descargado en forma continua desde la cámara de secado y fue recolectado en una botella. Se determinó que el porcentaje de disolución en agua a la temperatura ambiente era > 35,9%

Si bien el invento ha sido descrito en detalle con respecto a realizaciones específicas suyas, los peritos en la especialidad apreciarán, después de comprender lo anterior, que se pueden discurrir fácilmente alteraciones, variaciones y equivalentes de estas realizaciones. Por consiguiente, el campo de acción de este invento debería ser estimado como el de las reivindicaciones anexas y todos sus equivalentes.

REIVINDICACIONES

1. Un método para purificar rebaudiosida A **CARACTERIZADO** por incluir los pasos de:

combinar rebaudiosida A sin refinar y un solvente orgánico acuoso para formar una solución de rebaudiosida A, en que la solución orgánica acuosa comprende agua en una cantidad de alrededor de 10% hasta alrededor de 25% en peso; y

cristalizar desde la solución de rebaudiosida A en un solo paso, una composición de rebaudiosida A substancialmente pura que comprende rebaudiosida A con una pureza superior a alrededor de 95% en peso en una base seca.

2. El método de la reivindicación 1, **CARACTERIZADO** por incluir, además, el paso de calentar la solución de rebaudiosida A.

3. El método de la reivindicación 2, **CARACTERIZADO** por incluir, además, el paso de enfriar la solución de rebaudiosida A.

4. El método de la reivindicación 1, **CARACTERIZADO** porque la solución de rebaudiosida A en el paso único de cristalización puede ser o no agitada.

5. El método de la reivindicación 1, **CARACTERIZADO** por incluir, además, el paso (opcional) de sembrar la solución de rebaudiosida A a una temperatura apropiada, con una cantidad de rebaudiosida A suficiente para promover la cristalización de rebaudiosida A.

6. El método de la reivindicación 1, **CARACTERIZADO** por incluir, además, los pasos de separar y lavar la composición de rebaudiosida A substancialmente pura.

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7. El método de la reivindicación 6, **CARACTERIZADO** además por incluir el paso de secar la composición de rebaudiosida A substancialmente pura.

8. El método de la reivindicación 1, **CARACTERIZADO** porque la rebaudiosida A sin refinar no comprende substancialmente ninguna impureza de rebaudiosida D, y el método comprende además, formar una lechada con la composición de rebaudiosida A substancialmente pura en un solvente orgánico acuoso o en un solvente orgánico.

9. El método de la reivindicación 8, **CARACTERIZADO** además por comprender los pasos de separar y lavar la composición de rebaudiosida A substancialmente pura.

10. El método de la reivindicación 9, **CARACTERIZADO** por comprender el paso de secar la composición de una rebaudiosida A substancialmente pura.

11. El método de la reivindicación 1, **CARACTERIZADO** porque el solvente orgánico acuoso comprende una mezcla de por lo menos un solvente orgánico y agua.

12. El método de la reivindicación 11, **CARACTERIZADO** porque por lo menos un solvente orgánico comprende un alcohol.

13. El método de la reivindicación 12, **CARACTERIZADO** porque el alcohol comprende etanol.

14. El método de la reivindicación 12, **CARACTERIZADO** porque el alcohol comprende metanol.

15. El método de la reivindicación 12, **CARACTERIZADO** porque el alcohol comprende una mezcla de etanol y metanol.

16. El método de la reivindicación 15, **CARACTERIZADO** porque el etanol y el metanol están presentes en la solución

orgánica acuosa en una relación en peso desde alrededor de 20 partes a alrededor de 1 parte de etanol, con aproximadamente una parte de metanol.

17. El método de la reivindicación 15, **CARACTERIZADO** porque el etanol y el metanol están presentes en la solución orgánica acuosa en una relación en peso desde alrededor de 3 partes a alrededor de una parte de etanol, con alrededor de una parte de metanol.

18. El método de la reivindicación 1, **CARACTERIZADO** porque el por lo menos un solvente orgánico comprende un solvente orgánico elegido del grupo constituido por acetona, acetonitrilo, metanol, etanol, 1-propanol, isopropanol, 1 butanol, 2-butanol, ter-butanol, y mezclas de ellos.

19. El método de la reivindicación 1, **CARACTERIZADO** porque el solvente orgánico acuoso y la rebaudiosida A sin refinar están presentes en la solución de rebaudiosida A en una relación en peso desde alrededor de 4 hasta alrededor de 10 partes de solvente orgánico, con alrededor de 1 parte de rebaudiosida A sin refinar.

20. El método de la reivindicación 1, **CARACTERIZADO** porque el solvente orgánico acuoso y la rebaudiosida A sin refinar están presentes en la solución de rebaudiosida A en una relación en peso desde alrededor de 3 hasta alrededor de 5 partes de solvente orgánico acuoso, con alrededor de 1 parte de rebaudiosida A sin refinar.

21. El método de la reivindicación 1, **CARACTERIZADO** porque el solvente orgánico acuoso comprende agua en una cantidad desde alrededor de 10% hasta alrededor de 25% en peso.

22. El método de la reivindicación 1, **CARACTERIZADO** porque la mezcla de rebaudiosida A sin refinar comprende

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rebaudiosida A en una pureza desde alrededor de 40% hasta alrededor de 95% en peso.

23. El método de la reivindicación 1, **CARACTERIZADO** porque la mezcla de rebaudiosida A sin refinar comprende rebaudiosida A en una pureza desde alrededor de 60% hasta alrededor de 85% en peso.

24. El método de la reivindicación 1, **CARACTERIZADO** porque la mezcla de rebaudiosida A sin refinar comprende rebaudiosida A en una pureza desde alrededor de 70% hasta alrededor de 85% en peso.

25. El método de la reivindicación 1, **CARACTERIZADO** porque el método es llevado a cabo a una temperatura aproximada a la temperatura ambiente.

26. El método de la reivindicación 2, **CARACTERIZADO** porque el paso de calentar la solución de rebaudiosida A comprende calentar la solución de rebaudiosida A, hasta una temperatura en un margen de variación desde alrededor de 20°C hasta alrededor de 40°C.

27. El método de la reivindicación 2, **CARACTERIZADO** porque el paso de calentar la solución de rebaudiosida A comprende calentar la solución de rebaudiosida A, hasta una temperatura en un margen de variación desde alrededor de 40°C hasta alrededor de 60°C.

28. El método de la reivindicación 2, **CARACTERIZADO** porque el paso de calentar la solución de rebaudiosida A comprende calentar la solución de rebaudiosida A, hasta una temperatura aproximada a la temperatura de reflujo.

29. El método de la reivindicación 2, **CARACTERIZADO** porque el paso de enfriar la solución de rebaudiosida A comprende

enfriar la solución de rebaudiosida A, hasta una temperatura en un margen de variación desde alrededor de 4°C hasta alrededor de 25°C.

30. El método de la reivindicación 3, **CARACTERIZADO** porque el paso de enfriar la solución de rebaudiosida A comprende enfriar la solución de rebaudiosida A durante alrededor de 0,5 horas hasta alrededor de 24 horas.

31. El método de la reivindicación 1, **CARACTERIZADO** porque el producto de rebaudiosida A substancialmente pura comprende rebaudiosida A con una pureza superior a 97% de rebaudiosida A en peso en una base seca.

32. El método de la reivindicación 1, **CARACTERIZADO** porque el producto de rebaudiosida A substancialmente pura comprende rebaudiosida A con una pureza superior a 98% de rebaudiosida A en peso en una base seca.

33. El método de la reivindicación 1, **CARACTERIZADO** porque el producto de rebaudiosida A substancialmente pura comprende rebaudiosida A con una pureza superior a 99% de rebaudiosida A en peso en una base seca.

34. El método de la reivindicación 1, **CARACTERIZADO** porque comprende además, los pasos de:

calentar la mezcla de solvente orgánico acuoso y rebaudiosida A;

enfriar la solución de rebaudiosida A;

separar y lavar una composición de rebaudiosida A substancialmente pura; y

secar la composición de rebaudiosida A substancialmente pura.

35. Una composición de rebaudiosida A substancialmente pura preparada según el método de la reivindicación 1, **CARACTERIZADA** porque la composición de rebaudiosida A substancialmente pura comprende un polimorfo con un patrón de difracción de rayos X substancialmente similar a la Figura 7.

36. Una composición de rebaudiosida A substancialmente pura, preparada según el método de la reivindicación 1, **CARACTERIZADA** porque la composición de rebaudiosida A substancialmente pura comprende un polimorfo con un patrón de difracción de rayos X substancialmente similar a la Figura 8.

37. Una composición de rebaudiosida A substancialmente pura, preparada según el método de la reivindicación 1, **CARACTERIZADA** porque la composición de rebaudiosida A substancialmente pura comprende un polimorfo con un patrón de difracción de rayos X substancialmente similar a la Figura 9.

38. Una composición de rebaudiosida A substancialmente pura, preparada según el método de la reivindicación 1, **CARACTERIZADA** porque la composición de rebaudiosida A substancialmente pura comprende un polimorfo con un patrón de difracción de rayos X substancialmente similar a la Figura 10.

39. Una composición de rebaudiosida A substancialmente pura preparada según el método de la reivindicación 1, **CARACTERIZADA** porque la composición de rebaudiosida A substancialmente pura comprende un polimorfo con un patrón de difracción de rayos X substancialmente similar a la Figura 11.

40. El método de la reivindicación 1, **CARACTERIZADO** porque comprende además el paso de formar una forma amorfa de la composición de rebaudiosida A substancialmente pura.

41. La composición de la reivindicación 38, **CARACTERIZADA** porque el paso de formar una forma amorfa de la

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composición de rebaudiosida A substancialmente pura comprende un método elegido del grupo constituido por molienda con molinos de bolas, precipitación, liofilización, criomolienda, y secado por aspersión.

42. Una composición de rebaudiosida A substancialmente pura, **CARACTERIZADA** porque es preparada según el método de la reivindicación 1.

p.p.: THE COCA-COLA COMPANY

REIVINDICACIONES

1.- Un método para purificar rebaudiosida A que comprende los pasos de:

5 combinar rebaudiosida A cruda y una solución orgánica acuosa para formar una solución de rebaudiosida A, la rebaudiosida A cruda comprendiendo rebaudiosida A en una pureza de alrededor de 40% a alrededor de 85% en peso sobre una base seca, y la solución orgánica acuosa comprendiendo agua en una cantidad de alrededor de 10% a alrededor de 25% en peso; y

 cristalizar la solución de rebaudiosida A en un solo paso una composición de rebaudiosida A que comprende rebaudiosida A en una pureza mayor de alrededor de 95% en peso sobre una base seca.

15 2.- El método de conformidad con la reivindicación 1, que comprende además el paso de calentar la solución de rebaudiosida A.

 3.- El método de conformidad con la reivindicación 2, que comprende además el paso de enfriar la solución de rebaudiosida A.

20 4.- El método de conformidad con la reivindicación 1, en donde la solución de rebaudiosida A en el único paso de cristalización está agitada o no agitada.

 5.- El método de conformidad con la reivindicación 1, que comprende además el paso de sembrar la solución de rebaudiosida A a una

HOJA MODIFICADA

temperatura apropiada con una cantidad de rebaudiosida A suficiente para promover la cristalización de rebaudiosida A.

6.- El método de conformidad con la reivindicación 1, que comprende además los pasos de separar y lavar la composición de rebaudiosida A substancialmente pura.

7.- El método de conformidad con la reivindicación 6, que comprende además el paso de secar la composición de rebaudiosida A substancialmente pura.

8.- El método de conformidad con la reivindicación 1, en donde la rebaudiosida A cruda comprende substancialmente nada de impureza de rebaudiosida D y el método comprende además formar en suspensión la composición de rebaudiosida A substancialmente pura en una solución orgánica acuosa o en un solvente orgánico.

9.- El método de conformidad con la reivindicación 8, que comprende además los pasos de separar y lavar la composición de rebaudiosida A substancialmente pura.

10.- El método de conformidad con la reivindicación 9, que comprende además el paso de secar la composición de una rebaudiosida A substancialmente pura.

11.- El método de conformidad con la reivindicación 11, en donde la solución orgánica acuosa comprende una mezcla de cuando menos un solvente orgánico y agua.

HOJA MODIFICADA

12.- El método de conformidad con la reivindicación 11, en donde cuando menos un solvente orgánico comprende un alcohol.

13.- El método de conformidad con la reivindicación 12, en donde el alcohol comprende etanol.

5 14.- El método de conformidad con la reivindicación 12, en donde el alcohol comprende metanol.

15.- El método de conformidad con la reivindicación 12, en donde el alcohol comprende una mezcla de etanol y metano

10 16.- El método de conformidad con la reivindicación 15, en donde el etanol y metanol están presentes en la solución orgánica acuosa en una relación en peso de alrededor de 20 partes a alrededor de 1 parte de etanol a alrededor de 1 parte de metanol.

15 17.- El método de conformidad con la reivindicación 15, en donde el etanol y metanol están presentes en la solución orgánica acuosa en una relación en peso de alrededor de 3 partes a alrededor de 1 parte de etanol a alrededor de 1 parte de metanol.

20 18.- El método de conformidad con la reivindicación 1, en donde la cuando menos una solución orgánica acuosa comprende un solvente orgánico seleccionado del grupo que consiste en acetona, acetonitrilo, metanol, etanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, ter-butanol, y mezclas de los mismos.

19.- El método de conformidad con la reivindicación 1, en donde la solución orgánica acuosa y la rebaudiosida A cruda están presentes en la solución de rebaudiosida A en una relación en peso de alrededor de 4 a alrededor de 10 partes de solución orgánica acuosa a alrededor de 1 parte de rebaudiosida A cruda.

20.- El método de conformidad con la reivindicación 1, en donde la solución orgánica acuosa y la rebaudiosida A cruda están presentes en la solución de rebaudiosida A en una relación en peso de alrededor de 3 a alrededor de 5 partes de solución orgánica acuosa a alrededor de 1 parte de rebaudiosida A cruda.

21.- El método de conformidad con la reivindicación 1, en donde la solución orgánica acuosa comprende agua en una cantidad de alrededor de 105 a alrededor de 25% en peso.

22.- Un método para purificar rebaudiosida A que comprende los pasos de:

combinar rebaudiosida A cruda en una solución orgánica acuosa para formar una solución de rebaudiosida A, la rebaudiosida A cruda comprendiendo rebaudiosida A en una pureza de alrededor de 40% a alrededor de 85% en peso sobre una base seca, y la solución orgánica acuosa comprendiendo agua en una cantidad de alrededor de 10% a alrededor de 25% en peso; y

cristalizar de la solución de rebaudiosida A en un solo paso una composición de rebaudiosida A que comprende rebaudiosida a en una pureza mayor de alrededor de 95% en peso sobre una base seca, en donde el método se lleva a cabo aproximadamente a temperatura ambiente.

5 23.- El método de conformidad con la reivindicación 2, en donde el paso de calentar la solución de rebaudiosida A comprende calentar la solución de rebaudiosida A a una temperatura en la escala de alrededor de 20°C a alrededor de 40°C.

10 24.- El método de conformidad con la reivindicación 2, en donde el paso de calentar la solución de rebaudiosida A comprende calentar la solución de rebaudiosida A a una temperatura en una escala de alrededor de 40°C a alrededor de 60°C.

15 25.- El método de conformidad con la reivindicación 2, en donde el paso de calentar la solución de rebaudiosida A comprende calentar la solución de rebaudiosida A a alrededor de una temperatura de reflujo.

20 26.- El método de conformidad con la reivindicación 3, en donde el paso de enfriar la solución de rebaudiosida A comprende enfriar la solución de rebaudiosida A a una temperatura en una escala de alrededor de 4°C a alrededor de 25°C.

27.- El método de conformidad con la reivindicación 3, en donde el paso de enfriar la solución de rebaudiosida A comprende enfriar la solución de rebaudiosida A durante alrededor de 0.5 horas a alrededor de 24 horas.

28.- El método de conformidad con la reivindicación 1, en donde el producto de rebaudiosida A substancialmente puro comprende rebaudiosida A en una pureza mayor de alrededor de 97% de rebaudiosida A en peso sobre un base seca.

29.- El método de conformidad con la reivindicación 1, en donde el producto de rebaudiosida A substancialmente puro comprende rebaudiosida A en una pureza mayor de alrededor de 98% de rebaudiosida A en peso sobre una base seca.

30.- El método de conformidad con la reivindicación 1, en donde el producto de rebaudiosida A substancialmente puro comprende rebaudiosida A en una pureza mayor de alrededor de 99% de rebaudiosida A en peso sobre una base seca.

31.- El método de conformidad con la reivindicación 1, que comprende además los pasos de:

- calentar la solución de rebaudiosida A;
- enfriar la solución de rebaudiosida A;

separar y lavar una composición de rebaudiosida A substancialmente pura; y secar la composición de rebaudiosida A substancialmente pura.

32.- Una composición de rebaudiosida A substancialmente pura
5 hecha de conformidad con el método de la reivindicación 1, en donde la composición de rebaudiosida A substancialmente pura comprende un polimorfo que tiene un patrón de difracción de rayos X substancialmente similar a la Figura 8.

33.- Una composición de rebaudiosida A substancialmente pura
10 hecha de conformidad con el método de la reivindicación 1, en donde la composición de rebaudiosida A substancialmente pura comprende un polimorfo que tiene un patrón de difracción de rayos X substancialmente similar a la Figura 9.

34.- Una composición de rebaudiosida A substancialmente pura
15 hecha de conformidad con el método de la reivindicación 1, en donde la composición de rebaudiosida A substancialmente pura comprende un polimorfo que tiene un patrón de difracción de rayos X substancialmente similar a la Figura 10.

35.- Una composición de rebaudiosida A substancialmente pura
20 hecha de conformidad con el método de la reivindicación 1, en donde la composición de rebaudiosida A substancialmente pura comprende una forma

amorfa que tiene un patrón de difracción de rayos X substancialmente similar a la Figura 11.

36.- El método de conformidad con la reivindicación 1, que comprende además el paso de formar una forma amorfa de la composición de rebaudiosida A substancialmente pura.

37.- La composición de conformidad con la reivindicación 35, en donde el paso de formar una forma amorfa de la composición de rebaudiosida A substancialmente pura comprende un método seleccionado del grupo que consiste en molienda de bolas, precipitación, liofilización, criomolienda, y secado por aspersión.

38.- Una composición de rebaudiosida A substancialmente pura hecha de conformidad con el método de la reivindicación 1.

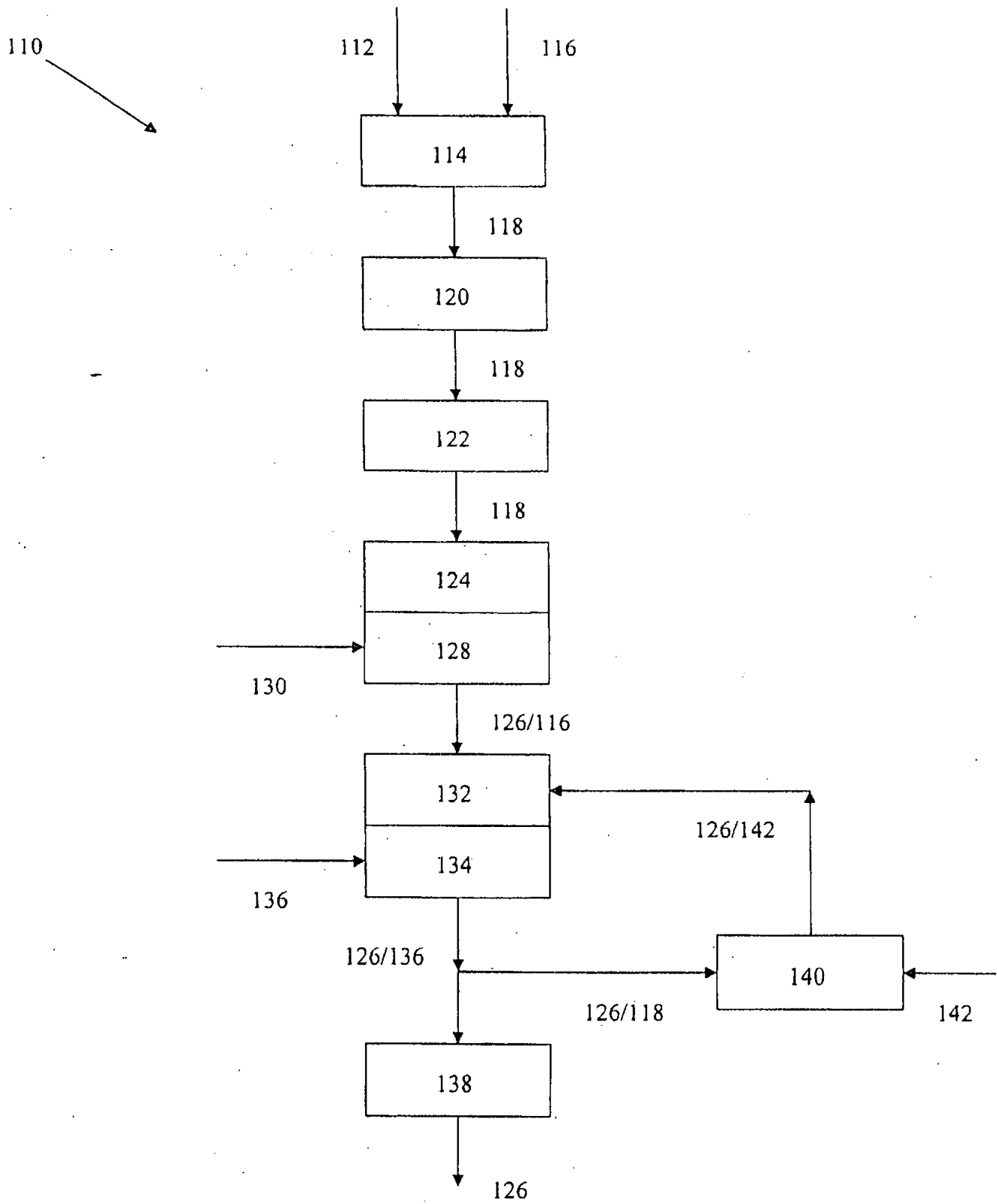


FIGURA 1

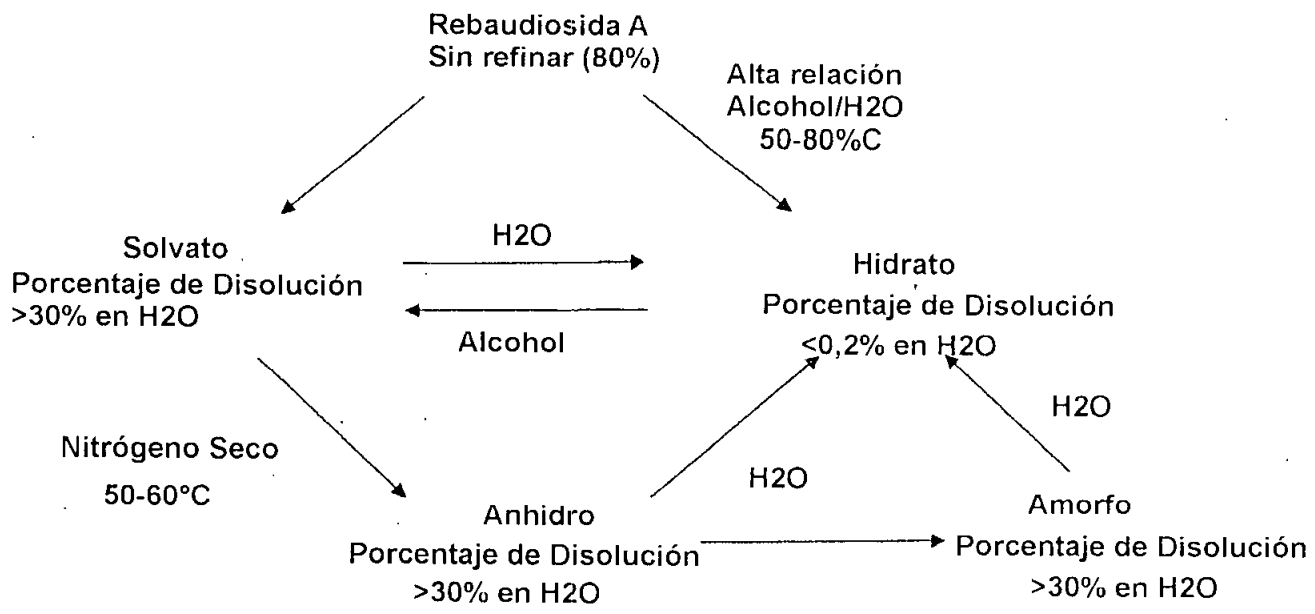


FIGURA 2

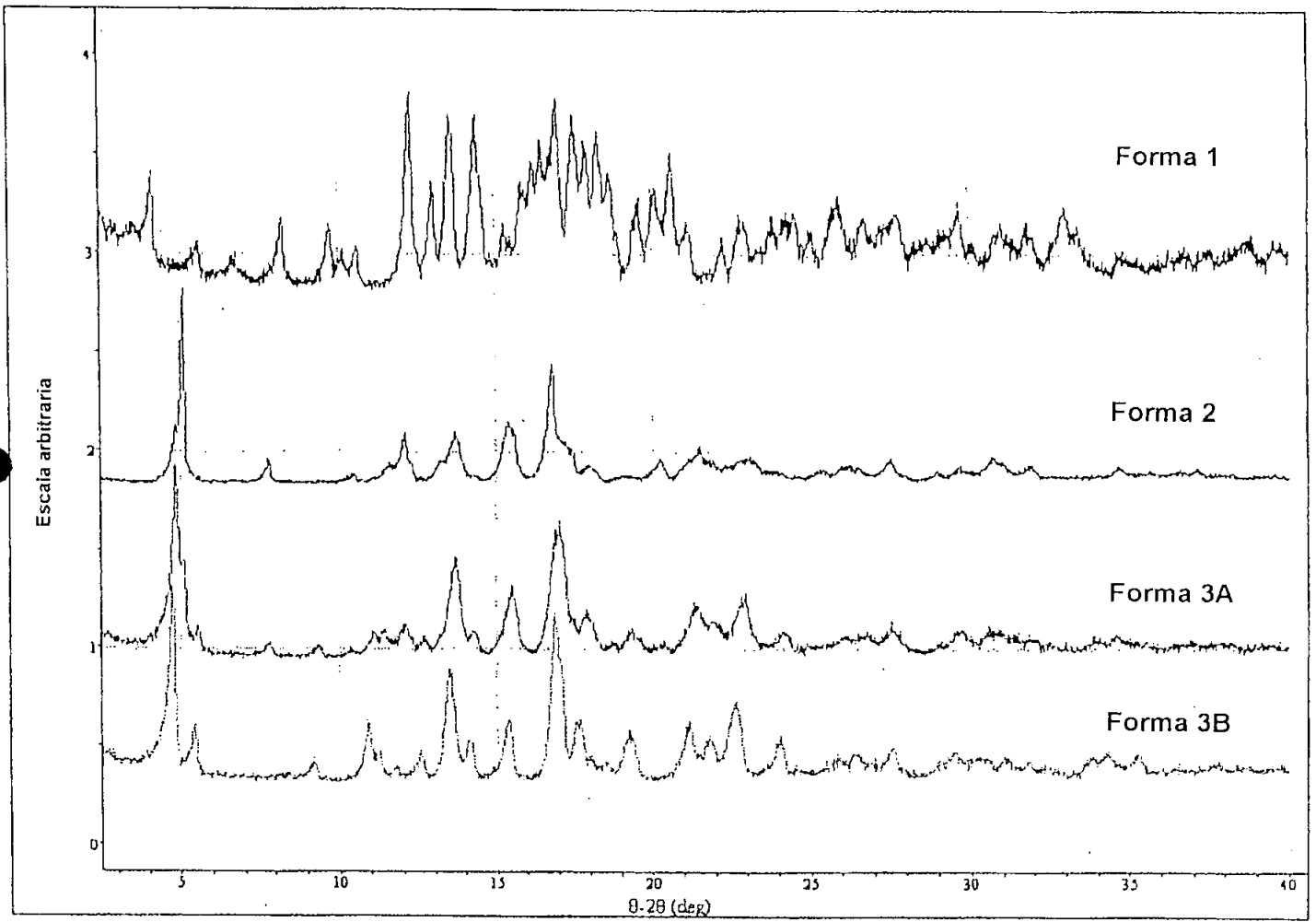


FIGURA 3

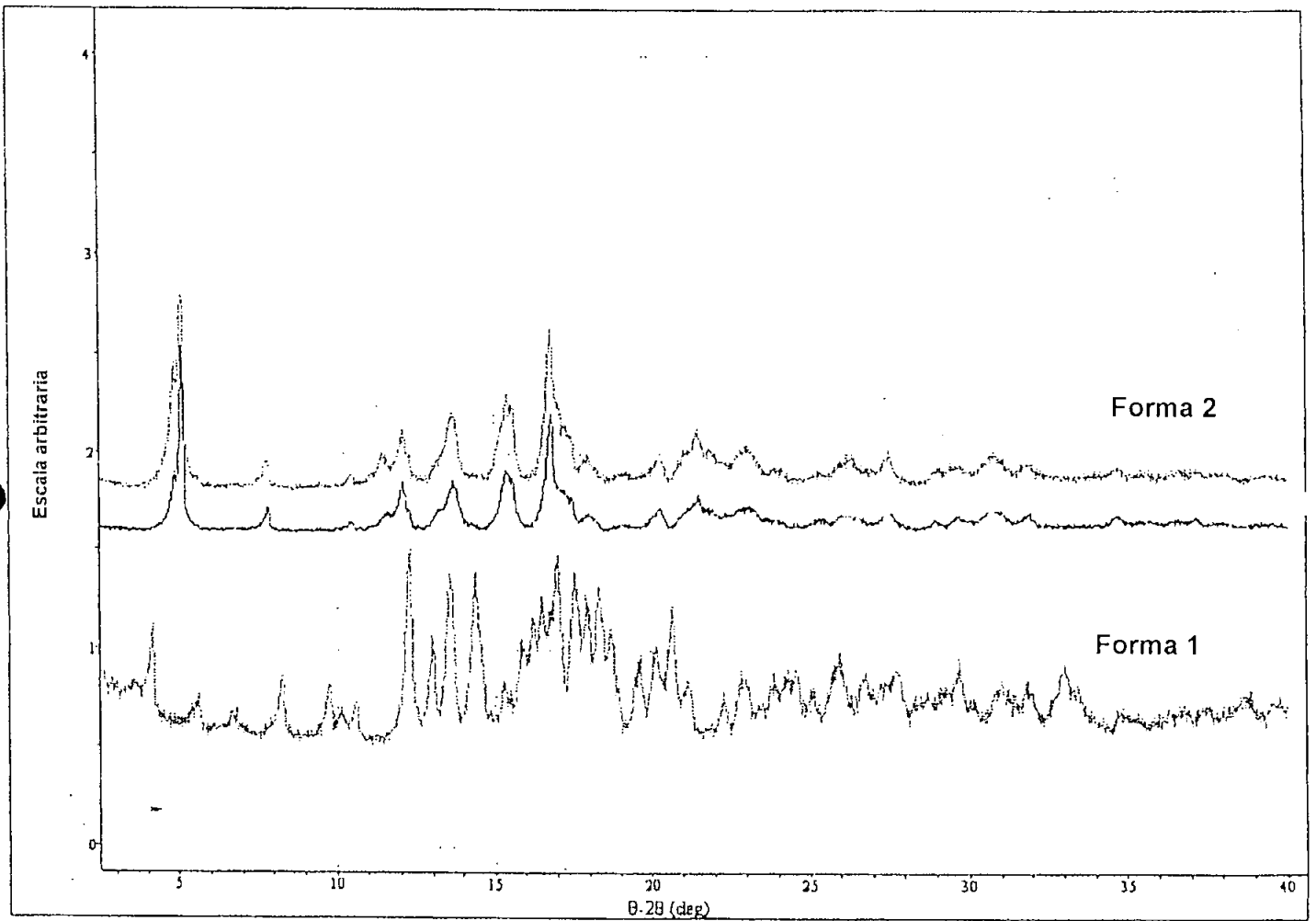


FIGURA 4

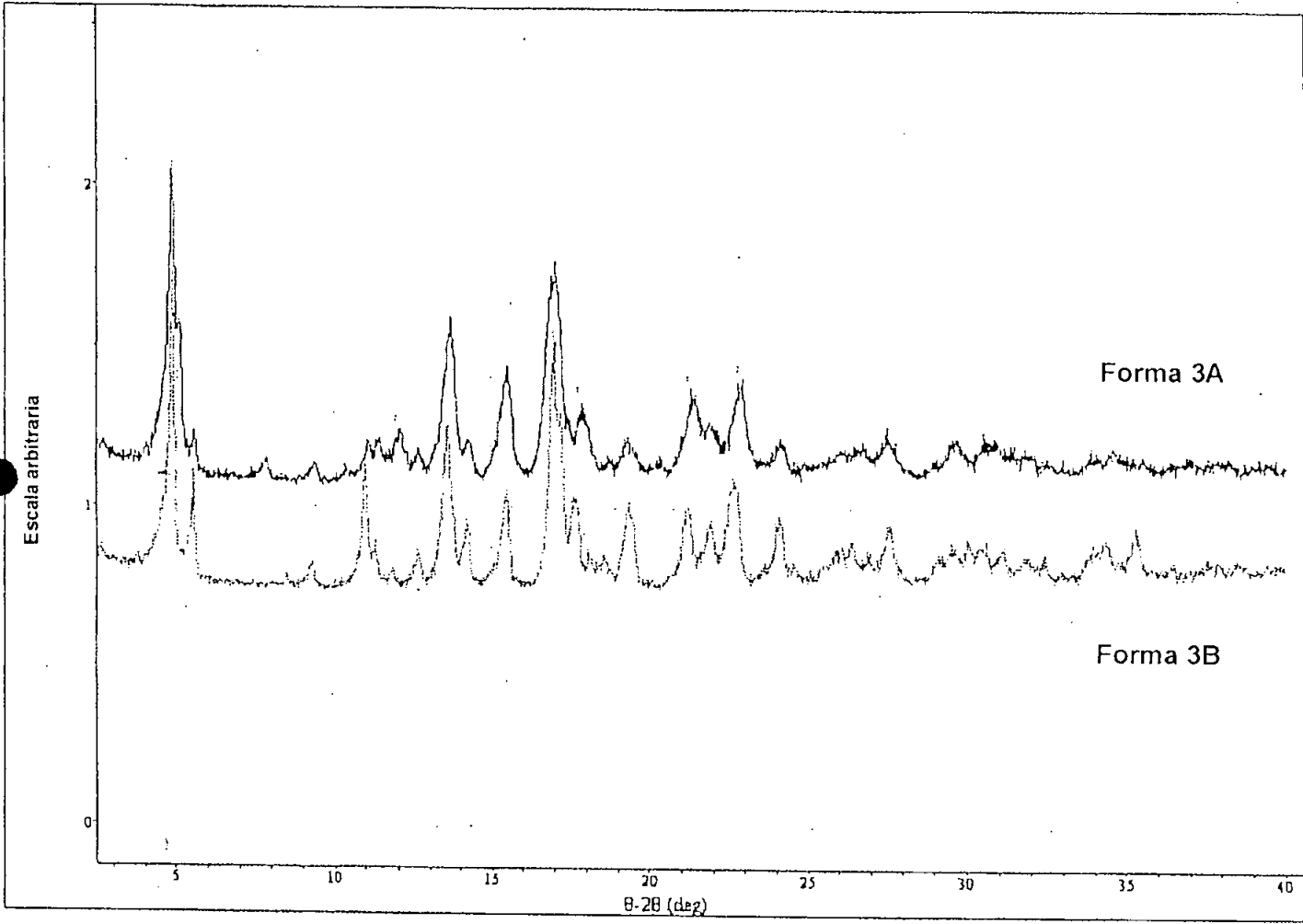


FIGURA 5

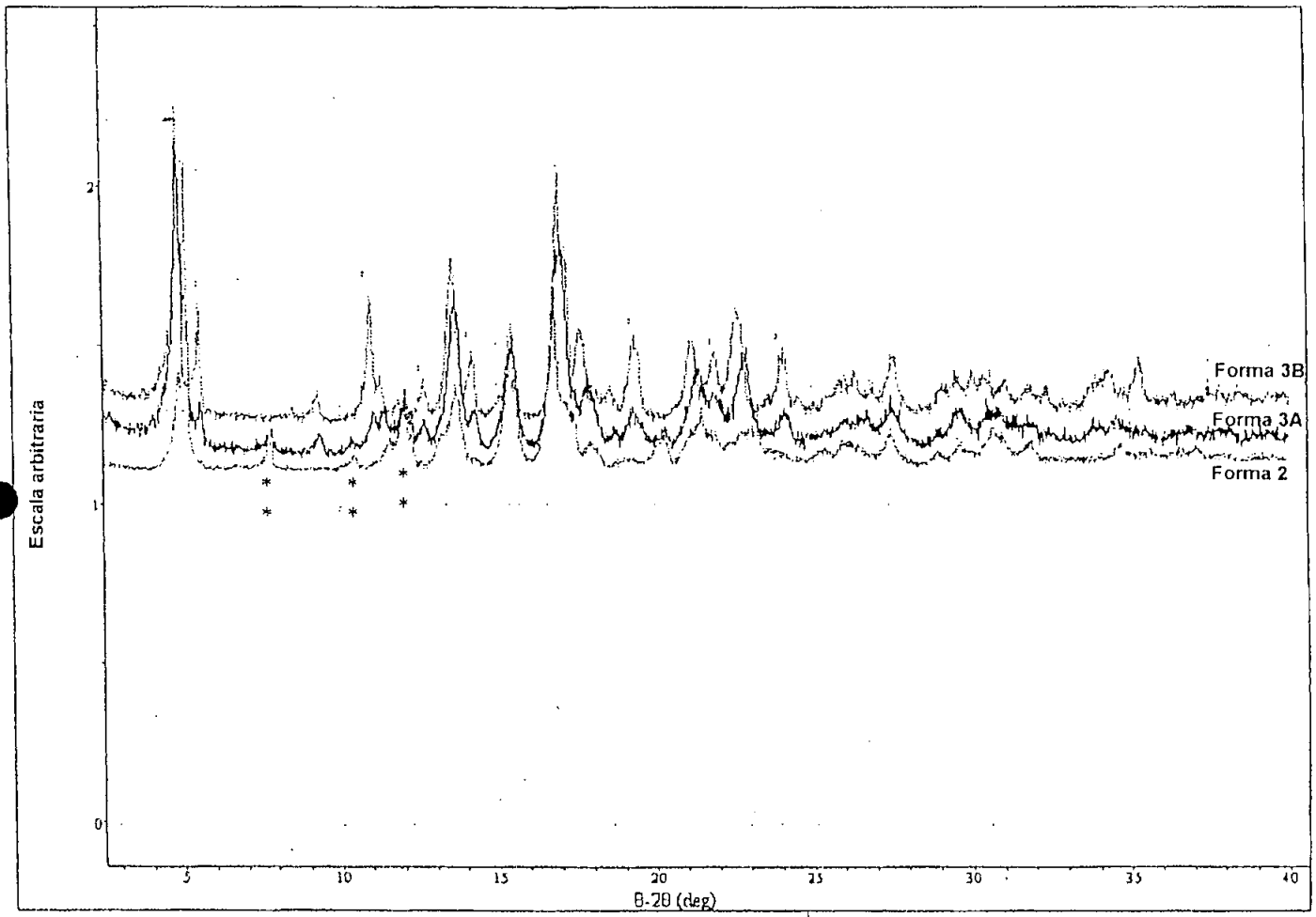


FIGURA 6

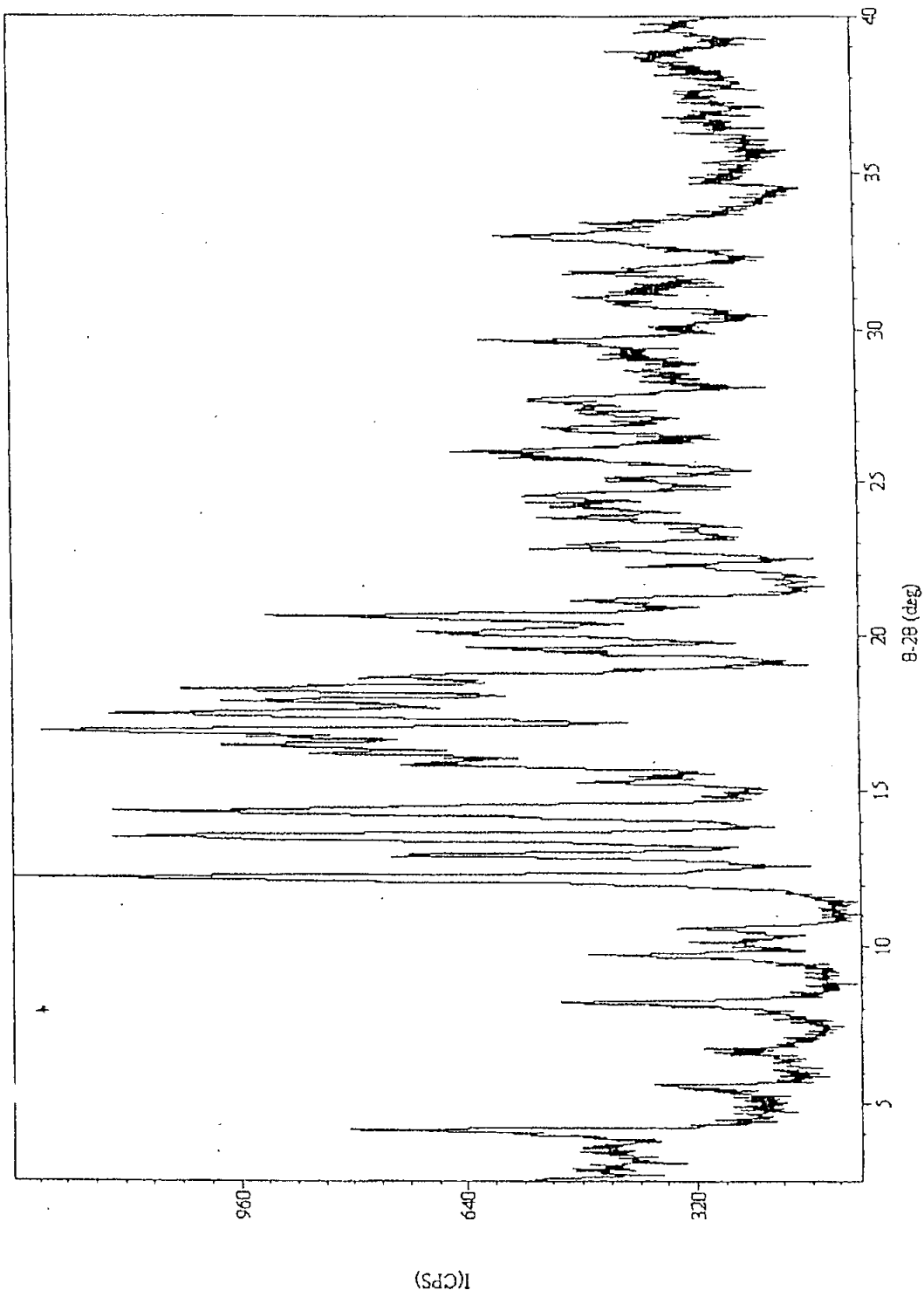


FIGURA 7

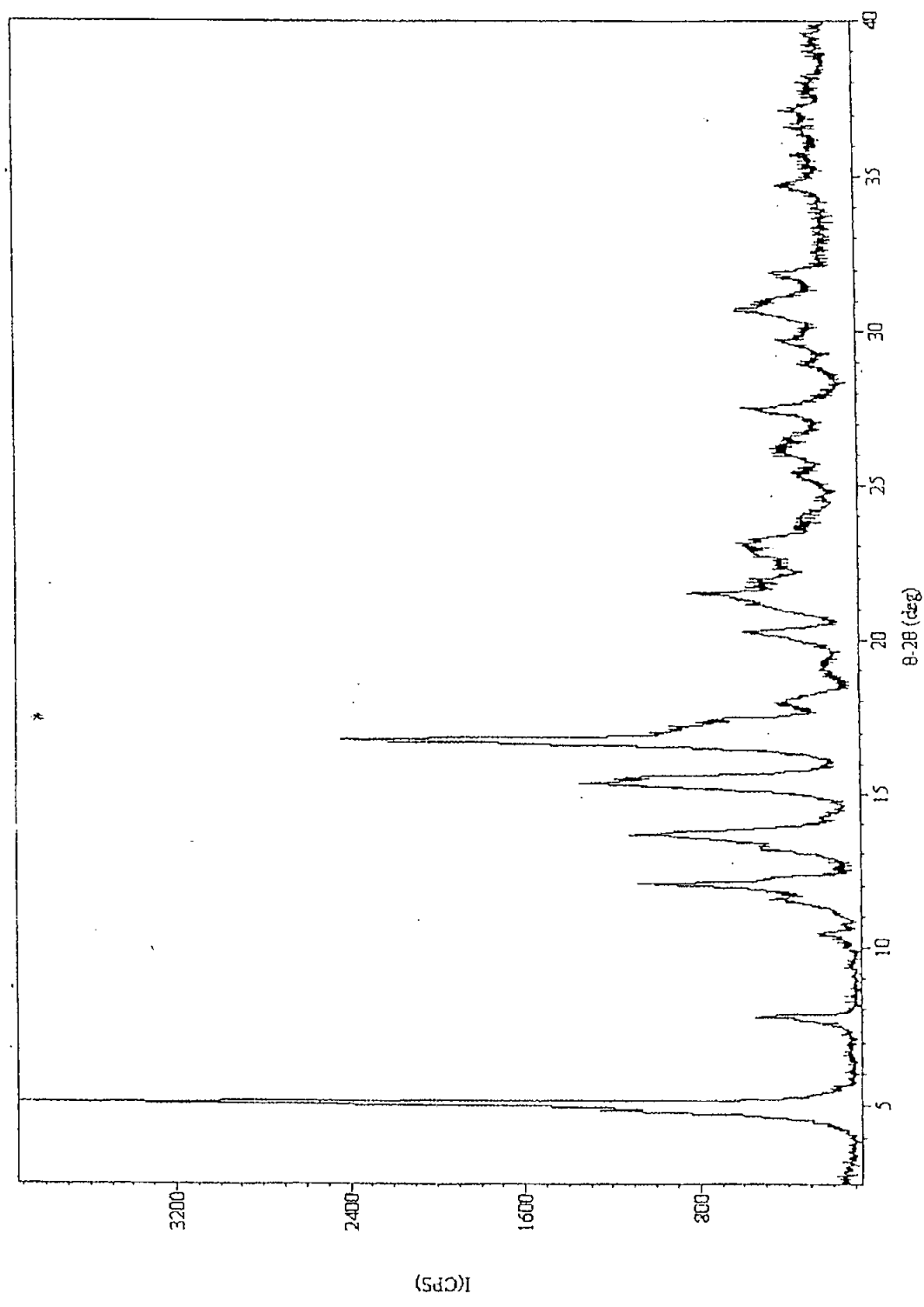


FIGURA 8

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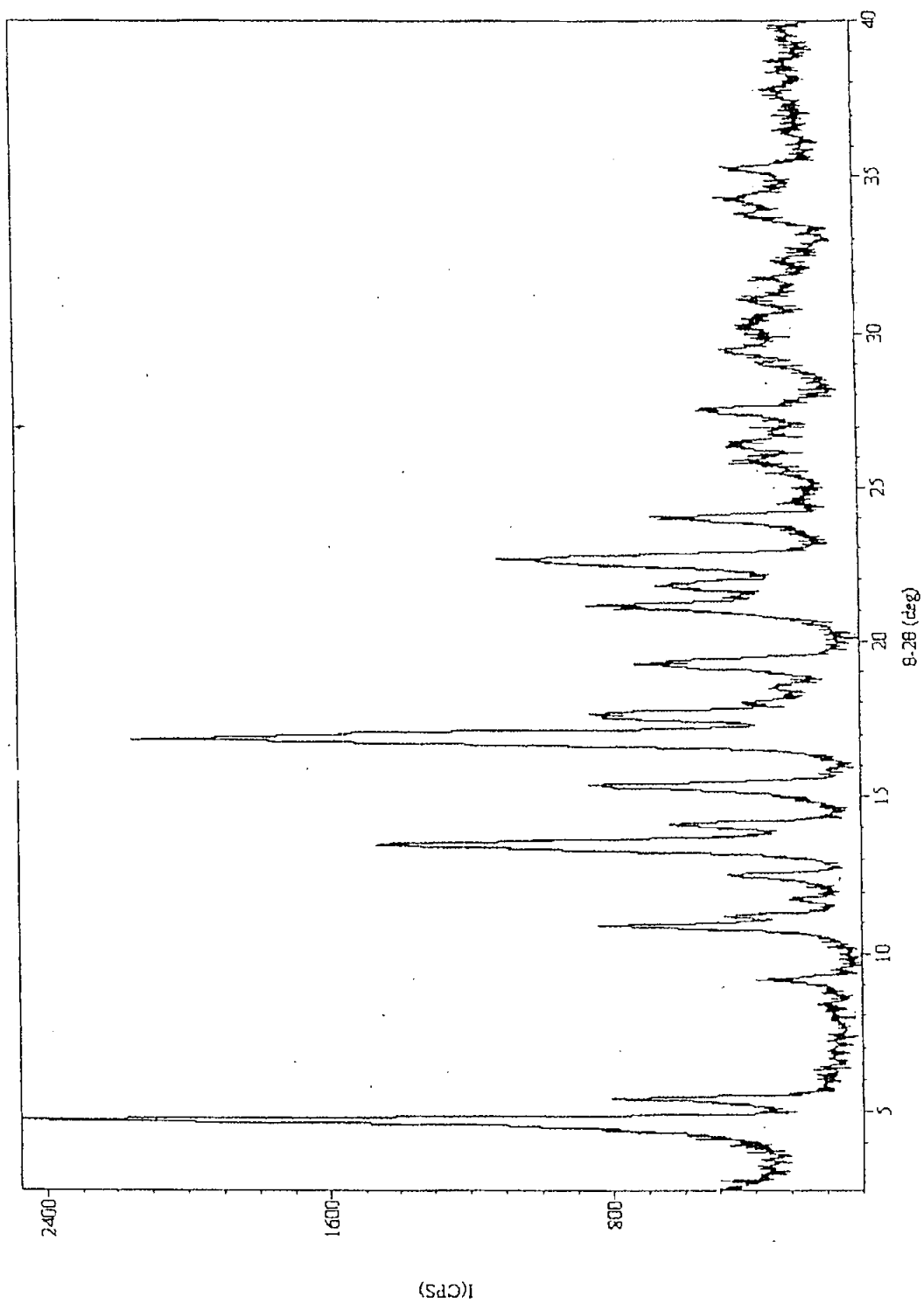


FIGURA 9

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10/11

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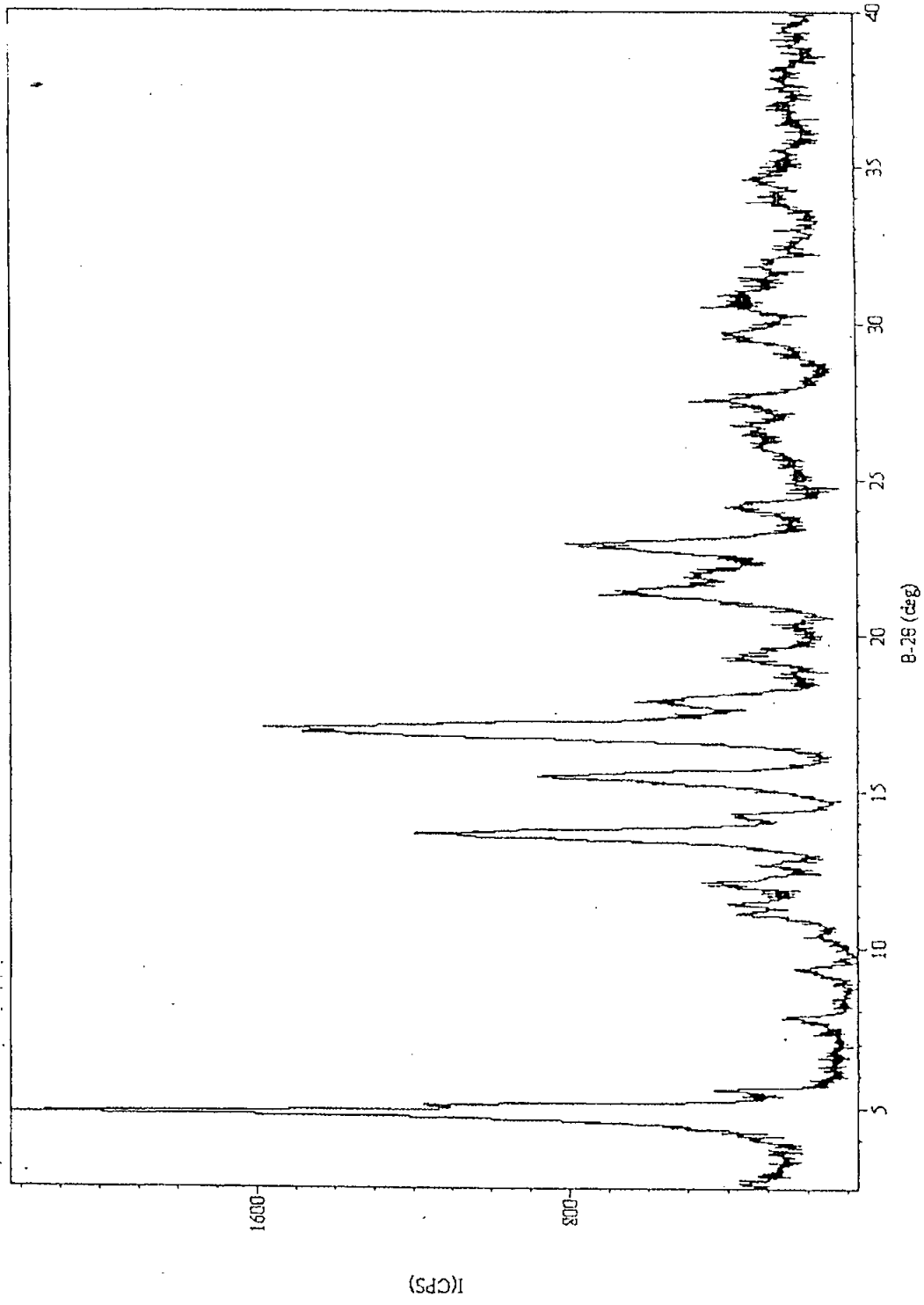


FIGURA 10

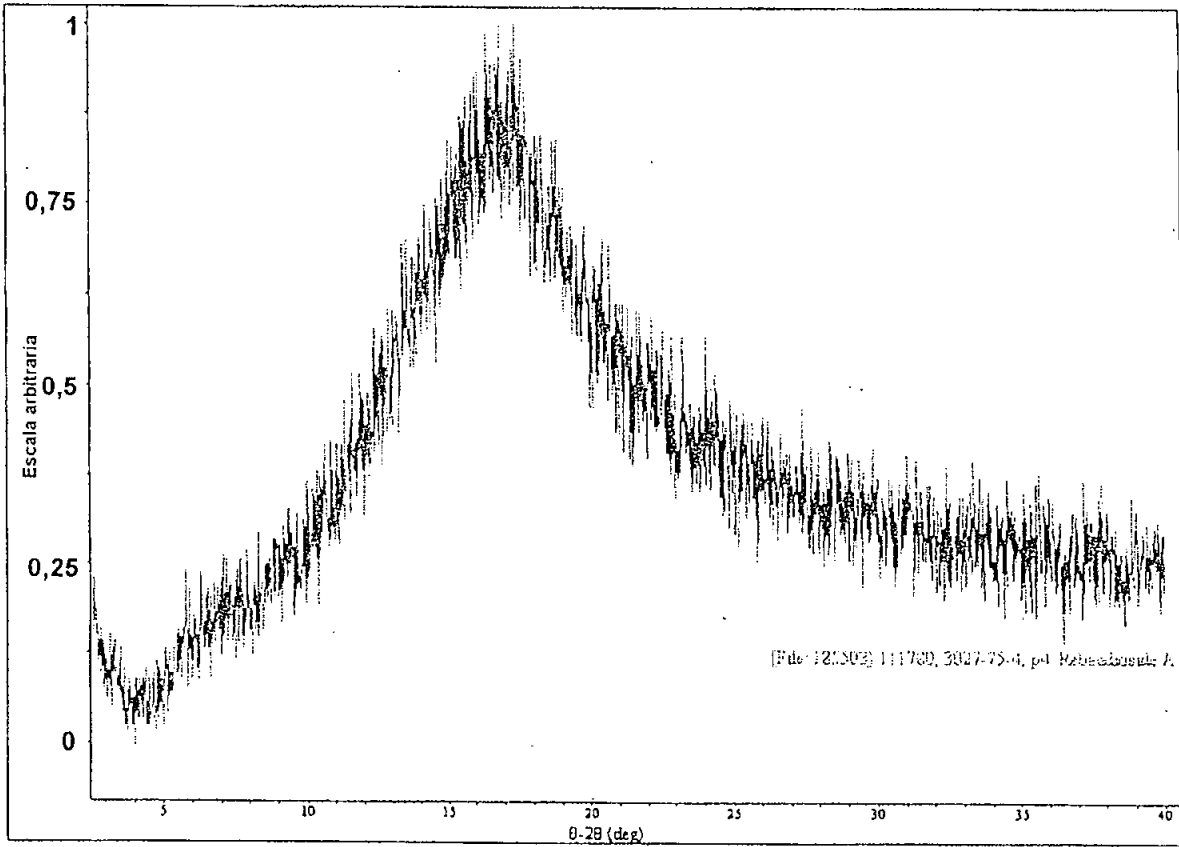


FIGURA 11

RESUMEN DEL INVENTO

Realizaciones ilustrativas de este invento abarcan un método para purificar rebaudiosida A sin refinar. En particular, este invento se refiere a un método para purificar composiciones de rebaudiosida A sin refinar que comprenden purezas desde alrededor de 40% a alrededor de 95% de rebaudiosida A para obtener un producto de rebaudiosida A substancialmente puro con un solo paso de cristalización. Se publican también formas polimórficas y amorfas resultantes de rebaudiosida A y métodos para preparar formas polimórficas y amorfas de rebaudiosida A desde composiciones de rebaudiosida A sin refinar y composiciones de rebaudiosida A substancialmente pura.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PAPPAS, Peter G.
Sutherland Asbill & Brennan LLP
999 Peachtree Street, NE
Atlanta, GA 30309-3996
ETATS-UNIS D'AMERIQUE

RECEIVED

OCT 17 2008

SUTHERLAND ASBILL & BRENNAN LLP

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**NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY**

(PCT Rule 71.1)

Date of mailing
(day/month/year)

13.10.2008

Applicant's or agent's file reference
25040-2775

IMPORTANT NOTIFICATION

International application No.
PCT/US2007/069548

International filing date (day/month/year)
23.05.2007

Priority date (day/month/year)
19.06.2006

Applicant

THE COCA-COLA COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the International
preliminary examining authority:



European Patent Office
D-80298 Munich
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Authorized Officer

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PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 25040-2775	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/US2007/069548	International filing date (day/month/year) 23.05.2007	Priority date (day/month/year) 19.06.2006
International Patent Classification (IPC) or national classification and IPC INV. A23L1/236		
Applicant THE COCA-COLA COMPANY		
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>9</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ sent to the applicant and to the International Bureau) a total of <u>11</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).		
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application		
Date of submission of the demand 2008-05-23	Date of completion of this report 13.10.2008	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Groh, Björn Telephone No. +49 89 2399-7855 	

INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY

International application No.
PCT/US2007/069548

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

2, 4, 5, 8, 10, 11, 13-33	as originally filed
1, 3, 6, 7, 9, 12	received on 23.05.2008 with letter of 23.05.2008

Claims, Numbers

1-38	received on 23.05.2008 with letter of 23.05.2008
------	--

Drawings, Sheets

1/11-11/11	as originally filed
------------	---------------------

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☒ the claims, Nos. 39-42
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>5,14-17,22,35</u>
	No: Claims	<u>1-4,6-13,18-21,23-36,38</u>
Inventive step (IS)	Yes: Claims	<u>22</u>
	No: Claims	<u>1-21,23-38</u>
Industrial applicability (IA)	Yes: Claims	<u>1-42</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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Re Item V.

1 Amendments

- 1.1 The expression "aqueous organic solvent" of original claim 1 was replaced with "aqueous organic solution" in the present claim. Both expressions were used more than once in the application as originally filed. Since (A) solvent is understood to comprise the meaning of 'mixture of two liquids', and (B) the definition of "aqueous organic solvent" in the original description (see p. 6, lines 10-15) was kept and assigned to "aqueous organic solution", and (C) the amendment from 'solvent' to 'solution' was applied consistently throughout the application, this amendment appears to be allowable (Art. 41(2) PCT).
- 1.2 The claims were restricted. The application (including specifying examples within / outside the invention) needs to be adapted to the present / latest set of claims.
- 1.3 A new independent claim (present claim 22) was created based on original claims 1 and 22-24. Present claim 22 comprises all subject matter of present claim 1 and should be phrased as dependent claim thereof.

2 Reference is made to the following documents:

D1: US 2006/083838 A1 (JACKSON MEL C [US]) 20 April 2006;
D2: CA-A1-2 278 083 (ALBERTA RES COUNCIL [CA]) 20 Jan. 2001.

3 General / Interpretation

- 3.1 The method claims are phrased in an open way ("... comprising ..."), consequently the claimed method may contain additional steps, which contribute the purity of the rebaudioside A. Therefore, additional method steps can not disqualify a document from being novelty destroying.
- 3.2 The feature "crystallizing from the rebaudioside A solution in a single step" does not

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exclude nor limit any other process steps.

4 Novelty (Art. 33(2) PCT)

4.1 In view of D1

A method for purifying rebaudioside A is known from D1. That method comprises the step of using an ethanol - water mix as solvent and crystallising rebaudioside A from that solvent. The purity of the final product (rebaudioside A) depends on the quality of educt (purity of rebaudioside A to start with). A final product (rebaudioside A) with a 100% purity can be obtained (see Table 3).

With a **single** reflux step and using a higher quality Stevia starting material (defined to be approximately 85% or higher rebaudioside A content, see § 12 of D1) a 100% rebaudioside A product is typically obtained, see § 55.

Furthermore, in case a final product with a rebaudioside A concentration of less than 99% is acceptable (for example 95%), then the stirred wash step can be omitted, see § 55 of D1.

Pure rebaudioside A produced by the *same* methods (presently claimed and prior art) will result in products which consequently show a 'substantially similar' X-ray diffraction pattern.

Present claims 1-4,6-13,18-21, 23-36 and 38 are not new over D1.

4.2 In view of D2

From prior art D2 it is known that rebaudioside A can be purified from a methanol - water mixture (see claims 1 to 5 and example 5).

The purity of the final product (rebaudioside A) depends on the quality of educt (purity of rebaudioside A to start with). A final product (rebaudioside A) with a 98.6% purity

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can be obtained (see example 5).

Pure rebaudioside A produced by the *same* methods (presently claimed and prior art) will result in products which consequently show a 'substantially similar' X-ray diffraction pattern.

Present claims Present claims 32-35 and 38 are not new over D1.

5 Inventive step (Art. 33(3) PCT)

The argumentation concerning Art. 33(3) PCT will depend on how novelty can be achieved (for example how/which amendments may be made).

- 5.1 It is known to use water-soluble organic solvents, such as methanol and ethanol to purify rebaudioside A (see D2 claim 3; and D1 claims, page 22: "Table 2-continued" and p. 4 last sentence).

Since it is already known (for example D1, see above), how to purify rebaudioside A upto a 100% purity, the objective technical problem can be formulated to provide an alternative method to the ones known in the art.

A difference might be that the present method uses upto 25% water.

However, it is known from D1 (see page 22: "Table 2-continued") that increasing concentrations of water (0 through 10%) will increase the purity of the rebaudioside A. Consequently it is obvious to further increase the water content to maintain or ensure (in case of lower quality starting material) a high purity of rebaudioside A.

Claims 1-21,23-38 do not involve an inventive step over the prior art.

Since it is not evident which process steps define the invention, the applicant is asked to phrase the independent claims in the two-part form, or at least provide such information in an accompanying letter.

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- 5.2 A method for purifying rebaudioside A, as defined in claim 22, characterised in that the method is carried out at room temperature is not derivable in an obvious way from the prior art, which generally teach to use an elevated temperature (such as 79-80°C in D1).

Claim 22 appears to involve an inventive step.

6 Other

6.1 Result-to-be-achieved / desiderata

- A. Claim 1 and dependent claims are defined by the result "purity greater than about 95%" to-be-achieved.
- B. Claims 35 to 39 and dependent claim(s) are defined by a graphically. illustrated X-ray diffraction pattern to be obtained.

Only exceptionally, when the invention can not be defined in another way without unduly restricting the scope or the claims, result-to-be-achieved type of claims may be acceptable (see PCT International Preliminary Examination - Guidelines, chapter III, point 4.7).

Any of the claim groups A and B could have been defined in precise way without using the result-to-be-achieved type of definitions:

to A: Method claims of set A must contain **method** steps, which enable the result "purity greater than about 95%".

Consequently the feature "purity greater than about 95%" is regarded as '... **suitable for** obtaining a purity greater than about 95%'.

to B: Product claims of set B could have been defined more precisely by defining the claimed product by its *inherent* chemical properties (such as crystal water, mono-, di- or polymeric structure, etc.) and/or physical (such as crystal or

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amorphous form, isomeric forms, etc.) properties.

Claims 35 to 39 do not fulfil the requirements of Art. 6 PCT.

6.2 Lack of disclosure

The application as filed is silent about **how** to obtain specifically one of the various rebaudioside A compositions described in claim 32 to 35, which are characterised based on different X-ray diffraction figures only.

How can (at least) four allegedly different compositions be obtained by one and the same method ?

Claims 32 to 35 do not fulfil the requirements of Art. 5 PCT.

6.3 Claims 32 to 36

- a. The expression "substantially pure" is a relative term, which is not precise enough to define the extend of a patentable claim (Art. 6 PCT).
- b. The expression "substantially similar" is a relative term, which is not precise enough to define the extend of a patentable claim (Art. 6 PCT).
- c. The definition of a composition by reference to a graphically illustrated result (Figures 7 to 11) of a method is not precise enough to define the extend of a patentable claim (Art. 6 PCT and Rule 6.2 a PCT).
Furthermore, reference to a graphically result which lacks the definition and scale of the y-axis "arbitrary scale" (!) is not precise enough to define the extend of a patentable claim (Art. 6 PCT).

6.4 Concerning claim 38

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The expression "substantially pure" is not clear enough to define the extend of the product claim (Art. 6 PCT).

6.5 Description

The last paragraph on page 33 renders the subject matter claimed vague, because it refers to unspecified alterations, variations, equivalents, etc. That paragraph is not necessary, unclear and should be deleted (Art. 6 PCT and Rule 9.1 iv PCT).

The applicant communicated that the last paragraph on page 33 was deleted, however in the version sent by mail (26.05.08) such amendment was missing.

- 6.6** In order to facilitate examination of conformity of any amendments (during PCT chapter II or during the National phase) with the requirements of Article 41 (2) PCT, the applicant is requested to clearly identify all amendments, whether they are amendments by addition, replacement, combination (e.g. of claims) or deletion. The applicant should indicate in detail the passages in the application as filed, on which these amendments are based on.

REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A

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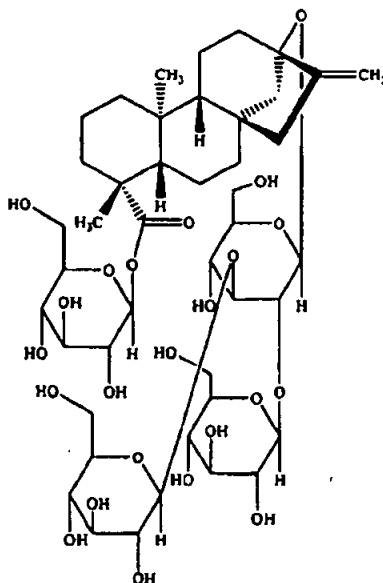
FIELD OF INVENTION

This invention relates generally to polymorphic and amorphous forms of rebaudioside A, methods for purifying rebaudioside A, and methods for preparing polymorphic and amorphous forms of rebaudioside A. More particularly, this invention relates to polymorphic and amorphous forms of rebaudioside A and methods for the purification or crystallization of rebaudioside A with aqueous organic solutions or organic solvents to obtain a product in high yield and high purity.

BACKGROUND OF INVENTION

Rebaudioside A is a high-potency diterpenoid glycoside sweetener having the chemical structure:

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Rebaudioside A is isolated and extracted, along with other steviol glycosides, from the *Stevia rebaudiana* (Bertoni) plant ("Stevia"), which is commercially cultivated in Japan, Singapore, Taiwan, Malaysia, South Korea, China, Israel, India, Brazil, Australia, and Paraguay. It is an alternative non-caloric sweetener with functional and

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rebaudioside A, methods for purifying rebaudioside A, and methods for making polymorphic and amorphous forms of rebaudioside A.

In a particular embodiment, the method for purifying rebaudioside A comprises a simple crystallization. In one embodiment, a method for purifying rebaudioside A
5 comprises combining crude rebaudioside A and an aqueous organic solution to form a rebaudioside A solution, the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight, and crystallizing from the crude rebaudioside A solution, in a single step, a substantially pure rebaudioside A in a purity greater than about 95% by weight on a dry basis.

10 In other particular embodiments, different polymorphic and amorphous forms of rebaudioside A and methods for preparing different polymorphic and amorphous forms of rebaudioside A are provided.

Other objects, features, and advantages of the invention will be apparent from the following detailed description, drawings, and claims. Unless otherwise defined, all
15 technical and scientific terms and abbreviations used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and compositions similar or equivalent to those described herein can be used in the practice of the present invention, suitable methods and compositions are described without intending that any such methods and compositions
20 limit the invention herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustrating a method for purifying rebaudioside A in accordance with an embodiment of this invention.

Fig. 2 is a schematic of the formation and conversion of rebaudioside A
25 polymorphic and amorphous forms of rebaudioside A in accordance with an embodiment of this invention.

Fig. 3 is a powder x-ray diffraction scan comparing four rebaudioside A polymorphs, Forms 1, 2, 3A and 3B, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

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anion exchange resin. Accordingly, the method of purification depends on the impurities present in the crude rebaudioside A starting material.

In an exemplary embodiment of a method for purifying rebaudioside A 110, illustrated in Figure 1, crude rebaudioside A 112 may be combined 114 with an aqueous organic solution 116 to form a rebaudioside A solution 118. The aqueous organic solution 116 comprises water in an amount from about 10 % to about 25 % by weight and at least one organic solvent. Alternatively, the aqueous organic solution 116 may comprise water in an amount from about 15 % to about 20 % by weight and at least one organic solvent.

10 Aqueous organic solutions, as used herein, refer to mixtures of water and at least one organic solvent. Non-limiting examples of organic solvents include alcohol, acetone, and acetonitrile. Alcohol, as used herein, refers to any straight, branched, or cyclic; substituted or unsubstituted alkyl, alkenyl, or alkynyl group attached to at least one hydroxyl moiety. Non-limiting examples of alcohols include ethanol, methanol, 15 isopropanol, 1-propanol, 1-butanol, 2-butanol, tert-butanol, and isobutanol.

In an exemplary embodiment, the aqueous organic solution 116 comprises a mixture of water and at least one organic solvent. In another exemplary embodiment, at least one organic solvent comprises an alcohol, the alcohol comprising ethanol, methanol, or mixtures thereof. In exemplary embodiments wherein the at least one organic solvent comprises a mixture of ethanol and methanol, the ethanol and methanol may be combined in the aqueous organic solvent in a weight ratio ranging from about 20 parts to about 1 part ethanol to about 1 part methanol. In another exemplary embodiment, the ethanol and methanol may be combined in the aqueous organic solvent in a weight ratio ranging from about 3 parts to about 1 part ethanol to about 1 part methanol.

20 In an exemplary embodiment, the rebaudioside A solution 118 comprises the aqueous organic solution 116 and the crude rebaudioside A 112 in a weight ratio ranging from about 10 to about 4 parts aqueous organic solution to about 1 part crude rebaudioside A. In another exemplary embodiment, the rebaudioside A solution 118 30 comprises the aqueous organic solution 116 and the crude rebaudioside A 112 in a

weight ratio ranging from about 5 to about 3 parts aqueous organic solution to about 1 part crude rebaudioside A.

In an exemplary embodiment, the method 110 may be carried out at approximately room temperature. In another embodiment, the method 110 further comprises the step of heating 120 the rebaudioside A solution 118. In an embodiment, the step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution to a temperature in a range from about 20°C to about 70°C, from about 20°C to about 60°C, from about 20°C to about 40°C, or from about 40°C to about 60°C. In another embodiment, the step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution to about reflux temperature. The step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution for about 0.25 hours to about 8 hours. In another exemplary embodiment, wherein the method for purifying rebaudioside A 110 comprises the step of heating 120 the rebaudioside A solution 118, the method further comprises the step of cooling 122 the rebaudioside A solution. In an embodiment, the step of cooling 122 the rebaudioside A solution 118 comprises cooling the rebaudioside A solution to a temperature in the range from about 4°C to about 25°C. The step of cooling 122 the rebaudioside A solution 118 comprises cooling the rebaudioside A solution for about 0.5 hours to about 24 hours.

The method for purifying rebaudioside A 110 further comprises the step of crystallizing 124 from the rebaudioside A solution 118 in a single step a substantially pure rebaudioside A composition 126 comprising rebaudioside A in an amount greater than about 85 % by weight on a dry basis, greater than about 90 % by weight on a dry basis, greater than about 95 % by weight on a dry basis, greater than about 97 % by weight on a dry basis, greater than about 98 % by weight on a dry basis, or greater than about 99 % by weight on a dry basis. The rebaudioside A solution 118 during the single crystallization step may be stirred or unstirred.

In an exemplary embodiment, the method 110 may further comprise the optional step of seeding 128 the rebaudioside A solution 118 at an appropriate temperature with substantially pure crystals of rebaudioside A 130 sufficient to promote crystallization of the rebaudioside A to form pure rebaudioside A. An amount of rebaudioside A 130 sufficient to promote crystallization of substantially pure

paddle dryer and microwave dryer. In an exemplary embodiment, the step of drying 138 comprises drying the substantially pure rebaudioside A composition 126 using a nitrogen or argon purge to remove the residual solvent 120 at a temperature in a range from about 40°C to about 60°C for about 5 hours to about 100 hours.

5 In yet another exemplary embodiment, wherein the crude rebaudioside A mixture 112 comprises substantially no rebaudioside D impurity, the method 110 further comprises the step of slurrying 140 the composition of substantially pure rebaudioside A 126 with an organic solvent or an aqueous organic solution 142 prior to the step of drying 138 the substantially pure rebaudioside A composition. The slurry
10 may be a mixture comprising a solid and an aqueous organic solution or organic solvent, wherein the solid comprises the substantially pure rebaudioside A composition 126 and is only sparingly soluble in the aqueous organic solution or organic solvent 142. In an embodiment, the substantially pure rebaudioside A composition 126 and aqueous organic solution or organic solvent 142 may be present in the slurry in a
15 weight ratio ranging from about 15 parts to about 1 part aqueous organic solution to about 1 part substantially pure rebaudioside A composition. In one embodiment, the slurry may be maintained at room temperature. In another embodiment, the step of slurrying 140 comprises heating the slurry to a temperature in a range from about 20°C to about 40°C. The substantially pure rebaudioside A composition 126 may be slurried
20 for about 0.5 hours to about 24 hours.

In still yet another exemplary embodiment, the method further comprises the steps of separating 132 the substantially pure rebaudioside A composition 126 from the aqueous organic solution 142 of the slurry and washing 134 the substantially pure rebaudioside A composition followed by the step of drying 138 the substantially pure
25 rebaudioside A composition.

If further purification is desired, the method of purifying rebaudioside A 110 described herein may be repeated or the substantially pure rebaudioside A composition may be further purified using an alternative purification method, such as the column chromatography.

30 Purity, as used herein, represents the weight percentage of rebaudioside A present in a rebaudioside A composition in raw or purified form. In one embodiment, a

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degrees show this shifting as well. Not wishing to be bound by any theory, the shifting of the peaks may be an indication that Form 3A is partially desolvated, thus containing a mixture of both the solvate and Form 2 crystals.

5 Figs. 7-10 are XRPD scans of the individual polymorphs Form 1, Form 2, Form 3A, and Form 3B, respectively, from a substantially pure rebaudioside A composition obtained from the purification process described hereinabove.

10 As illustrated in Fig. 2, the type of polymorph formed may be dependent on the factors such as the composition of the aqueous organic solution, the temperature of the crystallization step, and the temperature during the drying step. Not wishing to be bound by any theory, Form 1 and Form 3 are believed to be formed during the single crystallization step while Form 2 is believed to be formed during the drying step after conversion from Form 1 and Form 3.

15 Low temperatures during the crystallization step, in the range of about 20°C to about 50°C, and a low ratio of water to the organic solvent in the aqueous organic solution results in the formation of Form 3. High temperatures during the crystallization step, in the range of about 50°C to about 80°C, and a high ratio of water to the organic solvent in the aqueous organic solution results in the formation of the Form 1. Form 1 can be converted to Form 3 by slurring in an anhydrous solvent at about room temperature for about 2 to about 16 hours or by slurring in an anhydrous
20 solvent at about reflux temperature for about 0.5 to about 3 hours. Form 3 can be converted to Form 1 by slurring the polymorph in water at about room temperature for approximately 16 hours or at about reflux temperature for about 2 to about 3 hours. Form 3 can be converted to the Form 2 during the drying process; however, increasing either the drying temperature above about 70°C or the drying time of a substantially
25 pure rebaudioside A composition can result in decomposition of the rebaudioside A and increase the remaining rebaudioside B impurity in the substantially pure rebaudioside A composition. Form 2 can be converted to Form 1 with the addition of water.

30 In addition to the at least three polymorphic forms of rebaudioside A, the purification of rebaudioside A may result in the formation of an amorphous form of rebaudioside A, Form 4, as shown in Fig. 11. Form 4 has a broad amorphous halo that identifies the composition as being amorphous.

CLAIMS

1. A method for purifying rebaudioside A comprising the steps of:
combining crude rebaudioside A and an aqueous organic solution to form a rebaudioside A solution, the crude rebaudioside A comprising rebaudioside A in a purity from about 40 % to about 85 % by weight on a dry basis, and the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight; and
crystallizing from the rebaudioside A solution in a single step a rebaudioside A composition comprising rebaudioside A in a purity greater than about 95 % by weight on a dry basis.
2. The method of claim 1, further comprising the step of heating the rebaudioside A solution.
3. The method of claim 2, further comprising the step of cooling the rebaudioside A solution.
4. The method of claim 1, wherein rebaudioside A solution in the single crystallization step is stirred or unstirred.
5. The method of claim 1, further comprising the step of seeding the rebaudioside A solution at an appropriate temperature with an amount of rebaudioside A sufficient to promote crystallization of rebaudioside A.
6. The method of claim 1, further comprising the steps of separating and washing the substantially pure rebaudioside A composition.
7. The method of claim 6, further comprising the step of drying the substantially pure rebaudioside A composition.

8. The method of claim 1, wherein the crude rebaudioside A comprises substantially no rebaudioside D impurity, and the method further comprises slurrying the substantially pure rebaudioside A composition in an aqueous organic solution or in an organic solvent.

9. The method of claim 8, further comprising the steps of separating and washing the substantially pure rebaudioside A composition.

10. The method of claim 9, further comprising the step of drying the composition of a substantially pure rebaudioside A.

11. The method of claim 1, wherein the aqueous organic solution comprises a mixture of at least one organic solvent and water.

12. The method of claim 11, wherein at least one organic solvent comprises an alcohol.

13. The method of claim 12, wherein the alcohol comprises ethanol.

14. The method of claim 12, wherein the alcohol comprises methanol.

15. The method of claim 12, wherein the alcohol comprises a mixture of ethanol and methanol.

16. The method of claim 15, wherein the ethanol and methanol are present in the aqueous organic solution in a weight ratio from about 20 parts to about 1 parts ethanol to about 1 part methanol.

17. The method of claim 15, wherein the ethanol and methanol are present in the aqueous organic solution in a weight ratio from about 3 parts to about 1 part ethanol to about 1 part methanol.

18. The method of claim 1, wherein the at least one aqueous organic solution comprises an organic solvent selected from the group consisting of acetone, acetonitrile, methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, tert-butanol, and mixtures thereof.

19. The method of claim 1, wherein the aqueous organic solution and the crude rebaudioside A are present in the rebaudioside A solution in a weight ratio from about 4 to about 10 parts aqueous organic solution to about 1 part crude rebaudioside A.

20. The method of claim 1, wherein the aqueous organic solution and the crude rebaudioside A are present in the rebaudioside A solution in a weight ratio from about 3 to about 5 parts aqueous organic solution to about 1 part crude rebaudioside A.

21. The method of claim 1, wherein aqueous organic solution comprises water in an amount from about 10 % to about 25 % by weight.

22. A method for purifying rebaudioside A comprising the steps of combining crude rebaudioside A and an aqueous organic solution to form a rebaudioside A solution, the crude rebaudioside A comprising rebaudioside A in a purity from about 40 % to about 85 % by weight on a dry basis, and the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight; and

crystallizing from the rebaudioside A solution in a single step a rebaudioside A composition comprising rebaudioside A in a purity greater than about 95 % by weight on a dry basis, wherein the method is carried out at approximately room temperature.

23. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to a temperature in a range from about 20°C to about 40°C.

24. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to a temperature in a range from about 40°C to about 60°C.

25. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to about a reflux temperature.

26. The method of claim 3, wherein the step of cooling the rebaudioside A solution comprises cooling the rebaudioside A solution to a temperature in a range from about 4°C to about 25°C.

27. The method of claim 3, wherein the step of cooling the rebaudioside A solution comprises cooling the rebaudioside A solution for about 0.5 hours to about 24 hours.

28. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 97 % rebaudioside A by weight on a dry basis.

29. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 98 % rebaudioside A by weight on a dry basis.

30. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 99 % rebaudioside A by weight on a dry basis.

31. The method of claim 1, further comprising the steps of:
heating the rebaudioside A solution;
cooling the rebaudioside A solution;
separating and washing a substantially pure rebaudioside A composition; and
drying the substantially pure rebaudioside A composition.

32. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 8.

33. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 9.

34. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 10.

35. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises an amorphous form having an X-ray diffraction pattern substantially similar to Figure 11.

36. The method of claim 1, further comprising the step of forming an amorphous form of the substantially pure rebaudioside A composition.

37. The composition of claim 35, wherein the step of forming an amorphous form of the substantially pure rebaudioside A composition comprises a method selected from the group consisting of ball milling, precipitation, lyophilization, cryogrinding, and spray-drying.

38. A substantially pure rebaudioside A composition made according to the method of claim 1.

TRATADO SOBRE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

De la AGENCIA INTERNACIONAL

Para:

PAPPAS, Peter G.
Sutherland Asbill & Brennan LLP
999 Peachtree Street, NE
Atlanta, GA 30309-3996
ESTADOS UNIDOS DE AMERICA

**RECIBIDO
OCT 17 2008**

SUTHERLAND ASBILL & BRENNAN LLP

PCT

NOTIFICACIÓN DE TRANSMISIÓN DEL
EXAMEN PRELIMINAR INTERNACIONAL
SOBRE PATENTABILIDAD

(Regla PCT 71.1)

Fecha de Envío
(*dia/mes/año*) 13.10.2008

Expediente de Referencia del Solicitante o Agente
25040-2775

NOTIFICACIÓN IMPORTANTE

Solicitud Internacional No.
PCT/US2007/069548

Fecha de Solicitud Internacional
(*dia/mes/año*) 23.05.2007

Fecha Prioridad (*dia/mes/año*)
19.06.2006

Solicitante
THE COCA-COLA COMPANY

1. El solicitante queda notificado por el presente que esta Autoridad Examinadora Preliminar Internacional se transmite aquí con el informe preliminar internacional sobre la patentabilidad y sus anexos, si hay, establecidos en la solicitud internacional.
2. Una copia del informe y sus anexos, si hay, está siendo transmitida a la Agencia Internacional para comunicación a todas las Oficinas elegidas.
3. Cuando sea requerido por cualquiera de las Oficinas Elegidas, la Agencia Internacional preparará una traducción al inglés del informe (pero no de los anexos) y transmitirá dicha traducción a esas Oficinas.
4. **RECORDATORIO**

El solicitante deberá entrar a fase nacional ante cada oficina elegida realizando ciertos actos (presentar traducciones y pagando tarifas nacionales) dentro de 30 meses de la fecha de prioridad (o más tarde en algunas oficinas) (Artículo 39(1)) (ver también el recordatorio enviado por la Agencia Internacional con el Formato PCT/IB/301).

Donde se requiera enviar una traducción de la solicitud internacional a una Oficina elegida, esa traducción deberá contener una traducción de cualquier anexo al informe preliminar internacional sobre la patentabilidad. Es responsabilidad del solicitante preparar y enviar dicha traducción directamente a cada Oficina elegida que le concierna.

Para más detalles sobre tiempos límites aplicables y requerimientos de las Oficinas elegidas, ver Volumen II de la *Guía del Solicitante PCT*.

La atención del solicitante se dirige al Artículo 33(5), el cual proporciona que los criterios de novedad, nivel inventivo y aplicabilidad industrial como se describe en el Artículo 33(2) a (4) solo tienen como objeto el examen preliminar internacional y que "cualquier Estado Contratante puede aplicar criterios adicionales o diferentes para decidir si, en ese Estado, la invención reivindicada es patentable o no" (ver también Artículo 27(5)). Tales criterios adicionales pueden relacionarse, por ejemplo, a exenciones de patentabilidad, requerimientos para permitir la divulgación, claridad y soporte de las reivindicaciones.

Nombre y dirección postal de la autoridad examinadora del reporte preliminar internacional:

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**TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES
PCT**

**INFORME DE EXAMEN PRELIMINAR INTERNACIONAL SOBRE
PATENTABILIDAD**

(Capítulo II del tratado de Cooperación para Patentes)

(Artículo 36 y Regla 70 PCT)

Expediente del Solicitante o Apoderado 25040-2775		PARA PROCEDIMIENTO POSTERIOR	Véase Formulario PCT/IPEA/416
No. Solicitud Internacional PCT/US2007/069548	Fecha Internacional de Presentación (día/mes/año) 23.05.2007	Fecha de Prioridad (día/mes/año) 19.06.2006	
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC INV. A23L1/236			
Solicitante THE COCA-COLA COMPANY			

1. Este informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional bajo el Artículo 35 y se envía al solicitante según Artículo 36. 2. Este INFORME comprende un total de <u>9</u> hojas, incluyendo esta portada 3. Este INFORME también viene acompañado de ANEXOS que comprenden: a. ☒ (enviados al solicitante y a la Oficina Internacional) un total de <u>11</u> hojas, como sigue: ☒ hojas de la descripción, reivindicaciones y/o dibujos que han sido corregidas y son la base para este informe y/o hojas que contienen rectificaciones autorizadas por esta Autoridad (ver regla 70.16 y Sección 607 de las Instrucciones Administrativas) ☐ hojas que sustituyen hojas anteriores, pero las cuales esta Autoridad considera contienen una corrección que va más allá de lo divulgado en la solicitud internacional como se presentó, según se indica en el ítem 4 de la casilla I y la Casilla Suplementaria. b. ☐ (enviados solamente a la Oficina Internacional) un total de (indique tipo y número de portador(es) electrónico(s)) _____, que contienen un listado de una secuencia y/o tablas relacionadas con el mismo, solo en forma legible por computador, como se indica en la casilla suplementaria Relacionada con el Listado de la Secuencia (ver Sección 802 de las Instrucciones Administrativas).																									
4. Este informe contiene datos con respecto a los siguientes puntos: <table><tr><td>☒</td><td>Casilla No. I</td><td>Base del Informe</td></tr><tr><td>☐</td><td>Casilla No. II</td><td>Prioridad</td></tr><tr><td>☐</td><td>Casilla No. III</td><td>Sin elaboración de una opinión sobre novedad, actividad inventiva y posibilidad de aplicación industrial</td></tr><tr><td>☐</td><td>Casilla No. IV</td><td>Falta de uniformidad de la invención</td></tr><tr><td>☒</td><td>Casilla No. V</td><td>Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración</td></tr><tr><td>☐</td><td>Casilla No. VI</td><td>Ciertos documentos enumerados</td></tr><tr><td>☐</td><td>Casilla No. VII</td><td>Ciertas deficiencias de la solicitud internacional</td></tr><tr><td>☐</td><td>Casilla No. VIII</td><td>Ciertas observaciones relacionadas con la solicitud internacional</td></tr></table>		☒	Casilla No. I	Base del Informe	☐	Casilla No. II	Prioridad	☐	Casilla No. III	Sin elaboración de una opinión sobre novedad, actividad inventiva y posibilidad de aplicación industrial	☐	Casilla No. IV	Falta de uniformidad de la invención	☒	Casilla No. V	Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración	☐	Casilla No. VI	Ciertos documentos enumerados	☐	Casilla No. VII	Ciertas deficiencias de la solicitud internacional	☐	Casilla No. VIII	Ciertas observaciones relacionadas con la solicitud internacional
☒	Casilla No. I	Base del Informe																							
☐	Casilla No. II	Prioridad																							
☐	Casilla No. III	Sin elaboración de una opinión sobre novedad, actividad inventiva y posibilidad de aplicación industrial																							
☐	Casilla No. IV	Falta de uniformidad de la invención																							
☒	Casilla No. V	Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración																							
☐	Casilla No. VI	Ciertos documentos enumerados																							
☐	Casilla No. VII	Ciertas deficiencias de la solicitud internacional																							
☐	Casilla No. VIII	Ciertas observaciones relacionadas con la solicitud internacional																							

Fecha de presentación de la petición 2008-05-23	Fecha de la preparación de este informe 13.10.2008
Nombre y dirección postal de la autoridad examinadora del reporte preliminar internacional: Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Funcionario Autorizado Groh, Bjorn Teléfono No. +49 89 2399 - 7855

**INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL
SOBRE PATENTABILIDAD**

Solicitud Internacional No.
PCT/US2007/069548

Casilla No. I Bases para este informe.

1. Respecto al **Idioma**, la base para el examen preliminar fue:

- ☒ Solicitud internacional en el idioma en el que fue presentada originalmente
- ☐ Traducción de la solicitud internacional, traducida del idioma original a , siendo este idioma de traducción proporcionado para los propósitos de
- ☐ La búsqueda internacional (Reglas 12.3(a) y 23.1(b))
- ☐ Publicación de la solicitud internacional (Regla 12.4(a))
- ☐ Examen preliminar internacional (bajo las Reglas 55.2 y/o 55.3)

2. Respecto a los **elementos*** de la solicitud internacional, este reporte es basado en (*hojas de reemplazo que han sido presentadas a la Oficina receptora en respuesta a una invitación bajo el Artículo 14 se referencian en este informe como "presentadas originalmente" y no se anexan a este informe*):

Descripción, Páginas

2,4,5,8,10,11,13-33 como se presentaron originalmente
1,3,6,7,9,12 recibidas el 23.05.2008 con una carta del 23.05.2008

Reivindicaciones, Números

1-38 recibidas el 23.05.2008 con una carta del 23.05.2008

Dibujos, Hojas

1/11-11/11 como se presentaron originalmente

- ☐ Un listado de una secuencia y/o cualquier tabla relacionada – Ver Casilla Suplementaria relacionada con el Listado de la Secuencia.

3. ☒ Las correcciones han dado como resultado la cancelación de

- ☐ la descripción, páginas
- ☒ las reivindicaciones, Nos. 39-42
- ☐ los dibujos, hojas/figuras
- ☐ el listado de la secuencia (*especifique*):
- ☐ cualquier tabla relacionada con el listado de la secuencia (*especifique*):

4. ☐ Este informe se ha establecido como si (algunas de) las correcciones anexas a este informe, y enumeradas debajo no se hubieran hecho, ya que se consideran como que van más allá de la divulgación, según se indica en la casilla Suplementaria (Regla 70.2(c))

- ☐ la descripción, páginas
- ☐ las reivindicaciones, Nos.
- ☐ los dibujos, hojas/figuras
- ☐ el listado de la secuencia (*especifique*):
- ☐ cualquier tabla relacionada con el listado de la secuencia (*especifique*):

5. ☐ Esta opinión se ha establecido teniendo en cuenta la **rectificación de un error obvio** autorizado por o notificado a esta Autoridad bajo la Regla 91 (Regla 70.2 (e)).

**INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL
SOBRE PATENTABILIDAD**

Solicitud Internacional No.
PCT/US2007/069548

**Casilla No. V Declaración razonable de acuerdo a el Artículo 35(2) con relación a la novedad,
el nivel inventivo o la aplicabilidad industrial; citas y explicaciones apoyando esta declaración**

1. Declaración

Novedad (N)	Si:	Reivindicaciones	<u>5,14-17,22,35</u>
	No:	Reivindicaciones	<u>1-4,6-13,18-21,23-36,38</u>
Nivel Inventivo (IS)	Si:	Reivindicaciones	<u>22</u>
	No:	Reivindicaciones	<u>1-21,23-38</u>
Aplicabilidad Industrial (IA)	Si:	Reivindicaciones	<u>1-42</u>
	No:	Reivindicaciones	

2. Citas y explicaciones (Regla 70.7)

Ver hoja separada

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Re Ítem V.

1. Modificaciones

1.1. La expresión "solvente orgánico acuoso" de la reivindicación original 1 fue reemplazada con "solución orgánica acuosa" en la presente reivindicación. Ambas expresiones fueron usadas más de una vez en la solicitud como fue originalmente presentada. Desde que (A) solvente se entiende que comprende el significado de 'mezcla de dos líquidos', y (B) la definición de "solvente orgánico acuoso" en la descripción original (ver página 6, línea 10-15) fue mantenido y asignado a "solución orgánica acuosa", y (C) la forma de modificación 'solvente' a 'solución' fue usada constantemente a través de la solicitud, esta modificación parece ser permisible (Art. 41(2) PCT).

1.2. Las reivindicaciones fueron restringidas. La solicitud (incluyendo ejemplos específicos dentro de si/fuera de la invención) necesita ser adaptada a la presente/ última serie de reivindicaciones.

1.3. Una nueva reivindicación independiente (presente reivindicación 22) fue creada basada en las reivindicaciones originales 1 y de la 22 a la 24. La presente reivindicación 22 comprende toda la materia de la presente reivindicación 1 y debería ser parafraseada como una reivindicación dependiente por eso mismo.

2. Se hace referencia a los siguiente documentos:

D1: US 2006/083838 A1 (JACKSON MEL C [EU]) 20 de abril de 2006;

D2: CA-A1-2 278 083 (ALBERTA RES COUNCIL [CA]) 20 de enero de 2001.

3. General / Interpretación

3.1. El método en que las reivindicaciones están parafraseadas en una forma abierta ("...caracterizado por..."), consecuentemente el método reivindicado puede contener pasos adicionales, los cuales contribuirían a la pureza de la rebaudioside A. Por consiguiente, los pasos adicionales del método no pueden descalificar la forma de un documento siendo la destrucción de la novedad.

3.2. la expresión "solución de rebaudiosida A en el paso único de cristalización" no

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excluye ni limita ningún otro paso del proceso.

4. Novedad (Art. 33(2) PCT)

4.1 A la vista de D1

D1 da a conocer un método para purificar rebaudiósido A. Dicho método comprende el paso de usar una mezcla de etanol-agua como solvente y cristalizar el rebaudiósido A de dicho solvente. La pureza del producto final (rebaudiósido A) depende de la calidad de eyección (pureza inicial del rebaudiósido A). Se puede obtener un producto final (rebaudiósido A) con una pureza del 100% (ver Tabla 3).

Con un **único** paso de reflujo y utilizando un material inicial de estevia de mayor calidad (definida en aproximadamente 85% ó mayor contenido de rebaudiósido A, ver §12 de D1) se obtiene de manera típica un producto de 100% rebaudiósido A, ver §55.

Además, en el evento de que se acepte un producto final con una concentración de rebaudiósido A inferior a 99% (por ejemplo 95), entonces el paso de lavado por agitación podría ser omitido, ver §55 de D1.

El rebaudiósido A puro producido por los *mismos* métodos (los actualmente reivindicados y los del arte previo) daría como resultado productos que por consiguiente mostrarían un patrón de difracción de rayos X "sustancialmente similar"

Las presentes reivindicaciones 1-4, 6-13, 18-21, 23-36 y 38 no son nuevas sobre D1.

4.2 A la vista de D2

Del arte previo D2 se conoce que el rebaudiósido A puede ser purificado de una mezcla de metanol-agua (ver reivindicaciones 1 a 5 y ejemplo 5).

La pureza del producto final (rebaudiósido A) depende de la calidad de eyección (pureza inicial del rebaudiósido A). Se puede obtener un producto final (rebaudiósido A) con una pureza del 98.6% (ver ejemplo 5)

9
16
1

El rebaudiósido A puro producido por los *mismos* métodos (los actualmente reivindicados y los del arte previo) daría como resultado productos que por consiguiente mostrarían un patrón de difracción de rayos X "sustancialmente similar"

Las reivindicaciones actuales 32-35 y 38 no son nuevas sobre D2.

5. Nivel Inventivo (Art. 33(3) PCT)

Los argumentos relacionados con el Art. 33(3) PCT dependerán de cómo se puede lograr la novedad (por ejemplo cómo/cuáles modificaciones pueden ser llevadas a cabo).

- 5.1 Se conoce el uso de solventes orgánicos solubles en agua, tales como metanol y etanol para purificar el rebaudiósido A (ver D2 reivindicación 3 y las reivindicaciones de D1, página 22: "Tabla 2-continuación y página 4 última oración).

Puesto que ya es conocido (por ejemplo D1, ver arriba), cómo purificar el rebaudiósido A hasta un 100% de pureza, el problema técnico objetivo puede ser formulado para proveer un método alternativo a lo que se conoce en el arte.

Una diferencia podría ser que el presente método utiliza hasta un 25% de agua.

Sin embargo, se conoce por D1 (ver página 22: "Tabla 2-continuación) que el incremento de las concentraciones de agua (de 0 a 10%) aumentan la pureza del rebaudiósido A. En consecuencia, resulta obvio incrementar el contenido de agua para mantener ó asegurar (en caso de un material inicial de menor calidad) un rebaudiósido A de alta pureza.

La reivindicaciones 1-21, 23-38 no involucran un nivel inventivo sobre el arte previo.

En vista de que no se evidencia cuales pasos del proceso definen la invención, se requiere al solicitante que redacte las reivindicaciones independientes en forma de dos partes, ó que al menos suministre dicha información en una carta anexa.

- 5.2. Un método para purificar rebaudiósido A, como se define en la reivindicación 22, caracterizado en que el método es llevado a cabo a una temperatura ambiente, lo cual no se deriva de manera obvia del arte previo, que generalmente enseña utilizar una temperatura elevada (tal como 79-80°C en D1)

La reivindicación 22 aparenta implicar un nivel inventivo.

6. Otros

6.1 Resultados a alcanzar/ ó deseados.

- A. La reivindicación 1 y sus reivindicaciones dependientes están definidas por el resultado "pureza mayor que 95% aproximadamente" a alcanzar.
- B. Las reivindicaciones 35 a 39 y sus reivindicaciones dependientes están definidas por un patrón de difracción de rayos X a obtener, ilustrado de manera gráfica.

Cuando la invención no puede ser definida de otra forma, solamente en casos especiales, las reivindicaciones del tipo resultado a obtener pueden ser aceptables sin restringir excesivamente el alcance de las reivindicaciones (ver Examen Preliminar Internacional PCT – Guías, Capítulo III, punto 4.7).

Cualquiera de las reivindicaciones de los grupos A y B podría haber sido definida de manera precisa sin utilizar las definiciones de tipo resultado a obtener:

Para A: Reivindicaciones de método del grupo A deben contener los **pasos** del método, lo cuales permiten el resultado "pureza mayor que 95% aproximadamente".
En consecuencia, la característica "pureza mayor que 95% aproximadamente" es considerada como "apropiada para obtener una pureza mayor a 95% aproximadamente"

Para B: Las reivindicaciones de producto del grupo B podrían haber sido delimitadas de manera más precisa mediante la definición del producto reclamado por sus propiedades químicas *inherentes* (tales como agua cristalina, estructuras mono-, di- ó poliméricas, etc.) y/ó físicas (tales como formas isoméricas, cristalinas ó

amorphas, etc).

Las reivindicaciones 35 a 39 no cumplen con los requisitos del Art. 6 del PCT.

6.2 Falta de divulgación.

La solicitud tal como fue presentada no menciona **cómo** obtener específicamente una de las varias composiciones de rebaudiósido A descritas en las reivindicaciones 32 a 35, las cuales son caracterizadas únicamente con base en figuras de difracción de rayos X diferentes.

¿Cómo pueden (al menos) cuatro composiciones supuestamente diferentes ser obtenidas por una y el mismo método?

Las reivindicaciones 32 a 35 no cumplen con los requisitos del Art. 5 del PCT.

6.3 Reivindicaciones 32 a 36

- a. La expresión "sustancialmente puro" es un término relativo, el cual no es lo suficientemente preciso para definir la ampliación de una reivindicación patentable. (Art. 6 del PCT).
- b. La expresión "sustancialmente similar" es un término relativo, el cual no es lo suficientemente preciso para definir la ampliación de una reivindicación patentable. (Art. 6 del PCT).
- c. La definición de una composición por medio de la referencia a un resultado de un método ilustrado gráficamente (Figuras 7 a 1) no es lo suficientemente preciso para definir la ampliación de una reivindicación patentable (Art. 6 y Regla 6.2 a del PCT). Además, la referencia a un resultado representado de manera gráfica, el cual carece de definición y escala del eje Y "escala arbitraria" (!) no es lo suficientemente preciso para definir la ampliación de una reivindicación patentable (Art. 6 del PCT).

6.4 Con relación a la reivindicación 38

La expresión "sustancialmente puro" no es lo suficientemente clara para definir la ampliación de una reivindicación de producto (Art. 6 del PCT).

6.5 Descripción

El último párrafo en la página 33 presenta la materia objeto reivindicada de manera imprecisa, ya que se refiere a alteraciones no especificadas, variaciones, equivalentes, etc. Dicho párrafo no es necesario ni claro y debería ser eliminado (Art. 6 y Regla 9.1 iv del PCT). El solicitante informó que el último párrafo en la página 33 había sido borrado, sin embargo en la versión enviada por correo electrónico (26.05.08) dicha modificación no fue presentada.

- 6.6 Con el fin de facilitar el examen de cumplimiento de cualquier modificación (durante el Capítulo II del PCT ó durante la Fase Nacional) con los requisitos del Artículo 21 (2) del PCT, se requiere al solicitante que identifique claramente todas las modificaciones, ya sea que sean modificaciones por adición, reemplazo, combinación (de reivindicaciones por ejemplo) ó eliminación. El solicitante deberá indicar en detalle los textos en la solicitud como fue presentada, sobre los cuales se basan estas modificaciones.

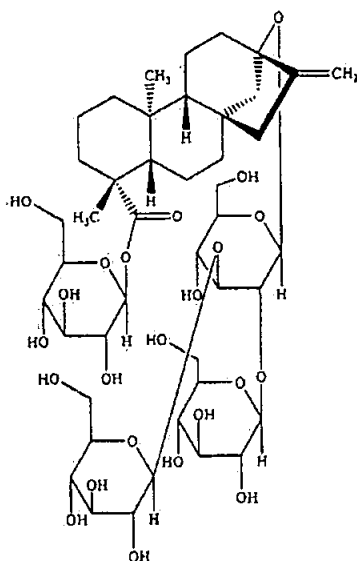
MEMORIA DESCRIPTIVA

CAMPO DEL INVENTO

Este invento se refiere en general a formas polimórficas y amorfas de rebaudiosida A, a métodos para purificar la rebaudiosida A y métodos para preparar formas polimórficas y amorfas de rebaudiosida A. Más específicamente, este invento se refiere a formas polimórficas y amorfas de rebaudiosida A, y a métodos para la purificación o cristalización de rebaudiosida A con solventes orgánicos acuosos o con solventes orgánicos para obtener un producto de alto rendimiento y alta pureza.

ANTECEDENTES DEL INVENTO

La rebaudiosida A es un endulzante glicósido diterpenoide de alto poder que tiene la estructura química:



La rebaudiosida A es aislada y extraída, junto con otros glicósidos de esteviol, de la planta *Stevia rebaudiana* (Bertoni) ("Stevia"), cultivada comercialmente en Japón, Singapur, Taiwán, Malasia, Corea del Sur, China, India, Brasil, Australia y Paraguay. Es un endulzante no-calórico alternativo

publicación de patente norteamericana N° 2007/0082103 revela un método para purificar rebaudiosida A mediante recristalización desde etanol acuoso, aseverando que una recristalización en dos pasos desde rebaudiosida sin refinar (60%) da como resultado la formación de rebaudiosida A >98% pura con un rendimiento de 97%. Estos métodos de la especialidad anterior, sin embargo, no proporcionan una composición de rebaudiosida A substancialmente pura usando un paso de recristalización único.

En consecuencia, se necesita un método sencillo, eficiente y económico para producir rebaudiosida A substancialmente pura.

RESEÑA DEL INVENTO

Realizaciones ejemplares del invento tratan la necesidad identificada anteriormente, proporcionando una rebaudiosida A substancialmente pura, formas polimórficas y amorfas de rebaudiosida A, métodos para purificar rebaudiosida A, y métodos para preparar formas polimórficas y amorfas de rebaudiosida A.

En una realización en particular, el método de purificación de rebaudiosida A comprende una cristalización simple. En una realización, un método para purificar rebaudiosida A comprende combinar rebaudiosida A sin refinar y un solvente orgánico acuoso para formar una solución de rebaudiosida A, en que la solución orgánica acuosa comprende agua en una cantidad desde alrededor de 10% hasta 25% en peso, aproximadamente, y cristalizar desde la solución de rebaudiosida A sin refinar, en un solo paso, una rebaudiosida A substancialmente pura con una pureza superior a 95% en peso en una base seca.

En otras realizaciones particulares, se proporcionan diferentes formas polimórficas y amorfas de rebaudiosida A y

hasta alrededor de 25% en peso y, por lo menos, un solvente orgánico. Alternativamente, la solución orgánica acuosa 116 puede comprender agua en una cantidad desde alrededor de 15% hasta alrededor de 20% en peso y por lo menos un solvente orgánico.

Solventes orgánico acuosos, en la forma usada aquí se refieren a mezclas de agua y por lo menos un solvente orgánico. Ejemplos no limitantes de solventes orgánicos incluyen alcohol, acetona, y acetonitrilo. Alcohol, como se usa aquí, se refiere, a cualquier grupo alquilo, alquenilo o alquinilo lineal, ramificado o cíclico, substituido o insubstituido, unido a, por lo menos, una porción hidroxilo. Ejemplos no limitantes de alcoholes incluyen etanol, metanol, isopropanol, 1-propanol, 1-butanol-2-butanol, ter-butanol e isobutanol.

En una realización ilustrativa, la solución orgánica acuosa 116 comprende una mezcla de agua y por lo menos un solvente orgánico. En otra realización ilustrativa, por lo menos un solvente orgánico comprende un alcohol, el alcohol comprende etanol, metanol, o mezclas suyas. En realizaciones ilustrativas en que el por lo menos un solvente orgánico comprende una mezcla de etanol y metanol, el etanol y metanol pueden ser combinados en el solvente orgánico con una proporción en peso que varía desde alrededor de 20 partes por una parte de etanol hasta alrededor de una parte de metanol. En otra realización ilustrativa, el etanol y metanol pueden ser combinados en el solvente orgánico acuoso en una proporción en peso que varía desde alrededor de 3 partes a 1 parte de etanol, hasta alrededor de 1 parte de metanol.

En una realización ilustrativa, la solución de rebaudiosida A 118 comprende el solvente orgánico acuoso 116 y la rebaudiosida A sin refinar 112 en una relación en peso que varía desde alrededor de 10 hasta alrededor de 4 partes de solvente

orgánico acuoso con alrededor de 1 parte de rebaudiosida A sin refinar. En otra realización ilustrativa, la solución de rebaudiosida A 118 comprende la solución orgánica acuosa 116 y la rebaudiosida A sin refinar 1 112 en una relación en peso que varía desde alrededor de 5 hasta 3 partes de solvente orgánico acuoso con alrededor de una parte de rebaudiosida A sin refinar.

En una realización ilustrativa, el método 110 puede ser llevado a cabo a una temperatura aproximada a la temperatura ambiente. En otra realización, el método 110 comprende adicionalmente el paso de calentar 120 de la solución de rebaudiosida A 118. En una realización, el paso de calentar 120 de la solución de rebaudiosida A 118, comprende calentar la solución de rebaudiosida A hasta una temperatura que varía desde alrededor desde 20°C hasta alrededor de 70°C, desde alrededor de 20°C hasta alrededor de 60°C, desde alrededor de 20°C hasta alrededor de 40°C, o desde alrededor de 40°C hasta alrededor de 60°C. En otra realización, el paso de calentar 120 de la solución de rebaudiosida A 118 comprende calentar la solución de rebaudiosida A hasta una temperatura aproximada a la temperatura de reflujo. El paso de calentar 120 de la solución de rebaudiosida A 118 comprende calentar la solución de rebaudiosida A durante aproximadamente 0,25 horas hasta alrededor de 8 horas. En otra realización ilustrativa, donde el método para purificar rebaudiosida A 110 comprende el paso de calentar 120 de la solución de rebaudiosida A 118, en que el método comprende adicionalmente el paso de enfriar 122 la solución de rebaudiosida A. En una realización, el paso de enfriar 122 la solución de rebaudiosida A, comprende enfriar la solución de rebaudiosida A hasta una temperatura dentro del margen de variación desde alrededor de 4°C hasta alrededor de 25°C. El paso de enfriar 122

En otra realización ilustrativa más, el método 110 comprende adicionalmente el paso de secar 138 la composición de rebaudiosida A substancialmente pura 126. Tales métodos son conocidos por los peritos en la especialidad e incluyen, pero no se limitan, al uso de un secador rotatorio al vacío, secador de lecho fluido, secador de túnel rotatorio, secador de placas, secador de bandejas, secador tipo Nauta, secador de rociado, secador instantáneo, secador de micrón, secador tipo recipiente, secador de paleta de baja y alta velocidad y secador por microondas. En una realización ilustrativa, el paso de secado 138 comprende secar la composición de rebaudiosida A substancialmente pura 126 usando una purga de nitrógeno o argón para eliminar el solvente residual 120 a una temperatura en un margen de variación de alrededor de 40°C hasta alrededor de 60°C durante 5 horas, aproximadamente, hasta alrededor de 100 horas.

En otra realización ilustrativa más, donde la mezcla de rebaudiosida A sin refinar 112 no comprende substancialmente ninguna impureza de rebaudiosida D, el método 110 comprende además el paso de formar una lechada 140 con la composición de rebaudiosida A substancialmente pura 126, con un solvente orgánico o con un solvente orgánico acuoso 142 previo al paso de secar 138 la composición de rebaudiosida A substancialmente pura. La lechada puede ser una mezcla que comprende un sólido y un solvente orgánico acuoso o un solvente orgánico donde el sólido comprende la composición de rebaudiosida A substancialmente pura 126 y es sólo escasamente soluble en el solvente orgánico acuoso o en el solvente orgánico 142. En una realización, una composición de rebaudiosida A substancialmente pura 126 y el solvente orgánico acuoso o el solvente orgánico 142 pueden estar presentes en la lechada en una relación en peso en un margen de

desplazamiento. Sin que se desee ser forzado por ninguna teoría, el desplazamiento de los valores máximos puede ser una indicación de que la Forma A estar desolvatado parcialmente, conteniendo así una mezcla tanto del solvato como de los cristales de Forma 2.

Las Figuras 7-10 son exploraciones XRPD de los polimorfos individuales de Forma 1, Forma 2, Forma 3A, y Forma 3B, respectivamente, desde una composición de rebaudiosida A substancialmente pura obtenida del proceso de purificación descrito aquí anteriormente.

Como se ilustra en la Figura 2, el tipo de polimorfo formado puede ser dependiente de factores tales como la composición de la solución orgánica acuosa, la temperatura del paso de cristalización, y la temperatura durante el paso de secado. Sin que se desee ser forzado por ninguna teoría, se cree que la Forma 1 y la Forma 3 se forman durante el paso de cristalización único, en tanto que se cree que la Forma 2 se forma durante el paso de secado después de la conversión desde la Forma 1 y la Forma 3.

Las temperaturas bajas durante el paso de cristalización, entre alrededor de 20° C y alrededor de 50°C, y una baja relación de agua con el solvente orgánico en el solvente orgánico acuoso da como resultado en la formación de la Forma 3. Altas temperaturas durante el paso de cristalización, entre alrededor de 50°C hasta alrededor de 80°C, y la alta relación entre agua y solvente orgánico en el solvente orgánico acuoso dan como resultado la formación de la Forma 1. La Forma 1 puede ser convertida en la Forma 3 formando una lechada en un solvente anhidro a una temperatura próxima a la temperatura ambiente durante alrededor de 2 hasta alrededor de 16 horas, o formando una lechada en un solvente anhidro a una temperatura próxima al

REIVINDICACIONES

1.- Un método para purificar rebaudiosida A que comprende los pasos de:

5 combinar rebaudiosida A cruda y una solución orgánica acuosa para formar una solución de rebaudiosida A, la rebaudiosida A cruda comprendiendo rebaudiosida A en una pureza de alrededor de 40% a alrededor de 85% en peso sobre una base seca, y la solución orgánica acuosa comprendiendo agua en una cantidad de alrededor de 10% a alrededor de 25%
10 en peso; y

 cristalizar la solución de rebaudiosida A en un solo paso una composición de rebaudiosida A que comprende rebaudiosida A en una pureza mayor de alrededor de 95% en peso sobre una base seca.

 2.- El método de conformidad con la reivindicación 1, que
15 comprende además el paso de calentar la solución de rebaudiosida A.

 3.- El método de conformidad con la reivindicación 2, que comprende además el paso de enfriar la solución de rebaudiosida A.

 4.- El método de conformidad con la reivindicación 1, en donde la solución de rebaudiosida A en el único paso de cristalización está agitada o no
20 agitada.

 5.- El método de conformidad con la reivindicación 1, que comprende además el paso de sembrar la solución de rebaudiosida A a una

HOJA MODIFICADA

temperatura apropiada con una cantidad de rebaudiosida A suficiente para promover la cristalización de rebaudiosida A.

6.- El método de conformidad con la reivindicación 1, que comprende además los pasos de separar y lavar la composición de rebaudiosida A substancialmente pura.

7.- El método de conformidad con la reivindicación 6, que comprende además el paso de secar la composición de rebaudiosida A substancialmente pura.

8.- El método de conformidad con la reivindicación 1, en donde la rebaudiosida A cruda comprende substancialmente nada de impureza de rebaudiosida D y el método comprende además formar en suspensión la composición de rebaudiosida A substancialmente pura en una solución orgánica acuosa o en un solvente orgánico.

9.- El método de conformidad con la reivindicación 8, que comprende además los pasos de separar y lavar la composición de rebaudiosida A substancialmente pura.

10.- El método de conformidad con la reivindicación 9, que comprende además el paso de secar la composición de una rebaudiosida A substancialmente pura.

11.- El método de conformidad con la reivindicación 11, en donde la solución orgánica acuosa comprende una mezcla de cuando menos un solvente orgánico y agua.

- 12.- El método de conformidad con la reivindicación 11, en donde cuando menos un solvente orgánico comprende un alcohol.
- 13.- El método de conformidad con la reivindicación 12, en donde el alcohol comprende etanol.
- 5 14.- El método de conformidad con la reivindicación 12, en donde el alcohol comprende metanol.
- 15.- El método de conformidad con la reivindicación 12, en donde el alcohol comprende una mezcla de etanol y metano
- 16.- El método de conformidad con la reivindicación 15, en donde
 - 10 el etanol y metanol están presentes en la solución orgánica acuosa en una relación en peso de alrededor de 20 partes a alrededor de 1 parte de etanol a alrededor de 1 parte de metanol.
- 17.- El método de conformidad con la reivindicación 15, en donde el etanol y metanol están presentes en la solución orgánica acuosa en una
 - 15 relación en peso de alrededor de 3 partes a alrededor de 1 parte de etanol a alrededor de 1 parte de metanol.
- 18.- El método de conformidad con la reivindicación 1, en donde la cuando menos una solución orgánica acuosa comprende un solvente orgánico seleccionado del grupo que consiste en acetona, acetonitrilo, metanol,
 - 20 etanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, ter-butanol, y mezclas de los mismos.

19.- El método de conformidad con la reivindicación 1, en donde la solución orgánica acuosa y la rebaudiosida A cruda están presentes en la solución de rebaudiosida A en una relación en peso de alrededor de 4 a alrededor de 10 partes de solución orgánica acuosa a alrededor de 1 parte de rebaudiosida A cruda.

20.- El método de conformidad con la reivindicación 1, en donde la solución orgánica acuosa y la rebaudiosida A cruda están presentes en la solución de rebaudiosida A en una relación en peso de alrededor de 3 a alrededor de 5 partes de solución orgánica acuosa a alrededor de 1 parte de rebaudiosida A cruda.

21.- El método de conformidad con la reivindicación 1, en donde la solución orgánica acuosa comprende agua en una cantidad de alrededor de 105 a alrededor de 25% en peso.

22.- Un método para purificar rebaudiosida A que comprende los pasos de:

combinar rebaudiosida A cruda en una solución orgánica acuosa para formar una solución de rebaudiosida A, la rebaudiosida A cruda comprendiendo rebaudiosida A en una pureza de alrededor de 40% a alrededor de 85% en peso sobre una base seca, y la solución orgánica acuosa comprendiendo agua en una cantidad de alrededor de 10% a alrededor de 25% en peso; y

cristalizar de la solución de rebaudiosida A en un solo paso una composición de rebaudiosida A que comprende rebaudiosida a en una pureza mayor de alrededor de 95% en peso sobre una base seca, en donde el método se lleva a cabo aproximadamente a temperatura ambiente.

5 23.- El método de conformidad con la reivindicación 2, en donde el paso de calentar la solución de rebaudiosida A comprende calentar la solución de rebaudiosida A a una temperatura en la escala de alrededor de 20°C a alrededor de 40°C.

10 24.- El método de conformidad con la reivindicación 2, en donde el paso de calentar la solución de rebaudiosida A comprende calentar la solución de rebaudiosida A a una temperatura en una escala de alrededor de 40°C a alrededor de 60°C.

15 25.- El método de conformidad con la reivindicación 2, en donde el paso de calentar la solución de rebaudiosida A comprende calentar la solución de rebaudiosida A a alrededor de una temperatura de reflujo.

20 26.- El método de conformidad con la reivindicación 3, en donde el paso de enfriar la solución de rebaudiosida A comprende enfriar la solución de rebaudiosida A a una temperatura en una escala de alrededor de 4°C a alrededor de 25°C.

27.- El método de conformidad con la reivindicación 3, en donde el paso de enfriar la solución de rebaudiosida A comprende enfriar la solución de rebaudiosida A durante alrededor de 0.5 horas a alrededor de 24 horas.

28.- El método de conformidad con la reivindicación 1, en donde
5 el producto de rebaudiosida A substancialmente puro comprende rebaudiosida A en una pureza mayor de alrededor de 97% de rebaudiosida A en peso sobre un base seca.

29.- El método de conformidad con la reivindicación 1, en donde el producto de rebaudiosida A substancialmente puro comprende rebaudiosida
10 A en una pureza mayor de alrededor de 98% de rebaudiosida A en peso sobre una base seca.

30.- El método de conformidad con la reivindicación 1, en donde el producto de rebaudiosida A substancialmente puro comprende rebaudiosida
15 A en una pureza mayor de alrededor de 99% de rebaudiosida A en peso sobre una base seca.

31.- El método de conformidad con la reivindicación 1, que comprende además los pasos de:

calentar la solución de rebaudiosida A;

20 enfriar la solución de rebaudiosida A;

separar y lavar una composición de rebaudiosida A substancialmente pura; y secar la composición de rebaudiosida A substancialmente pura.

32.- Una composición de rebaudiosida A substancialmente pura
5 hecha de conformidad con el método de la reivindicación 1, en donde la composición de rebaudiosida A substancialmente pura comprende un polimorfo que tiene un patrón de difracción de rayos X substancialmente similar a la Figura 8.

33.- Una composición de rebaudiosida A substancialmente pura
10 hecha de conformidad con el método de la reivindicación 1, en donde la composición de rebaudiosida A substancialmente pura comprende un polimorfo que tiene un patrón de difracción de rayos X substancialmente similar a la Figura 9.

34.- Una composición de rebaudiosida A substancialmente pura
15 hecha de conformidad con el método de la reivindicación 1, en donde la composición de rebaudiosida A substancialmente pura comprende un polimorfo que tiene un patrón de difracción de rayos X substancialmente similar a la Figura 10.

35.- Una composición de rebaudiosida A substancialmente pura
20 hecha de conformidad con el método de la reivindicación 1, en donde la composición de rebaudiosida A substancialmente pura comprende una forma

amorfa que tiene un patrón de difracción de rayos X substancialmente similar a la Figura 11.

36.- El método de conformidad con la reivindicación 1, que comprende además el paso de formar una forma amorfa de la composición de rebaudiosida A substancialmente pura.

37.- La composición de conformidad con la reivindicación 35, en donde el paso de formar una forma amorfa de la composición de rebaudiosida A substancialmente pura comprende un método seleccionado del grupo que consiste en molienda de bolas, precipitación, liofilización, criomolienda, y secado por aspersión.

38.- Una composición de rebaudiosida A substancialmente pura hecha de conformidad con el método de la reivindicación 1.

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of
international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION Applicant's or agent's file reference 25040-2775	
International application No. PCT/US2007/069548	International filing date (day/month/year) 23 May 2007
(Earliest) Priority date (day/month/year) 19 June 2006	
Title of invention REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) THE COCA-COLA COMPANY One C�ca-Cola Plaza, NW Atlanta, Georgia 30313 United States of America	
Telephone No. 404.676.2121	
Facsimile No. 404.676.8414	
Applicant's registration No. with the Office	
State (that is, country) of nationality: United States of America	State (that is, country) of residence: United States of America
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
State (that is, country) of nationality:	
State (that is, country) of residence:	
☐ Further applicants are indicated on a continuation sheet.	

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE							
The following person is ☒ agent ☐ common representative and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination. ☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked. ☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.							
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> SUTHERLAND ASBILL & BRENNAN LLP Peter G. Pappas, Esq. 999 Peachtree Street, NE Atlanta, Georgia 30309-3996 United States of America	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">Telephone No.</td> <td style="padding: 2px;">404.853.8064</td> </tr> <tr> <td style="padding: 2px;">Facsimile No.</td> <td style="padding: 2px;">404.853.8806</td> </tr> <tr> <td style="padding: 2px;">Agent's registration No. with the Office</td> <td style="padding: 2px;"></td> </tr> </table>	Telephone No.	404.853.8064	Facsimile No.	404.853.8806	Agent's registration No. with the Office	
Telephone No.	404.853.8064						
Facsimile No.	404.853.8806						
Agent's registration No. with the Office							
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.							
Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION							
Statement concerning amendments:* 1. The applicant wishes the international preliminary examination to start on the basis of: ☒ the international application as originally filed the description ☐ as originally filed ☒ as amended under Article 34 the claims ☐ as originally filed ☐ as amended under Article 19 (together with any accompanying statement) ☒ as amended under Article 34 the drawings ☒ as originally filed ☐ as amended under Article 34 2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed. 3. ☐ Where the IPEA wishes to start the international preliminary examination at the same time as the international search in accordance with Rule 69.1(b), the applicant requests the IPEA to postpone the start of the international preliminary examination until the expiration of the applicable time limit under Rule 69.1(d). 4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a). * Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.							
Language for the purposes of international preliminary examination: <u>English</u> ☒ which is the language in which the international application was filed. ☐ which is the language of a translation furnished for the purposes of international search. ☐ which is the language of publication of the international application. ☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.							
Box No. V ELECTION OF STATES							
The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.							

Box No. VI CHECK LIST

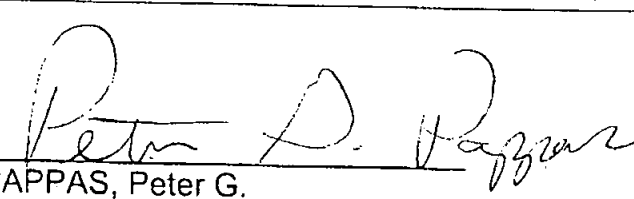
The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:		For International Preliminary Examining Authority use only	
		received	not received
1.	translation of international application : sheets	☐	☐
2.	amendments under Article 34 : 5 sheets	☐	☐
3.	copy (or, where required, translation) of amendments under Article 19 : sheets	☐	☐
4.	copy (or, where required, translation) of statement under Article 19 : sheets	☐	☐
5.	letter : 9 sheets	☐	☐
6.	other (specify) Specification : 6 sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet	5. ☐ statement explaining lack of signature
2. ☐ original separate power of attorney	6. ☐ sequence listing in electronic form
3. ☐ original general power of attorney	7. ☐ tables in electronic form related to a sequence listing
4. ☐ copy of general power of attorney; reference number, if any:	8. ☐ other (specify):

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).


PAPPAS, Peter G.

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1. Date of actual receipt of DEMAND:	
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):	
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.	6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.	7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.	8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

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**IN THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
OF THE EUROPEAN PATENT OFFICE
FOR THE PATENT COOPERATION TREATY**

International Application of: **THE COCA-COLA COMPANY**
Title: **Rebaudioside A Composition and Method for
Purifying Rebaudioside A**
International Application No.: **PCT/US2007/069548**
Filing Date: **23 May 2007 (23.05.2007)**
Agent's Docket No.: **25040-2775**

**VIA FACSIMILE TRANSMISSION - 011.49.89.2399.4465
AND FEDERAL EXPRESS INTERNATIONAL**

**International Preliminary Examination Authority
European Patent Office
D-80298 Munich**

**AMENDMENT UNDER ARTICLE 34 AND
REPLY TO WRITTEN OPINION OF THE ISA**

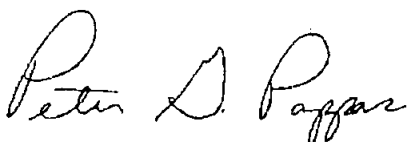
Sir:

Responsive to the Written Opinion of the International Searching Authority mailed **25 February 2008**, please substitute original pages 1, 3, 6-7, 9, 12, 33-39 with the enclosed replacement pages 1, 3, 6, 7, 9, 12, 34-38 and consider the accompanying remarks.

By FedEx International Air today, the originals of this response are being forwarded to the International Preliminary Examining Authority in the European Patent Office. Applicant requests that the IPEA consider **May 23, 2008** (the date of transmission via facsimile) as the date of receipt of this Reply to the Opinion.

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to **European Patent Office**, Fax No. **011-49-89-2399-4465** on May 23, 2008.



Peter G. Pappas, Reg. No. 33205

I. Amendments to the Specification

The specification was amended to correct obvious typographical errors. Specifically, "aqueous organic solvent(s)" was amended to "aqueous organic solution(s)" in several locations, including at page 1, line 10; page 3, line 5; page 6, lines 10, 27, and 28; page 7, line 1; page 9, lines 8, 10, 12, 14, 15, and 23; page 12, lines 15 and 17. It is obvious that this was a typographical error because, for example, in original claim 1 at line 3, "the aqueous organic solution" is described clearly referred back to the introduction of "an aqueous organic solvent" in the previous lines. The same is found at page 3, line 6; page 5, line 10; page 5, line 31; page 6, lines 5, 6, 7, 16, 30; page 8, line 11; page 10, line 15; and page 12, line 8.

The final paragraph on page 33 was deleted in order to comply with Art. 6 and Rule 9.1 iv. Therefore, the subject matter is no longer rendered vague by this paragraph.

II. Amendments to the Claims

Original claims 22-24 and 35 have been cancelled, and original claims 25-34 and 36-42 have been renumbered as claims 22-38. Dependencies/antecedent bases have been amended accordingly.

Independent claim 1 has been amended to more clearly reflect Applicants' claimed invention. Specifically claim 1 has been amended to provide that "the crude rebaudioside A comprise[es] rebaudioside A in a purity from about 40 % to about 85 % by weight on a dry basis." Support for this amendment may be found throughout the original claims, including original claims 22 and 23, and the specification, including page 5, lines 21-23.

Claim 1 also has been amended by changing "the aqueous organic solvent" to "the aqueous organic solution" in order to correct a typographical error. Support for this amendment may be found throughout the original claims, including the subsequent text of original claim 1 which states "the aqueous organic *solution*" and specification, including at page 6, lines 3-9. Claims 8, 11, 18-22, and 31 similarly have been amended. Support for these amendments may be found throughout the specification, including at page 6, lines 3-9 and in numerous other places in the specification as recited in the previous section of this response.

Claim 5 has been amended to delete optional. Support for this amendment may be found in the specification at page 7, lines 28-31.

Original dependent claim 41, now claim 37 has been amended to correct the dependency. Claim 37 now properly refers to the *composition* of claim 35.

II. The Claims as Amended Are Fully Compliant with PCT Article 6

III. Applicant's Claims are Novel and Inventive over the Cited Prior Art

The claimed purification process is novel and inventive over D1 to D6, alone or in combination.

Novelty

D1 generally discloses a recrystallization process that isolates highly pure rebaudioside A from an ethanol and water solution. As noted in the Written Opinion, the processes described by D1 may produce 100 % rebaudioside A. In order to obtain highly pure or 100 % rebaudioside A, however, the processes of D1 must be adjusted to compensate for the purity of the crude rebaudioside A starting material. These adjustments include repeating the initial reflux step and adding an ethanol "stirred wash" step to the process. Specifically, D1 teaches that multiple steps are necessary to obtain substantially pure (> 95 %) rebaudioside A when the crude rebaudioside A starting material purity is below 85 %. With a *single* step, Applicants' method produces substantially pure (> 95 %) rebaudioside A from crude rebaudioside A starting materials with purities from about 40 % to about 85 %. Applicants' process does not require any of the additional steps required by D1 to compensate for low purities of crude rebaudioside A starting material.

For instance, Example 1 of D1 requires three reflux steps to obtain at least 95 % pure rebaudioside A from crude rebaudioside A starting material with purities ranging from 71.85 to 81.58 %. Similarly, Example 9 of D1 teaches the necessity of two reflux steps in order to produce at least 95 % pure rebaudioside A from 82.3 % pure crude rebaudioside A starting material. Unlike D1, Applicants' process produces similar results with only a single step. For instance, the process of Applicants' Example B11 converts 80.37 % pure crude rebaudioside A starting material into pure rebaudioside A (> 97 %) with only one ten-minute reflux step. Furthermore, Applicants' Example E1 describes the isolation of pure

rebaudioside A (> 97 %) from 41 % pure crude rebaudioside A starting material after only a single room temperature stirring step. D1 does not describe a method that produces substantially pure rebaudioside A (> 95%) from crude rebaudioside A starting materials with purities from about 40 % to about 85 % in a *single* step.

In lieu of multiple reflux steps, D1 also teaches following the initial reflux with a "stirred wash" in absolute ethanol in order to increase the purity of the final rebaudioside A product. In Example 2, D1 subjected 5 g samples of 81.67 % and 89.95 % pure crude rebaudioside A starting material to a 1-hour reflux in 20 mL of an ethanol and water mixture (of varying percentages) followed by a "stirred wash" in 16 mL of absolute ethanol for 15 minutes at room temperature. The samples were held at room temperature for 96 hours before the "stirred wash" in ethanol. Despite the use of these two steps, the final purity of the rebaudioside A produced from the 81.67 % pure crude starting material only exceeded 95 % (96.24 %) when the reflux solvent was a 90/10 ethanol/water solution. Not surprisingly, the purer rebaudioside A starting material (89.95 %) produced at least 95 % pure rebaudioside A regardless of the reflux solvent's composition. Accordingly, D1 teaches that a "15 minute wash in absolute ethanol is sufficient," only when "higher quality *Stevia* starting material" is used. Paragraph [00121]. After citing the inefficiency of the "stirred wash" for purifying 81.67 % pure crude rebaudioside A starting material, D1 discloses that "for lower quality *Stevia* starting material, it is necessary to use an additional reflux stage to produce 99+ % pure rebaudioside A." Paragraph [0122].

D1 discloses in Example 5 that the results of Example 2 may be improved by reducing the samples' standing time between the reflux and "stirred wash" steps. Example 5 produced pure rebaudioside A (99.44—99.68%) from 81.58 % pure crude rebaudioside starting material. Example 6 of D1 reproduced these results on a larger scale. Like Example 2, however, the methods of Examples 5 and 6 involve two steps—a reflux and a "stirred wash" in ethanol.

In addition to Examples 2, 5, and 6, D1 also discloses the use of the "stirred wash" in ethanol in Examples 7 and 8. It is important to note that the "stirred wash" in ethanol in all of these examples is another procedural step in the method, instead of a common laboratory rinsing technique. D1 teaches in Examples 2 and 8 the importance of maintaining an

approximate 1:4 mass to volume ratio during the "stirred wash" step. Since approximately 20 % of the 5 g sample remained in solution after the initial reflux step, Example 2 used 16 mL of ethanol for the "stirred wash" of the remaining 4 g. D1's Examples 5 and 6 also used 16 mL or 1600 mL, respectively, of ethanol in the "stirred wash" for the same reason. Example 7 of D1 used 40 mLs of ethanol in the stirred wash for 10 g of starting material. Also, Example 8 demonstrates that mass to solvent ratios of 1:5 or 1:6 may be even more beneficial. The lowest mass to solvent ratio disclosed by Example 8 of D1 for the ethanol "stirred wash" was 1:3.

Even at the lowest mass to solvent ratio disclosed for the ethanol "stirred wash," the amount of ethanol used in the "stirred wash" far exceeds any common laboratory rinsing that may accompany recrystallization. Following recrystallization, common laboratory technique calls for rinsing the crystals prior to drying in order to remove any residual impurities or aqueous solvent. The crystals are typically rinsed twice with a small amount of an organic solvent. Typically, the amount of organic solvent used for rinsing does not exceed a 1:1 mass to volume ratio. Accordingly, the "stirred wash" of D1 is an additional procedural step, and not a common laboratory rinsing.

D1 does not disclose a process capable of isolating pure (> 95 %) rebaudioside A from crude rebaudioside A starting materials with purities from about 40% to about 85% in a *single* step. When the purity of the crude rebaudioside A starting material is between 40 and 85 %, D1 teaches the necessity of either multiple reflux steps or an initial reflux followed by at least one "stirred wash" in ethanol. Unlike D1, the Applicants' processes convert crude rebaudioside A starting materials with purities from about 40 % to about 85 % into pure rebaudioside A (> 95 %) with a *single* step. Applicants' method is therefore novel in view of D1.

D2 discloses a multiple step process that isolates individual sweet glycosides from the *Stevia rebaudiana* plant. D2 discloses that recrystallization of sweet glycosides from methanol produces an undesirable product unless the Giovanetto water extraction method is first performed to remove unwanted impurities. Although preceded by the Giovanetto water extraction, D2's final recrystallization step must be repeated in order to obtain at least 90 % pure rebaudioside A. Applicants' method generates at least 95% pure rebaudioside A from

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crude rebaudioside A starting materials with purities from about 40 % to about 85 % in a *single-step* recrystallization without the benefit of any preliminary water extraction. The method described by Applicants does not require a preliminary water extraction or multiple recrystallization steps as taught by D2. Therefore, Applicants' claims are novel in view of D2.

D3 (Japanese Patent No. 56121455) discloses a recrystallization process that isolates stevioside from aqueous methanol. The products produced by D3's method consist of at least 84 % stevioside, less than 2 % rebaudioside A, and 8—13 % water. Therefore, D3's method does not produce substantially pure rebaudioside A (> 95%) as described by Applicants. Unlike D3, Applicants' method minimizes the presence of stevioside in order to yield substantially pure rebaudioside A (> 95%). Since stevioside constitutes a majority of D3's product, the Applicants' method does not generate substantially similar x-ray diffraction patterns. Therefore, Applicants' method is novel in view of D3.

D4 (WO 2006/0382231) generally discloses the treatment of an aqueous extract of *Stevia* leaves with a divalent basic salt to generate a precipitate that is exposed to an ion exchange resin to isolate stevioside. D4 does not employ organic solvents. The method of D4 isolates stevioside with purities ranging from 45 % to 64 %. D4 does not address the isolation of rebaudioside A. Accordingly, the products of D4's method do not generate x-ray diffraction patterns substantially similar to those described by Applicants. Without the use of organic solvents, it is not possible for the method of D4 to generate the Applicants' claimed solvates of rebaudioside A. Furthermore, the Applicants' substantially pure (> 95%) rebaudioside A and D4's impure stevioside (45—64 %) do not generate substantially similar x-ray diffraction patterns. Accordingly, Applicants' method is novel in view of D4.

D5 (US Patent No. 4,082,858) describes the recovery of rebaudioside A from *Stevia* and its use as a sweetener in various foods and pharmaceuticals. Although D5 discloses a successful method for isolating rebaudioside A, D5 does not describe any of the rebaudioside A polymorphs claimed by Applicants. Furthermore, D5 only describes rebaudioside A as "[s]oluble in water." Column 3, Line 56. Since rebaudioside A polymorphs have varying water solubilities, D5's failure to disclose specific water solubility data demonstrates an unawareness of rebaudioside A polymorphism. Accordingly, D5 does not describe a process

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that may be tuned to produce a desired rebaudioside A polymorph. Therefore, Applicants' claims are novel in view of D5.

D6 (Japanese Patent No. 56-121453) describes a method for separating a crystalline mixture of stevioside and rebaudioside A that exploits the crystals' varying water solubilities. D6 teaches that a recrystallization similar to Applicants' method is not a preferred method for separating pure rebaudioside A from stevioside, because the recrystallization process must be repeated and produces low purities and low yields. In order to instigate the separation of rebaudioside A and stevioside, D6 discloses the combination of rebaudioside A and stevioside with different crystal forms of each compound. D6 does not describe the combination of different crystal forms of the same compound. Applicants disclose a rebaudioside A composition consisting of different polymorphic and amorphous forms of rebaudioside A. The Applicants' process can be modified in order produce the desired crystal structure. D6 discloses an x-ray diffraction pattern for the α -crystal structure of rebaudioside A, however, it is not substantially similar to applicant's Figures 8, 9, 10, or 11. Original claim 35 has been cancelled, because Figure 1(D) of D6 is substantially similar to Applicants' Figure 7. Therefore, Applicants' claim set as amended is novel in view of D6.

Inventive Step

In Figures 1-5, and 8 of D1, which define the claimed laboratory and industrial process, each flowchart contains an "iteration decision." This step requires either the reflux step or the "stirred wash" in ethanol to be repeated. The "iteration step" is included because "[i]n embodiments that use lower quality *Stevia* starting material, a second reflux stage is typically added before a stirred wash stage to maximize purity of the Reb A final product." Paragraph [0034]. Due to the fact that D1 fails to present any examples that produce substantially pure rebaudioside A (> 97 %) from crude rebaudioside A starting material with purities from about 40 % to about 85 %, D1 discloses that "for lower quality *Stevia* starting material, it is necessary to use an additional reflux stage to produce 99+ % purity Reb A." Paragraph [0122]. This specific statement referred to starting rebaudioside A material with a purity of 80 %. Therefore, Applicants' single-step method that produces substantially pure

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rebaudioside A (> 95 %) from crude rebaudioside A with purities from about 40 % to about 85 % involves an inventive step over D1.

Like D1, D2 describes a multiple-step process designed to isolate rebaudioside A from the *Stevia* plant. D2 discloses the use of methanol to recrystallize rebaudioside A, however, the recrystallization "can be repeated again to further increase the purity of the precipitated Rebaudioside A to a level higher than about 90 % and more preferably higher than 95 %." Page 7, Lines 9-11. Therefore, D2 teaches that multiple steps are needed to obtain substantially pure rebaudioside A (> 97 %). Applicants' single-step method therefore possesses an inventive step over D2.

D3 also uses a methanol solution to extract sweet-tasting glycosides from the *Stevia* plant. Unlike Applicants' method, D3 teaches the isolation of a crystal that consists mainly of stevioside instead of rebaudioside A. For example, Embodiment 1 of D3 teaches a crystal consisting of 88 % stevioside, 8.5 % water, and only 0.8 % rebaudioside A. Applicants' method is not obvious in view of D3, because the presently claimed method isolates substantially pure rebaudioside A instead of stevioside.

Unlike Applicants' method, D4 does not use recrystallization to isolate rebaudioside A. Rather D4, uses water and cation exchange resins to isolate stevioside in purities ranging from 45 % to 64 %. Since D4 isolates an entirely different product using an entirely different method, the Applicants' claimed process is not obvious over D4 alone or in combination with the other references.

D5 describes a method for isolation rebaudioside A crystals, but makes no mention of polymorphism. Therefore, Applicants' claims are non-obvious over D5.

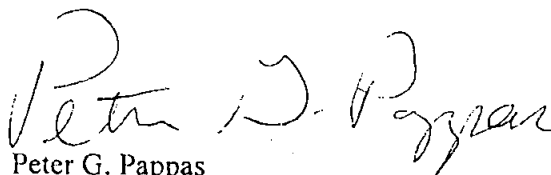
D6 teaches away from the recrystallization techniques described by Applicants. D6 discloses that because repeated recrystallization steps are needed to obtain high-purity rebaudioside A, "such methods not only take time and energy for recrystallization but also result in low purity and yield of the obtained product." Page 229, Column 2. The Applicants' method overcomes these disadvantages. Therefore, the present claimed method possesses an inventive step over D6.

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IV. Conclusion

* It is respectfully submitted that claims 1-38 meet all of the PCT requirements. Prompt issuance of a favorable International Preliminary Report on Patentability is therefore requested.

Respectfully submitted,



Peter G. Pappas
Agent for Applicant

May 23, 2008

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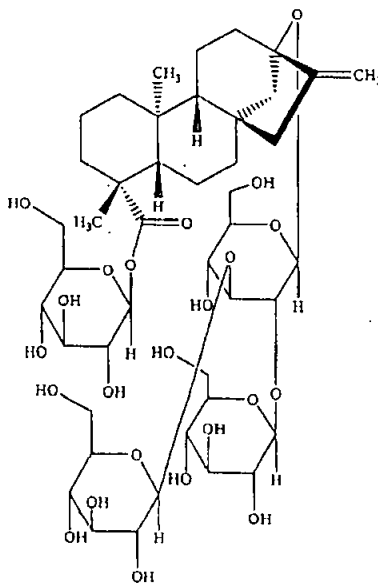
REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A

FIELD OF INVENTION

This invention relates generally to polymorphic and amorphous forms of rebaudioside A, methods for purifying rebaudioside A, and methods for preparing polymorphic and amorphous forms of rebaudioside A. More particularly, this invention relates to polymorphic and amorphous forms of rebaudioside A and methods for the purification or crystallization of rebaudioside A with aqueous organic solutions or organic solvents to obtain a product in high yield and high purity.

BACKGROUND OF INVENTION

Rebaudioside A is a high-potency diterpenoid glycoside sweetener having the chemical structure:



Rebaudioside A is isolated and extracted, along with other steviol glycosides, from the *Stevia rebaudiana* (Bertoni) plant ("Stevia"), which is commercially cultivated in Japan, Singapore, Taiwan, Malaysia, South Korea, China, Israel, India, Brazil, Australia, and Paraguay. It is an alternative non-caloric sweetener with functional and

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rebaudioside A, methods for purifying rebaudioside A, and methods for making polymorphic and amorphous forms of rebaudioside A.

In a particular embodiment, the method for purifying rebaudioside A comprises a simple crystallization. In one embodiment, a method for purifying rebaudioside A comprises combining crude rebaudioside A and an aqueous organic solution to form a rebaudioside A solution, the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight, and crystallizing from the crude rebaudioside A solution, in a single step, a substantially pure rebaudioside A in a purity greater than about 95% by weight on a dry basis.

In other particular embodiments, different polymorphic and amorphous forms of rebaudioside A and methods for preparing different polymorphic and amorphous forms of rebaudioside A are provided.

Other objects, features, and advantages of the invention will be apparent from the following detailed description, drawings, and claims. Unless otherwise defined, all technical and scientific terms and abbreviations used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and compositions similar or equivalent to those described herein can be used in the practice of the present invention, suitable methods and compositions are described without intending that any such methods and compositions limit the invention herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustrating a method for purifying rebaudioside A in accordance with an embodiment of this invention.

Fig. 2 is a schematic of the formation and conversion of rebaudioside A polymorphic and amorphous forms of rebaudioside A in accordance with an embodiment of this invention.

Fig. 3 is a powder x-ray diffraction scan comparing four rebaudioside A polymorphs, Forms 1, 2, 3A and 3B, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

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anion exchange resin. Accordingly, the method of purification depends on the impurities present in the crude rebaudioside A starting material.

In an exemplary embodiment of a method for purifying rebaudioside A 110, illustrated in Figure 1, crude rebaudioside A 112 may be combined 114 with an aqueous organic solution 116 to form a rebaudioside A solution 118. The aqueous organic solution 116 comprises water in an amount from about 10 % to about 25 % by weight and at least one organic solvent. Alternatively, the aqueous organic solution 116 may comprise water in an amount from about 15 % to about 20 % by weight and at least one organic solvent.

10 Aqueous organic solutions, as used herein, refer to mixtures of water and at least one organic solvent. Non-limiting examples of organic solvents include alcohol, acetone, and acetonitrile. Alcohol, as used herein, refers to any straight, branched, or cyclic; substituted or unsubstituted alkyl, alkenyl, or alkynyl group attached to at least one hydroxyl moiety. Non-limiting examples of alcohols include ethanol, methanol, 15 isopropanol, 1-propanol, 1-butanol, 2-butanol, tert-butanol, and isobutanol.

In an exemplary embodiment, the aqueous organic solution 116 comprises a mixture of water and at least one organic solvent. In another exemplary embodiment, at least one organic solvent comprises an alcohol, the alcohol comprising ethanol, methanol, or mixtures thereof. In exemplary embodiments wherein the at least one 20 organic solvent comprises a mixture of ethanol and methanol, the ethanol and methanol may be combined in the aqueous organic solvent in a weight ratio ranging from about 20 parts to about 1 part ethanol to about 1 part methanol. In another exemplary embodiment, the ethanol and methanol may be combined in the aqueous organic solvent in a weight ratio ranging from about 3 parts to about 1 part ethanol to about 1 25 part methanol.

In an exemplary embodiment, the rebaudioside A solution 118 comprises the aqueous organic solution 116 and the crude rebaudioside A 112 in a weight ratio ranging from about 10 to about 4 parts aqueous organic solution to about 1 part crude rebaudioside A. In another exemplary embodiment, the rebaudioside A solution 118 30 comprises the aqueous organic solution 116 and the crude rebaudioside A 112 in a

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weight ratio ranging from about 5 to about 3 parts aqueous organic solution to about 1 part crude rebaudioside A.

In an exemplary embodiment, the method 110 may be carried out at approximately room temperature. In another embodiment, the method 110 further comprises the step of heating 120 the rebaudioside A solution 118. In an embodiment, the step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution to a temperature in a range from about 20°C to about 70°C, from about 20°C to about 60°C, from about 20°C to about 40°C, or from about 40°C to about 60°C. In another embodiment, the step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution to about reflux temperature. The step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution for about 0.25 hours to about 8 hours. In another exemplary embodiment, wherein the method for purifying rebaudioside A 110 comprises the step of heating 120 the rebaudioside A solution 118, the method further comprises the step of cooling 122 the rebaudioside A solution. In an embodiment, the step of cooling 122 the rebaudioside A solution 118 comprises cooling the rebaudioside A solution to a temperature in the range from about 4°C to about 25°C. The step of cooling 122 the rebaudioside A solution 118 comprises cooling the rebaudioside A solution for about 0.5 hours to about 24 hours.

The method for purifying rebaudioside A 110 further comprises the step of crystallizing 124 from the rebaudioside A solution 118 in a single step a substantially pure rebaudioside A composition 126 comprising rebaudioside A in an amount greater than about 85 % by weight on a dry basis, greater than about 90 % by weight on a dry basis, greater than about 95 % by weight on a dry basis, greater than about 97 % by weight on a dry basis, greater than about 98 % by weight on a dry basis, or greater than about 99 % by weight on a dry basis. The rebaudioside A solution 118 during the single crystallization step may be stirred or unstirred.

In an exemplary embodiment, the method 110 may further comprise the optional step of seeding 128 the rebaudioside A solution 118 at an appropriate temperature with substantially pure crystals of rebaudioside A 130 sufficient to promote crystallization of the rebaudioside A to form pure rebaudioside A. An amount of rebaudioside A 130 sufficient to promote crystallization of substantially pure

paddle dryer and microwave dryer. In an exemplary embodiment, the step of drying 138 comprises drying the substantially pure rebaudioside A composition 126 using a nitrogen or argon purge to remove the residual solvent 120 at a temperature in a range from about 40°C to about 60°C for about 5 hours to about 100 hours.

5 In yet another exemplary embodiment, wherein the crude rebaudioside A mixture 112 comprises substantially no rebaudioside D impurity, the method 110 further comprises the step of slurring 140 the composition of substantially pure rebaudioside A 126 with an organic solvent or an aqueous organic solution 142 prior to the step of drying 138 the substantially pure rebaudioside A composition. The slurry
10 may be a mixture comprising a solid and an aqueous organic solution or organic solvent, wherein the solid comprises the substantially pure rebaudioside A composition 126 and is only sparingly soluble in the aqueous organic solution or organic solvent 142. In an embodiment, the substantially pure rebaudioside A composition 126 and aqueous organic solution or organic solvent 142 may be present in the slurry in a
15 weight ratio ranging from about 15 parts to about 1 part aqueous organic solution to about 1 part substantially pure rebaudioside A composition. In one embodiment, the slurry may be maintained at room temperature. In another embodiment, the step of slurring 140 comprises heating the slurry to a temperature in a range from about 20°C to about 40°C. The substantially pure rebaudioside A composition 126 may be slurried
20 for about 0.5 hours to about 24 hours.

In still yet another exemplary embodiment, the method further comprises the steps of separating 132 the substantially pure rebaudioside A composition 126 from the aqueous organic solution 142 of the slurry and washing 134 the substantially pure rebaudioside A composition followed by the step of drying 138 the substantially pure
25 rebaudioside A composition.

If further purification is desired, the method of purifying rebaudioside A 110 described herein may be repeated or the substantially pure rebaudioside A composition may be further purified using an alternative purification method, such as the column chromatography.

30 Purity, as used herein, represents the weight percentage of rebaudioside A present in a rebaudioside A composition in raw or purified form. In one embodiment, a

degrees show this shifting as well. Not wishing to be bound by any theory, the shifting of the peaks may be an indication that Form 3A is partially desolvated, thus containing a mixture of both the solvate and Form 2 crystals.

5 Figs. 7-10 are XRPD scans of the individual polymorphs Form 1, Form 2, Form 3A, and Form 3B, respectively, from a substantially pure rebaudioside A composition obtained from the purification process described hereinabove.

10 As illustrated in Fig. 2, the type of polymorph formed may be dependent on the factors such as the composition of the aqueous organic solution, the temperature of the crystallization step, and the temperature during the drying step. Not wishing to be bound by any theory, Form 1 and Form 3 are believed to be formed during the single crystallization step while Form 2 is believed to be formed during the drying step after conversion from Form 1 and Form 3.

15 Low temperatures during the crystallization step, in the range of about 20°C to about 50°C, and a low ratio of water to the organic solvent in the aqueous organic solution results in the formation of Form 3. High temperatures during the crystallization step, in the range of about 50°C to about 80°C, and a high ratio of water to the organic solvent in the aqueous organic solution results in the formation of the Form 1. Form 1 can be converted to Form 3 by slurrying in an anhydrous solvent at about room temperature for about 2 to about 16 hours or by slurrying in an anhydrous
20 solvent at about reflux temperature for about 0.5 to about 3 hours. Form 3 can be converted to Form 1 by slurrying the polymorph in water at about room temperature for approximately 16 hours or at about reflux temperature for about 2 to about 3 hours. Form 3 can be converted to the Form 2 during the drying process; however, increasing either the drying temperature above about 70°C or the drying time of a substantially
25 pure rebaudioside A composition can result in decomposition of the rebaudioside A and increase the remaining rebaudioside B impurity in the substantially pure rebaudioside A composition. Form 2 can be converted to Form 1 with the addition of water.

30 In addition to the at least three polymorphic forms of rebaudioside A, the purification of rebaudioside A may result in the formation of an amorphous form of rebaudioside A, Form 4, as shown in Fig. 11. Form 4 has a broad amorphous halo that identifies the composition as being amorphous.

CLAIMS

1. A method for purifying rebaudioside A comprising the steps of:
combining crude rebaudioside A and an aqueous organic solution to form a rebaudioside A solution, the crude rebaudioside A comprising rebaudioside A in a purity from about 40 % to about 85 % by weight on a dry basis, and the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight; and
crystallizing from the rebaudioside A solution in a single step a rebaudioside A composition comprising rebaudioside A in a purity greater than about 95 % by weight on a dry basis.
2. The method of claim 1, further comprising the step of heating the rebaudioside A solution.
3. The method of claim 2, further comprising the step of cooling the rebaudioside A solution.
4. The method of claim 1, wherein rebaudioside A solution in the single crystallization step is stirred or unstirred.
5. The method of claim 1, further comprising the step of seeding the rebaudioside A solution at an appropriate temperature with an amount of rebaudioside A sufficient to promote crystallization of rebaudioside A.
6. The method of claim 1, further comprising the steps of separating and washing the substantially pure rebaudioside A composition.
7. The method of claim 6, further comprising the step of drying the substantially pure rebaudioside A composition.

8. The method of claim 1, wherein the crude rebaudioside A comprises substantially no rebaudioside D impurity, and the method further comprises slurrying the substantially pure rebaudioside A composition in an aqueous organic solution or in an organic solvent.

9. The method of claim 8, further comprising the steps of separating and washing the substantially pure rebaudioside A composition.

10. The method of claim 9, further comprising the step of drying the composition of a substantially pure rebaudioside A.

11. The method of claim 1, wherein the aqueous organic solution comprises a mixture of at least one organic solvent and water.

12. The method of claim 11, wherein at least one organic solvent comprises an alcohol.

13. The method of claim 12, wherein the alcohol comprises ethanol.

14. The method of claim 12, wherein the alcohol comprises methanol.

15. The method of claim 12, wherein the alcohol comprises a mixture of ethanol and methanol.

16. The method of claim 15, wherein the ethanol and methanol are present in the aqueous organic solution in a weight ratio from about 20 parts to about 1 parts ethanol to about 1 part methanol.

17. The method of claim 15, wherein the ethanol and methanol are present in the aqueous organic solution in a weight ratio from about 3 parts to about 1 part ethanol to about 1 part methanol.

18. The method of claim 1, wherein the at least one aqueous organic solution comprises an organic solvent selected from the group consisting of acetone, acetonitrile, methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, tert-butanol, and mixtures thereof.

19. The method of claim 1, wherein the aqueous organic solution and the crude rebaudioside A are present in the rebaudioside A solution in a weight ratio from about 4 to about 10 parts aqueous organic solution to about 1 part crude rebaudioside A.

20. The method of claim 1, wherein the aqueous organic solution and the crude rebaudioside A are present in the rebaudioside A solution in a weight ratio from about 3 to about 5 parts aqueous organic solution to about 1 part crude rebaudioside A.

21. The method of claim 1, wherein aqueous organic solution comprises water in an amount from about 10 % to about 25 % by weight.

22. A method for purifying rebaudioside A comprising the steps of combining crude rebaudioside A and an aqueous organic solution to form a rebaudioside A solution, the crude rebaudioside A comprising rebaudioside A in a purity from about 40 % to about 85 % by weight on a dry basis, and the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight; and

crystallizing from the rebaudioside A solution in a single step a rebaudioside A composition comprising rebaudioside A in a purity greater than about 95 % by weight on a dry basis, wherein the method is carried out at approximately room temperature.

23. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to a temperature in a range from about 20°C to about 40°C.

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24. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to a temperature in a range from about 40°C to about 60°C.

25. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to about a reflux temperature.

26. The method of claim 3, wherein the step of cooling the rebaudioside A solution comprises cooling the rebaudioside A solution to a temperature in a range from about 4°C to about 25°C.

27. The method of claim 3, wherein the step of cooling the rebaudioside A solution comprises cooling the rebaudioside A solution for about 0.5 hours to about 24 hours.

28. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 97 % rebaudioside A by weight on a dry basis.

29. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 98 % rebaudioside A by weight on a dry basis.

30. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 99 % rebaudioside A by weight on a dry basis.

31. The method of claim 1, further comprising the steps of:
heating the rebaudioside A solution;
cooling the rebaudioside A solution;
separating and washing a substantially pure rebaudioside A composition; and
drying the substantially pure rebaudioside A composition.

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32. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 8.

33. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 9.

34. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 10.

35. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises an amorphous form having an X-ray diffraction pattern substantially similar to Figure 11.

36. The method of claim 1, further comprising the step of forming an amorphous form of the substantially pure rebaudioside A composition.

37. The composition of claim 35, wherein the step of forming an amorphous form of the substantially pure rebaudioside A composition comprises a method selected from the group consisting of ball milling, precipitation, lyophilization, cryogrinding, and spray-drying.

38. A substantially pure rebaudioside A composition made according to the method of claim 1.

REBAUDIOSIDE A COMPOSITION AND
METHOD FOR PURIFYING REBAUDIOSIDE A

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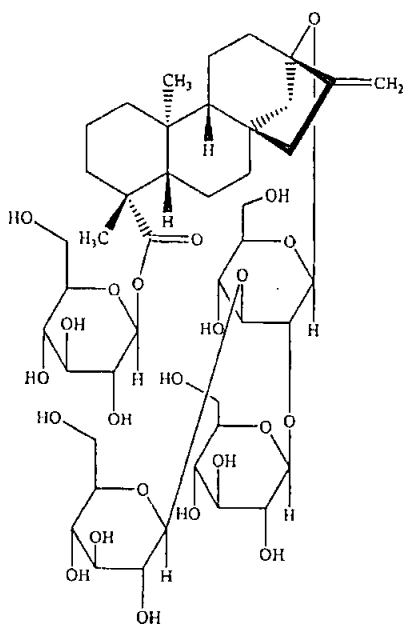
FIELD OF INVENTION

This invention relates generally to polymorphic and amorphous forms of rebaudioside A, methods for purifying rebaudioside A, and methods for preparing polymorphic and amorphous forms of rebaudioside A. More particularly, this invention relates to polymorphic and amorphous forms of rebaudioside A and methods for the purification or crystallization of rebaudioside A with aqueous organic solvents solutions or organic solvents to obtain a product in high yield and high purity.

BACKGROUND OF INVENTION

Rebaudioside A is a high-potency diterpenoid glycoside sweetener having the chemical structure:

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Rebaudioside A is isolated and extracted, along with other steviol glycosides, from the *Stevia rebaudiana* (Bertoni) plant ("Stevia"), which is commercially cultivated in Japan, Singapore, Taiwan, Malaysia, South Korea, China, Israel, India, Brazil, Australia, and Paraguay. It is an alternative non-caloric sweetener with functional and

rebaudioside A, methods for purifying rebaudioside A, and methods for making polymorphic and amorphous forms of rebaudioside A.

In a particular embodiment, the method for purifying rebaudioside A comprises a simple crystallization. In one embodiment, a method for purifying rebaudioside A comprises combining crude rebaudioside A and an aqueous organic ~~solvent~~solution to form a rebaudioside A solution, the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight, and crystallizing from the crude rebaudioside A solution, in a single step, a substantially pure rebaudioside A in a purity greater than about 95% by weight on a dry basis.

In other particular embodiments, different polymorphic and amorphous forms of rebaudioside A and methods for preparing different polymorphic and amorphous forms of rebaudioside A are provided.

Other objects, features, and advantages of the invention will be apparent from the following detailed description, drawings, and claims. Unless otherwise defined, all technical and scientific terms and abbreviations used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and compositions similar or equivalent to those described herein can be used in the practice of the present invention, suitable methods and compositions are described without intending that any such methods and compositions limit the invention herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustrating a method for purifying rebaudioside A in accordance with an embodiment of this invention.

Fig. 2 is a schematic of the formation and conversion of rebaudioside A polymorphic and amorphous forms of rebaudioside A in accordance with an embodiment of this invention.

Fig. 3 is a powder x-ray diffraction scan comparing four rebaudioside A polymorphs, Forms 1, 2, 3A and 3B, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

anion exchange resin. Accordingly, the method of purification depends on the impurities present in the crude rebaudioside A starting material.

In an exemplary embodiment of a method for purifying rebaudioside A 110, illustrated in Figure 1, crude rebaudioside A 112 may be combined 114 with an aqueous organic solution 116 to form a rebaudioside A solution 118. The aqueous organic solution 116 comprises water in an amount from about 10 % to about 25 % by weight and at least one organic solvent. Alternatively, the aqueous organic solution 116 may comprise water in an amount from about 15 % to about 20 % by weight and at least one organic solvent.

10 Aqueous organic ~~solvents~~solutions, as used herein, refer to mixtures of water and at least one organic solvent. Non-limiting examples of organic solvents include alcohol, acetone, and acetonitrile. Alcohol, as used herein, refers to any straight, branched, or cyclic; substituted or unsubstituted alkyl, alkenyl, or alkynyl group attached to at least one hydroxyl moiety. Non-limiting examples of alcohols include
15 ethanol, methanol, isopropanol, 1-propanol, 1-butanol, 2-butanol, tert-butanol, and isobutanol.

In an exemplary embodiment, the aqueous organic solution 116 comprises a mixture of water and at least one organic solvent. In another exemplary embodiment, at least one organic solvent comprises an alcohol, the alcohol comprising ethanol, methanol, or mixtures thereof. In exemplary embodiments wherein the at least one
20 organic solvent comprises a mixture of ethanol and methanol, the ethanol and methanol may be combined in the aqueous organic solvent in a weight ratio ranging from about 20 parts to about 1 part ethanol to about 1 part methanol. In another exemplary embodiment, the ethanol and methanol may be combined in the aqueous organic
25 solvent in a weight ratio ranging from about 3 parts to about 1 part ethanol to about 1 part methanol.

In an exemplary embodiment, the rebaudioside A solution 118 comprises the aqueous organic ~~solvents~~solution 116 and the crude rebaudioside A 112 in a weight ratio ranging from about 10 to about 4 parts aqueous organic ~~solvents~~solution to about 1 part
30 crude rebaudioside A. In another exemplary embodiment, the rebaudioside A solution 118 comprises the aqueous organic solution 116 and the crude rebaudioside A 112 in a

weight ratio ranging from about 5 to about 3 parts aqueous organic solventsolution to about 1 part crude rebaudioside A.

In an exemplary embodiment, the method 110 may be carried out at approximately room temperature. In another embodiment, the method 110 further
5 comprises the step of heating 120 the rebaudioside A solution 118. In an embodiment, the step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution to a temperature in a range from about 20°C to about 70°C, from about 20°C to about 60°C, from about 20°C to about 40°C, or from about 40°C to about 60°C. In another embodiment, the step of heating 120 the rebaudioside A
10 solution 118 comprises heating the rebaudioside A solution to about reflux temperature. The step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution for about 0.25 hours to about 8 hours. In another exemplary embodiment, wherein the method for purifying rebaudioside A 110 comprises the step of heating 120 the rebaudioside A solution 118, the method further comprises the step
15 of cooling 122 the rebaudioside A solution. In an embodiment, the step of cooling 122 the rebaudioside A solution 118 comprises cooling the rebaudioside A solution to a temperature in the range from about 4°C to about 25°C. The step of cooling 122 the rebaudioside A solution 118 comprises cooling the rebaudioside A solution for about 0.5 hours to about 24 hours.

20 The method for purifying rebaudioside A 110 further comprises the step of crystallizing 124 from the rebaudioside A solution 118 in a single step a substantially pure rebaudioside A composition 126 comprising rebaudioside A in an amount greater than about 85 % by weight on a dry basis, greater than about 90 % by weight on a dry basis, greater than about 95 % by weight on a dry basis, greater than about 97 % by
25 weight on a dry basis, greater than about 98 % by weight on a dry basis, or greater than about 99 % by weight on a dry basis. The rebaudioside A solution 118 during the single crystallization step may be stirred or unstirred.

In an exemplary embodiment, the method 110 may further comprise the optional step of seeding 128 the rebaudioside A solution 118 at an appropriate
30 temperature with substantially pure crystals of rebaudioside A 130 sufficient to promote crystallization of the rebaudioside A to form pure rebaudioside A. An amount of rebaudioside A 130 sufficient to promote crystallization of substantially pure

paddle dryer and microwave dryer. In an exemplary embodiment, the step of drying 138 comprises drying the substantially pure rebaudioside A composition 126 using a nitrogen or argon purge to remove the residual solvent 120 at a temperature in a range from about 40°C to about 60°C for about 5 hours to about 100 hours.

5 In yet another exemplary embodiment, wherein the crude rebaudioside A mixture 112 comprises substantially no rebaudioside D impurity, the method 110 further comprises the step of slurrying 140 the composition of substantially pure rebaudioside A 126 with an organic solvent or an aqueous organic solvent solution 142 prior to the step of drying 138 the substantially pure rebaudioside A composition. The
10 slurry may be a mixture comprising a solid and an aqueous organic solvent solution or organic solvent, wherein the solid comprises the substantially pure rebaudioside A composition 126 and is only sparingly soluble in the aqueous organic solvent solution or organic solvent 142. In an embodiment, the substantially pure rebaudioside A composition 126 and aqueous organic solvent solution or organic solvent 142 may be
15 present in the slurry in a weight ratio ranging from about 15 parts to about 1 part aqueous organic solvent solution to about 1 part substantially pure rebaudioside A composition. In one embodiment, the slurry may be maintained at room temperature. In another embodiment, the step of slurrying 140 comprises heating the slurry to a temperature in a range from about 20°C to about 40°C. The substantially pure
20 rebaudioside A composition 126 may be slurried for about 0.5 hours to about 24 hours.

In still yet another exemplary embodiment, the method further comprises the steps of separating 132 the substantially pure rebaudioside A composition 126 from the aqueous organic solvent solution 142 of the slurry and washing 134 the substantially pure rebaudioside A composition followed by the step of drying 138 the substantially
25 pure rebaudioside A composition.

If further purification is desired, the method of purifying rebaudioside A 110 described herein may be repeated or the substantially pure rebaudioside A composition may be further purified using an alternative purification method, such as the column chromatography.

30 Purity, as used herein, represents the weight percentage of rebaudioside A present in a rebaudioside A composition in raw or purified form. In one embodiment, a

degrees show this shifting as well. Not wishing to be bound by any theory, the shifting of the peaks may be an indication that Form 3A is partially desolvated, thus containing a mixture of both the solvate and Form 2 crystals.

5 Figs. 7-10 are XRPD scans of the individual polymorphs Form 1, Form 2, Form 3A, and Form 3B, respectively, from a substantially pure rebaudioside A composition obtained from the purification process described hereinabove.

As illustrated in Fig. 2, the type of polymorph formed may be dependent on the factors such as the composition of the aqueous organic solution, the temperature of the crystallization step, and the temperature during the drying step. Not wishing to be
10 bound by any theory, Form 1 and Form 3 are believed to be formed during the single crystallization step while Form 2 is believed to be formed during the drying step after conversion from Form 1 and Form 3.

Low temperatures during the crystallization step, in the range of about 20°C to about 50°C, and a low ratio of water to the organic solvent in the aqueous organic
15 solvent solution results in the formation of Form 3. High temperatures during the crystallization step, in the range of about 50°C to about 80°C, and a high ratio of water to the organic solvent in the aqueous organic solvent solution results in the formation of the Form 1. Form 1 can be converted to Form 3 by slurrying in an anhydrous solvent at about room temperature for about 2 to about 16 hours or by slurrying in an anhydrous
20 solvent at about reflux temperature for about 0.5 to about 3 hours. Form 3 can be converted to Form 1 by slurrying the polymorph in water at about room temperature for approximately 16 hours or at about reflux temperature for about 2 to about 3 hours. Form 3 can be converted to the Form 2 during the drying process; however, increasing either the drying temperature above about 70°C or the drying time of a substantially
25 pure rebaudioside A composition can result in decomposition of the rebaudioside A and increase the remaining rebaudioside B impurity in the substantially pure rebaudioside A composition. Form 2 can be converted to Form 1 with the addition of water.

In addition to the at least three polymorphic forms of rebaudioside A, the purification of rebaudioside A may result in the formation of an amorphous form of
30 rebaudioside A, Form 4, as shown in Fig. 11. Form 4 has a broad amorphous halo that identifies the composition as being amorphous.

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CLAIMS

1. A method for purifying rebaudioside A comprising the steps of:
combining crude rebaudioside A and an aqueous organic ~~solvent~~solution to form a rebaudioside A solution, the crude rebaudioside A comprising rebaudioside A in a purity from about 40 % to about 85 % by weight on a dry basis, and the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight; and
crystallizing from the rebaudioside A solution in a single step a ~~substantially pure~~ rebaudioside A composition comprising rebaudioside A in a purity greater than about 95 % by weight on a dry basis.
2. The method of claim 1, further comprising the step of heating the rebaudioside A solution.
3. The method of claim 2, further comprising the step of cooling the rebaudioside A solution.
4. The method of claim 1, wherein rebaudioside A solution in the single crystallization step is stirred or unstirred.
5. The method of claim 1, further comprising the step of seeding ~~(optional)~~ the rebaudioside A solution at an appropriate temperature with an amount of rebaudioside A sufficient to promote crystallization of rebaudioside A.
6. The method of claim 1, further comprising the steps of separating and washing the substantially pure rebaudioside A composition.
7. The method of claim 6, further comprising the step of drying the substantially pure rebaudioside A composition.

8. The method of claim 1, wherein the crude rebaudioside A comprises substantially no rebaudioside D impurity, and the method further comprises slurrying the substantially pure rebaudioside A composition in an aqueous organic ~~solvent~~solution or in an organic solvent.

9. The method of claim 8, further comprising the steps of separating and washing the substantially pure rebaudioside A composition.

10. The method of claim 9, further comprising the step of drying the composition of a substantially pure rebaudioside A.

11. The method of claim 1, wherein the aqueous organic ~~solvent~~solution comprises a mixture of at least one organic solvent and water.

12. The method of claim 11, wherein at least one organic solvent comprises an alcohol.

13. The method of claim 12, wherein the alcohol comprises ethanol.

14. The method of claim 12, wherein the alcohol comprises methanol.

15. The method of claim 12, wherein the alcohol comprises a mixture of ethanol and methanol.

16. The method of claim 15, wherein the ethanol and methanol are present in the aqueous organic solution in a weight ratio from about 20 parts to about 1 parts ethanol to about 1 part methanol.

17. The method of claim 15, wherein the ethanol and methanol are present in the aqueous organic solution in a weight ratio from about 3 parts to about 1 part ethanol to about 1 part methanol.

18. The method of claim 1, wherein the at least one aqueous organic ~~solvent~~solution comprises an organic solvent selected from the group consisting of acetone, acetonitrile, methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, tert-butanol, and mixtures thereof.

19. The method of claim 1, wherein the aqueous organic ~~solvent~~solution and the crude rebaudioside A are present in the rebaudioside A solution in a weight ratio from about 4 to about 10 parts aqueous organic ~~solvent~~solution to about 1 part crude rebaudioside A.

20. The method of claim 1, wherein the aqueous organic ~~solvent~~solution and the crude rebaudioside A are present in the rebaudioside A solution in a weight ratio from about 3 to about 5 parts aqueous organic ~~solvent~~solution to about 1 part crude rebaudioside A.

21. The method of claim 1, wherein aqueous organic ~~solvent~~solution comprises water in an amount from about 10 % to about 25 % by weight.

22. ~~The method for purifying rebaudioside A comprising the steps of claim 1,~~
~~wherein~~
combining crude rebaudioside A and an aqueous organic solution to form a rebaudioside A solution, the crude rebaudioside A mixture comprising rebaudioside A in a purity from about 40 % to about 95 % by weight, 85 % by weight on a dry basis, and the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight; and

23. ~~The method of claim 1, wherein the crude rebaudioside A mixture comprises rebaudioside A in a purity from about 60 % to about 85 % by weight.~~

24. ~~The method of claim 1, wherein the crude rebaudioside A mixture comprises rebaudioside A in a purity from about 70 % to about 85 % by weight.~~

25. ~~The method of claim 1;~~ crystallizing from the rebaudioside A solution in a single step a rebaudioside A composition comprising rebaudioside A in a purity greater than about 95 % by weight on a dry basis, wherein the method is carried out at approximately room temperature.

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~~26-23~~ The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to a temperature in a range from about 20°C to about 40°C.

~~27-24~~ The method of claim 2, wherein the step of heating the ~~rebaudioside~~ rebaudioside A solution comprises heating the rebaudioside A solution to a temperature in a range from about 40°C to about 60°C.

~~28-25~~ The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to about a reflux temperature.

~~29-26~~ The method of claim 3, wherein the step of cooling the rebaudioside A solution comprises cooling the rebaudioside A solution to a temperature in a range from about 4°C to about 25°C.

~~30-27~~ The method of claim 3, wherein the step of cooling the rebaudioside A solution comprises cooling the rebaudioside A solution for about 0.5 hours to about 24 hours.

~~31-28~~ The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 97 % rebaudioside A by weight on a dry basis.

~~32-29~~ The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 98 % rebaudioside A by weight on a dry basis.

~~33-30~~ The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 99 % rebaudioside A by weight on a dry basis.

34. ~~31~~ The method of claim 1, further comprising the steps of:

heating the rebaudioside A ~~aqueous-organic solvent mixture~~ solution;

cooling the rebaudioside A solution;

separating and washing a substantially pure rebaudioside A composition; and

drying the substantially pure rebaudioside A composition.

~~35. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 7.~~

36. ~~32~~ A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 8.

37. ~~33~~ A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 9.

38. ~~34~~ A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 10.

39. ~~35~~ A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises an amorphous form having an X-ray diffraction pattern substantially similar to Figure 11.

40. ~~36~~ The method of claim 1, further comprising the step of forming an amorphous form of the substantially pure rebaudioside A composition.

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44. 37 The ~~method~~composition of claim ~~38~~35, wherein the step of forming an amorphous form of the substantially pure rebaudioside A composition comprises a method selected from the group consisting of ball milling, precipitation, lyophilization, cryogrinding, and spray-drying.

42. 38 A substantially pure rebaudioside A composition made according to the method of claim 1.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

PAPPAS, Peter G.
Sutherland Asbill & Brennan LLP
999 Peachtree Street, NE
Atlanta, GA 30309-3996
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RECEIVED

JUN 06 2008

**NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY**

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

03-06-2008

Applicant's or agent's file reference
25040-2775

IMPORTANT NOTIFICATION

International application No.

PCT/US2007/069548

International filing date (day/month/year)

23 May 2007 (23-05-2007)

Priority date (day/month/year)

19 June 2006 (19-06-2006)

Applicant

THE COCA-COLA COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

23 May 2008 (23-05-2008)

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☒ **ATTENTION:** That date of receipt is **after** the expiration of 19 months from the priority date. Consequently, in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the acts for entry into the national phase must therefore be performed within 20 months from the priority date (or later in some Offices). However, in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

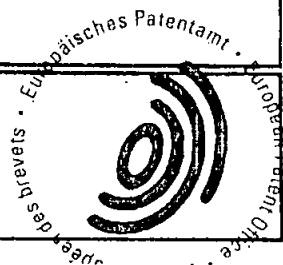
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From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Article 31(7) and Rule 61.3)

To:

PAPPAS, Peter, G.
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RECEIVED

JUL 15 2008

SUTHERLAND ASBILL & BRENNAN LLP

Date of mailing (day/month/year) 03 July 2008 (03.07.2008)		
Applicant's or agent's file reference 25040-2775		
IMPORTANT INFORMATION		
International application No. PCT/US2007/069548	International filing date (day/month/year) 23 May 2007 (23.05.2007)	Priority date (day/month/year) 19 June 2006 (19.06.2006)
Applicant THE COCA-COLA COMPANY		

- The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:
EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR
National: BG, CA, CN, CZ, DE, JP, KP, KR, MN, MY, NO, PL, RO, SK
- The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:
AP: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW
EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BH, BR, BW, BY, BZ, CH, CO, CR, CU, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, KE, KG, KM, KN, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MW, MX, MZ, NA, NG, NI, NZ, OM, PG, PH, PT, RS, RU, SC, SD, SE, SG, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
- Since the election(s) was (were) made after the expiration of 19 months from the priority date, the applicant is reminded that he must, subject to the following paragraph, enter the national phase within 20 months from the priority date (or later in some Offices) before some of the designated Offices in respect of which Article 22(1), as modified with effect of 1 April 2002, does not apply, by paying the national fee(s) and furnishing, if prescribed, a translation of the international application.
However, in respect of most other designated Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters, the *PCT Newsletter* and the WIPO Internet site, updated regularly.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Athina Nickitas-Etienne
Facsimile No. +41 22 338 82 70	e-mail: pt04.pct@wipo.int

022

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2007/069548

International filing date (day/month/year)
23.05.2007

Priority date (day/month/year)
19.06.2006

International Patent Classification (IPC) or both national classification and IPC
INV. A23L1/236 C07H1/08

Applicant
THE COCA-COLA COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Groh, Björn Telephone No. +49 89 2399-7855 
---	---	--

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/069548

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/069548

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>15-17</u>
	No: Claims	<u>1-14,18-42</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-42</u>
Industrial applicability (IA)	Yes: Claims	<u>1-42</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1 Reference is made to the following documents:

D1: US 2006/083838 A1 (JACKSON MEL C [US]) 20 April 2006 (2006-04-20)

D2: CA-A1-2 278 083 (ALBERTA RES COUNCIL [CA]) 20 January 2001 (2001-01-20)

2 Novelty (Art. 33(2) PCT)

2.1 In view of D1

A method for purifying rebaudioside A is known from D1. That method comprises the step of using an ethanol - water mix as solvent and crystallising rebaudioside A from that solvent. The purity of the final product (rebaudioside A) depends on the quality of educt (purity of rebaudioside A to start with). A final product (rebaudioside A) with a 100% purity can be obtained (see Table 3).

"Substantially pure" rebaudioside A produced by the *same* methods (presently claimed and prior art) will result in products which consequently show a 'substantially similar' X-ray diffraction pattern.

Present claims 1-4,6-13,18-42 are not new over D1.

2.2 In view of D2

From prior art D2 it is known that rebaudioside A can be purified from a methanol - water mixture (see claims 1 to 5 and example 5).

The purity of the final product (rebaudioside A) depends on the quality of educt (purity of rebaudioside A to start with). A final product (rebaudioside A) with a 98.6% purity can be obtained (see example 5).

"Substantially pure" rebaudioside A produced by the *same* methods (presently

claimed and prior art) will result in products which consequently show a 'substantially similar' X-ray diffraction pattern.

Present claims Present claims: 1-4,6-12,14,18-32,34-42 are not new over D1.

2.3 In view of other relevant documents of the search report

The claims mentioned above are also not new over other documents of the search report, if the claims (see search report right hand column) have an X-symbol in the left hand column.

3 Inventive step (Art. 33(3) PCT)

It is known to use water-soluble organic solvents, such as methanol and ethanol to purify rebaudioside A (see D2 claim 3; D1 claims; and other relevant documents of the search report cited as X-documents).

Since it is known, for example D1 (see above), how to purify rebaudioside A upto a 100% purity, the objective technical problem can be formulated to provide an alternative method to the ones known in the art.

A method using a methanol-ethanol mix for purification of rebaudioside A, instead of water-soluble organic solvents, such as methanol and ethanol does not involve an inventive step per se, unless a non-obvious technical effect was established which results due to this difference (use methanol-ethanol mix) of over the prior art.

The present set of claims does not involve an inventive step over the prior art.

4 Other

4.1 Result-to-be-achieved / desiderata

- 522
- A. Claim 1 and dependent claims are defined by the result "purity greater than about 95%" to-be-achieved.
 - B. Claims 35 to 39 and dependent claim(s) are defined by a graphically illustrated X-ray diffraction pattern to be obtained.

Only exceptionally, when the invention can not be defined in another way without unduly restricting the scope or the claims, result-to-be-achieved type of claims may be acceptable (see PCT International Preliminary Examination - Guidelines, chapter III, point 4.7).

Any of the claim groups A and B could have been defined in precise way without using the result-to-be-achieved type of definitions:

to A: Method claims of set A must contain **method** steps, which enable the result "purity greater than about 95%".

Consequently the feature "purity greater than about 95%" is regarded as '... **suitable for** obtaining a purity greater than about 95%'.

to B: Product claims of set B could have been defined more precisely by defining the claimed product by its *inherent* chemical properties (such as crystal water, mono-, di- or polymeric structure, etc.) and/or physical (such as crystal or amorphous form, isomeric forms, etc.) properties.

Claims 35 to 39 do not fulfil the requirements of Art. 6 PCT.

4.2 Claims 35 to 39

- a. The expression "substantially pure" is a relative term, which is not precise enough to define the extend of a patentable claim (Art. 6 PCT).
- b. The expression "substantially similar" is a relative term, which is not precise enough to define the extend of a patentable claim (Art. 6 PCT).
- c. The definition of a composition by reference to a graphically illustrated result (Figures 7 to 11) of a method is not precise enough to define the extend of a

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2007/069548

patentable claim (Art. 6 PCT and Rule 6.2 a PCT).

Furthermore, reference to a graphically result which lacks the definition and scale of the y-axis "arbitrary scale" (!) is not precise enough to define the extend of a patentable claim (Art. 6 PCT).

4.3 Claim 42

The expression "substantially pure" is not clear enough to define the extend of the product claim (Art. 6 PCT).

4.4 Claim 5

In claim 5 it is not clear (see Art. 6 PCT) if the seeding is optional or not (term in parenthesis).

4.5 Claim 41

The dependency needs to be corrected (claim 38 is not a method claim).

4.6 Description

The last paragraph on page 33 renders the subject matter claimed vague, because it refers to unspecified alterations, variations, equivalents, etc. That paragraph is not necessary, unclear and should be deleted (Art. 6 PCT and Rule 9.1 iv PCT).

- 4.7 In order to facilitate examination of conformity of any amendments (during PCT chapter II or during the National phase) with the requirements of Article 41 (2) PCT, the applicant is requested to clearly identify all amendments, whether they are amendments by addition, replacement, combination (e.g. of claims) or deletion. The applicant should indicate in detail the passages in the application as filed, on

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2007/069548

which these amendments are based on.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

Bitte beachten Sie, dass angeführte Nichtpatentliteratur (wie z. B. wissenschaftliche oder technische Dokumente) je nach geltendem Recht dem Urheberrechtsschutz und/oder anderen Schutzarten für schriftliche Werke unterliegen könnte. Die Vervielfältigung urheberrechtlich geschützter Texte, ihre Verwendung in anderen elektronischen oder gedruckten Publikationen und ihre Weitergabe an Dritte ist ohne ausdrückliche Zustimmung des Rechtsinhabers nicht gestattet.

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING AVAILABILITY OF THE PUBLICATION OF THE INTERNATIONAL APPLICATION

To:

PAPPAS, Peter, G.
Sutherland Asbill & Brennan LLP
999 Peachtree Street, NE
Atlanta, GA 30309-3996
ETATS-UNIS D'AMERIQUE

RECEIVED

APR 25 2008

SUTHERLAND ASBILL & BRENNAN LLP

IMPORTANT NOTICE

Date of mailing (day/month/year)
10 April 2008 (10.04.2008)

Applicant's or agent's file reference
25040-2775

International application No.
PCT/US2007/069548

International filing date (day/month/year)
23 May 2007 (23.05.2007)

Priority date (day/month/year)
19 June 2006 (19.06.2006)

Applicant

THE COCA-COLA COMPANY

The applicant is hereby notified that the International Bureau:

☐ has published the above-indicated international application on under
No. WO

☒ has republished the above-indicated international application on 10 April 2008 (10.04.2008) under
No. WO 2007/149672

For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48)
or (88) (as the case may be) on the front page of the published international application.

A copy of the international application is available for viewing and downloading on WIPO's website at the following address:
<http://www.wipo.int/pctdb> (under "Query" enter the PCT or WO number).

The applicant may also request a paper copy of the published international application from the International Bureau by submitting a written
request to PatentScope@wipo.int or to the address provided below.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Athina Nickitas-Etienne

Facsimile No. +41 22 338 82 70

e-mail: pt04.pct@wipo.int

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 December 2007 (27.12.2007)

PCT

(10) International Publication Number
WO 2007/149672 A3

(51) International Patent Classification:
A23L 1/236 (2006.01) C07H 1/08 (2006.01)

(74) Agents: PAPPAS, Peter, G. et al.; Sutherland Asbill & Brennan LLP, 999 Peachtree Street, NE, Atlanta, GA 30309-3996 (US).

(21) International Application Number:
PCT/US2007/069548

(22) International Filing Date: 23 May 2007 (23.05.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/805,216 19 June 2006 (19.06.2006) US
60/889,318 12 February 2007 (12.02.2007) US

(71) Applicant (for all designated States except US): THE COCA-COLA COMPANY [US/US]; Patents, One Coca-cola Plaza, NW, Atlanta, GA 30313 (US).

(72) Inventors: PRAKASH, Indra; 9750 Talisman Drive, Alpharetta, Georgia 30022 (US). DUBOIS, Grant, E.; 215 Quincy Lane, Roswell, GA 30076 (US). KING, George, A.; 1755 Wildwood Road, Atlanta, Georgia 30306 (US). UPRETI, Mani; 1943 Rotherham Way, Dunwoody, Georgia 30338 (US).

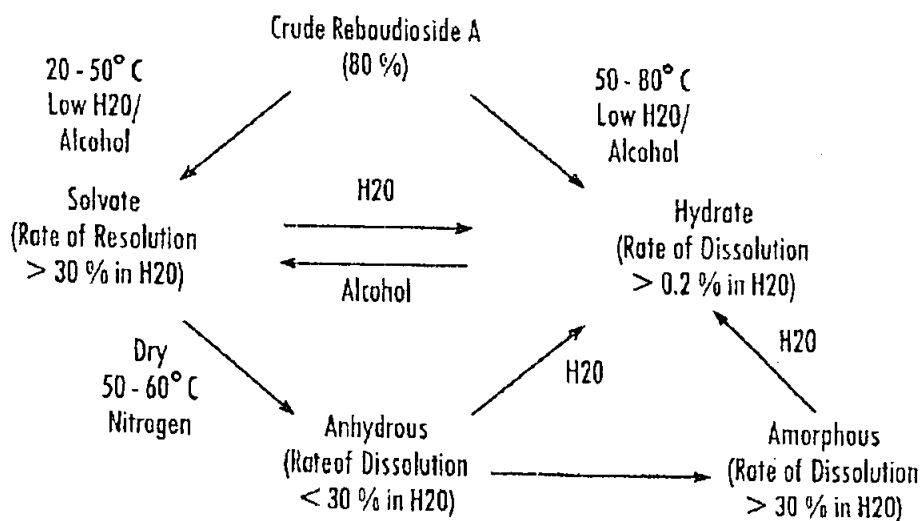
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

[Continued on next page]

(54) Title: REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A



(57) Abstract: Exemplary embodiments of this invention encompass a method for purifying crude rebaudioside A. In particular, this invention relates to a method for purifying crude rebaudioside A compositions comprising purities from approximately 40 % to approximately 95 % rebaudioside A to obtain a substantially pure rebaudioside A product with a single crystallization step. Resulting polymorph and amorphous forms of rebaudioside A and methods for preparing polymorph and amorphous forms of rebaudioside A from crude rebaudioside A compositions and substantially pure rebaudioside A compositions also are disclosed.

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WO 2007/149672 A3



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the International search report:
10 April 2008

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/069548

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23L1/236 C07H1/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A23L C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/083838 A1 (JACKSON MEL C [US] ET AL) 20 April 2006 (2006-04-20) claims 1-20; tables 3,6	1-4, 6-13, 18-42
X	CA 2 278 083 A1 (ALBERTA RES COUNCIL [CA]) 20 January 2001 (2001-01-20) claim 1; example 5	1-4, 6-12,14, 18-32, 34-42
X	DATABASE WPI Week 198145 Derwent Publications Ltd., London, GB; AN 1981-82360D XP002469089 & JP 56 121455 A (AJINOMOTO KK) 24 September 1981 (1981-09-24) abstract	1,35-39, 42

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

14 February 2008

Date of mailing of the international search report

25/02/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Groh, Björn

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/069548

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/038221 A (COUNCIL SCIENT IND RES [IN]; KUMAR JONNALA KOTESH [IN]; BABU GARIKAPAT) 13 April 2006 (2006-04-13) pages 4-7	35-39,42
X	US 4 082 858 A (MORITA TOYOSHIGE ET AL) 4 April 1978 (1978-04-04) claim 1; example 1	35-39,42
X	DATABASE WPI Week 198145 Derwent Publications Ltd., London, GB; AN 1981-823580 XP002469090 & JP 56 121453 A (AJINOMOTO KK) 24 September 1981 (1981-09-24) abstract	1,13,14, 35-39,42
A	DATABASE WPI Week 197727 Derwent Publications Ltd., London, GB; AN 1977-47639Y XP002469091 & JP 52 062300 A (AJINOMOTO KK) 23 May 1977 (1977-05-23) abstract	5

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/069548

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006083838 A1	20-04-2006	AU 2005295234 A1	27-04-2006
		CA 2583909 A1	27-04-2006
		EP 1809124 A2	25-07-2007
		KR 20070067199 A	27-06-2007
		WO 2006045023 A2	27-04-2006
CA 2278083 A1	20-01-2001	NONE	
JP 56121455 A	24-09-1981	NONE	
WO 2006038221 A	13-04-2006	NONE	
US 4082858 A	04-04-1978	JP 973099 C	28-09-1979
		JP 51142570 A	08-12-1976
		JP 52027226 B	19-07-1977
JP 56121453 A	24-09-1981	NONE	
JP 52062300 A	23-05-1977	NONE	

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PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 25040-2775	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2007/069548	International filing date (day/month/year) 23/05/2007	(Earliest) Priority Date (day/month/year) 19/06/2006
Applicant THE COCA-COLA COMPANY		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6b(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 2
☒ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

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PCT/US2007/069548

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23L1/236 C07H1/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A23L C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/083838 A1 (JACKSON MEL C [US] ET AL) 20 April 2006 (2006-04-20) claims 1-20; tables 3,6 -----	1-4, 6-13, 18-42
X	CA 2 278 083 A1 (ALBERTA RES COUNCIL [CA]) 20 January 2001 (2001-01-20) claim 1; example 5 -----	1-4, 6-12, 14, 18-32, 34-42
X	DATABASE WPI Week 198145 Derwent Publications Ltd., London, GB; AN 1981-82360D XP002469089 & JP 56 121455 A (AJINOMOTO KK) 24 September 1981 (1981-09-24) abstract ----- -/--	1, 35-39, 42

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

14 February 2008

Date of mailing of the international search report

25/02/2008

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Groh, Björn

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PCT/US2007/069548

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/038221 A (COUNCIL SCIENT IND RES [IN]; KUMAR JONNALA KOTESH [IN]; BABU GARIKAPAT) 13 April 2006 (2006-04-13) . pages 4-7	35-39, 42
X	US 4 082 858 A (MORITA TOYOSHIGE ET AL) 4 April 1978 (1978-04-04) claim 1; example 1	35-39, 42
X	DATABASE WPI Week 198145 Derwent Publications Ltd., London, GB; AN 1981-82358D XP002469090 & JP 56 121453 A (AJINOMOTO KK) 24 September 1981 (1981-09-24) abstract	1, 13, 14, 35-39, 42
A	DATABASE WPI Week 197727 Derwent Publications Ltd., London, GB; AN 1977-47639Y XP002469091 & JP 52 062300 A (AJINOMOTO KK) 23 May 1977 (1977-05-23) abstract	5

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PCT/US2007/069548

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2006083838	A1	20-04-2006	AU 2005295234 A1	27-04-2006
			CA 2583909 A1	27-04-2006
			EP 1809124 A2	25-07-2007
			KR 20070067199 A	27-06-2007
			WO 2006045023 A2	27-04-2006
CA 2278083	A1	20-01-2001	NONE	
JP 56121455	A	24-09-1981	NONE	
WO 2006038221	A	13-04-2006	NONE	
US 4082858	A	04-04-1978	JP 973099 C	28-09-1979
			JP 51142570 A	08-12-1976
			JP 52027226 B	19-07-1977
JP 56121453	A	24-09-1981	NONE	
JP 52062300	A	23-05-1977	NONE	

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

SUTHERLAND ASBILL & BRENNAN LLP
Attn. Pappas, Peter G.
999 Peachtree Street, NE
Atlanta, Georgia 30309-3996
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

RECEIVED

FEB 25 2008

(PCT Rule 44.1)

SUTHERLAND ASBILL & BRENNAN LLP

Date of mailing
(day/month/year)

25/02/2008

Applicant's or agent's file reference

25040-2775

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2007/069548

International filing date
(day/month/year)

23/05/2007

Applicant

THE COCA-COLA COMPANY

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Eleonora Longo

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

PAPPAS, Peter, G.
Sutherland Asbill & Brennan LLP
999 Peachtree Street
Atlanta, GA 30309-
ETATS-UNIS D'AMERIQUE

RECEIVED

FEB 01 2008

SUTHERLAND ASBILL &
BRENNAN LLP
IMPORTANT NOTICE

Date of mailing (day/month/year)

24 January 2008 (24.01.2008)

Applicant's or agent's file reference

25040-2775

International application No.

PCT/US2007/069548

International filing date (day/month/year)

23 May 2007 (23.05.2007)

Priority date (day/month/year)

19 June 2006 (19.06.2006)

Applicant

THE COCA-COLA COMPANY

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does apply**, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:

None

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

CH, LU, TZ, UG

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 20 MONTHS from the priority date.

In practice, time limits other than the 20-month time limit will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For regular updates on the applicable time limits (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Yoshiko Kuwahara

Facsimile No. +41 22 338 82 70

e-mail: pt07.pct@wipo.int

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PATENT COOPERATION TREATY

From the RECEIVING OFFICE

To:
PETER G. PAPPAS
SUTHERLAND ASBILL & BRENNAN LLP
999 PEACHTREE STREET, NE
ATLANTA, GEORGIA 30309-3996

PCT

INVITATION TO CORRECT DEFECTS IN
THE INTERNATIONAL APPLICATION

(PCT Articles 3(4)(i) and 14(1) and Rule 26)

Date of mailing (day/month/year) 24 Jul 2007	
Applicant's or agent's file reference 25040-2775	REPLY DUE within 1 months/days from the above date of mailing
International application No. PCT/US2007/069548	International filing date (day/month/year) 23 May 2007
Applicant THE COCA-COLA COMPANY	

1. ☒ The applicant is hereby invited, within the time limit indicated above, to correct, in the international application as filed, the defects specified on the attached:

☐ Annex A

☐ Annex B1 (text matter of the international application as filed)

☒ Annex C1 (drawings of the international application as filed)

2. ☐ The applicant is hereby invited, within the time limit indicated above, to correct, in the translation of the international application furnished under Rule 12.3 or 12.4, the defects specified on the attached:

☐ Annex A

☐ Annex B2 (text matter of the translation of the international application)

☐ Annex C2 (drawings of the translation of the international application)

Additional observations (if necessary):

HOW TO CORRECT THE DEFECTS?

Correction must be submitted by filing a replacement sheet embodying the correction and a letter accompanying the replacement sheet, which shall draw attention to the difference between the replaced sheet and the replacement sheet. A correction may be stated in a letter only if it is of such a nature that it can be transferred from the letter to the record copy without adversely affecting the clarity and direct reproducibility of the sheet onto which the correction is to be transferred (Rule 26.4).

ATTENTION

Failure to correct the defects will result in the international application being considered withdrawn by this receiving Office (see Rule 26.5 for further details).

A copy of this invitation and any attachments has been sent to the International Bureau

☒ and the International Searching Authority

Name and mailing address of the receiving Office Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-3201	Authorized officer Zeta Adams Telephone No. 703-308-9013
---	--

ANNEX C1 TO FORM PCT/RO/106

International application No.
PCT/US2007/069548

This receiving Office has found that, with regard to the presentation of the drawings of the international application as filed, the physical requirements are not complied with to the extent that compliance therewith is necessary for:

1. ☒ reasonably uniform international publication (Rules 11 and 26.3(a)(i)) (defects to be specified):

Sheets containing drawings:

- a. ☐ the sheets do not admit of direct reproduction
- b. ☐ the sheets are not free from creases, cracks, folds
- c. ☐ one side of the sheets is not left unused
- d. ☐ the paper of the sheets is not flexible/strong/white/smooth/non-shiny/durable
- e. ☐ the drawings do not commence on a new sheet
- f. ☐ the sheets are not connected as prescribed (Rule 11.4(b))
- g. ☐ the sheets are not A4 size (29.7cm x 21cm)
- h. ☐ the minimum margins on the sheets are not as prescribed (top: 2.5cm; left side: 2.5cm; right side: 1.5cm; bottom: 1cm)
- i. ☐ the file reference number indicated on the sheets does not appear in the left-hand corner of the sheets, within 1.5 cm of the top of the sheets
- j. ☐ the file reference number exceeds the maximum of 12 characters
- k. ☐ the sheets are not free from frames around usable or used surfaces
- l. ☒ the sheets are not numbered in consecutive Arabic numerals (e.g. 1/3, 2/3, 3/3)
- m. ☐ the sheet numbers are not centered at the top or bottom of the sheets
- n. ☐ the sheet numbers are in the margin (see h. above for the size of the margins)
- o. ☐ the sheets contain alterations/overwritings/interlineations/too many erasures
- p. ☐ the sheets contain photocopy marks

Drawings (Rule 11.13):

- a. ☐ do not admit of direct reproduction
- b. ☐ contain unnecessary text matter
- c. ☐ contain words so placed as to prevent translation without interference with lines thereof
- d. ☐ are not executed in durable black color; the lines are not uniformly thick and well-defined
- e. ☐ contain cross-sections not properly hatched
- f. ☐ would not be properly distinguishable in reduced reproduction
- g. ☐ contain scales not represented graphically
- h. ☒ contain numbers, letters and reference lines lacking simplicity and clarity
- i. ☐ contain lines drafted without the aid of drafting instruments
- j. ☐ contain disproportionate elements of a figure not necessary for clarity
- k. ☐ contain numbers and letters of height less than 0.32 cm
- l. ☐ contain letters not conforming to the Latin, and where customary, Greek alphabets
- m. ☐ contain figures on two or more sheets which form a single complete figure but which are not able to be assembled without concealing parts thereof
- n. ☐ contain figures which are not properly arranged and clearly separated
- o. ☐ contain different figures not numbered in consecutive Arabic numerals
- p. ☐ contain different figures not numbered independently of the numbering of the sheets
- q. ☐ are not restricted to reference signs mentioned in the description
- r. ☐ do not contain reference signs that are mentioned in the description
- s. ☐ contain the same feature denoted by different reference signs
- t. ☐ are not arranged in an upright position, clearly separated from one another
- u. ☐ are not presented sideways with the top of the figures at the left side of the sheets

2. ☐ satisfactory reproduction (Rules 11 and 26.3(b)(i))

Further observations (if necessary):

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE ACTING AS
RECEIVING OFFICE FOR THE INTERNATIONAL APPLICATION

International Application of: **THE COCA-COLA COMPANY**
Title: **Rebaudioside A Composition and Method for
Purifying Rebaudioside A**
International Application No.: **PCT/US2007/069548**
Filing Date: **23 May 2007 (23.05.2007)**
Agent's Docket No.: **25040-2775**

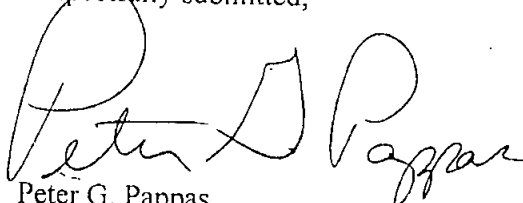
**TRANSMITTAL OF RESPONSE TO INVITATION
TO CORRECT DEFECTS IN THE INTERNATIONAL APPLICATION**

VIA FACSIMILE TRANSMISSION (571) 273-3201
AND FEDERAL EXPRESS INTERNATIONAL
United States Patent and Trademark Office
Customer Service Window - Mail Stop PCT
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Dear Sir:

Agent for Applicant respectfully submits the attached FORMAL DRAWINGS that
contain CORRECTIONS TO THE DEFECTS as enumerated upon form PCT/RO/106 dated
July 24, 2007.

Respectfully submitted,



Peter G. Pappas
Agent for Applicant

August 24, 2007

SUTHERLAND ASBILL & BRENNAN LLP
999 Peachtree Street, N.E.
Atlanta, Georgia 30309-3996
United States of America
Telephone: (404) 853-8000
Facsimile: (404) 853-8806

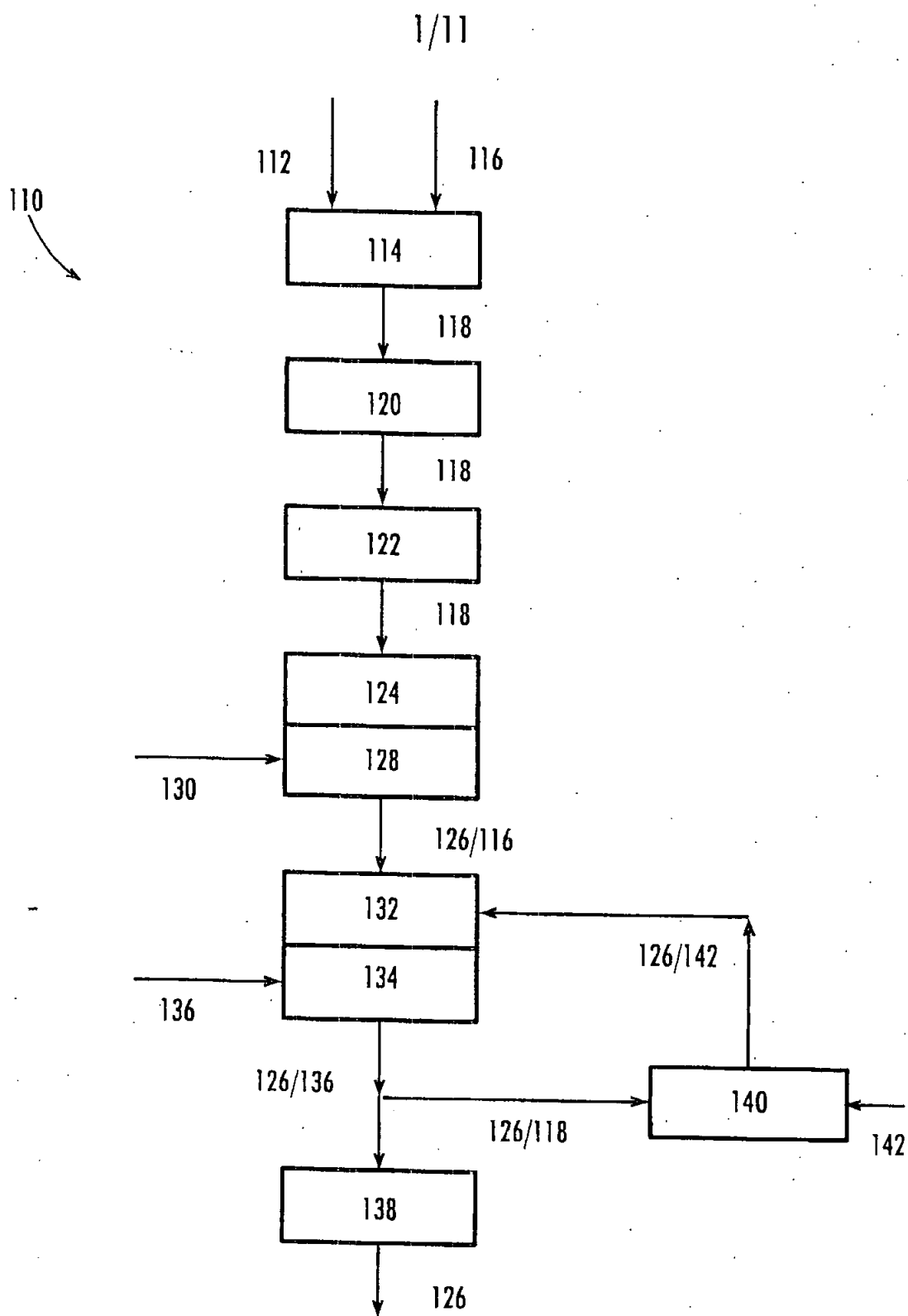


Fig. 1

2/11

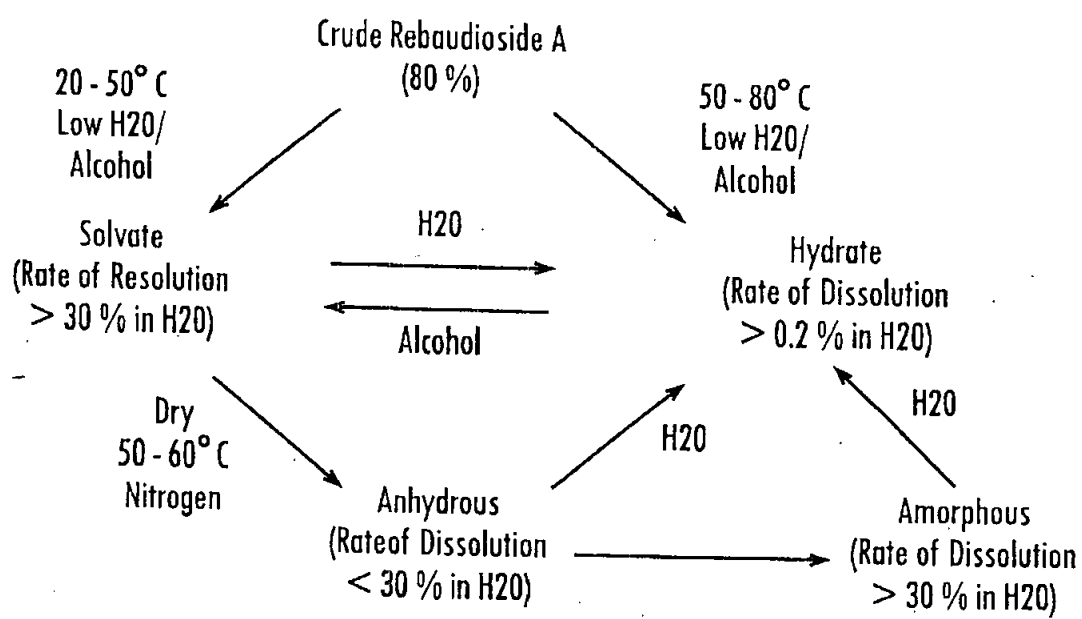


Fig. 2

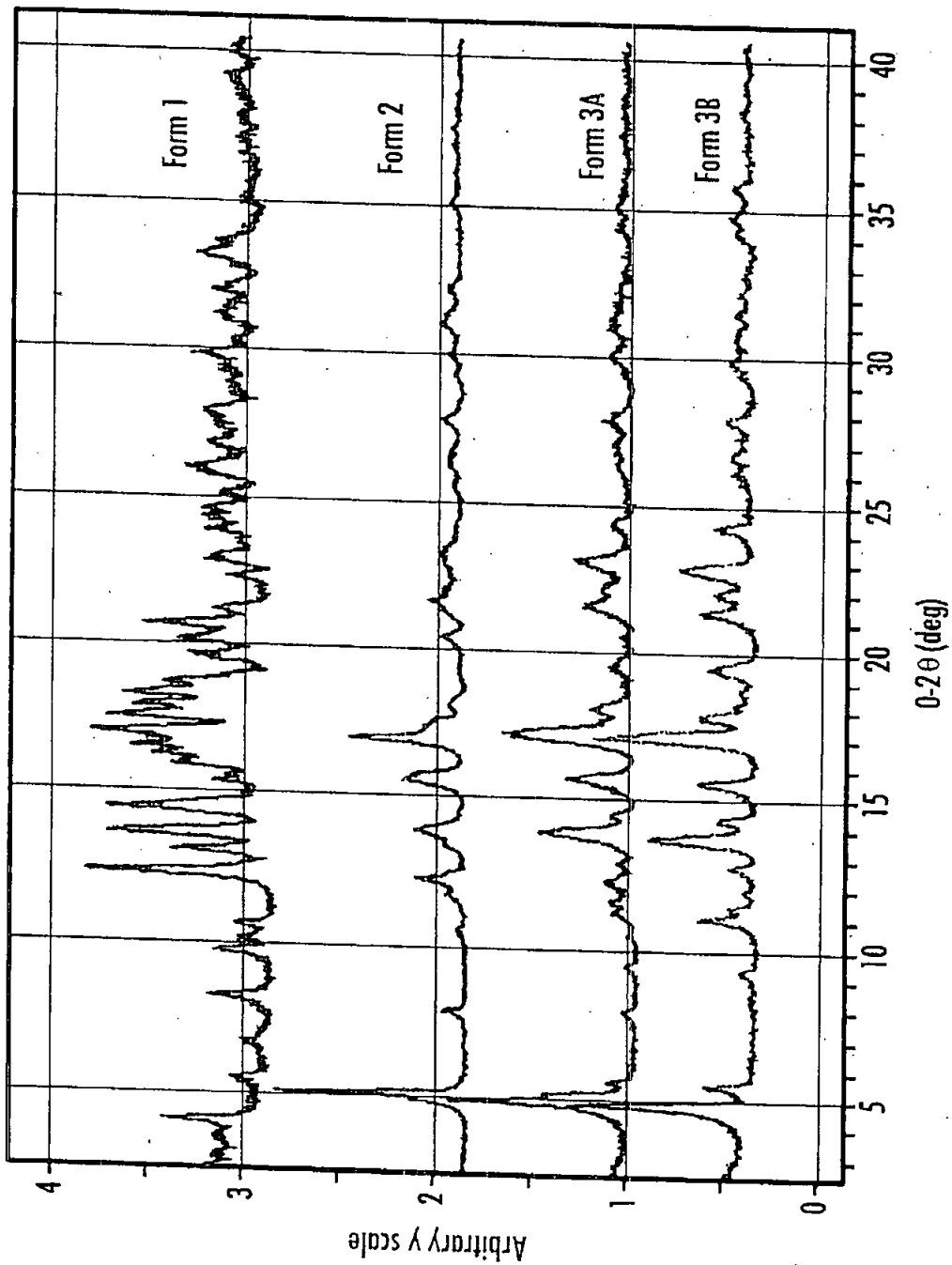


Fig. 3

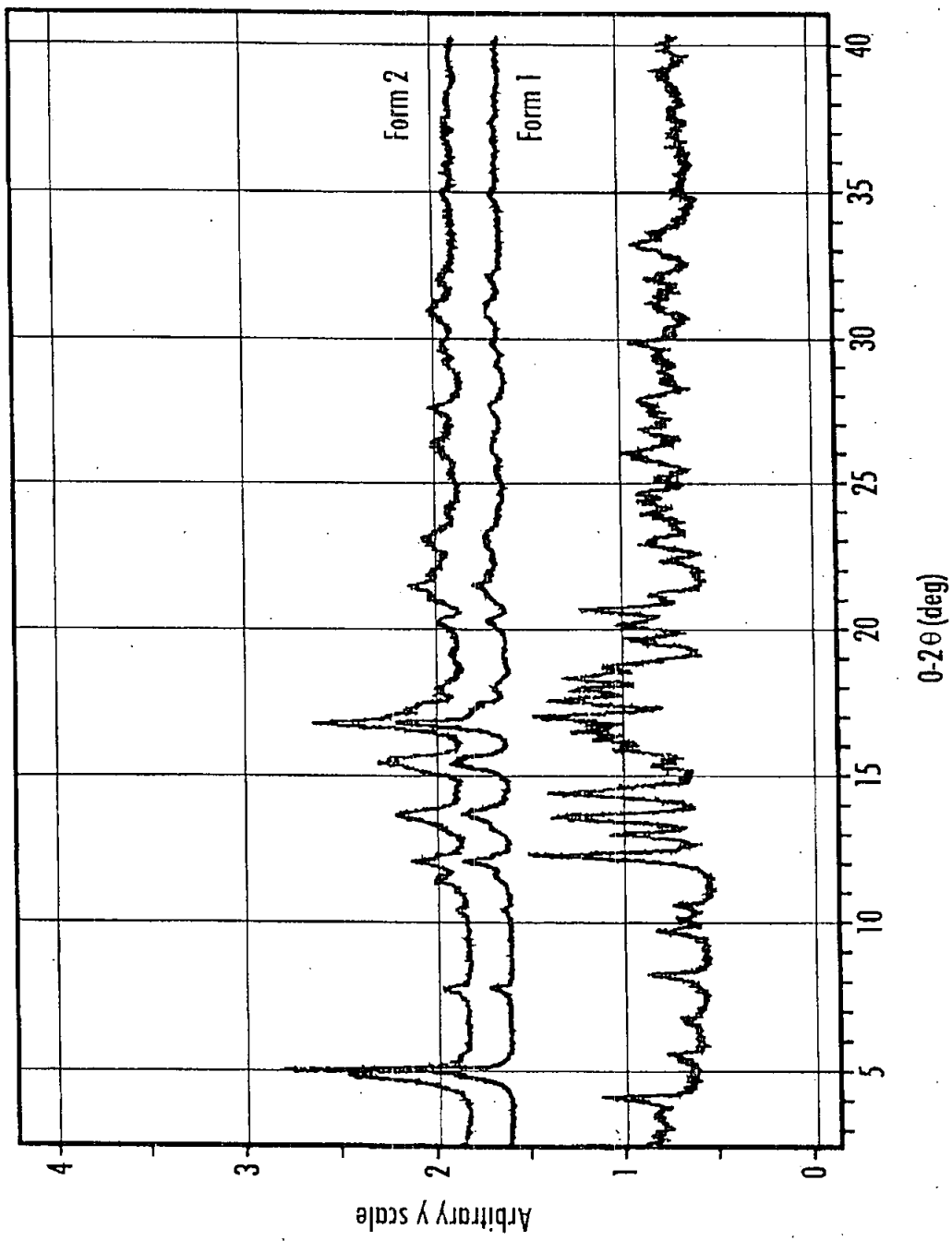


Fig. 4

250

5/11

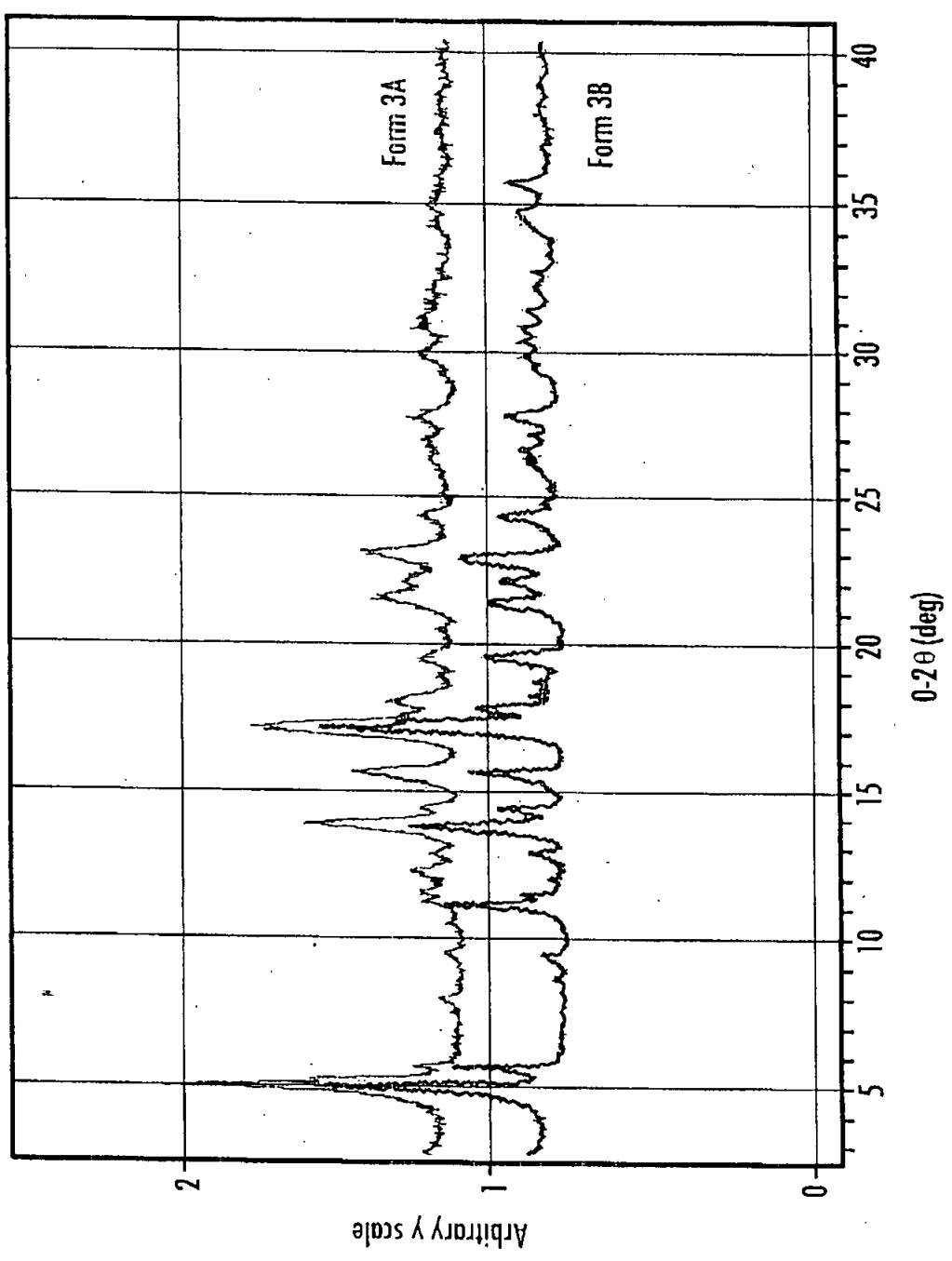


Fig. 5

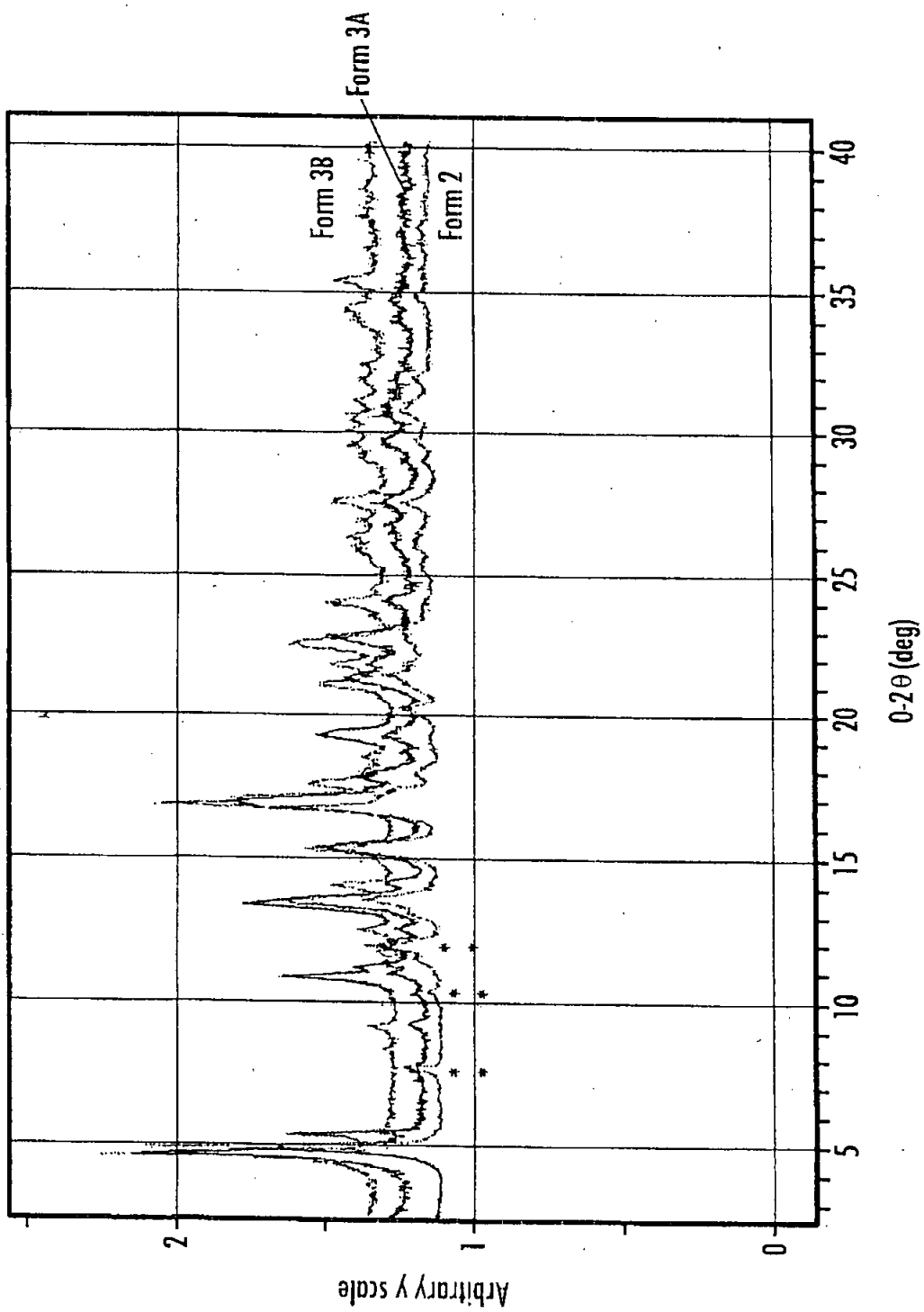


Fig. 6

25-1

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7/11

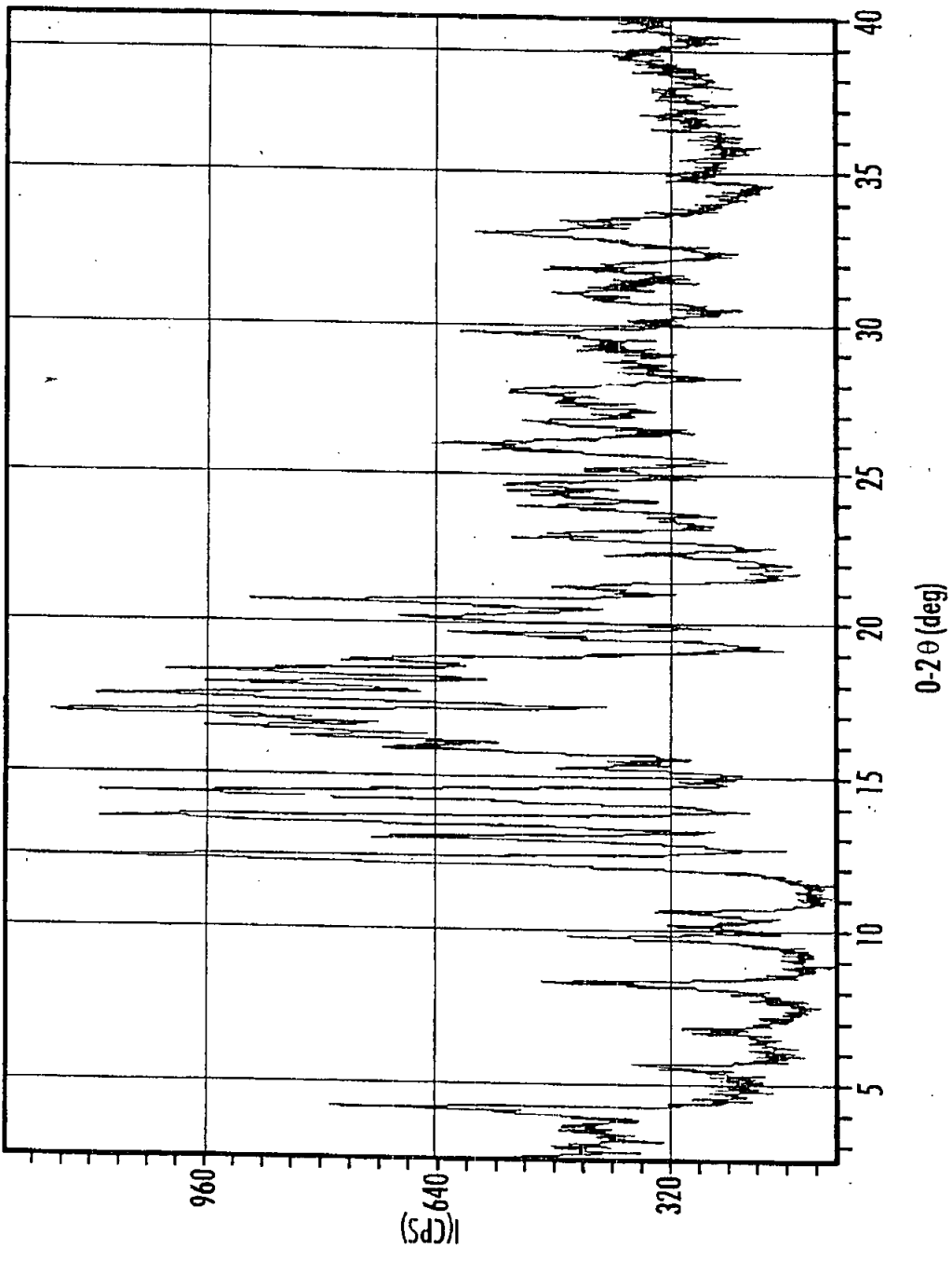


Fig. 7

253

8/11

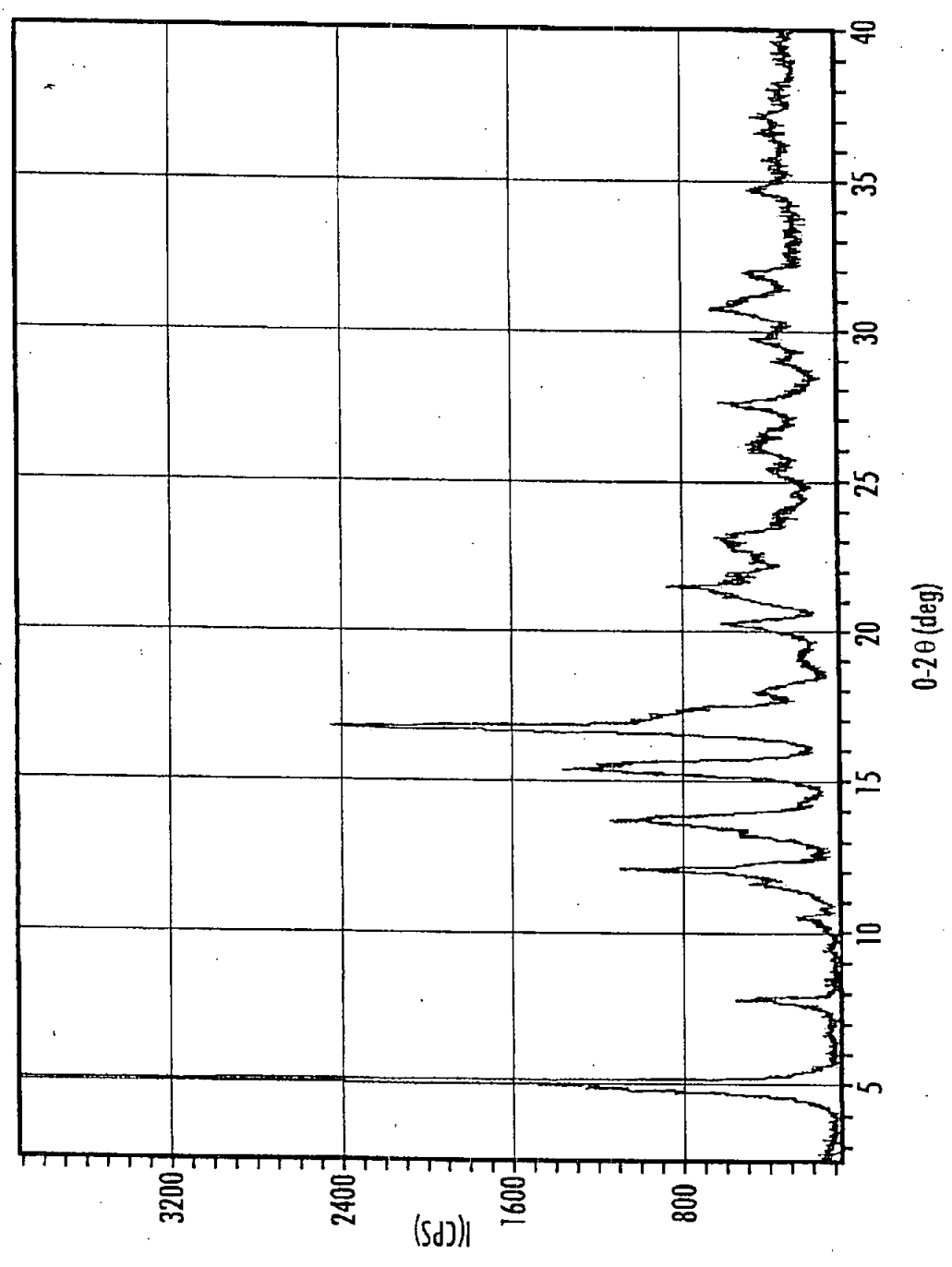


Fig. 8

254

9/11

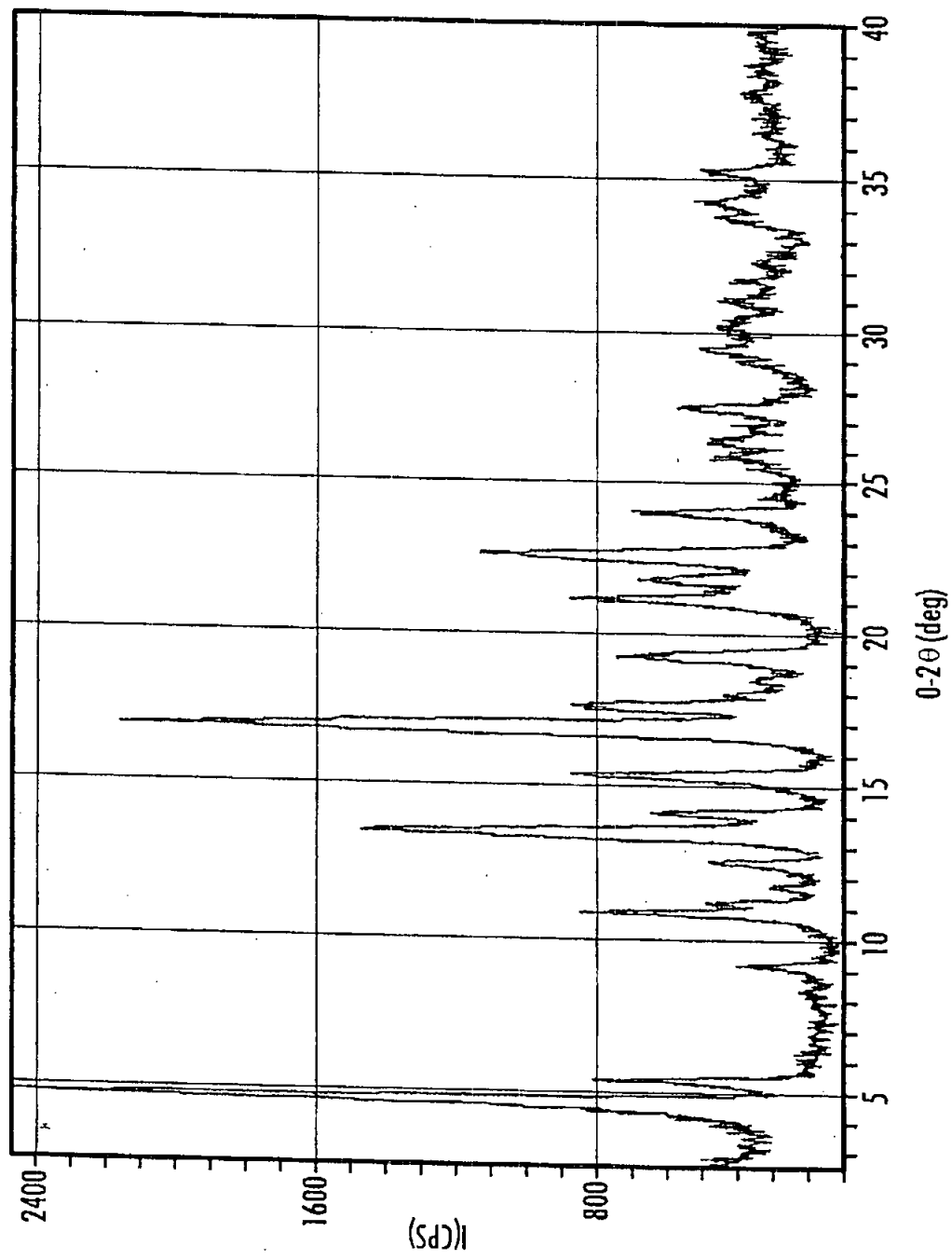


Fig. 9

255

10/11

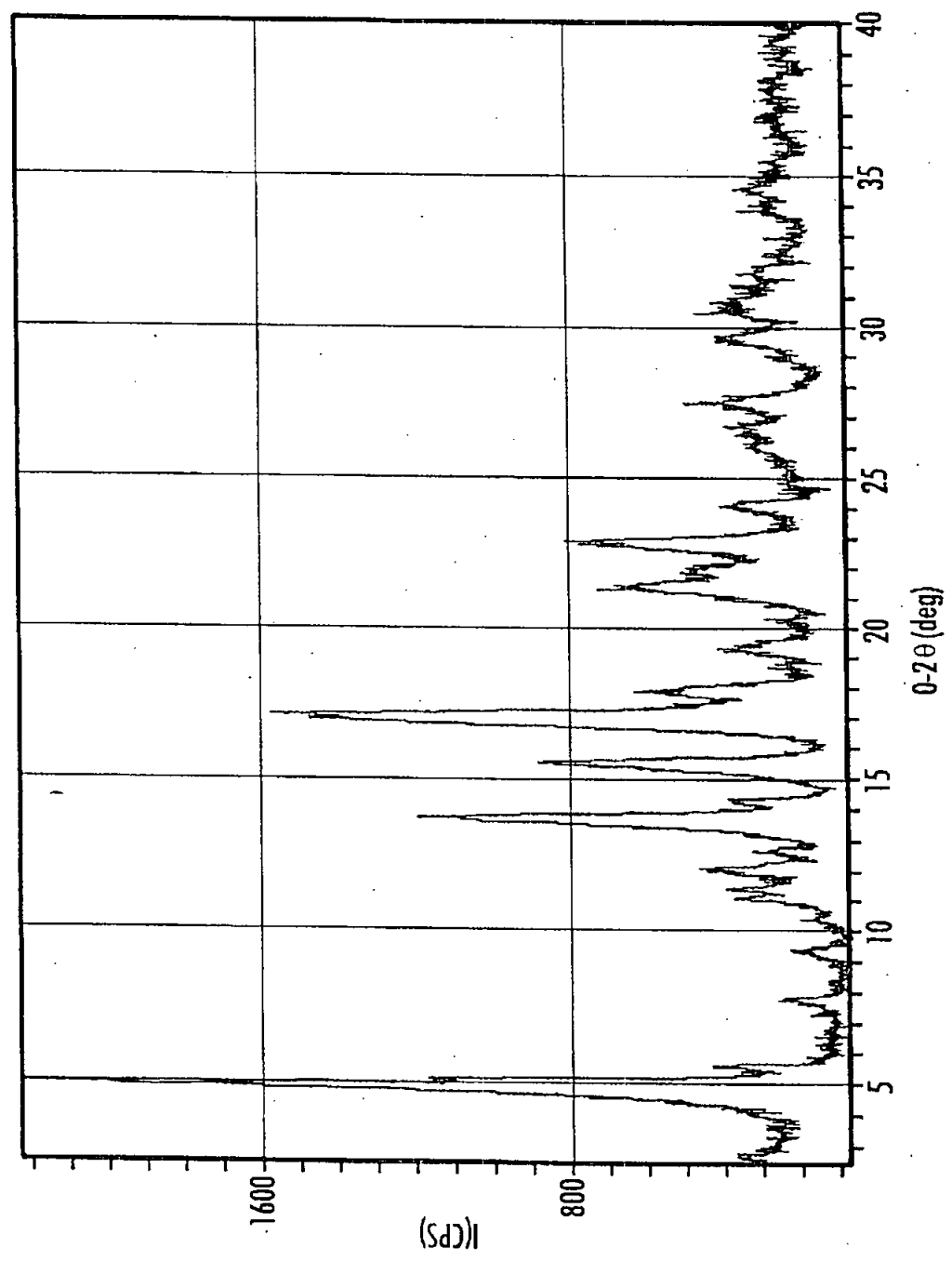
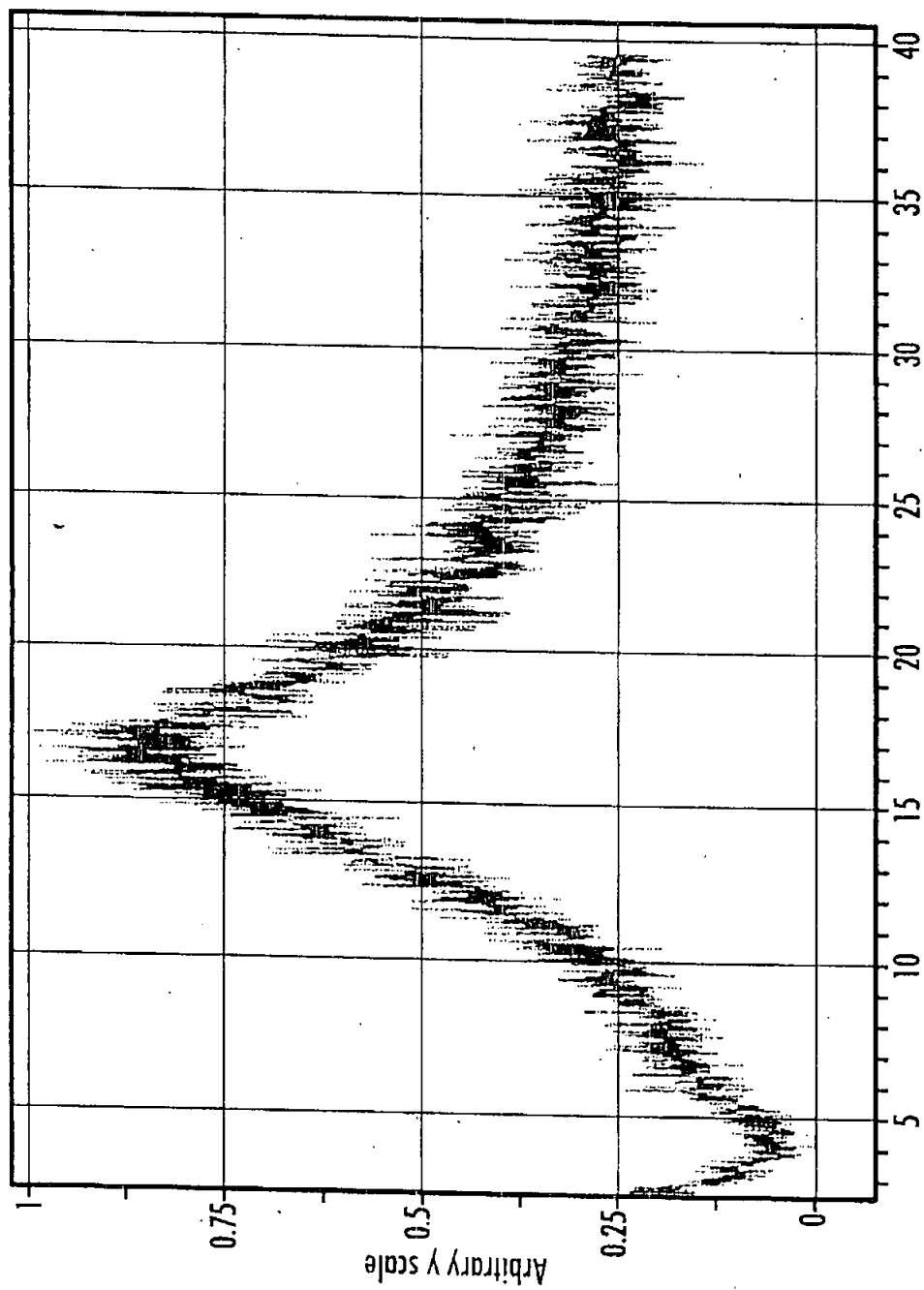


Fig. 10



0-2θ (deg)

Fig. 11

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

PAPPAS, Peter, G
Sutherland Asbill & Brennan LLP
999 Peachtree Street NE
Atlanta, GA 30309-3996
ETATS-UNIS D'AMERIQUE

RECEIVED

SEP 07 2007

SUTHERLAND ASBILL &
BRENNAN LLP

Date of mailing (day/month/year)

27 August 2007 (27.08.2007)

IMPORTANT NOTIFICATION

Applicant's or agent's file reference

25040-2775

International application No.

PCT/US2007/069548

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

THE COCA-COLA COMPANY (for all designated States except US)

International filing date:

23 May 2007 (23.05.2007)

Priority date(s) claimed:

19 June 2006 (19.06.2006)

12 February 2007 (12.02.2007)

Date of receipt of the record copy by the International Bureau:

20 July 2007 (20.07.2007)

List of designated Offices:

AP: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW

EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR

OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

National: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

ATTENTION: The applicant should carefully check the data appearing in this notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau. In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- time limits for entry into the national phase - see updated important information (as of April 2002)
- requirements regarding priority documents (if applicable)

A copy of this notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Peretti Eliott

Facsimile No. +41 22 338 90 90

e-mail pt07.pct@wipo.int

Telephone No. +41 22 338 74 07

INFORMATION ON ENTERING THE NATIONAL PHASE

The applicant is reminded that the **"national phase"** must be entered before each of the designated Offices indicated on the cover sheet of this notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with **other special requirements** applicable in certain Offices. It is the **applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The **applicable time limit** for entering the national phase will, **subject to what is said in the following paragraph**, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, **time limits other than the 30-month time limit will continue to apply, for various periods of time**, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit)**, Office by Office, refer to the *PCT Gazette* ("Section IV" part published on a weekly basis), to the *PCT Newsletter* (on a monthly basis) and to the relevant National Chapters in Volume II of the *PCT Applicant's Guide* (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages of the site, including those of the *Gazette*, *Newsletter* and *Guide*, at <http://www.wipo.int/pct/en/index.html>.

Information about the requirements for filing a **demand for international preliminary examination** is set out in the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before the date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau and if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances (Rule 17.1(c)).

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit (and all other PCT time limits) is the filing date of the earliest application whose priority is claimed (Article 2(xi)(b)).

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF RECEIPT
OF SEARCH COPY

(PCT Rule 25.1)

To:

SUTHERLAND ASBILL & BRENNAN LLP
Attn. Pappas, Peter G.
999 Peachtree Street, NE
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SUTHERLAND ASBILL & BRENNAN LLP

Date of mailing
(day/month/year)

27/08/2007

Applicant's or agent's file reference

25040-2775

IMPORTANT NOTIFICATION

International application No.

PCT/US2007/069548

International filing date (day/month/year)

23/05/2007

Priority date (day/month/year)

19/06/2006

Applicant

THE COCA-COLA COMPANY

1. Where the International Searching Authority and the receiving Office are not the same office:

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

Where the International Searching Authority and the receiving Office are the same office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

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2. ☐ The search copy was accompanied by a nucleotide and/or amino acid sequence listing or tables related thereto in electronic form.
3. ☐ The search copy contained a nucleotide and/or amino acid sequence listing or tables related thereto in electronic form.
4. Time limit for establishment of international search report and written opinion of the International Searching Authority
The applicant is informed that the time limit for establishing the international search report and the written opinion of the International Searching Authority is three months from the date of receipt indicated above or nine months from the priority date, whichever time limit expires later (Rules 42.1 and 43bis.1(a)).
5. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the receiving Office.

Name and mailing address of the International Searching Authority

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NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

From the INTERNATIONAL BUREAU

To:

PAPPAS, Peter, G.
Sutherland Asbill & Brennan LLP
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Atlanta, GA 30309-3996
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(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 28 August 2007 (28.08.2007)	
Applicant's or agent's file reference 25040-2775	IMPORTANT NOTIFICATION
International application No. PCT/US2007/069548	International filing date (day/month/year) 23 May 2007 (23.05.2007)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 19 June 2006 (19.06.2006)
Applicant THE COCA-COLA COMPANY	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
19 June 2006 (19.06.2006)	60/805,216	US	24 July 2007 (24.07.2007)
12 February 2007 (12.02.2007)	60/889,318	US	24 July 2007 (24.07.2007)

The International Bureau of WIPO
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From the INTERNATIONAL BUREAU

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NOTIFICATION CONCERNING
AVAILABILITY OF THE PUBLICATION
OF THE INTERNATIONAL APPLICATION

To:

PAPPAS, Peter, G.
Sutherland Asbill & Brennan LLP
999 Peachtree Street NE
Atlanta, GA 30309-3916
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JAN 16 2008

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IMPORTANT NOTICE

Date of mailing (day/month/year) 27 December 2007 (27.12.2007)			
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Applicant THE COCA-COLA COMPANY			

The applicant is hereby notified that the International Bureau:

- ☒ has published the above-indicated international application on 27 December 2007 (27.12.2007) under No. WO 2007/149672
- ☐ has republished the above-indicated international application on under No. WO
For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48) or (88) (as the case may be) on the front page of the published international application.

A copy of the international application is available for viewing and downloading on WIPO's website at the following address:
<http://www.wipo.int/pctdb> (under "Query" enter the PCT or WO number).

The applicant may also request a paper copy of the published international application from the International Bureau by submitting a written request to PatentScope@wipo.int or to the address provided below.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Yoshiko Kuwahara e-mail: pt07.pct@wipo.int
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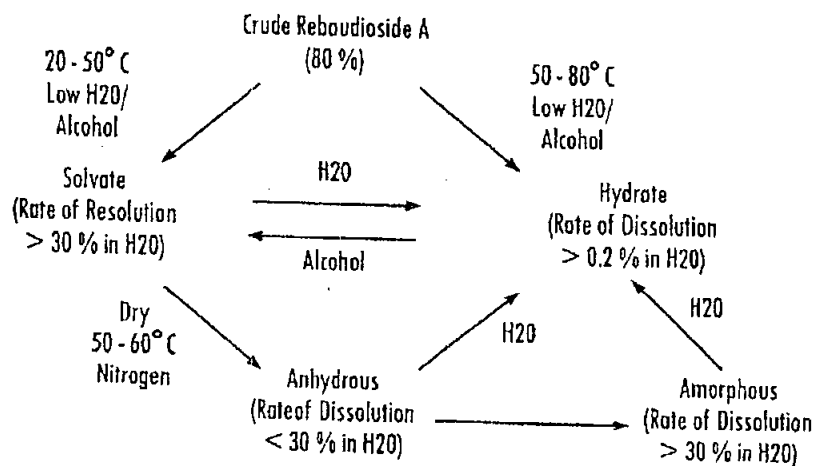
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A



(57) Abstract: Exemplary embodiments of this invention encompass a method for purifying crude rebaudioside A. In particular, this invention relates to a method for purifying crude rebaudioside A compositions comprising purities from approximately 40 % to approximately 95 % rebaudioside A to obtain a substantially pure rebaudioside A product with a single crystallization step. Resulting polymorph and amorphous forms of rebaudioside A and methods for preparing polymorph and amorphous forms of rebaudioside A from crude rebaudioside A compositions and substantially pure rebaudioside A compositions also are disclosed.

REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A

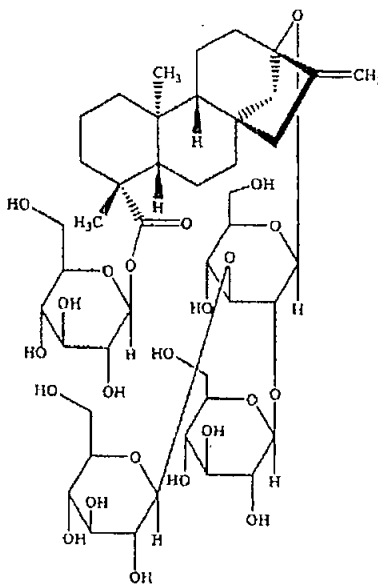
5 FIELD OF INVENTION

This invention relates generally to polymorphic and amorphous forms of rebaudioside A, methods for purifying rebaudioside A, and methods for preparing polymorphic and amorphous forms of rebaudioside A. More particularly, this invention relates to polymorphic and amorphous forms of rebaudioside A and methods
10 for the purification or crystallization of rebaudioside A with aqueous organic solvents or organic solvents to obtain a product in high yield and high purity.

BACKGROUND OF INVENTION

Rebaudioside A is a high-potency diterpenoid glycoside sweetener having the chemical structure:

15



Rebaudioside A is isolated and extracted, along with other steviol glycosides, from the *Stevia rebaudiana* (Bertoni) plant ("Stevia"), which is commercially cultivated in
20 Japan, Singapore, Taiwan, Malaysia, South Korea, China, Israel, India, Brazil, Australia, and Paraguay. It is an alternative non-caloric sweetener with functional and

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sensory properties superior to those of many high-potency sweeteners. Processed forms of *Stevia* can be 70 to 400 times more potent than sugar; however, *Stevia* also has a bitter component. Of the four major diterpenoid glycoside sweeteners present in *Stevia*, rebaudioside A has been identified as the least bitter, and with the least persistent aftertaste. Bitterness often is significantly due to the impurities in extracts.

Rebaudioside A is generally available at ≤ 80 % pure. The primary impurities comprise stevioside, steviolbioside, rebaudioside B, rebaudioside C, rebaudioside D, dulcoside A, rebaudioside F, and other steviol glycosides. It is very difficult to obtain a high purity of rebaudioside A in high recovery because the rebaudioside A and the impurities have similar solubilities.

Previously reported efforts to purify rebaudioside A from mixtures of rebaudioside A and stevioside require numerous repeated purification steps. U.S. Patent No. 5,962,678 discloses the re-crystallization of rebaudioside A using an anhydrous methanol solution to obtain an 80 % pure rebaudioside A. By repeating the re-crystallization with anhydrous methanol numerous times, the purity of rebaudioside A may be increased to over 95 %. U.S. Patent Publication No. 2006/0083838 discloses purification of rebaudioside A through re-crystallization with a solvent comprising ethanol and between 4 and 15 % water. Japanese Patent Application No. 55-23756 discloses a method for purifying rebaudioside A and stevioside by crystallization from aqueous ethanol (> 70 %) to obtain an 80 % pure rebaudioside A. U.S. Patent Publication No. 2007/0082103 discloses a method for purifying rebaudioside A by recrystallization from aqueous ethanol, asserting a two-step recrystallization from crude rebaudioside (60 %) results in the formation of > 98 % pure rebaudioside at 97 % yield. These prior art methods, however, do not provide a substantially pure rebaudioside A composition using only a single recrystallization step.

Accordingly, there exists a need for a simple, efficient, and economical method for producing substantially pure rebaudioside A.

SUMMARY OF INVENTION

Exemplary embodiments of the invention address the above-identified need by providing a substantially pure rebaudioside A, polymorphic and amorphous forms of

rebaudioside A, methods for purifying rebaudioside A, and methods for making polymorphic and amorphous forms of rebaudioside A.

In a particular embodiment, the method for purifying rebaudioside A comprises a simple crystallization. In one embodiment, a method for purifying rebaudioside A comprises combining crude rebaudioside A and an aqueous organic solvent to form a rebaudioside A solution, the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight, and crystallizing from the crude rebaudioside A solution, in a single step, a substantially pure rebaudioside A in a purity greater than about 95% by weight on a dry basis.

In other particular embodiments, different polymorphic and amorphous forms of rebaudioside A and methods for preparing different polymorphic and amorphous forms of rebaudioside A are provided.

Other objects, features, and advantages of the invention will be apparent from the following detailed description, drawings, and claims. Unless otherwise defined, all technical and scientific terms and abbreviations used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and compositions similar or equivalent to those described herein can be used in the practice of the present invention, suitable methods and compositions are described without intending that any such methods and compositions limit the invention herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustrating a method for purifying rebaudioside A in accordance with an embodiment of this invention.

Fig. 2 is a schematic of the formation and conversion of rebaudioside A polymorphic and amorphous forms of rebaudioside A in accordance with an embodiment of this invention.

Fig. 3 is a powder x-ray diffraction scan comparing four rebaudioside A polymorphs, Forms 1, 2, 3A and 3B, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 4 is a powder x-ray diffraction scan comparing rebaudioside A polymorphs, Form 1 and Form 2, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 5 is a powder x-ray diffraction scan comparing rebaudioside A polymorphs, Form 3A and Form 3B, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 6 is a powder x-ray diffraction scan comparing rebaudioside A polymorphs, Forms 2, 3A and 3B, on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 7 is a powder x-ray diffraction scan of rebaudioside A polymorph Form 1 on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 8 is a powder x-ray diffraction scan of rebaudioside A polymorph Form 2 on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 9 is a powder x-ray diffraction scan of rebaudioside A polymorph Form 3A on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 10 is a powder x-ray diffraction scan of rebaudioside A polymorph Form 3B on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

Fig. 11 is a powder x-ray diffraction scan of rebaudioside A amorphous Form 4 on a plot of the scattering intensity versus the scattering angle 2θ in accordance with an embodiment of this invention.

DETAILED DESCRIPTION OF INVENTION

Rebaudioside A is a natural high-potency sweetener that generally is available at moderate cost at $\leq 80\%$ purity and at $> 80\%$ purity only at high cost. Commercial samples of rebaudioside A often have a bitter taste that is believed to be due to impurities. Accordingly, there exists a need for a substantially pure rebaudioside A and

a simple and economic method for purifying rebaudioside A in order to obtain a substantially pure rebaudioside A suitable for use as a natural high-potency sweetener.

As used herein, the term "substantially" or "substantially pure" refers to a rebaudioside A composition that includes at least about 85 % by dry weight of the rebaudioside A, in another embodiment at least about 90 % by dry weight, in another embodiment from about 95 % to about 98 % by dry weight, and in yet another embodiment from about 99 % to about 100 % by dry weight.

Exemplary embodiments of this invention satisfy these needs by providing a method for purifying crude rebaudioside A to substantially pure rebaudioside A by crystallizing a crude rebaudioside A from an aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight and crystallizing in at least one step a substantially pure rebaudioside A. Other exemplary embodiments of this invention encompass a composition of a substantially pure rebaudioside A and compositions comprising one, or more than one, polymorph(s) of rebaudioside A. Still other exemplary embodiments of this invention encompass an amorphous form of rebaudioside A and methods of preparing amorphous forms of rebaudioside A. In yet another embodiment, a method for converting one form of polymorph into another form of polymorph or amorphous form is provided. Exemplary embodiments of this invention are described in detail below and illustrated in Figures 1-11.

20

Method of Purifying Crude Rebaudioside A Mixture

Crude rebaudioside A products are commercially available comprising rebaudioside A in purities from about 40 % to about 95 % by weight, about 60 % to about 85 % by weight, or about 70 % to about 85 % by weight. It is envisioned that crude rebaudioside A in its raw form as extracted from Stevia plants, may be purified by recrystallization. The primary impurities, identified by HPLC, are stevioside, rebaudioside B, rebaudioside C, and rebaudioside D. Rebaudioside D impurities can be removed by increasing the amount of water in an aqueous organic recrystallization solvent; however, excessive water content in the crystallization solvent will result in a lower recovery of rebaudioside A. Rebaudioside B impurity can be reduced significantly by slurring the crude rebaudioside A in an organic solvent or an aqueous organic solution or through treatment of the crude rebaudioside A solution with an

anion exchange resin. Accordingly, the method of purification depends on the impurities present in the crude rebaudioside A starting material.

In an exemplary embodiment of a method for purifying rebaudioside A 110, illustrated in Figure 1, crude rebaudioside A 112 may be combined 114 with an aqueous organic solution 116 to form a rebaudioside A solution 118. The aqueous organic solution 116 comprises water in an amount from about 10 % to about 25 % by weight and at least one organic solvent. Alternatively, the aqueous organic solution 116 may comprise water in an amount from about 15 % to about 20 % by weight and at least one organic solvent.

Aqueous organic solvents, as used herein, refer to mixtures of water and at least one organic solvent. Non-limiting examples of organic solvents include alcohol, acetone, and acetonitrile. Alcohol, as used herein, refers to any straight, branched, or cyclic; substituted or unsubstituted alkyl, alkenyl, or alkynyl group attached to at least one hydroxyl moiety. Non-limiting examples of alcohols include ethanol, methanol, isopropanol, 1-propanol, 1-butanol, 2-butanol, tert-butanol, and isobutanol.

In an exemplary embodiment, the aqueous organic solution 116 comprises a mixture of water and at least one organic solvent. In another exemplary embodiment, at least one organic solvent comprises an alcohol, the alcohol comprising ethanol, methanol, or mixtures thereof. In exemplary embodiments wherein the at least one organic solvent comprises a mixture of ethanol and methanol, the ethanol and methanol may be combined in the aqueous organic solvent in a weight ratio ranging from about 20 parts to about 1 part ethanol to about 1 part methanol. In another exemplary embodiment, the ethanol and methanol may be combined in the aqueous organic solvent in a weight ratio ranging from about 3 parts to about 1 part ethanol to about 1 part methanol.

In an exemplary embodiment, the rebaudioside A solution 118 comprises the aqueous organic solvent 116 and the crude rebaudioside A 112 in a weight ratio ranging from about 10 to about 4 parts aqueous organic solvent to about 1 part crude rebaudioside A. In another exemplary embodiment, the rebaudioside A solution 118 comprises the aqueous organic solution 116 and the crude rebaudioside A 112 in a

weight ratio ranging from about 5 to about 3 parts aqueous organic solvent to about 1 part crude rebaudioside A.

In an exemplary embodiment, the method 110 may be carried out at approximately room temperature. In another embodiment, the method 110 further comprises the step of heating 120 the rebaudioside A solution 118. In an embodiment, the step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution to a temperature in a range from about 20°C to about 70°C, from about 20°C to about 60°C, from about 20°C to about 40°C, or from about 40°C to about 60°C. In another embodiment, the step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution to about reflux temperature. The step of heating 120 the rebaudioside A solution 118 comprises heating the rebaudioside A solution for about 0.25 hours to about 8 hours. In another exemplary embodiment, wherein the method for purifying rebaudioside A 110 comprises the step of heating 120 the rebaudioside A solution 118, the method further comprises the step of cooling 122 the rebaudioside A solution. In an embodiment, the step of cooling 122 the rebaudioside A solution 118 comprises cooling the rebaudioside A solution to a temperature in the range from about 4°C to about 25°C. The step of cooling 122 the rebaudioside A solution 118 comprises cooling the rebaudioside A solution for about 0.5 hours to about 24 hours.

The method for purifying rebaudioside A 110 further comprises the step of crystallizing 124 from the rebaudioside A solution 118 in a single step a substantially pure rebaudioside A composition 126 comprising rebaudioside A in an amount greater than about 85 % by weight on a dry basis, greater than about 90 % by weight on a dry basis, greater than about 95 % by weight on a dry basis, greater than about 97 % by weight on a dry basis, greater than about 98 % by weight on a dry basis, or greater than about 99 % by weight on a dry basis. The rebaudioside A solution 118 during the single crystallization step may be stirred or unstirred.

In an exemplary embodiment, the method 110 may further comprise the optional step of seeding 128 the rebaudioside A solution 118 at an appropriate temperature with substantially pure crystals of rebaudioside A 130 sufficient to promote crystallization of the rebaudioside A to form pure rebaudioside A. An amount of rebaudioside A 130 sufficient to promote crystallization of substantially pure

rebaudioside A 126 comprises an amount of rebaudioside A from about 0.0001 % to about 1 % by weight of the rebaudioside A present in the solution. In another embodiment, an amount of rebaudioside A 130 sufficient to promote crystallization of the rebaudioside A to form a composition of a substantially pure rebaudioside A 126

5 comprises an amount of rebaudioside A from about 0.01 % to about 1 % by weight. An appropriate temperature for the step of seeding 128 comprises a temperature in a range from about 18°C to about 35°C.

In another exemplary embodiment, the method further comprises the steps of separating 132 and washing 134 the substantially pure rebaudioside A composition 126.

10 The substantially pure rebaudioside A composition 126 may be separated from the aqueous organic solution 118 by a variety of solid-liquid separation techniques that utilize centrifugal force, that include, without limitation, vertical and horizontal perforated basket centrifuge, solid bowl centrifuge, decanter centrifuge, peeler type centrifuge, pusher type centrifuge, Heinkel type centrifuge, disc stack centrifuge and

15 cyclone separation. Additionally, separation may be enhanced by any pressure, vacuum, or gravity filtration methods, that include without limitation, the use of belt, drum, nutsche type, leaf, plate, Rosenmund type, sparkler type, and bag filters and filter press. Operation of the rebaudioside A solid-liquid separation device may be continuous, semi-continuous or in batch mode. The substantially pure rebaudioside A

20 composition 126 also may be washed 134 on the separation device using various aqueous organic solvents 136 and mixtures thereof. The substantially pure rebaudioside A composition 126 can be partially or totally dried on the separation device using any number of gases, including, without limitation, nitrogen or argon, to evaporate residual liquid solvent 136. The substantially pure rebaudioside A

25 composition 126 may be automatically or manually removed from the separation device using liquids, gases or mechanical means by either dissolving the solid or maintaining the solid form.

In still another exemplary embodiment, the method 110 further comprises the step of drying 138 the substantially pure rebaudioside A composition 126. Such

30 methods are known to those skilled in the art and include, but are not limited to, the use of a rotary vacuum dryer, fluid bed dryer, rotary tunnel dryer, plate dryer, tray dryer, Nauta type dryer, spray dryer, flash dryer, micron dryer, pan dryer, high and low speed

paddle dryer and microwave dryer. In an exemplary embodiment, the step of drying 138 comprises drying the substantially pure rebaudioside A composition 126 using a nitrogen or argon purge to remove the residual solvent 120 at a temperature in a range from about 40°C to about 60°C for about 5 hours to about 100 hours.

5 In yet another exemplary embodiment, wherein the crude rebaudioside A mixture 112 comprises substantially no rebaudioside D impurity, the method 110 further comprises the step of slurrying 140 the composition of substantially pure rebaudioside A 126 with an organic solvent or an aqueous organic solvent 142 prior to the step of drying 138 the substantially pure rebaudioside A composition. The slurry
10 may be a mixture comprising a solid and an aqueous organic solvent or organic solvent, wherein the solid comprises the substantially pure rebaudioside A composition 126 and is only sparingly soluble in the aqueous organic solvent or organic solvent 142. In an embodiment, the substantially pure rebaudioside A composition 126 and aqueous organic solvent or organic solvent 142 may be present in the slurry in a weight ratio
15 ranging from about 15 parts to about 1 part aqueous organic solvent to about 1 part substantially pure rebaudioside A composition. In one embodiment, the slurry may be maintained at room temperature. In another embodiment, the step of slurrying 140 comprises heating the slurry to a temperature in a range from about 20°C to about 40°C. The substantially pure rebaudioside A composition 126 may be slurried for about 0.5
20 hours to about 24 hours.

In still yet another exemplary embodiment, the method further comprises the steps of separating 132 the substantially pure rebaudioside A composition 126 from the aqueous organic solvent 142 of the slurry and washing 134 the substantially pure rebaudioside A composition followed by the step of drying 138 the substantially pure rebaudioside A composition.
25

If further purification is desired, the method of purifying rebaudioside A 110 described herein may be repeated or the substantially pure rebaudioside A composition may be further purified using an alternative purification method, such as the column chromatography.

30 Purity, as used herein, represents the weight percentage of rebaudioside A present in a rebaudioside A composition in raw or purified form. In one embodiment, a

rebaudioside A composition comprises rebaudioside A in a particular purity, with the remainder of the composition comprising a mixture of other steviol glycosides or any component that is not rebaudioside A. The purity of the composition may be measured using methods known to those of ordinary skill in the art. One such method includes high performance liquid chromatography (HPLC). Those of ordinary skill in the art also should appreciate that the moisture in the sample may affect the accuracy of purity measurements. Accordingly, the composition should be substantially dry when measured for purity. As used herein, a substantially dry composition comprises up to about 10 % by weight of moisture.

10 Rebaudioside A Polymorphic and Amorphous Forms

The purification of rebaudioside A using the method described hereinabove results in the formation of at least three different polymorphs of rebaudioside A: Form 1: a rebaudioside A hydrate; Form 2: an anhydrous rebaudioside A, and Form 3: a rebaudioside A solvate. Those of ordinary skill in the art will appreciate that both the aqueous organic solution and the temperatures of the purification process described herein may influence the resulting polymorphs of a substantially pure rebaudioside A composition.

Polymorphism is defined as the ability of a substance to exist as two or more crystalline states that have different arrangements and/or conformations of the molecules in the crystal lattice. Approximately 30 % of organic compounds are believed to exhibit polymorphism (Zell, et al., *Tetrahedron* 56(36)6603-16 (2000)). Polymorphism is important in the formulation of pharmaceuticals, pigments and dyes, sweeteners, explosives, and agrochemicals. Polymorphism may cause physical properties such as density, melting point, and rate of dissolution to change.

25 The polymorphs of rebaudioside A were identified by analysis of samples with powder x-ray diffraction (XRPD), a technique well known to those skilled in the art. Figs. 3-11 are XRPD scans of substantially pure rebaudioside A compositions obtained from the purification process described herein. The XRPD scans of rebaudioside A polymorphs were created by plotting the scattering intensity versus the scattering angle 2 θ . Samples were analyzed by XRPD using a Shimadzu XRD-6000 X-ray powder diffractometer using Cu K α radiation. The instrument was equipped with a long fine

focus X-ray tube. The tube voltage and amperage were set to 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1°, and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A θ -2 θ continuous scan at 3°/min (0.4 sec/0.02° step) from 2.5 to 40° 2 θ was used. A silicon standard was analyzed to check the instrument alignment. Data were collected and analyzed using XRD-60000 v. 4.1. The patterns exhibit resolution of reflections, indicating that the samples are comprised of crystalline material.

Fig. 3 shows representative patterns for Form 1, Form 2, and Forms 3A (methanol solvate) and 3B (ethanol solvate). The pattern for Form 2 (top pattern) is distinctively different from the other patterns. It should be noted that multiple polymorphs can exist within each classification of Forms 1, 2, and 3.

Fig. 4 highlights the differences between Forms 1 and 2. Additionally, the two patterns of Form 2 are shown to illustrate the reproducibility in generation of the different polymorphs under varying recrystallization conditions of the polymorphs.

Fig. 5 shows a significant similarity between the XRPD patterns of Forms 3A and 3B. Not wishing to be bound by any theory, it is possible that these polymorphs are isostructural solvates, wherein the only differences between the patterns are the shifting of certain peaks due to the variation of the solvent identity. This isostructural relationship between Forms 3A and 3B could be verified by indexing the patterns if necessary. The asterisks identify the peaks that are shifted to the right by about 0.2 degrees 2 θ in the pattern for Form 3A. In addition, several peaks in Form 3B are more intense than the corresponding peaks in Form 3A. For example, the peaks at 5.5, 11.0, 14.2, and 19.4 degrees are more intense for Form 3B than for Form 3A.

Fig. 6 compares Form 2 to Forms 3A and 3B from Fig. 5. Form 2 is more similar to Form 3A than to that of Form 3B. Although the peaks identified in Fig. 5 as being more intense in Form 3B than in Form 3A are not observed in the pattern of Form 2, there are at least three peaks (marked with a double-asterisks underneath the patterns) that show the reverse trend (i.e., the peaks are present in Form 2, small in Form 3A, and larger in Form 3B). Finally, a large peak in Form 3B at 17.6 degrees appears to be shifted slightly to the right in Form 3A (17.9 degrees) and shifted further to the right in Form 2 (18.0 degrees). Two other sets of peaks between 21 and 23

degrees show this shifting as well. Not wishing to be bound by any theory, the shifting of the peaks may be an indication that Form 3A is partially desolvated, thus containing a mixture of both the solvate and Form 2 crystals.

Figs. 7-10 are XRPD scans of the individual polymorphs Form 1, Form 2, Form 3A, and Form 3B, respectively, from a substantially pure rebaudioside A composition obtained from the purification process described hereinabove.

As illustrated in Fig. 2, the type of polymorph formed may be dependent on the factors such as the composition of the aqueous organic solution, the temperature of the crystallization step, and the temperature during the drying step. Not wishing to be bound by any theory, Form 1 and Form 3 are believed to be formed during the single crystallization step while Form 2 is believed to be formed during the drying step after conversion from Form 1 and Form 3.

Low temperatures during the crystallization step, in the range of about 20°C to about 50°C, and a low ratio of water to the organic solvent in the aqueous organic solvent results in the formation of Form 3. High temperatures during the crystallization step, in the range of about 50°C to about 80°C, and a high ratio of water to the organic solvent in the aqueous organic solvent results in the formation of the Form 1. Form 1 can be converted to Form 3 by slurring in an anhydrous solvent at about room temperature for about 2 to about 16 hours or by slurring in an anhydrous solvent at about reflux temperature for about 0.5 to about 3 hours. Form 3 can be converted to Form 1 by slurring the polymorph in water at about room temperature for approximately 16 hours or at about reflux temperature for about 2 to about 3 hours. Form 3 can be converted to the Form 2 during the drying process; however, increasing either the drying temperature above about 70°C or the drying time of a substantially pure rebaudioside A composition can result in decomposition of the rebaudioside A and increase the remaining rebaudioside B impurity in the substantially pure rebaudioside A composition. Form 2 can be converted to Form 1 with the addition of water.

In addition to the at least three polymorphic forms of rebaudioside A, the purification of rebaudioside A may result in the formation of an amorphous form of rebaudioside A, Form 4, as shown in Fig. 11. Form 4 has a broad amorphous halo that identifies the composition as being amorphous.

Amorphous, as used herein, describes a non-crystalline solid material. The amorphous form of rebaudioside A (Form 4) has an improved rate of dissolution as compared to the polymorphic forms of rebaudioside A (Forms 1, 2, or 3). Those of ordinary skill in the art should appreciate that the rate of dissolution of a sweetener composition may be important in the formulation of solid and liquid sweetenable compositions, non-limiting examples of which include chewing gum, baked goods, and beverages.

As described hereinabove, Form 4 may be obtained during the initial purification of rebaudioside A or directly from any individual polymorph or combination of polymorphs using methods well known to those of ordinary skill in the art. In addition, Form 4 may be obtained from a crude rebaudioside A composition or a substantially pure rebaudioside A composition obtained through purification means other than those described hereinabove. Non-limiting examples of methods for preparing amorphous forms of rebaudioside A include ball milling, precipitation, lyophilization, cryogrinding, and spray-drying of a rebaudioside A composition.

In a particular embodiment, the purification of rebaudioside A described hereinabove results in a composition comprising the amorphous rebaudioside A of Form 4. Those of ordinary skill in the art should appreciate that the parameters of the crystallization procedure may be modified to enhance the formation of Form 4.

In another particular embodiment, Form 4 can be prepared from a rebaudioside A composition by spray-drying a solution of the rebaudioside A composition. Briefly described, spray-drying generally requires the feed of a solution of rebaudioside A through a feed pump into a nozzle atomizer which atomizes the solution into a spray of droplets with the help of a constant flow of nitrogen/air. The moisture is evaporated from the droplets under controlled temperature conditions and airflow conditions in the drying chamber, resulting in the formation of dry particles of amorphous rebaudioside A. The purity of the amorphous rebaudioside A will depend upon the purity of the solution of rebaudioside A.

In another particular embodiment, Form 4 can be prepared from a rebaudioside A composition by milling non-amorphous forms of rebaudioside A. Milling is a mechanical process that is believed to produce localized areas of energy that convert

crystalline forms of rebaudioside A to the amorphous form. Exemplary milling techniques include ball milling or air jet milling, both techniques well known to those of ordinary skill in the art. Briefly described, non-amorphous forms of rebaudioside A are milled for a period of time and at a speed effective to form an amorphous rebaudioside A. These parameters may be determined by those of ordinary skill in the art. Typical milling time periods may range from about 15 minutes to about 2 hours, although other time periods also may be employed.

The material properties of the three rebaudioside A polymorphs and the rebaudioside A amorphous form are summarized in the following table:

Table 1: Rebaudioside A Polymorph and Amorphous Forms

	Form 1 Polymorph	Form 2 Polymorph	Form 3 Polymorph	Form 4 Amorphous
Rate of dissolution in H ₂ O at 25°C	Very low (<0.2 % in 60 minutes)	Intermediate (<30 % in 5 minutes)	High (> 30 % in 5 minutes)	High (> 35 % in 5 minutes)
Alcohol content	< 0.5 %	< 1 %	1-3 %	< 0.05 %
Moisture content	> 5 %	< 1 %	< 3 %	< 6 %

The above-described material properties are only illustrative of particular embodiments of the polymorphic and amorphous forms of rebaudioside A. Those of ordinary skill in the art should appreciate that the anhydrous rebaudioside A polymorph (Form 2), rebaudioside A solvate polymorph, and amorphous rebaudioside A are hygroscopic and may absorb moisture to an amount up to about 10 % by weight on a dry basis.

Those of ordinary skill in the art should appreciate that the rebaudioside A composition may be modified to obtain a desired mixture of rebaudioside A polymorphic and amorphous forms depending on the desired qualities of the rebaudioside A composition (i.e., rate of dissolution, etc.). In one embodiment, a substantially pure rebaudioside A composition may comprise a particular polymorphic or amorphous form of rebaudioside A in an amount in the range of about 1 % to about 100 % by weight. For example, a substantially pure rebaudioside A composition may comprise a polymorphic or amorphous form of rebaudioside A in an amount greater than about 25 % by weight, more particularly in an amount greater than about 50 % by weight, still more particularly in an amount greater than about 75 % by weight, or still even more particularly in an amount greater than about 85 % by weight. Suitable amounts of rebaudioside A polymorphic or amorphous forms also may be used within

these ranges. In another embodiment, a substantially pure rebaudioside A composition may comprise a combination of particular polymorphic and/or amorphous form of rebaudioside A.

The present invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications, and equivalents thereof which, after reading the description therein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or the scope of the appended claims. Unless otherwise specified, percentages (%) are by weight.

EXAMPLES

The purity of the rebaudioside A compositions described in the examples hereinbelow was determined using HPLC. Methods of performing HPLC analysis are well known to those of ordinary skill in the art. Briefly described, the HPLC analysis was performed using a ZORBAX NH₂ column (150 x 4.6 mm, 5 μm) at a temperature of 30°C. The mobile phase comprised a solution of 20 % buffer (0.0125 % acetic acid and 0.0125 % ammonium acetate) and 80 % acetonitrile at a flow rate of 1.5 mL/min. 12 μL of each sample was injected in duplicate and the sample was analyzed using a UV detector at 210 nm (4 nm bandwidth) with a reference of 260 nm (100 nm bandwidth). The HPLC analysis required a run time ranging from 40 to 60 min.

A buffer solution of 0.0125 % acetic acid and 0.0125 % ammonium acetate was prepared by dissolving 0.125 g ammonium acetate and 125 μL glacial acetic acid in one liter of water. The retention time of rebaudioside B was adjusted by varying the ratio of ammonium acetate to acetic acid while maintaining a total of 0.025 % of both combined. Increasing the amount of acetic acid decreased the retention time of rebaudioside B.

The mobile phase was prepared by mixing the buffer solution with acetonitrile to achieve a rebaudioside A retention time of 7.0 ± 0.5 min. Initially, this was approximately 20 % buffer (200 mL of buffer and 800 mL of acetonitrile). Increasing the amount of acetonitrile by 1 to 2 % increased the retention time of rebaudioside A by about one minute.

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A diluent solution was prepared by mixing 750 mL of acetonitrile and 250 mL of the buffer solution. Rebaudioside A standards were prepared by diluting 20.0 ± 0.5 mg (recorded to the nearest 0.1 mg) of the rebaudioside A standard with 4 mL of the diluent solution to make a standard solution of approximately 5000 mg/L. The rebaudioside A standard solution was injected at 10.8, 11.4, 12.6 and 13.2 μ L. The moisture content was measured by Karl Fischer analysis every time a standard was prepared and corrections were made based on the solvent purity according to the certificate of analysis. Alternatively, rebaudioside A standards were prepared by diluting individual samples of 18, 19, 21 and 22 (each ± 0.2) mg of rebaudioside A standard with 4 mL of the diluent solution (correcting for moisture and purity). The individually prepared samples were injected at the same level as the samples (12 μ L).

Stevioside standards were prepared by diluting 12.5 ± 0.5 mg (recorded to the nearest 0.1 mg) of the stevioside standard with 5 mL of the diluent solution to make a standard solution of approximately 2500 mg/L standard (stock A) (correcting for moisture and purity). The stevioside standard was then diluted using one mL of stock A to ten mL of diluent to produce a 250 mg/L standard (stock B), and stock standards were diluted to final concentrations ranging from 2.5 to 50 mg/L.

Samples of the rebaudioside A compositions were prepared by diluting 125 ± 2 mg (recorded to the nearest 0.1 mg) of the rebaudioside A composition with 25 mL of the diluent solution to make a sample solution of approximately 5000 mg/L (correcting for moisture). If the samples were not analyzed immediately, they were stored without headspace, under nitrogen, and desiccated.

The following table provides a guideline for retention times (RT) for rebaudioside A and other steviol glycosides. However, those of ordinary skill in the art should appreciate that the retention times may be modified as needed.

Table 2: HPLC Retention Guidelines

Compound	RT (min)
Stevioside	4.53
Rebaudioside C	5.21
Rebaudioside F	5.62
Rebaudioside A	7.07
Rebaudioside D	15.79
Steviolbioside	18.35
Rebaudioside B	35.83

EXAMPLE SET A

Table 3: Summary of Examples A1-3

	Crude Rebaudioside A (g)	Ethanol (95 %)(mL)	Solvent Methanol (99 %)(mL)	Water (mL)	Heating T (°C)	Drying T (°C)	Yield (g)	HPLC Purity (wt/wt %)
A1	400	1200	400	320	50	50	130	98.9
A2	100	320	120	50	30-40	60	72	98.3
A3	50	160	60	25	~ 30	60	27.3	98.2

EXAMPLE A1

Crude rebaudioside A (77.4 % purity) mixture was obtained from a commercial source. The impurities (6.2 % stevioside, 5.6 % rebaudioside C, 0.6 % rebaudioside F, 1.0 % other steviol glycosides, 3.0 % rebaudioside D, 4.9 % rebaudioside B, 0.3 % steviolbioside) were identified and quantified using HPLC on a dry basis (moisture content 4.7 %).

Crude rebaudioside A (400 g), ethanol (95 %, 1200 mL), methanol (99 %, 400 mL) and water (320 mL) were combined and heated to 50°C for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystals were filtered and washed twice with ethanol (2 x 200 mL, 95%) and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm).

The final composition of substantially pure rebaudioside A (130 g) comprised 98.91 % rebaudioside A, 0.06 % stevioside, 0.03 % rebaudioside C, 0.12 %

rebaudioside F, 0.13 % other steviol glycosides, 0.1 % rebaudioside D, 0.49 % rebaudioside B and 0.03 % steviolbioside, all by weight.

EXAMPLE A2

5 Crude rebaudioside A (80.37 %) was obtained from a commercial source. The impurities (6.22 % stevioside, 2.28 % rebaudioside C, 0.35 % dulcoside A, 0.78 % rebaudioside F, 0.72 % other steviol glycosides, 3.33 % rebaudioside B, 0.07 % steviolbioside) were identified and quantified by HPLC on a dry basis (moisture content 3.4 %).

10 Crude rebaudioside A (100 g), ethanol (95%, 320 mL), methanol (99%, 120 mL) and water (50 mL) were combined and heated to 30-40°C for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystals were filtered and washed twice with ethanol (2 x 50 mL, 95 %). The wet filter cake (88 g) was slurried in ethanol (95 %, 1320 mL) for 16 hours, filtered, washed with ethanol (95 %, 2 x 100
15 mL) and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm).

20 The final composition of substantially pure rebaudioside A (72 g) comprised 98.29 % rebaudioside A, 0.03 % stevioside, 0.02 % rebaudioside C, 0.17 % rebaudioside F, 0.06 % rebaudioside D and 1.09 % rebaudioside B. Steviolbioside was not detected by HPLC.

EXAMPLE A3

25 Crude rebaudioside A (80.37 %) was obtained from a commercial source. The impurities (6.22 % stevioside, 2.28 % rebaudioside C, 0.35% dulcoside A, 0.78 % rebaudioside F, 0.72 % other steviol glycosides, 3.33 % rebaudioside B, 0.07 % steviolbioside) were identified and quantified by HPLC on a dry basis (moisture content 3.4 %).

30 Crude rebaudioside A (50 g), ethanol (95 %, 160 mL), methanol (99 %, 60 mL) and water (25 mL) were combined and heated to approximately 30°C for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystals were filtered and washed twice with ethanol (2 x 25 mL, 95 %). The wet filter cake (40 g) was

slurried in methanol (99 %, 600 mL) for 16 hours, filtered, washed with methanol (99 %, 2 x 25 mL) and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm).

The final composition of substantially pure rebaudioside A (27.3g) comprised 5 98.22 % rebaudioside A, 0.04 % stevioside, 0.04 % rebaudioside C, 0.18 % rebaudioside F, 0.08 % rebaudioside D and 1.03 % rebaudioside B. Steviolbioside was not detected by HPLC.

EXAMPLE SET B

Table 4: Summary of Examples B1-19

	Crude Rebaudioside A (g)	Solvent			Wash Solvent	Yield (g)	HPLC Purity (%)
		Ethanol (95%)(mL)	Organic Co- solvent (mL)	Water (mL)			
B1	5	16	Methanol (6)	2	EtOH/MeOH (4:1.5 v/v)	3.2	>97
B2	5	16	Methanol (4)	2	EtOH/MeOH (4:1 v/v)	3.1	>97
B3	5	9.5	1-Butanol (9.5)	1	EtOH/1-Butanol (1:1 v/v)	3.2	>95
B4	5	9.5	1-Butanol (9)	1	EtOH/MeOH (1:1 v/v)	3.5	>96
B5	5	12.5	Methanol (6)	2	*EtOH/MeOH (4:1 v/v)	3.3	>97
B6	5	12.5	Acetonitrile (6)	1.5	*EtOH/Acetonitrile (6:3 v/v)	3.4	>95
B7	5	14.5	Ethyl acetate (4)	4	*EtOH/Ethyl Acetate (7:2 v/v)	3.4	>95
B8	5	16	Methanol (6)	2	EtOH/MeOH (4:1.5 v/v)	3.2	>97
B9	5	16	Methanol (4)	2	EtOH/MeOH (4:1 v/v)	3.1	>97
B10	5	14.5	Methanol (4)	1.5	EtOH/MeOH (7:2 v/v)	3.4	>97
B11	5	16	Methanol (6)	1.5	EtOH/MeOH (8:3 v/v)	3.2	>97
B12	5	16	Methanol (6)	2	* EtOH/MeOH (8:3 v/v)	3.2	>96
B13	5	16	Methanol (6)	2	* EtOH/MeOH (8:3 v/v)	3.4	>96
B14	5	15	Methanol (5)	2.5	EtOH/MeOH (3:1 v/v)	3.2	>97
B15	5	15	Methanol (5)	3	EtOH/MeOH (3:1 v/v)	2.7	>97
B16	5	15	Methanol (6)	3.5	EtOH/MeOH (3:1 v/v)	2.6	>99
B17	5	15	Methanol (5)	4	EtOH/MeOH (3:1 v/v)	2.3	>99
B18	5	16	Methanol (6)	2.5	*EtOH/MeOH (8:3 v/v)	3.0	>97
B19	5	16	Methanol (6)	2.5	*EtOH/MeOH (8:3 v/v)	3.2	>98

EXAMPLE B1

Crude rebaudioside A (77.4 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5 mL, 4:1.5, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 97 % by HPLC).

EXAMPLE B2

Crude rebaudioside A (77.4 % purity, 5 g), ethanol (95 %, 16 mL), methanol (4 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5 mL, 4:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.1 g of purified product (> 97 % by HPLC).

EXAMPLE B3

Crude rebaudioside A (77.4 % purity, 5 g), ethanol (95 %, 9.5 mL), 1-butanol (9.5 mL) and water (1 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:1-butanol (5 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 95 % by HPLC).

EXAMPLE B4

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 9.5 mL), methanol (9 mL) and water (1 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.5 g of purified product (> 96 % by HPLC).

EXAMPLE B5

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 12.5 mL), methanol (6 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C. The solution was seeded with 10 mg of 98 % pure rebaudioside A and the mixture was left at 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5 mL, 4:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.3 g of purified product (> 97 % by HPLC).

EXAMPLE B6

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 12.5 mL), acetonitrile (6 mL) and water (1.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C. The solution was seeded with 10 mg of 98 % pure rebaudioside A and the mixture was left at 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:acetonitrile (5 mL, 6:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.4 g of purified product (> 95 % by HPLC).

EXAMPLE B7

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 14.5 mL), ethyl acetate (4 mL) and water (1.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C. The solution was seeded with 10 mg of 98 % pure rebaudioside A and the mixture was left at 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:acetonitrile (5 mL, 7:2, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.4 g of purified product (> 95 % by HPLC).

EXAMPLE B8

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.5 mL, 4:1.5, v/v) mixture and dried in a

vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 97 % by HPLC).

EXAMPLE B9

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (4 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 4:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.1 g of purified product (> 97 % by HPLC).

10 EXAMPLE B10

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 14.5 mL), methanol (4 mL) and water (1.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 7:2, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.4 g of purified product (> 97 % by HPLC).

EXAMPLE B11

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (1.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 97 % by HPLC).

EXAMPLE B12

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C and seeded with 10 mg of pure rebaudioside A (> 98 %). The mixture was kept at room temperature for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried

in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 98 % by HPLC).

EXAMPLE B13

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol
5 (6 mL) and water (2 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C and seeded with 10 mg of pure rebaudioside A (> 98 %). The mixture was kept at room temperature for 16 hours while stirring. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure
10 - (20 mm) to yield 3.4 g of purified product (> 96 % by HPLC).

EXAMPLE B14

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 15 mL), methanol
(5 mL) and water (2.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours while stirring. The white crystalline
15 product was filtered, washed twice with ethanol:methanol (5.0 mL, 3:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 97 % by HPLC).

EXAMPLE B15

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 15 mL), methanol
20 (5 mL) and water (3.0 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours while stirring. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 3:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 2.7 g of purified product (> 97 % by HPLC).

25 EXAMPLE B16

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 15 mL), methanol
(5 mL) and water (3.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours while stirring. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 3:1, v/v) mixture

and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 2.6 g of purified product (> 99 % by HPLC).

EXAMPLE B17

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 15 mL), methanol (5 mL) and water (4.0 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 16 hours while stirring. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 3:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 2.3 g of purified product (> 99 % by HPLC).

10 EXAMPLE B18

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (2.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C. This mixture was stirred at room temperature for 15-30 minutes during which time crystals started to appear. The stirring was stopped and the mixture was kept at room temperature for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.0 g of purified product (> 97 % by HPLC).

EXAMPLE B19

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 16 mL), methanol (6 mL) and water (2.5 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 2 hours. During this time crystals started to appear. The mixture was stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.2 g of purified product (> 98 % by HPLC).

EXAMPLE SET C

Table 5: Summary of Examples C1-9

	Crude Rebaudioside A (g)	Solvent			Wash Solvent	Yield (g)	HPLC Purity (%)
		Organic Solvent (mL)	Organic Co-solvent (mL)	Water (mL)			
C1	5	Isopropanol (9.5)	Methanol (9.5)	1	Isopropanol/MeOH (1:1 v/v)	3.85	>91
C2	5	<i>sec</i> -Butanol (9.5)	Methanol (9.5)	1	MeOH/ <i>sec</i> -Butanol (1:1 v/v)	4.0	>91
C3	5	1-Propanol (9.5)	Methanol (9.5)	1	MeOH/1-Propanol (1:1 v/v)	3.55	>91.2
C4	5	Ethanol (9.5)	1-Propanol (9.5)	1	EtOH/1-Propanol (1:1 v/v)	2.5	>94
C5	5	1-Butanol (9.5)	Methanol (9.5)	1	MeOH/1-Butanol (1:1 v/v)	3.7	>91.5
C6	5	Ethanol (9.5)	2-Propanol (9.5)	1	EtOH/2-Propanol (1:1 v/v)	2.4	>93.5
C7	5	Ethanol (9.5)	<i>sec</i> - Butanol (9.5)	1	EtOH/ <i>sec</i> -Butanol (1:1 v/v)	2.9	>93
C8	5	<i>tert</i> -Butanol (9.5)	Methanol (9.5)	1	MeOH/ <i>tert</i> -Butanol (1:1 v/v)	3.9	>83
C9	5	Ethanol (9.5)	<i>tert</i> - Butanol (9.5)	1	EtOH/ <i>tert</i> -Butanol (1:1 v/v)	2.9	>88

EXAMPLE C1

Crude rebaudioside A (80.37 % purity, 5 g), methanol (99 %, 9.5 mL), isopropanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with an ethanol:methanol (5.0 mL, 8:3, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.85 g of purified product (> 91.0 % by HPLC).

EXAMPLE C2

Crude rebaudioside A (80.37 % purity, 5 g), methanol (99 %, 9.5 mL), *sec*-butanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with a methanol: *sec*-butanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 4.0 g of purified product (> 91.0 % by HPLC).

EXAMPLE C3

Crude rebaudioside A (80.37 % purity, 5 g), methanol (99 %, 9.5 mL), 1-propanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with a methanol: 1-propanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.55 g of purified product (> 91.21 % by HPLC).

EXAMPLE C4

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 9.5 mL), 1-propanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with an ethanol: 1-propanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 2.5 g of purified product (> 94.0 % by HPLC).

EXAMPLE C5

Crude rebaudioside A (80.37 % purity, 5 g), methanol (99 %, 9.5 mL), 1-butanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with a methanol: 1-butanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.7 g of purified product (> 91.5 % by HPLC).

EXAMPLE C6

Crude rebaudioside A (80.37 % purity, 5 g), ethanol (95 %, 9.5 mL), 2-propanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with an ethanol: 2-propanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24

hours under reduced pressure (20 mm) to yield 2.4 g of purified product (> 93.5 % by HPLC).

EXAMPLE C7

Crude rebaudioside A (77.4 % purity, 5 g), ethanol (95 %, 9.5 mL), *sec*-butanol (9.5 mL) and water (1 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with an ethanol: *sec*-butanol (10.0 mL, 1:1, v/v) mixture and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 2.9 g of purified product (> 93.0 % by HPLC).

EXAMPLE C8

Crude rebaudioside A (77.4 % purity, 5 g), methanol (99 %, 9.5 mL), *tert*-butanol (9.5 mL) and water (1 mL) were combined and heated to about 40-50°C for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with methanol (99 %, 7.0 mL) and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 3.9 g of purified product (> 83.0 % by HPLC).

EXAMPLE C9

Crude rebaudioside A (77.4 % purity, 5 g), ethanol (95 %, 9.5 mL), *tert*-butanol (9.5 mL) and water (1 mL) were combined and heated to reflux for 10 minutes. The clear solution was cooled to 22°C for 2 hours and then stirred at room temperature for 16 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 7.0 mL) and dried in a vacuum oven at 50°C for 16-24 hours under reduced pressure (20 mm) to yield 2.9 g of purified product (> 88.0 % by HPLC).

EXAMPLE SET D

Table 6: Summary of Examples D1-12

	Crude Rebaudioside A (g)	Solvent		Wash Solvent	Yield (g)	HPLC Purity (%)
		Organic Solvent (mL)	Water (mL)			
D1	50	MeOH (180)	20	MeOH	29.8	96.2
D2	50	MeOH (160)	40	MeOH	31.2	95.5
D3	50	EtOH (188)	12	EtOH	37.3	93.4
D4	50	EtOH (184)	16	EtOH	31.7	95.3
D5	50	EtOH (180)	10	EtOH	35.7	94.7
D6	50	EtOH (176)	24	EtOH	38.2	97.3
D7	50	EtOH (172)	28	EtOH	32	98.1
D8	50	EtOH (160)	40	EtOH	19.8	99.5
D9	50	1-Propanol (180)	20	1-Propanol	27	92.9
D10	50	2-Propanol (180)	20	2-Propanol	34.9	91.4
D11	50	1-Butanol (180)	20	1-Butanol	40.6	93.1
D12	50	2-Butanol (180)	20	2-Butanol	40.4	90.5

EXAMPLE D1

5 Crude rebaudioside A (77.4 % purity, 50 g), methanol (99 %, 180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with methanol (99 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 29.8 g
10 of purified product (96.2 % by HPLC).

EXAMPLE D2

 Crude rebaudioside A (80.37 % purity, 50 g), methanol (99 %, 160 mL) and water (40 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 1 week. The white crystalline product
15 was filtered, washed twice with methanol (99 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 31.2 g of purified product (95.5 % by HPLC).

EXAMPLE D3

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 188 mL) and water (12 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 37.3 g of purified product (93.4 % by HPLC).

EXAMPLE D4

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 184 mL) and water (16 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 31.7 g of purified product (95.3 % by HPLC).

EXAMPLE D5

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 35.7 g of purified product (94.7 % by HPLC).

EXAMPLE D6

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 176 mL) and water (24 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 38.2 g of purified product (97.3 % by HPLC).

EXAMPLE D7

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 172 mL) and water (28 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 32.0 g of purified product (98.1 % by HPLC).

EXAMPLE D8

Crude rebaudioside A (80.37 % purity, 50 g), ethanol (95 %, 160 mL) and water (40 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with ethanol (95 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 19.8 g of purified product (99.5 % by HPLC).

EXAMPLE D9

Crude rebaudioside A (80.37 % purity, 50 g), 1-propanol (180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with 1-propanol (25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 27.0 g of purified product (92.9 % by HPLC).

EXAMPLE D10

Crude rebaudioside A (80.37 % purity, 50 g), 2-propanol (180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with 2-propanol (25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 34.9 g of purified product (91.4 % by HPLC).

EXAMPLE D11

Crude rebaudioside A (80.37 % purity, 50 g), 1-butanol (180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with 1-butanol (25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 40.6 g of purified product (93.1 % by HPLC).

EXAMPLE D12

Crude rebaudioside A (80.37 % purity, 50 g), 2-butanol (180 mL) and water (20 mL) were combined and heated to reflux for 30 minutes. The mixture was then allowed to cool to ambient temperature for 16-24 hours. The white crystalline product was filtered, washed twice with 2-butanol (25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 40.4 g of purified product (90.5 % by HPLC).

EXAMPLE SET E

Table 7: Summary of Examples E1-E3

	Crude Rebaudioside A (g)	Ethanol (95%)(mL)	Organic Co-solvent (mL)	Water (mL)	Methanol Slurry (mL)	Yield (g)	HPLC Purity (%)
E1	50	160	Methanol (60)	25	200	12.7	>97
E2	50	160	Methanol (60)	25	300	18.6	>97
E3	50	160	Methanol (60)	25	350	22.2	>97

EXAMPLE E1

Crude rebaudioside A (41 % purity, 50 g), ethanol (95 %, 160 mL), methanol (99.8 %, 60 mL) and water (25 mL) were combined by stirring at 22°C. A white product crystallized out in 5-20 hours. The mixture was stirred for additional 48 hours. The white crystalline product was filtered and washed twice with ethanol (95 %, 25 mL). The wet cake of white crystalline product then was slurried in methanol (99.8 %, 200 mL) for 16 hours, filtered, washed twice with methanol (99.8 %, 25 mL), and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 12.7 g of purified product (> 97 % by HPLC).

EXAMPLE E2

Crude rebaudioside A (48 % purity, 50 g), ethanol (95 %, 160 mL), methanol (99.8 %, 60 mL) and water (25 mL) was combined by stirring at 22°C. The white product crystallized out in 3-6 hours. The mixture was stirred for additional 48 hours.

- 5 The white crystalline product was filtered and washed twice with ethanol (95 %, 25 mL). The wet cake of white crystalline product then was slurried in methanol (99.8 %, 300 mL) for 16 hours, filtered, washed twice with methanol (99.8 %, 25 mL) and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 18.6 g of purified product (> 97 % by HPLC).

10 EXAMPLE E3

Crude rebaudioside A (55 % purity, 50 g), ethanol (95 %, 160 mL), methanol (99.8 %, 60 mL) and water (25 mL) was combined by stirring at 22°C. The white product crystallized out in 15-30 minutes. The mixture was stirred for an additional 48 hours. The white crystalline product was filtered and washed twice with ethanol (95 %, 25 mL). The wet cake of white crystalline product was slurried in methanol (99.8 %, 350 mL) for 16 hours, filtered, washed twice with methanol (99.8 %, 25 mL) and dried in a vacuum oven at 60°C for 16-24 hours under reduced pressure (20 mm) to yield 22.2 g of purified product (> 97 % by HPLC).

EXAMPLE F

- 20 A solution of substantially pure rebaudioside A obtained using the purification technique described hereinabove (>97 % pure by HPLC) was prepared in double distilled water (12.5 gm in 50 mL, 25 % concentration) by stirring the mixture at 40°C for 5 minutes. An amorphous form of rebaudioside A was formed by immediately using the clear solution for spray drying with the Lab-Plant spray drier SD-04 instrument (Lab-Plant Ltd., West Yorkshire, U.K.). The solution was fed through the feed pump into the nozzle atomizer, which atomized the rebaudioside A solution into a spray of droplets with the help of a constant flow of nitrogen / air. Moisture was evaporated from the droplets under controlled temperature conditions (about 90 to about 97°C) and airflow conditions in the drying chamber and resulted in the formation of dry particles.
- 25
- 30 This dry powder (11-12 g, H₂O 6.74 %) was discharged continuously from the drying

chamber and was collected in a bottle. The rate of dissolution in water at room temperature was determined to be > 35.0 %.

While the invention has been described in detail with respect to specific embodiments thereof, it will be appreciated that those skilled in the art, upon attaining an understanding of the foregoing, may readily conceive of alterations to, variations of, and equivalents to these embodiments. Accordingly, the scope of the present invention should be assessed as that of the appended claims and any equivalents thereof.

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We claim:

1. A method for purifying rebaudioside A comprising the steps of:
combining crude rebaudioside A and an aqueous organic solvent to form a rebaudioside A solution, the aqueous organic solution comprising water in an amount from about 10 % to about 25 % by weight; and
crystallizing from the rebaudioside A solution in a single step a substantially pure rebaudioside A composition comprising rebaudioside A in a purity greater than about 95 % by weight on a dry basis.
2. The method of claim 1, further comprising the step of heating the rebaudioside A solution.
3. The method of claim 2, further comprising the step of cooling the rebaudioside A solution.
4. The method of claim 1, wherein rebaudioside A solution in the single crystallization step is stirred or unstirred.
5. The method of claim 1, further comprising the step of seeding (optional) the rebaudioside A solution at an appropriate temperature with an amount of rebaudioside A sufficient to promote crystallization of rebaudioside A.
6. The method of claim 1, further comprising the steps of separating and washing the substantially pure rebaudioside A composition.
7. The method of claim 6, further comprising the step of drying the substantially pure rebaudioside A composition.

8. The method of claim 1, wherein the crude rebaudioside A comprises substantially no rebaudioside D impurity, and the method further comprises slurrying the substantially pure rebaudioside A composition in an aqueous organic solvent or in an organic solvent.
9. The method of claim 8, further comprising the steps of separating and washing the substantially pure rebaudioside A composition.
10. The method of claim 9, further comprising the step of drying the composition of a substantially pure rebaudioside A.
11. The method of claim 1, wherein the aqueous organic solvent comprises a mixture of at least one organic solvent and water.
12. The method of claim 11, wherein at least one organic solvent comprises an alcohol.
13. The method of claim 12, wherein the alcohol comprises ethanol.
14. The method of claim 12, wherein the alcohol comprises methanol.
15. The method of claim 12, wherein the alcohol comprises a mixture of ethanol and methanol.
16. The method of claim 15, wherein the ethanol and methanol are present in the aqueous organic solution in a weight ratio from about 20 parts to about 1 parts ethanol to about 1 part methanol.
17. The method of claim 15, wherein the ethanol and methanol are present in the aqueous organic solution in a weight ratio from about 3 parts to about 1 part ethanol to about 1 part methanol.

18. The method of claim 1, wherein the at least one aqueous organic solvent comprises an organic solvent selected from the group consisting of acetone, acetonitrile, methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, tert-butanol, and mixtures thereof.

19. The method of claim 1, wherein the aqueous organic solvent and the crude rebaudioside A are present in the rebaudioside A solution in a weight ratio from about 4 to about 10 parts aqueous organic solvent to about 1 part crude rebaudioside A.

20. The method of claim 1, wherein the aqueous organic solvent and the crude rebaudioside A are present in the rebaudioside A solution in a weight ratio from about 3 to about 5 parts aqueous organic solvent to about 1 part crude rebaudioside A.

21. The method of claim 1, wherein aqueous organic solvent comprises water in an amount from about 10 % to about 25 % by weight.

22. The method of claim 1, wherein the crude rebaudioside A mixture comprises rebaudioside A in a purity from about 40 % to about 95 % by weight.

23. The method of claim 1, wherein the crude rebaudioside A mixture comprises rebaudioside A in a purity from about 60 % to about 85 % by weight.

24. The method of claim 1, wherein the crude rebaudioside A mixture comprises rebaudioside A in a purity from about 70 % to about 85 % by weight.

25. The method of claim 1, wherein the method is carried out at approximately room temperature.

26. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to a temperature in a range from about 20°C to about 40°C.

27. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to a temperature in a range from about 40°C to about 60°C.

28. The method of claim 2, wherein the step of heating the rebaudioside A solution comprises heating the rebaudioside A solution to about a reflux temperature.

29. The method of claim 3, wherein the step of cooling the rebaudioside A solution comprises cooling the rebaudioside A solution to a temperature in a range from about 4°C to about 25°C.

30. The method of claim 3, wherein the step of cooling the rebaudioside A solution comprises cooling the rebaudioside A solution for about 0.5 hours to about 24 hours.

31. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 97 % rebaudioside A by weight on a dry basis.

32. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 98 % rebaudioside A by weight on a dry basis.

33. The method of claim 1, wherein the substantially pure rebaudioside A product comprises rebaudioside A in a purity greater than about 99 % rebaudioside A by weight on a dry basis.

34. The method of claim 1, further comprising the steps of:
heating the rebaudioside A aqueous organic solvent mixture;
cooling the rebaudioside A solution;
separating and washing a substantially pure rebaudioside A composition;
and
drying the substantially pure rebaudioside A composition.
35. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 7.
36. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 8.
37. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 9.
38. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises a polymorph having an X-ray diffraction pattern substantially similar to Figure 10.
39. A substantially pure rebaudioside A composition made according to the method of claim 1, wherein the substantially pure rebaudioside A composition comprises an amorphous form having an X-ray diffraction pattern substantially similar to Figure 11.
40. The method of claim 1, further comprising the step of forming an amorphous form of the substantially pure rebaudioside A composition.

41. The method of claim 38, wherein the step of forming an amorphous form of the substantially pure rebaudioside A composition comprises a method selected from the group consisting of ball milling, precipitation, lyophilization, cryogrinding, and spray-drying.

42. A substantially pure rebaudioside A composition made according to the method of claim 1.

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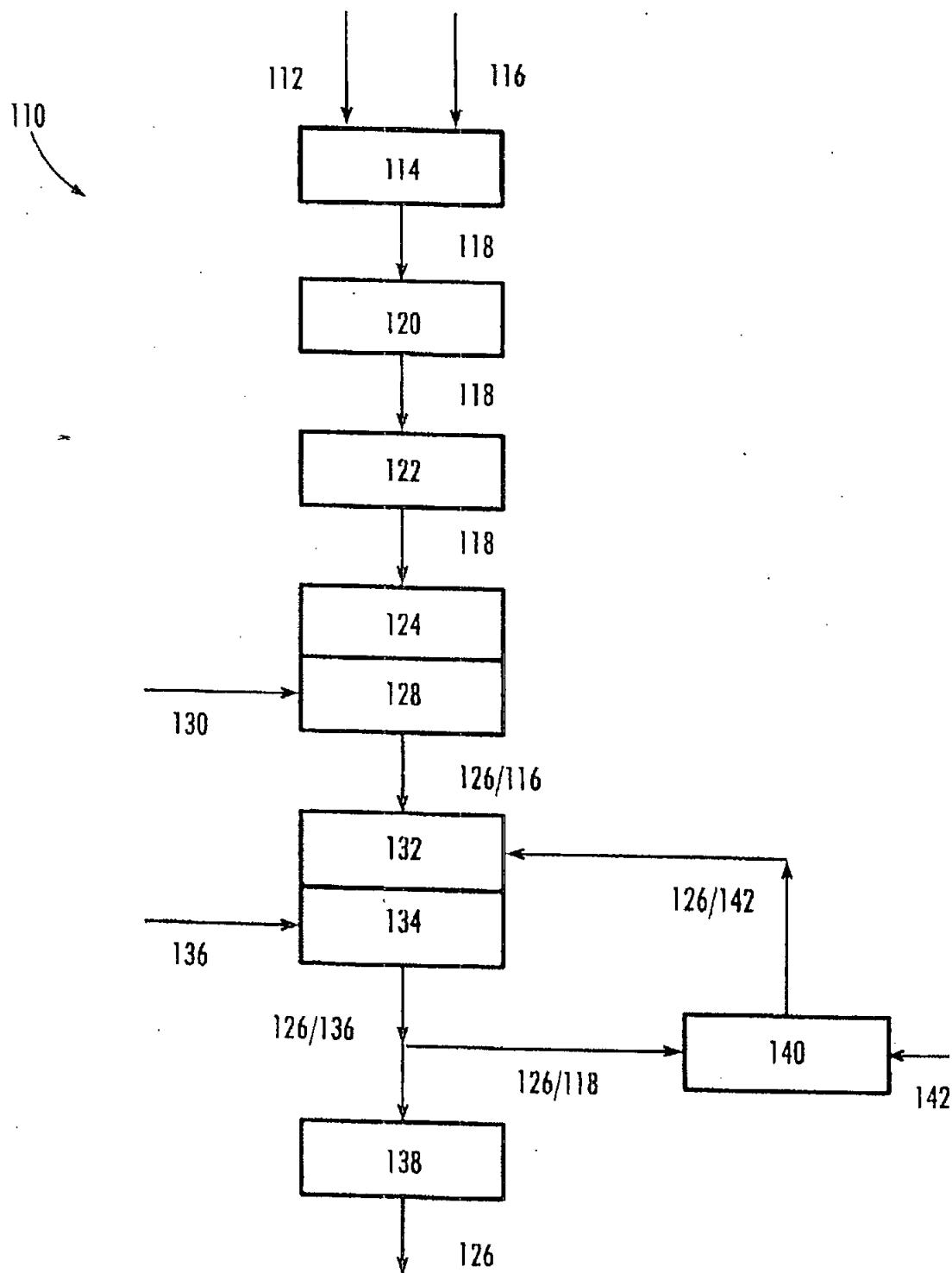


Fig. 1

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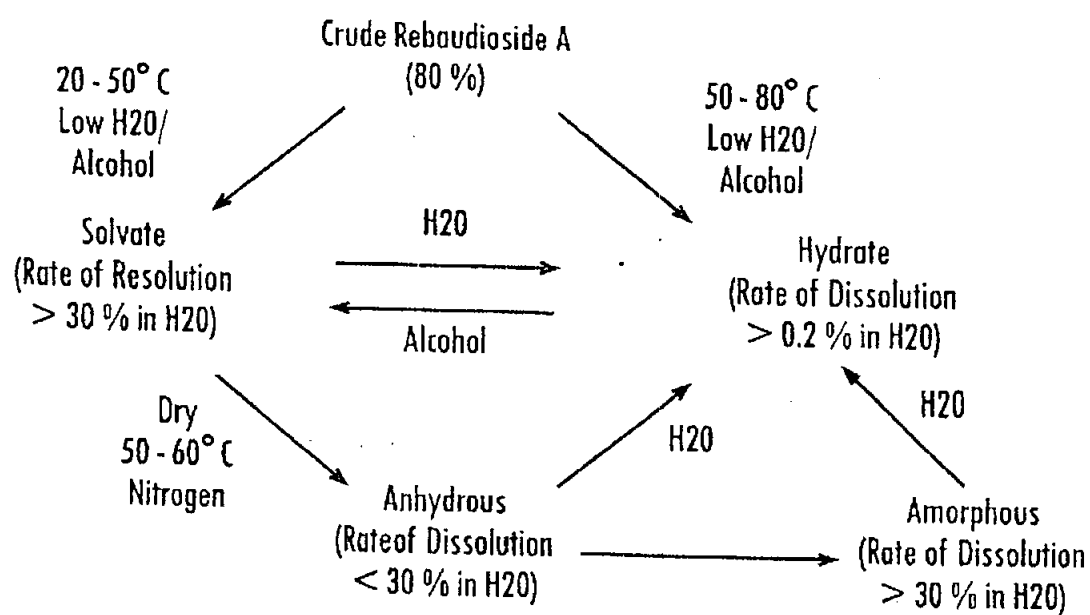


Fig. 2

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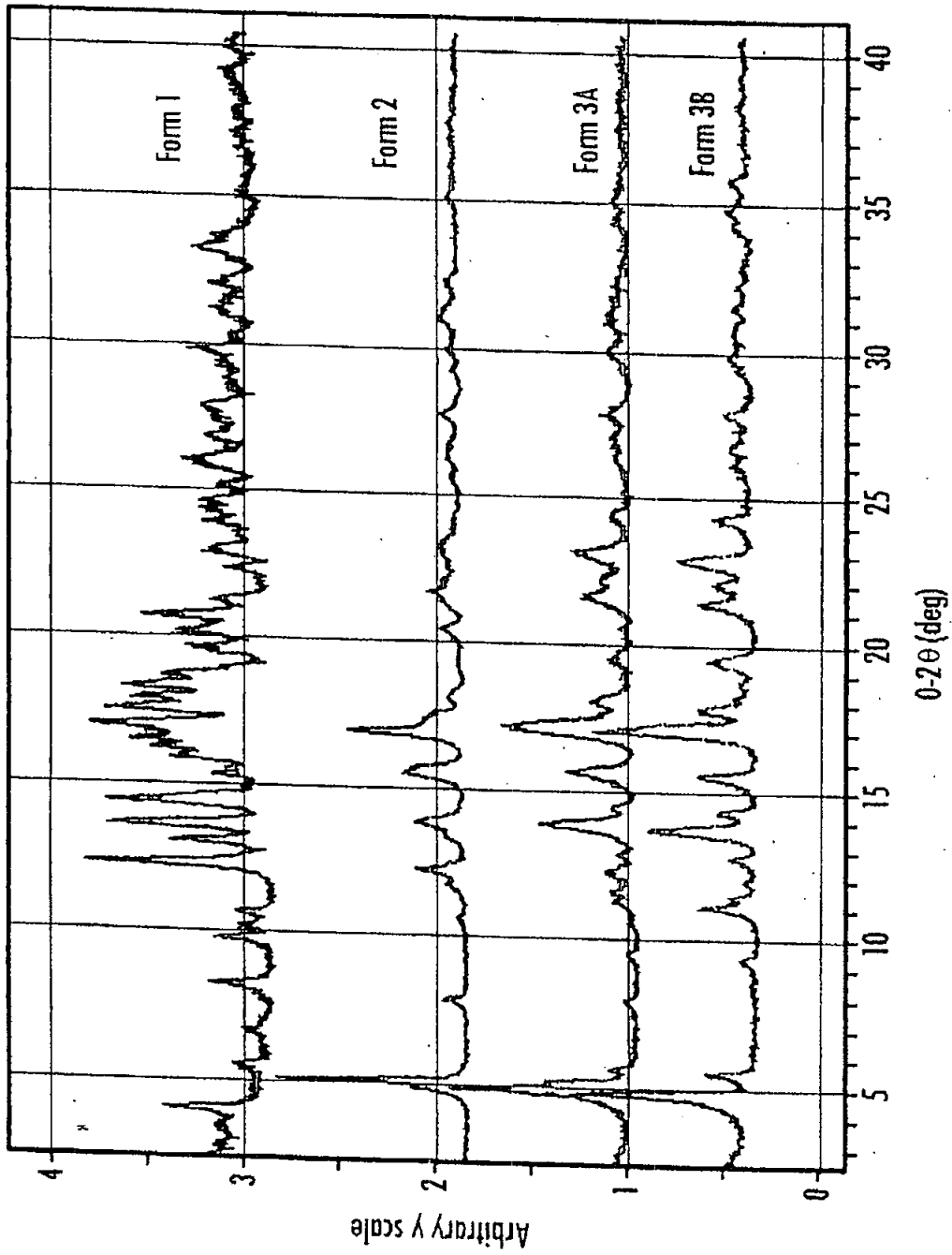


Fig. 3

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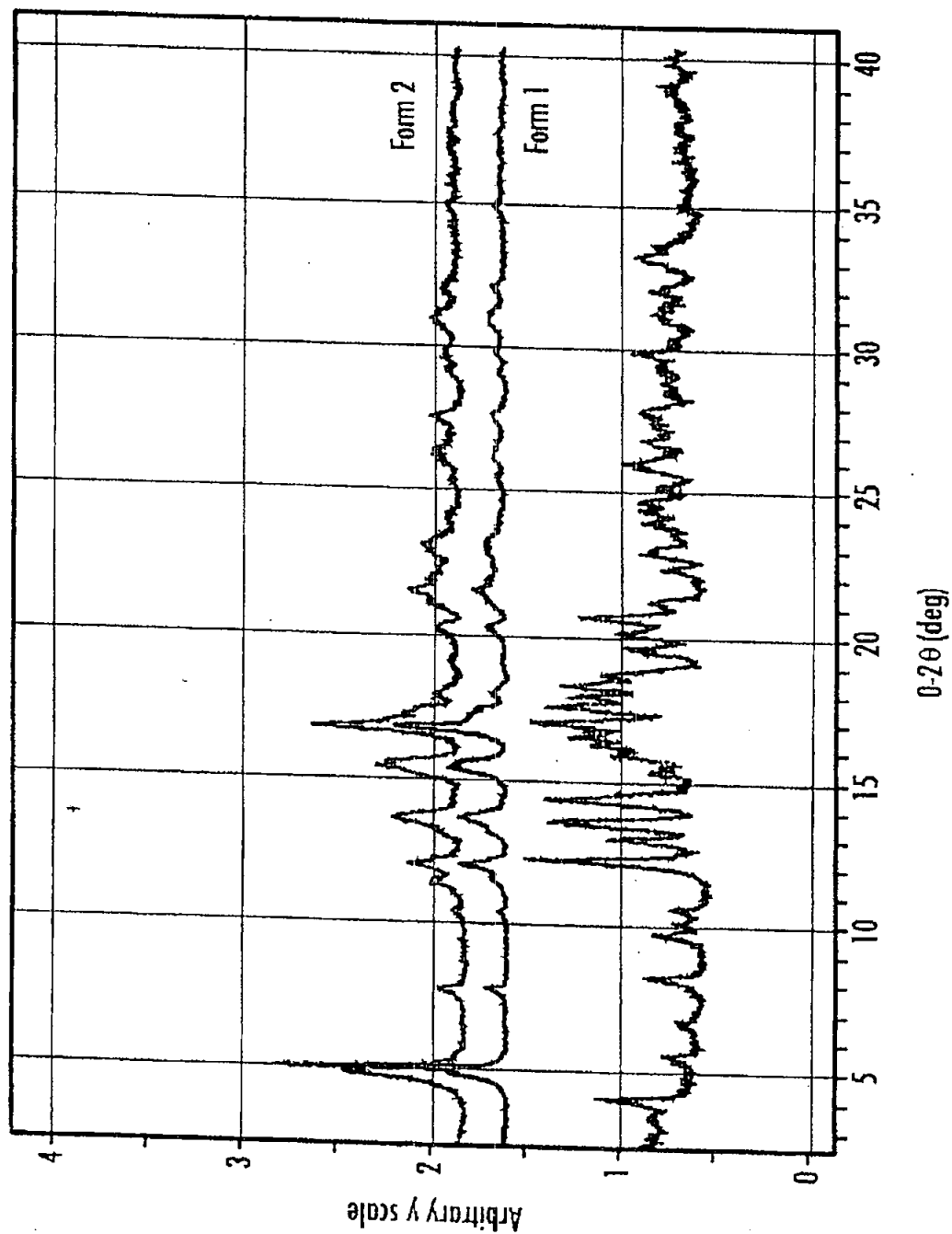


Fig. 4

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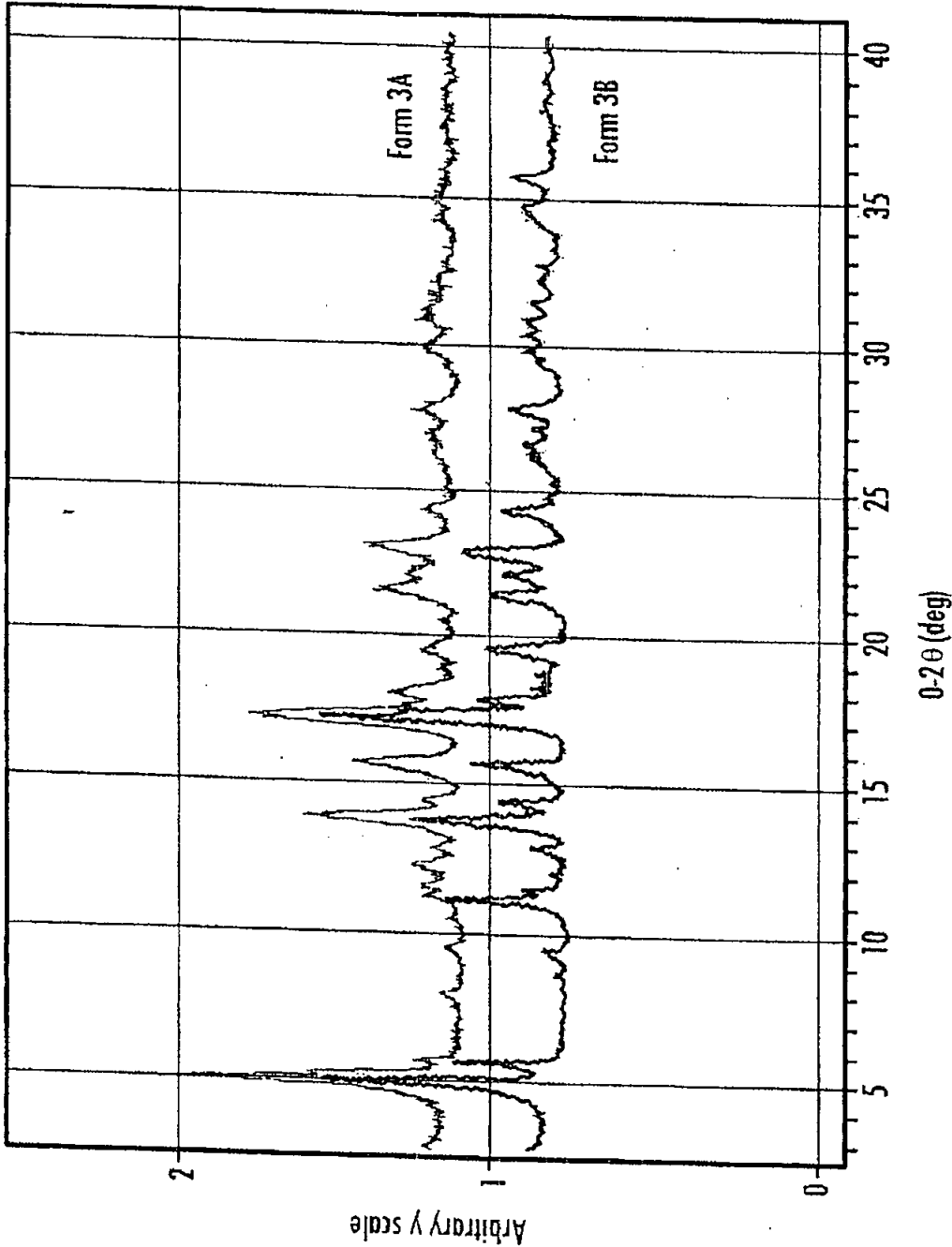


Fig. 5

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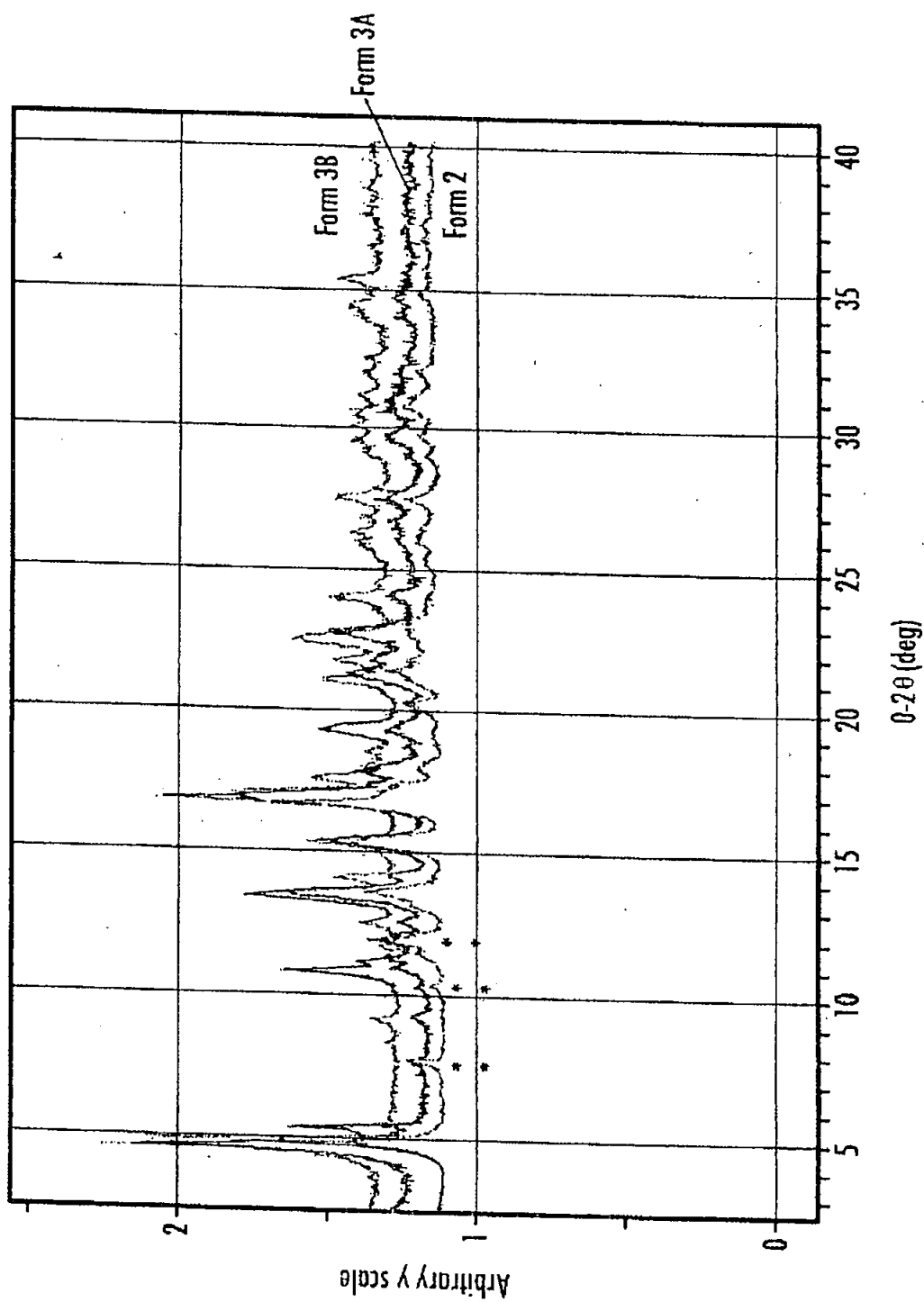


Fig. 6

203

208

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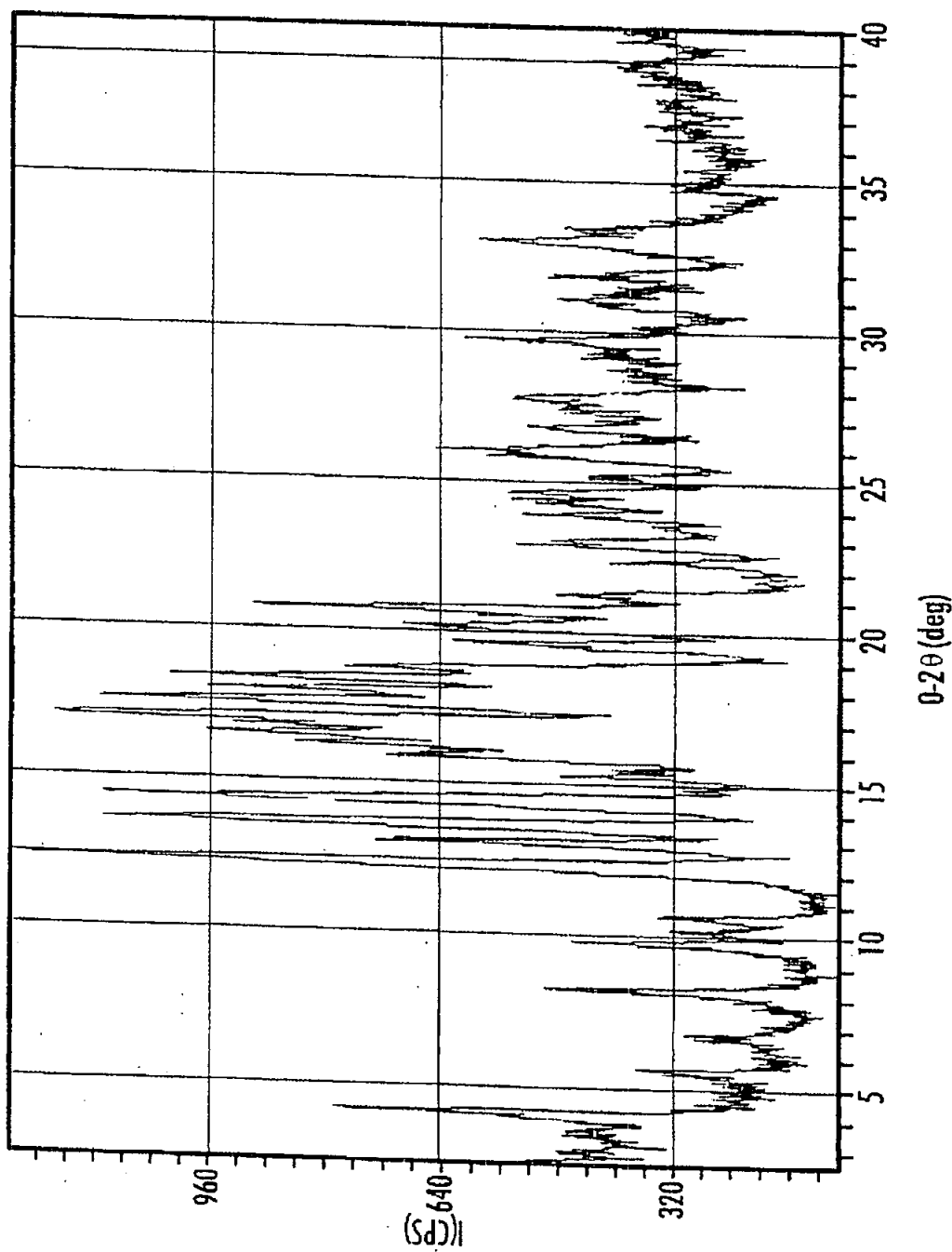


Fig. 7

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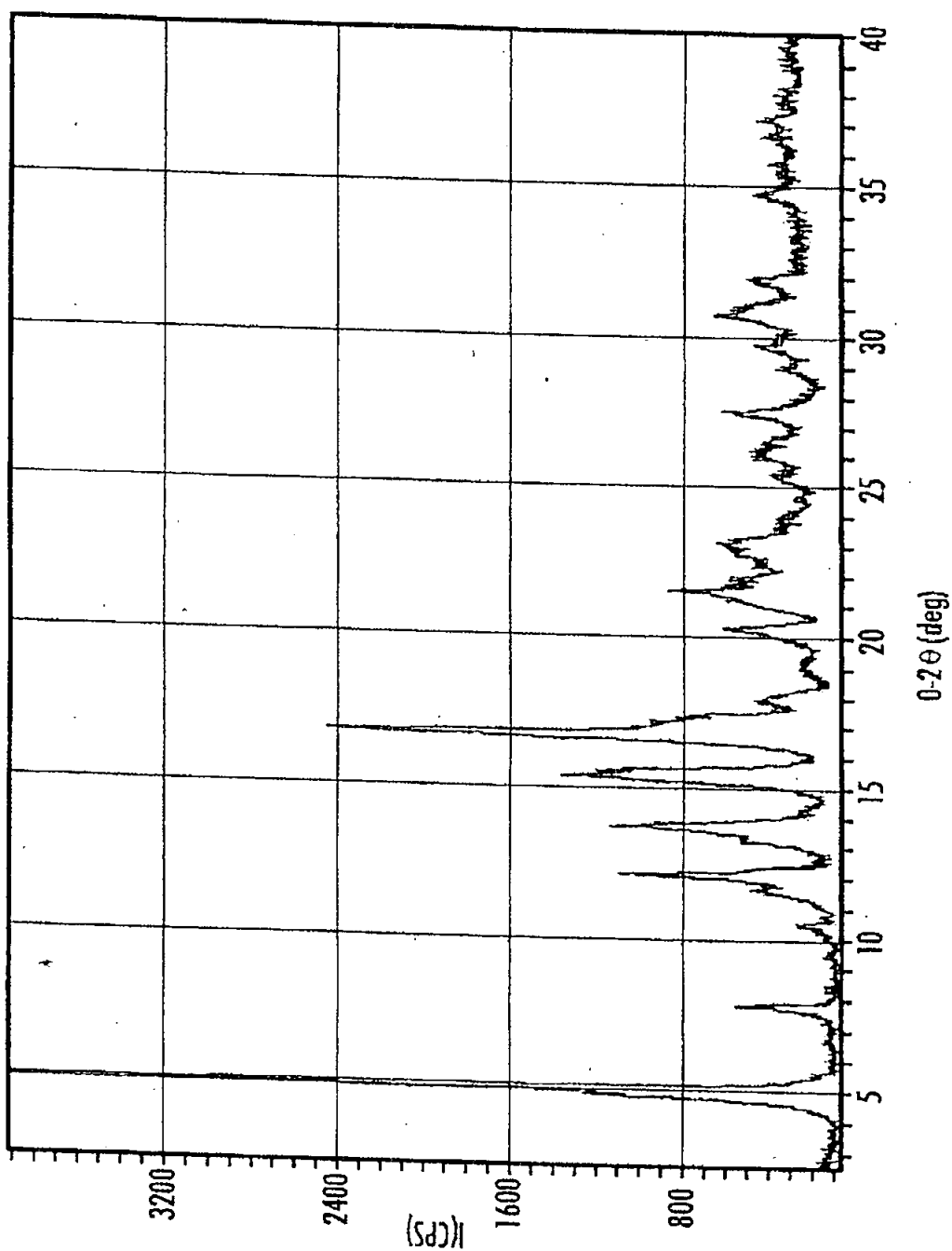


Fig. 8

607

9/11

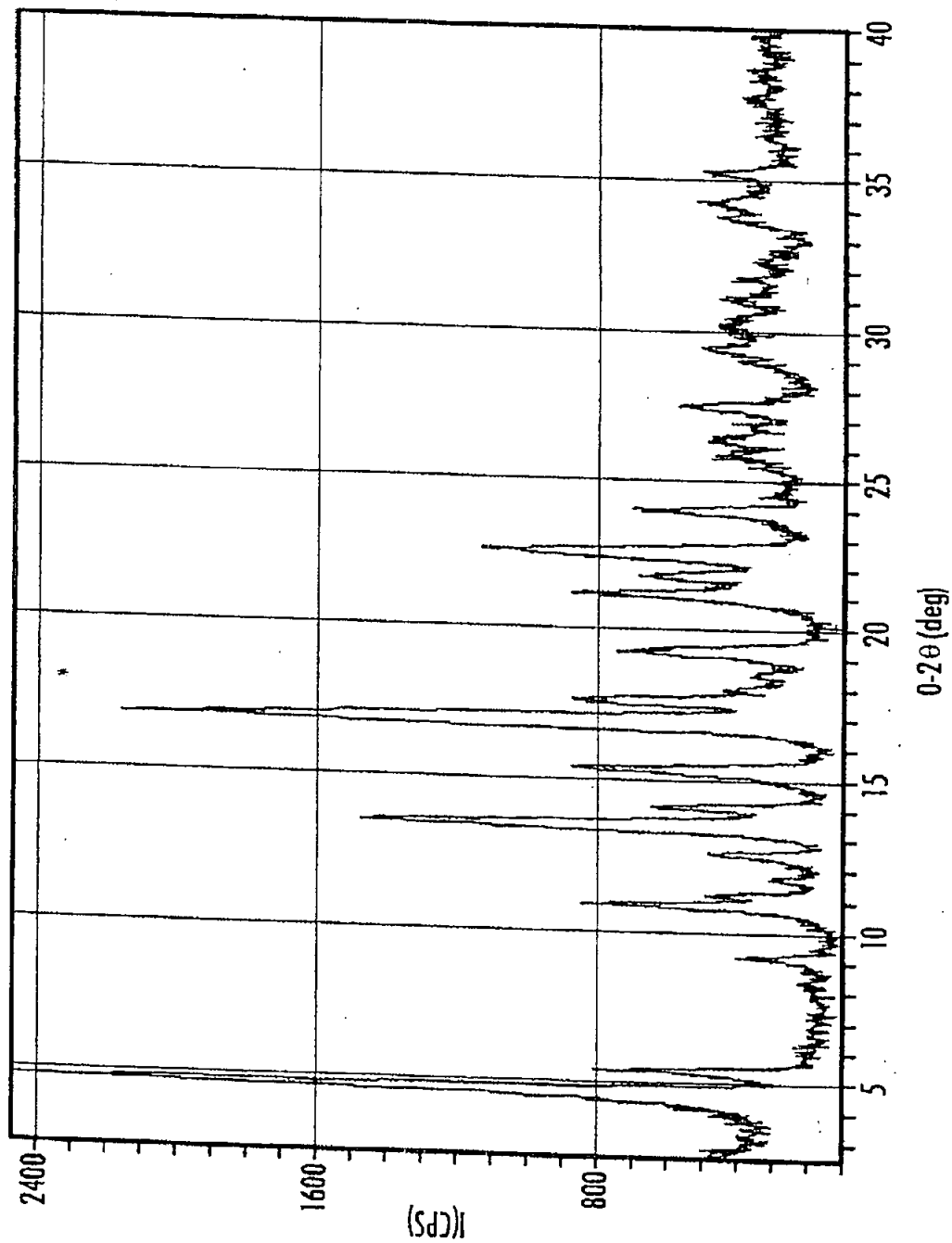


Fig. 9

310

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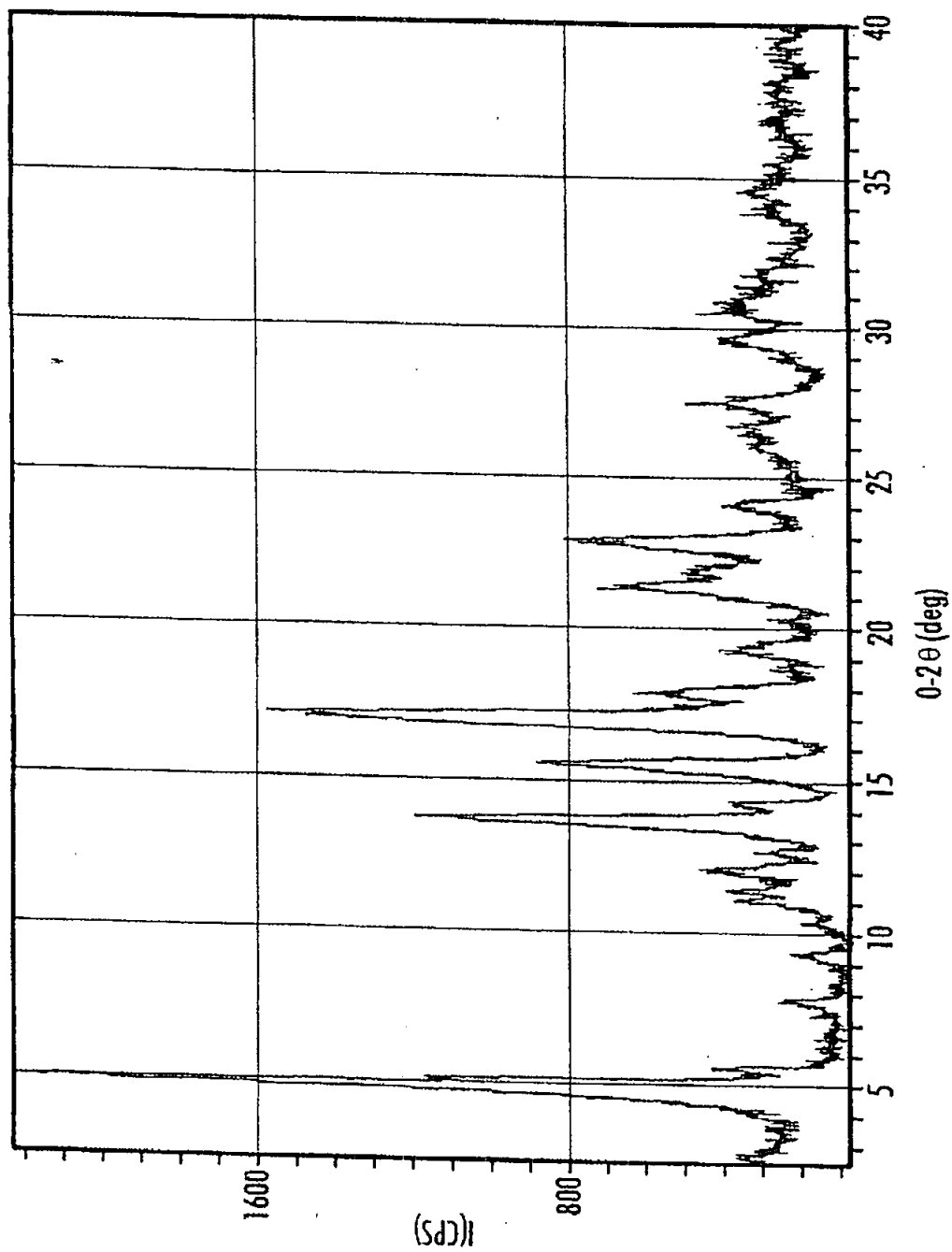


Fig. 10

11/11

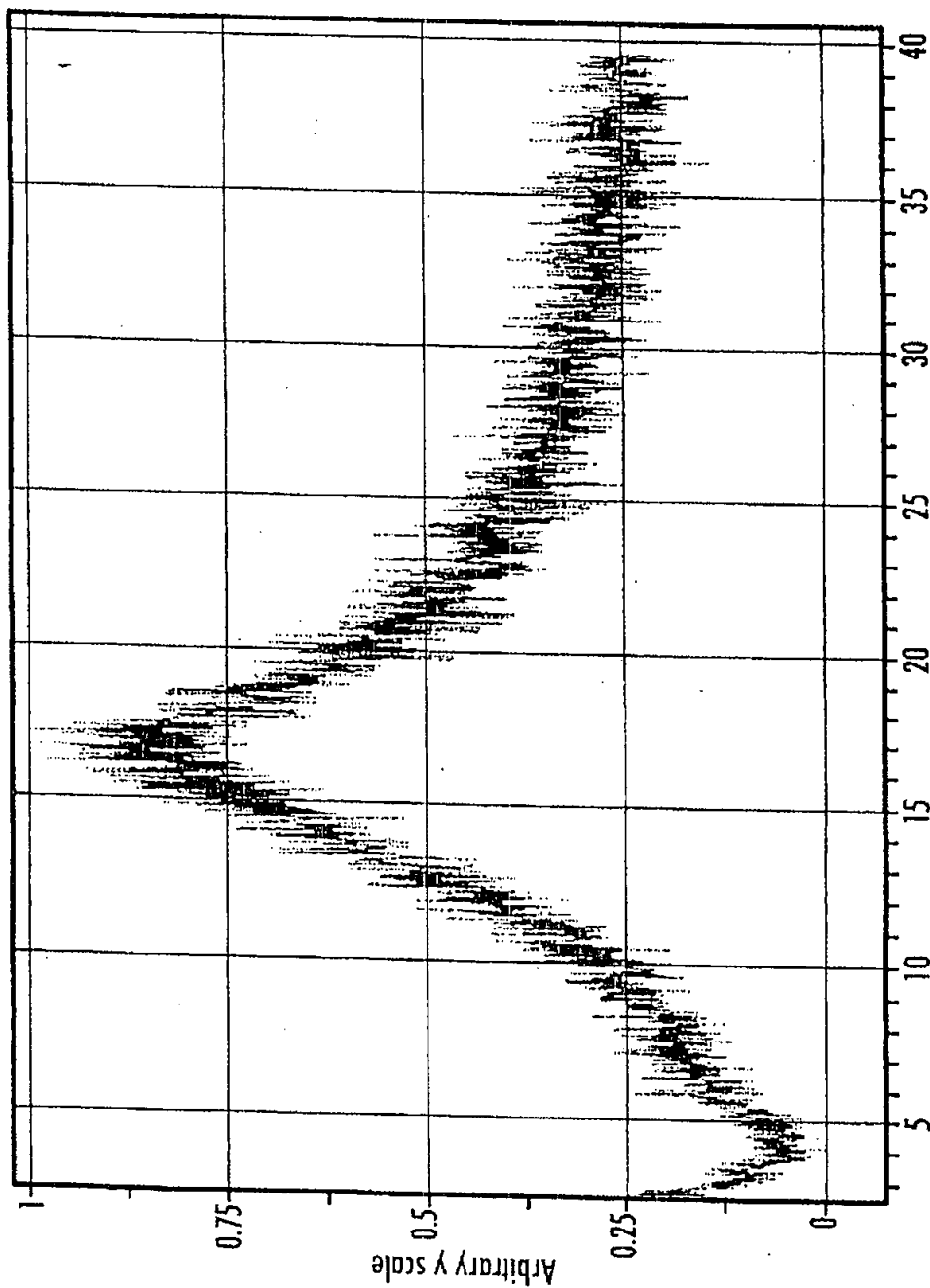


Fig. 11

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLE

To: PETER G. PAPPAS SUTHERLAND ASBILL & BRENNAN LLP 999 PEACHTREE STREET, NE ATLANTA, GEORGIA 30309-3996		Date of mailing <i>(day/month/year)</i>	24 Jul 2007
Confirmation No: 4152		REPLY DUE See paragraph 1 below	
Applicant's or agent's file reference 25040-2775		International filing date <i>(day/month/year)</i>	
International application No. PCT/US2007/069548		23 May 2007	
Applicant THE COCA-COLA COMPANY			

1. ☐ REPLY DUE within _____ months/days from the above date of mailing
- ☐ NO REPLY DUE, however, see below _____
- ☒ IMPORTANT COMMUNICATION
- ☐ INFORMATION ONLY

2. COMMUNICATION:

The applicant's attention is drawn to the fact that according to the national law of the United States of America, only the inventor is entitled to file a national application (Article 27(3)). The United States of America is designated in the international application, however, (i) The named inventor(s) is (are) not also indicated as applicant(s) for the purposes of the designation of the United States of America, and is (are) not indicated as being deceased; or (ii) no inventor is indicated. If no inventor is indicated as applicant for the purposes of the designation of the United States of America, the application may be rejected by the United States Patent and Trademark Office as a designated Office.

Name and mailing address of the receiving Office Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-3201	Authorized officer Zeta Adams Telephone No. 703-308-9013
--	---

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:

PETER G. PAPPAS
SUTHERLAND ASBILL & BRENNAN LLP
999 PEACHTREE STREET, NE
ATLANTA, GEORGIA 30309-3996

Confirmation No: 4152

NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE

(PCT Rule 20.2(c))

Applicant's or agent's file reference 25040-2775		Date of mailing (day/month/year) 24 Jul 2007	
International application No. PCT/US2007/069548		International filing date (day/month/year) 23 May 2007	Priority date (day/month/year) 19 Jun 2006
Applicant THE COCA-COLA COMPANY			
Title of the invention REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A			

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

☒ was transmitted to the International Bureau on 24 Jul 2007

☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:

☐ because the necessary national security clearance has not yet been obtained.

☐ because (reason to be specified):

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

3. FOREIGN TRANSMITTAL LICENSE INFORMATION Completed by: ZA

☐ Additional license for foreign transmittal not required. This subject matter is covered by a license already granted or the equivalent U.S. national application. Refer to that license for information concerning its scope.

☐ License for foreign transmittal not required. 37 CFR 5.11(c)(1) or 37 CFR 5.11(c)(2). However, a license may be required for additional subject matter. See 37 CFR 5.15(b).

☒ Foreign transmittal license granted. 35 U.S.C. 184; 37 CFR 5.11 on 18 Jul 2007 (date)

☐ 37 CFR 5.15(a) ☒ 37 CFR 5.15(b)

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:

PETER G. PAPPAS
SUTHERLAND ASBILL & BRENNAN LLP
999 PEACHTREE STREET, N.E.
ATLANTA, GEORGIA 30309-3900

RECEIVED

JUL 27 2007

SUTHERLAND ASBILL & BRENNAN LLP

NOTIFICATION CONCERNING PAYMENT OF PRESCRIBED FEES

(PCT Rules 14, 15 and 16 and Administrative
Instructions, Sections 102bis(c), 304,
323(b), 707(b) and 803)

Date of mailing (day/month/year) 24 Jul 2007		
Applicant's or agent's file reference 25040-2775	PAYMENT DUE see item 3 for time limits	
International application No. PCT/US2007/069548	International filing date/Date of receipt (day/month/year) 23 May 2007	Priority date (day/month/year) 19 Jun 2006
Applicant THE COCA-COLA COMPANY		

1. The applicant is hereby notified that this receiving Office has received:

☒ the payment of all the prescribed fees, and
 ☐ an overpayment, which will be refunded in due course.

☐ no or insufficient payment of the prescribed fees and the applicant is hereby invited to pay the balance due, as summarized under item 2, within the time limit(s) indicated under item 3.

2. Fees and payment calculation:

3,654.00	-	3,654.00	=	0.00
Total fees payable		Amount paid		Balance

☐ The details of the calculation are given in the Annex.

3. Time limit(s) for payment and amount(s) payable (Rules 14.1, 15.4 and 16.1(f)):

☐ within ONE MONTH from the date of receipt of the international application (for the transmittal fee (if any), the search fee and the international filing fee). The amount payable for each fee is the amount applicable on the date of receipt of the international application.

☐ within 16 MONTHS from the priority date (only for the fee for priority document). The applicant's attention is drawn to the fact that the request made by the applicant under Rule 17.1(b) will be considered not to have been made unless the fee is paid within that time limit.

4. Additional observations (if necessary):

☐ The search copy will not be transmitted to the International Searching Authority until the search fee is paid (therefore the start of the international search will be delayed) (Rule 23.1(a) and (b)).

Name and mailing address of the receiving Office Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-3201	Authorized officer Zeta Adams Telephone No. 703-308-9013
---	--

ANNEX TO FORM PCT/RO/102
CALCULATION OF THE PRESCRIBED FEES

International application No.
PCT/US2007/069548

T Transmittal Fee

Prescribed amount: 300.00 **T**
Amount paid: 300.00
Balance: = 0.00

☒ correct amount
☐ overpayment
☐ balance due

S Search Fee

Prescribed amount: 2,059.00 **S**
Amount paid: 2,059.00
Balance: = 0.00

☒ correct amount
☐ overpayment
☐ balance due

I International Filing Fee

Fixed amount for first 30 sheets: 931.00 **i1**
 $\frac{27}{\text{Number of sheets in excess of 30}} \times \frac{12.00}{\text{Fee per sheet}} = \frac{324.00}{\text{Fee per sheet}} \text{ **i2**}$
Additional component: 400 $\times \frac{0.00}{\text{Fee per sheet}} = \frac{0.00}{\text{Fee per sheet}} \text{ **i3**}$

Reduction where the international application is filed
(See PCT Applicant's Guide, Volume I, General Part,
for details on the availability of this reduction):

using the PCT-EASY software: 0.00 **r**

or

in electronic form where the text of the
description, claims and abstract is not in
character coded format: 0.00 **r**

or

in electronic form where the text of the
description, claims and abstract is in character
coded format: 0.00 **r**

Sub-total: = 1,255.00 **i1+i2+i3-r**

Prescribed total amount (The amount to be entered at I is the sub-total
entered at (i1+i2+i3-r), except where the applicant is (or all applicants
are) entitled to a reduction of 75% in which case the amount to be
entered at I is 25% of the sub-total (i1+i2+i3-r); certain applicants from
certain States are entitled to a reduction of 75% of the international
filing fee; see Notes to the Fee Calculation Sheet as annexed to the
Request Form, PCT/RO/101, for details): = 1,255.00 **I**

Amount paid: 1,255.00
Balance: = 0.00

☒ correct amount
☐ overpayment
☐ balance due

P Fee for Priority Document

Prescribed amount: 40.00 **P**
Amount paid: 40.00
Balance: = 0.00

☒ correct amount
☐ overpayment
☐ balance due

25040-2775

1/6

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.51.018.193 MT/FOP 20070401/0.20.5.9
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	25040-2775
I	Title of Invention	REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	THE COCA-COLA COMPANY
II-5	Address	Patents One Coca-Cola Plaza, NW Atlanta, Georgia 30313 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	404.676.2121
II-9	Facsimile No.	404.676.8414
III-1	Applicant and/or inventor	
III-1-1	This person is	inventor only
III-1-4	Name (LAST, First)	PRAKASH, Indra
III-1-5	Address	9750 Talisman Drive Alpharetta, Georgia 30022 United States of America

PCT REQUEST

Original (for SUBMISSION)

III-2	Applicant and/or inventor	
III-2-1	This person is	inventor only
III-2-4	Name (LAST, First)	DUBOIS, Grant, E.
III-2-5	Address	215 Quincy Lane Roswell, Georgia 30076 United States of America
III-3	Applicant and/or inventor	
III-3-1	This person is	inventor only
III-3-4	Name (LAST, First)	KING, George, A.
III-3-5	Address	1755 Wildwood Road Atlanta, Georgia 30306 United States of America
III-4	Applicant and/or inventor	
III-4-1	This person is	inventor only
III-4-4	Name (LAST, First)	UPRETI, Mani
III-4-5	Address	1943 Rotherham Way Dunwoody, Georgia 30338 United States of America
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	PAPPAS, Peter, G.
IV-1-2	Address	SUTHERLAND ASBILL & BRENNAN LLP 999 Peachtree Street, NE Atlanta, Georgia 30309-3996 United States of America
IV-1-3	Telephone No.	404.853.8000
IV-1-4	Facsimile No.	404.853.8006
IV-1-5	e-mail	pete.pappas@sablalaw.com
IV-1-6	Agent's registration No.	33,205
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	WARREN, Daniel, J. (34,272); WARREN, William, L. (36,714); GRIFFIN, III, Malvern, U. (38,899); KING, Kevin, W. (42,737); COOK, William T. (58,072); FANG, Lei (44,676); KORN, Russell, A. (54,236); KRAUSE, Michael, I. (53,157); LONG, William, F. (51,967); ONDRICK, Christina (46,198); WADE, Kathryn, H. (54,682); WALTERS, Robert, J. (40,862);

PCT REQUEST

Original (for SUBMISSION)

		LESTER, Elizabeth, A. (55,373); TSE, Kar, Yee (58,702); CHANG, Jason. V. (58,092); CHAN, Christopher, J. (44,070)
IV-3	Additional agent(s)	agent
IV-3-1	Name (LAST, First)	LONGO, Ivor, J.
IV-3-2	Address	THE COCA-COLA COMPANY Patents One Coca-Cola Plaza, NW Atlanta, Georgia 30313 United States of America
IV-3-3	Telephone No.	404.676.2121
IV-3-4	Facsimile No.	404.676.8414
IV-3-5	e-mail	ilongo@na.ko.com
IV-3-6	Agent's registration No.	46,869
IV-4	Additional agent(s)	agent
IV-4-1	Name (LAST, First)	TUBACH, Cheryl, J.
IV-4-2	Address	THE COCA-COLA COMPANY Patents One Coca-Cola Plaza, NW Atlanta, Georgia 30313 United States of America
IV-4-3	Telephone No.	404.676.2121
IV-4-4	Facsimile No.	404.676.8414
IV-4-5	e-mail	ctubach@na.ko.com
IV-4-6	Agent's registration No.	38,346
IV-5	Additional agent(s)	agent
IV-5-1	Name (LAST, First)	VO, Hoang, M.
IV-5-2	Address	THE COCA-COLA COMPANY Patents One Coca-Cola Plaza, NW Atlanta, Georgia 30313 United States of America
IV-5-3	Telephone No.	404.676.2121
IV-5-4	Facsimile No.	404.676.8414
IV-5-5	e-mail	hvo@na.ko.com
IV-5-6	Agent's registration No.	47,158

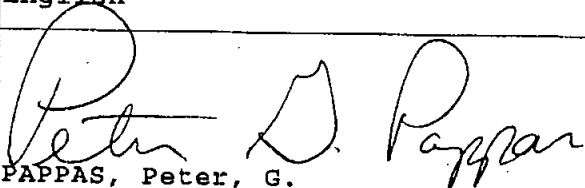
PCT REQUEST

Original (for SUBMISSION)

V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the International filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	19 June 2006 (19.06.2006)
VI-1-2	Number	60/805,216
VI-1-3	Country	US
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	12 February 2007 (12.02.2007)
VI-2-2	Number	60/889,318
VI-2-3	Country	US
VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2
VI-4	Incorporation by reference : where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

PCT REQUEST

Original (for SUBMISSION)

VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	33	-
IX-3	Claims	6	-
IX-4	Abstract	1	✓
IX-5	Drawings	11	-
IX-7	TOTAL	57	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract	2	
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	PAPPAS, Peter, G.	
X-1-2	Name of signatory		
X-1-3	Capacity		

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25040-2775

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PCI REQUEST

Original (for SUBMISSION)

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--



GERMANY
Tel. +49 (0)89 2399 - 0
Fax +49 (0)89 2399 - 4465



PAPPAS, Peter, G. et al.
Sutherland Asbill & Brennan LLP
999 Peachtree Street, NE
Atlanta, GA 30309-3996
ETATS-UNIS D'AMERIQUE

For any questions about
this communication:
Tel.: +31 (0)70 340 45 00

RECEIVED

NOV 06 2008

SUTHERLAND ASBILL & BRENNAN LLP

Date	31.10.08
------	----------

Reference	Application No./Patent No. 07797688.4 - 2114 PCT/US2007069548
Applicant/Proprietor The Coca-Cola Company	

Entry into the European phase before the European Patent Office

The following information describes the procedural steps required for entry into the European phase before the European Patent Office (EPO). You are advised to read it carefully because failure to take the necessary action in due time can lead to a loss of rights.

1. The above mentioned international patent application has been given the **European application No. 07797688.4**.
2. Applicants **without a residence or their principal place of business** in an EPC Contracting State may themselves initiate European processing of their international applications, provided they do so before expiry of the 31st month from the priority date.

During the European phase before the EPO as designated or elected Office, however, such applicants **must** be represented by a professional representative (Art. 133(2) and Art. 134(1) and (8) EPC).

Where, at the expiry of the time period laid down in Rule 163(5) EPC, the requirements of Article 133(2) EPC have not been complied with, the European patent application will be **refused**, pursuant to Rule 163(6) EPC.

Please note that a professional representative authorised to act before the EPO and who acted for the applicant during the international phase does not automatically become the representative for the European phase. Applicants are therefore strongly advised to appoint in good time any representative they wish to initiate the European phase for them; otherwise the EPO has to send all communications directly to the applicant.

3. Applicants **with a residence or their principal place of business** in an EPC Contracting State are not obliged to appoint for the European phase a professional representative authorised to act before the EPO. However, in view of the complexity of the procedure it is recommended that they do so.
4. Applicants and professional representatives are also strongly advised to initiate the European phase using **EPO Form 1200**. It is available free of charge from the EPO or via the EPO website at <http://www.epo.org>. Similarly, it can be generated with the **epoline® Online Filing Software**, obtainable free of charge from the EPO (<http://www.epoline.org>) The use of the form is not compulsory.

5. Where the EPO is acting as designated or elected Office (Art. 22(1) and (3) and Art. 39(1) PCT), to enter the European phase before the EPO, the following acts must be performed by the applicant within 31 months from the date of filing of the international application or (where applicable) the earliest priority date:
- Supply a translation of the international application into an EPO official language, if the International Bureau did not publish the application in such language (Art. 22(1) PCT and R. 159(1)(a) EPC);
 - Specify the application documents, as originally filed or as amended, on which the European grant procedure is to be based (R. 159(1)(c) EPC);
 - Pay the filing fee and, where a supplementary European search report has to be drawn up, the search fee (R. 159(1)(c) and (e) EPC);
 - Pay the designation fee for each designated Contracting State if the time limit laid down in Rule 39(1) EPC (i.e. six months after publication of the international search report) has expired before the 31-month period pursuant to Rule 159(1) EPC (R. 159(1)(d) EPC);
 - File the request for examination if the time limit laid down in Rule 70(1) EPC (i.e. six months after publication of the international search report) has expired before the 31-month period pursuant to Rule 159(1) EPC (R. 159(1)(f) EPC);
 - Pay the renewal fee in respect of the third year, if the fee has fallen due (see Rule 51(1) EPC) before expiry of the 31-month period pursuant to Rule 159(1) EPC (R. 159(1)(g) EPC);
 - File, where applicable, the certificate of exhibition referred to in Article 55(2) and Rule 25 EPC (R. 159(1)(h) EPC);
 - Pay the claims fees for the sixteenth and each subsequent claim when the application documents on which the European grant procedure is to be based comprise more than fifteen claims (R. 162(1) EPC).

If either the translation of the international application or the request for examination is not filed in due time, or if the filing fee or the search fee is not paid in due time, or no designation fee is paid in due time, the European patent application shall be deemed to be withdrawn (R. 160(1) EPC).

If the renewal fee is not paid in due time, it may still be paid within six months of the due date, provided that an additional fee is also paid within that period (R. 51(2) EPC).

If the claims fees are not paid in due time, they may still be paid within one month from a communication of the EPO pointing out the failure to observe the time limit (R. 162(2) EPC).

6. For an overview of search and examination fees, see the Notice from the European Patent Office dated 1 March 2006 (OJ EPO 2006, 192). The amounts of the fees are regularly published in the Official Journal of the EPO and are available on the EPO internet site at <http://www.epo.org>. At any time, payments to the EPO can be validly made by anybody.
7. If the applicant had appointed a representative during the application's international phase, the present Form will be sent to the representative, asking him to inform the applicant accordingly.

All subsequent communications will be sent to the applicant, or if the EPO is informed of his appointment in time, to the applicant's European representative.

8. For more details about time limits and procedural acts before the EPO as designated or elected Office, see the EPO brochure "How to get an European patent", Guide for applicants - Part 2, PCT procedure before the EPO - "Euro-PCT" (EPO PCT Guide). This brochure, the list of professional representatives before the EPO, Form 1200 and details of the latest fees are available on the Internet under <http://www.epo.org>.

Receiving Section



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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPL NO.	FILING OR 371 (c) DATE	ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	DRAWINGS	TOT CLMS	IND CLMS
60/805,216	06/19/2006		200	25040-1594	10		

29052
SUTHERLAND ASBILL & BRENNAN LLP
999 PEACHTREE STREET, N.E.
ATLANTA, GA 30309

RECEIVED

JUL 12 2006

SUTHERLAND ASBILL &
BRENNAN LLP

CONFIRMATION NO. 8756

FILING RECEIPT



OC000000019537795

Date Mailed: 07/10/2006

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Grant E. DuBois, Roswell, GA;
George A. King, Atlanta, GA;
Indra Prakash, Alpharetta, GA;

Assignment For Published Patent Application

THE COCA-COLA COMPANY, Atlanta, GA

Power of Attorney: The patent practitioners associated with Customer Number 29052.

If Required, Foreign Filing License Granted: 07/07/2006

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US60/805,216**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: Not applicable

Early-Publication Request: Not applicable

Title

Rebaudioside A Composition And Method For Purifying Rebaudioside A

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER Title 35, United States Code, Section 184 Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls,

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Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

625



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
60/889,318	02/12/2007		250	25040-2264		

CONFIRMATION NO. 3127

UPDATED FILING RECEIPT

29052

SUTHERLAND ASBILL & BRENNAN LLP
999 PEACHTREE STREET, N.E.
ATLANTA, GA 30309

RECEIVED

OC000000026584081

NOV 08 2007

Date Mailed: 11/05/2007

**SUTHERLAND ASBILL &
BRENNAN LLP**

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections

Applicant(s)

Indra Prakash, Alpharetta, GA;
Grant E. DuBois, Roswell, GA;
George A. King, Atlanta, GA;
Mani Upreti, Dunwoody, GA;

Power of Attorney: The patent practitioners associated with Customer Number 29052

If Required, Foreign Filing License Granted: 02/20/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 60/889,318**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Rebaudioside A Composition and Method for Purifying Rebaudioside A

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An International (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process simplifies the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international

053

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LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and

Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

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**UNITED STATES PATENT AND TRADEMARK OFFICE**UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

NOVEMBER 15, 2006

PTAS

500179553AELIZABETH A. LESTER
999 PEACHTREE STREET NE
ATLANTA, GA 30313

500179553A

UNITED STATES PATENT AND TRADEMARK OFFICE
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PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 11/15/2006

REEL/FRAME: 018521/0107
NUMBER OF PAGES: 6BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: 25040-1594ASSIGNOR:
PRAKASH, INDRA

DOC DATE: 11/01/2006

ASSIGNOR:
DUBOIS, GRANT E.

DOC DATE: 11/01/2006

ASSIGNOR:
KING, GEORGE A.

DOC DATE: 11/01/2006

ASSIGNEE:
THE COCA-COLA COMPANY
ONE COCA-COLA PLAZA, NW
ATLANTA, GEORGIA 30313

RightFax

11/16/06 7:50

PAGE 003/005

Fax Server

018521/0107 PAGE 2

SERIAL NUMBER: 60805216

FILING DATE: 06/19/2006

PATENT NUMBER:

ISSUE DATE:

TITLE: REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A

ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

11/15/2006
500179553

SUBMISSION TYPE:	NEW ASSIGNMENT								
NATURE OF CONVEYANCE:	ASSIGNMENT								
CONVEYING PARTY DATA									
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Name	Execution Date								
Indra Prakash	11/01/2006								
Grant E. DuBois	11/01/2006								
George A. King	11/01/2006								
RECEIVING PARTY DATA									
Name:	The Coca-Cola Company								
Street Address:	One Coca-Cola Plaza, NW								
City:	Atlanta								
State/Country:	GEORGIA								
Postal Code:	30313								
PROPERTY NUMBERS Total: 1									
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Property Type	Number								
Application Number:	60805216								
CORRESPONDENCE DATA									
Fax Number:	(404)853-8806								
<i>Correspondence will be sent via US Mail when the fax attempt is unsuccessful.</i>									
Phone:	404-853-8012								
Email:	elizabeth.lester@sablaw.com								
Correspondent Name:	Elizabeth A. Lester								
Address Line 1:	999 Peachtree Street NE								
Address Line 4:	Atlanta, GEORGIA 30313								
ATTORNEY DOCKET NUMBER:	25040-1594								
NAME OF SUBMITTER:	Elizabeth Lester								
Total Attachments: 4 source=1594Assignment#page1.tif source=1594Assignment#page2.tif									

CH: \$40.00 60805216

335

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PAGE 005/005

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ASSIGNMENT

WHEREAS, we, **Indra Prakash**, a citizen of the United States of America, residing at 9750 Talisman Drive, Alpharetta, GA 30022; **Grant E. DuBois**, a citizen of the United States of America, residing at 215 Quincy Lane, Roswell, Georgia 30076; and **George A. King**, a citizen of the United States of America, residing at 1755 Wildwood Road, Atlanta, GA 30306 (hereinafter, "ASSIGNORS"), have invented certain inventions and improvements disclosed in a provisional patent application entitled "**REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A**," filed in the United States Patent and Trademark Office on the 19th day of June, 2006, under Provisional Application No. 60/805,216; and

WHEREAS, **The Coca-Cola Company**, a corporation of the State of Delaware, having a principal place of business at One Coca-Cola Plaza, NW, Atlanta, GA 30313 (hereinafter, "ASSIGNEE"), is desirous of acquiring an interest in the same;

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, ASSIGNORS, by these presents do sell, assign and transfer unto ASSIGNEE the full, exclusive and entire right, title, and interest in and to said provisional application, and in and to all inventions and improvements disclosed and described in said provisional application, and in and to all U.S. non-provisional applications claiming benefit of said provisional application, including any continuations, divisionals, and reissues thereof, and all Letters Patents of the United States resulting from any of said applications;

For the same consideration, we, by these presents do sell, assign, and transfer to ASSIGNEE the full, exclusive, and entire right, title and interest in and to any foreign application or applications corresponding to said provisional application, in whole or in part, in countries other than the United States, in and to any Letters Patent and similar protective rights granted on said foreign applications, and in and to the right to claim any applicable priority rights arising from or required for said foreign applications under the terms of any applicable conventions, treaties, statutes, or regulations; said foreign applications to be filed and issued in the name of ASSIGNEE or its designee insofar as permitted by applicable law.

tcc

Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"
Attorney Docket No. 25040-1594
Page 2 of 4

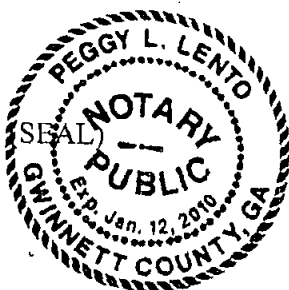
AND, for the same consideration, we agree to sign all lawful papers, execute all nonprovisional applications and other applications, make all assignments and rightful oaths, and generally do everything possible to aid ASSIGNEE its successors, assigns, and nominees, to obtain and enforce proper protection for all said inventions and improvements in all countries throughout the world.

Date: 11/1/06

Indra Prakash
Indra Prakash

STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 15 day of November, 2006, personally appeared **Indra Prakash**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.



Peggy L. Lento
NOTARY PUBLIC

My Commission Expires: 1-12-2010

903

Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"
Attorney Docket No. 25040-1594
Page 3 of 4

Date: 11-1-06

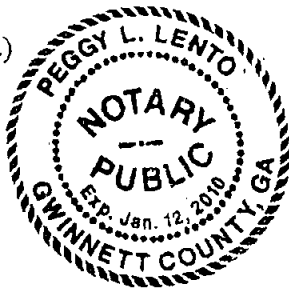
Grant E. DuBois
Grant E. DuBois

STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of November, 2006, personally appeared **Grant E. DuBois**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.

Peggy L. Lento
NOTARY PUBLIC

(SEAL)



My Commission Expires: 1-12-2010

553

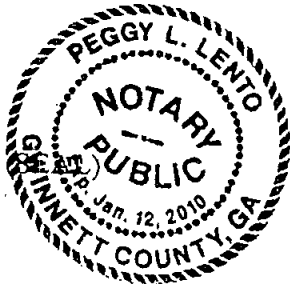
Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"
Attorney Docket No. 25040-1594
Page 4 of 4

Date: 11.01.06

George A. King
George A. King

STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of November, 2006, personally appeared **George A. King**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.



Peggy L. Lento
NOTARY PUBLIC

My Commission Expires: 1-12-2010

045

TO: ELIZABETH A. LESTER-SUTHERLAND AND ASBILL & COMPANY: 999 PEACHTREE STREET, NE



UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

JUNE 12, 2007

PTAS
ELIZABETH A. LESTER-SUTHERLAND ASBILL &
999 PEACHTREE STREET, NE
ATLANTA, GA 30309

500294152A
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RECORDATION DATE: 06/12/2007

REEL/FRAME: 019414/0618
NUMBER OF PAGES: 7

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: 25040-2776

ASSIGNOR:
PRAKASH, INDRA

DOC DATE: 06/01/2007

ASSIGNOR:
DUBOIS, GRANT E.

DOC DATE: 06/01/2007

ASSIGNOR:
KING, GEORGE A.

DOC DATE: 06/01/2007

ASSIGNOR:
UPRETI, MANI

DOC DATE: 06/01/2007

ASSIGNEE:
THE COCA-COLA COMPANY
ONE COCA-COLA PLAZA, NW

175

ELIZABETH A. LESTER-SUTHERLAND AND ASBILL & COMPANY: 999 PEACOCK TREE STREET, NE
ATLANTA, GEORGIA 30313

019414/0618 PAGE 2

SERIAL NUMBER: 11751627	FILING DATE:
PATENT NUMBER:	ISSUE DATE:
TITLE: REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A	
SERIAL NUMBER: 60805216	FILING DATE: 06/19/2006
PATENT NUMBER:	ISSUE DATE:
TITLE: REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A	
SERIAL NUMBER: 60889318	FILING DATE: 02/12/2007
PATENT NUMBER:	ISSUE DATE:
TITLE: REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A	

ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

273

TO: ELIZABETH A. LESTER-SUTHERLAND ASBILL & COMPANY: 999 PEACHTREE STREET, NE

PATENT ASSIGNMENT

Electronic Version v1.1 06/12/2007
Stylesheet Version v1.1 500294152

SUBMISSION TYPE:	NEW ASSIGNMENT										
NATURE OF CONVEYANCE:	ASSIGNMENT										
CONVEYING PARTY DATA											
<table border="1"><thead><tr><th>Name</th><th>Execution Date</th></tr></thead><tbody><tr><td>Indra Prakash</td><td>06/01/2007</td></tr><tr><td>Grant E. DuBois</td><td>06/01/2007</td></tr><tr><td>George A. King</td><td>06/01/2007</td></tr><tr><td>Mani Upreti</td><td>06/01/2007</td></tr></tbody></table>		Name	Execution Date	Indra Prakash	06/01/2007	Grant E. DuBois	06/01/2007	George A. King	06/01/2007	Mani Upreti	06/01/2007
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<table border="1"><tr><td>Name:</td><td>The Coca-Cola Company</td></tr><tr><td>Street Address:</td><td>One Coca-Cola Plaza, NW</td></tr><tr><td>City:</td><td>Atlanta</td></tr><tr><td>State/Country:</td><td>GEORGIA</td></tr><tr><td>Postal Code:</td><td>30313</td></tr></table>		Name:	The Coca-Cola Company	Street Address:	One Coca-Cola Plaza, NW	City:	Atlanta	State/Country:	GEORGIA	Postal Code:	30313
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Application Number:	11751627										
Application Number:	60805216										
Application Number:	60889318										
CORRESPONDENCE DATA											
Fax Number: (404)853-8806 <i>Correspondence will be sent via US Mail when the fax attempt is unsuccessful.</i>											
Phone: 4048538012											
Email: elizabeth.lester@sablaw.com											
Correspondent Name: Elizabeth A. Lester-Sutherland Asbill &											
Address Line 1: 999 Peachtree Street, NE											
Address Line 4: Atlanta, GEORGIA 30309											
ATTORNEY DOCKET NUMBER:	25040-2776										
NAME OF SUBMITTER:	Elizabeth A. Lester										

CH \$120.00 11751627

573

0:ELIZABETH A. LESTER-SUTHERLAND ASBILL & COMPANY:999 PEACHTREE STREET, NE

Total Attachments: 5
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H+E

ASSIGNMENT

WHEREAS, we, **Indra Prakash**, a citizen of the United States of America, residing at 9750 Talisman Drive, Alpharetta, GA 30022; **Grant E. DuBois**, a citizen of the United States of America, residing at 215 Quincy Lane, Roswell, Georgia 30076; **George A. King**, a citizen of the United States of America, residing at 1755 Wildwood Road, Atlanta, GA 30306; and **Mani Upreti**, a citizen of the India, residing at 1943 Rotherham Way, Dunwoody, GA 30338 (hereinafter, "ASSIGNORS"), have invented certain inventions and improvements disclosed in an application for Letters Patent entitled "**REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A**," filed in the United States Patent and Trademark Office on May 21, 2007 and assigned Application No. 11/751,627, which claims priority to U.S. Provisional Application No. 60/805,216, which was filed on June 19, 2006 and U.S. Provisional Application No. 60/889,318, which was filed on February 12, 2007 (hereinafter, "APPLICATIONS"); and

WHEREAS, **The Coca-Cola Company**, a corporation of the State of Delaware, having a principal place of business at One Coca-Cola Plaza, NW, Atlanta, GA 30313 (hereinafter, "ASSIGNEE"), is desirous of acquiring an interest in the same;

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, ASSIGNORS, by these presents do sell, assign and transfer unto ASSIGNEE the full, exclusive and entire right, title, and interest in and to said APPLICATIONS, in and to any divisions, continuations, and reissues thereof, and in and to all inventions and improvements disclosed and described in said APPLICATIONS, preparatory to obtaining Letters Patent of the United States therefor, and ASSIGNORS hereby request the Commissioner of Patents and Trademarks to issue any and all Letters Patent of the United States resulting from said APPLICATIONS, or from a division, continuation, or reissue thereof, to ASSIGNEE, as the assignee, for its interest and for the sole use and benefit of ASSIGNEE and its assigns and legal representatives;

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Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"
Application No. 11/751,627
Attorney Docket No. 25040-2776
Page 2 of 5

For the same consideration, ASSIGNORS, by these presents do sell, assign, and transfer to ASSIGNEE the full, exclusive, and entire right, title and interest in and to any foreign application or applications corresponding to said APPLICATIONS, in whole or in part, in countries other than the United States, in and to any Letters Patent and similar protective rights granted on said foreign applications, and in and to the right to claim any applicable priority rights arising from or required for said foreign applications under the terms of any applicable conventions, treaties, statutes, or regulations; said foreign applications to be filed and issued in the name of ASSIGNEE, or its designee insofar as permitted by applicable law.

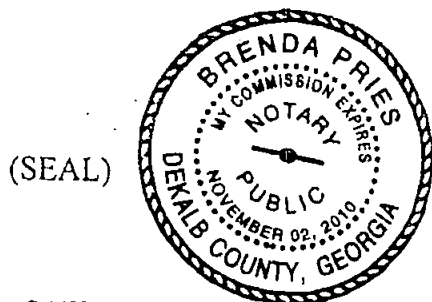
AND, for the same consideration, ASSIGNORS agree to sign all lawful papers, execute all division, continuing, reissue and other applications, make all assignments and rightful oaths, and generally do everything possible to aid ASSIGNEE, its successors, assigns, and nominees, to obtain and enforce proper protection for all said inventions and improvements in all countries throughout the world.

Date: 6/1/07

Indra M. Prakash
Indra Prakash

STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of June, 2007, personally appeared **Indra Prakash**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.



AO 1697279.1

Brenda Pries
NOTARY PUBLIC

My Commission Expires: 11/02/2010

94E

Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"
Application No. 11/751,627
Attorney Docket No. 25040-2776
Page 3 of 5

Date: 6-1-07

Grant E. DuBois
Grant E. DuBois

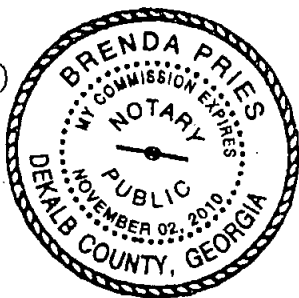
STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of June, 2007, personally appeared **Grant E. DuBois**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.

Brenda Pries
NOTARY PUBLIC

My Commission Expires: 11/02/2010

(SEAL)



343

Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"
Application No. 11/751,627
Attorney Docket No. 25040-2776
Page 4 of 5

Date: 1 June 2007

George A. King
George A. King

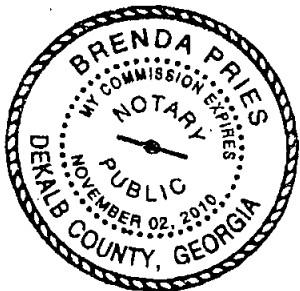
STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of June, 2007, personally appeared **George A. King**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.

Brenda Pries
NOTARY PUBLIC

My Commission Expires: 11/02/2010

(SEAL)



343

Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"
Application No. 11/751,627
Attorney Docket No. 25040-2776
Page 5 of 5

Date: 06/01/07

Mani Upreti
Mani Upreti

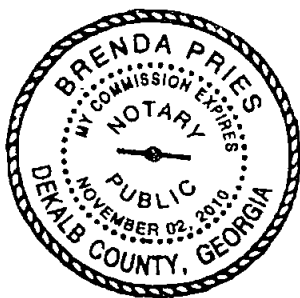
STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of June, 2007, personally appeared **Mani Upreti**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.

Brenda Pries
NOTARY PUBLIC

My Commission Expires: 11/02/2010

(SEAL)



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: United States of America

This public document

2. has been signed by M. K. Carter

3. acting in the capacity of Certifying Officer

4. bears the seal/stamp of U. S. Patent and Trademark Office

Certified

5. at Washington, D.C.

6. the sixteenth of December, 2008

7. by Assistant Authentication Officer, United States Department of State

8. No 09008279-14

9. Seal/Stamp:

10. Signature:

Fernesia T. Crawford

Fernesia T. Crawford

A 7160438

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

December 05, 2008

**THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE
RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON
JUNE 12, 2007.**

By Authority of the

**Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office**



M. K. CARTER

Certifying Officer



PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT										
NATURE OF CONVEYANCE:	ASSIGNMENT										
CONVEYING PARTY DATA											
<table border="1"><thead><tr><th>Name</th><th>Execution Date</th></tr></thead><tbody><tr><td>Indra Prakash</td><td>06/01/2007</td></tr><tr><td>Grant E. DuBois</td><td>06/01/2007</td></tr><tr><td>George A. King</td><td>06/01/2007</td></tr><tr><td>Mani Upreti</td><td>06/01/2007</td></tr></tbody></table>	Name	Execution Date	Indra Prakash	06/01/2007	Grant E. DuBois	06/01/2007	George A. King	06/01/2007	Mani Upreti	06/01/2007	
Name	Execution Date										
Indra Prakash	06/01/2007										
Grant E. DuBois	06/01/2007										
George A. King	06/01/2007										
Mani Upreti	06/01/2007										
RECEIVING PARTY DATA											
Name:	The Coca-Cola Company										
Street Address:	One Coca-Cola Plaza, NW										
City:	Atlanta										
State/Country:	GEORGIA										
Postal Code:	30313										
PROPERTY NUMBERS Total: 3											
<table border="1"><thead><tr><th>Property Type</th><th>Number</th></tr></thead><tbody><tr><td>Application Number:</td><td>11751627</td></tr><tr><td>Application Number:</td><td>60805216</td></tr><tr><td>Application Number:</td><td>60889318</td></tr></tbody></table>	Property Type	Number	Application Number:	11751627	Application Number:	60805216	Application Number:	60889318			
Property Type	Number										
Application Number:	11751627										
Application Number:	60805216										
Application Number:	60889318										
CORRESPONDENCE DATA											
Fax Number:	(404)853-8806										
<i>Correspondence will be sent via US Mail when the fax attempt is unsuccessful.</i>											
Phone:	4048538012										
Email:	elizabeth.lester@sablalaw.com										
Correspondent Name:	Elizabeth A. Lester-Sutherland Asbill &										
Address Line 1:	999 Peachtree Street, NE										
Address Line 4:	Atlanta, GEORGIA 30309										
ATTORNEY DOCKET NUMBER:	25040-2776										
NAME OF SUBMITTER:	Elizabeth A. Lester										

500294152

PATENT
REEL: 019414 FRAME: 0618

CH \$120.00 11751627

555

Total Attachments: 5
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source=assign#page5.tif

ASSIGNMENT

WHEREAS, we, **Indra Prakash**, a citizen of the United States of America, residing at 9750 Talisman Drive, Alpharetta, GA 30022; **Grant E. DuBois**, a citizen of the United States of America, residing at 215 Quincy Lane, Roswell, Georgia 30076; **George A. King**, a citizen of the United States of America, residing at 1755 Wildwood Road, Atlanta, GA 30306; and **Mani Upreti**, a citizen of the India, residing at 1943 Rotherham Way, Dunwoody, GA 30338 (hereinafter, "ASSIGNORS"), have invented certain inventions and improvements disclosed in an application for Letters Patent entitled "**REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A**," filed in the United States Patent and Trademark Office on May 21, 2007 and assigned Application No. 11/751,627, which claims priority to U.S. Provisional Application No. 60/805,216, which was filed on June 19, 2006 and U.S. Provisional Application No. 60/889,318, which was filed on February 12, 2007 (hereinafter, "APPLICATIONS"); and

WHEREAS, **The Coca-Cola Company**, a corporation of the State of Delaware, having a principal place of business at One Coca-Cola Plaza, NW, Atlanta, GA 30313 (hereinafter, "ASSIGNEE"), is desirous of acquiring an interest in the same;

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, ASSIGNORS, by these presents do sell, assign and transfer unto ASSIGNEE the full, exclusive and entire right, title, and interest in and to said APPLICATIONS, in and to any divisions, continuations, and reissues thereof, and in and to all inventions and improvements disclosed and described in said APPLICATIONS, preparatory to obtaining Letters Patent of the United States therefor, and ASSIGNORS hereby request the Commissioner of Patents and Trademarks to issue any and all Letters Patent of the United States resulting from said APPLICATIONS, or from a division, continuation, or reissue thereof, to ASSIGNEE, as the assignee, for its interest and for the sole use and benefit of ASSIGNEE and its assigns and legal representatives;

Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"

Application No. 11/751,627

Attorney Docket No. 25040-2776

Page 2 of 5

For the same consideration, ASSIGNORS, by these presents do sell, assign, and transfer to ASSIGNEE the full, exclusive, and entire right, title and interest in and to any foreign application or applications corresponding to said APPLICATIONS, in whole or in part, in countries other than the United States, in and to any Letters Patent and similar protective rights granted on said foreign applications, and in and to the right to claim any applicable priority rights arising from or required for said foreign applications under the terms of any applicable conventions, treaties, statutes, or regulations; said foreign applications to be filed and issued in the name of ASSIGNEE, or its designee insofar as permitted by applicable law.

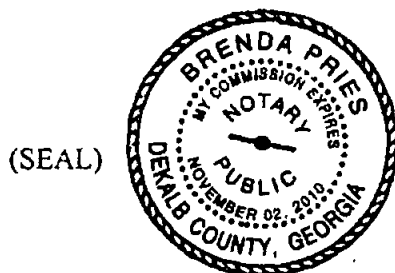
AND, for the same consideration, ASSIGNORS agree to sign all lawful papers, execute all division, continuing, reissue and other applications, make all assignments and rightful oaths, and generally do everything possible to aid ASSIGNEE, its successors, assigns, and nominees, to obtain and enforce proper protection for all said inventions and improvements in all countries throughout the world.

Date: 6/1/07

Indra Prakash
Indra Prakash

STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of June, 2007, personally appeared **Indra Prakash**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.



AO 1697279.1

Brenda Pries
NOTARY PUBLIC

My Commission Expires: 11/02/2010

PATENT
REEL: 019414 FRAME: 0621

255

Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"
Application No. 11/751,627
Attorney Docket No. 25040-2776
Page 3 of 5

Date: 6-1-07

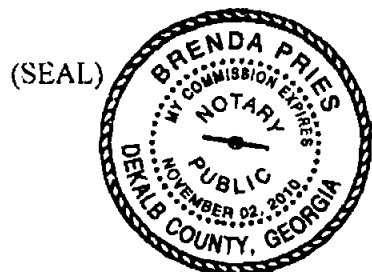
Grant E. DuBois
Grant E. DuBois

STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of June, 2007, personally appeared **Grant E. DuBois**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.

Brenda Pries
NOTARY PUBLIC

My Commission Expires: 11/02/2010



Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"

Application No. 11/751,627

Attorney Docket No. 25040-2776

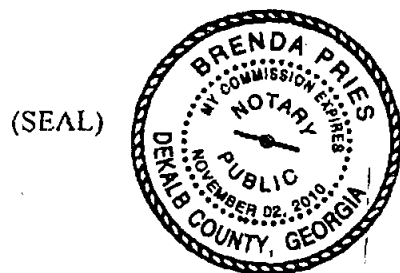
Page 4 of 5

Date: 1 June 2007

George A. King
George A. King

STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of June, 2007, personally appeared **George A. King**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.



Brenda Pries
NOTARY PUBLIC

My Commission Expires: 11/02/2010

Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"

Application No. 11/751,627

Attorney Docket No. 25040-2776

Page 5 of 5

Date: 06/01/07

Mani Upreti
Mani Upreti

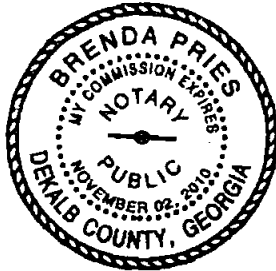
STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 15th day of June, 2007, personally appeared **Mani Upreti**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.

Brenda Pries
NOTARY PUBLIC

My Commission Expires: 11/02/2010

(SEAL)



AO 1697279.1

RECORDED: 06/12/2007

PATENT
REEL: 019414 FRAME: 0624

655

032

TRADUCCION AL ESPAÑOL del Documento de Cesión a **The Coca-Cola Company**, firmado por los Cedentes y el Cesionario.

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

- 1. País: Estados Unidos de América
- 2. Este documento público ha sido firmado por M. K. Carter
- 3. actuando en capacidad de Funcionario que Certifica
- 4. lleva el sello/timbre de la Oficina de Marcas y Patentes de Estados Unidos

Certificado

- 5. en Washington D.C.
- 6. el dieciséis de diciembre de 2008
- 7. por el Funcionario Asistente de Autenticación, Departamento de Estado de Estados Unidos
- 8. No. 09008279-14
- 9. Sello/timbre:
- 10. Firma:

(Firma)

Fernesia T. Crawford

130

LOS ESTADOS UNIDOS DE AMÉRICA

A TODO AQUEL A QUIEN PUEDA LLEGARLE LA PRESENTE:

DEPARTAMENTO DE COMERCIO DE ESTADOS UNIDOS

Oficina de Marcas y Patentes de Estados Unidos

Diciembre 5 de 2008

ESTE ES PARA CERTIFICAR QUE ANEXA SE ENCUENTRA UNA COPIA VERDADERA DE LOS ARCHIVOS DE ESTA OFICINA DEL DOCUMENTO REGISTRADO EL 12 DE JUNIO DE 2007.

Por autoridad del

Subsecretario de Comercio para la Propiedad Intelectual

y Director de la Oficina de Marcas y Patentes de Estados Unidos

(Firma)

M. K. CARTER

Funcionario que Certifica

293

CESIÓN DE PATENTE

Versión electrónica v1.1

Versión de la hoja v1.1

TIPO DE PRESENTACIÓN:	CESIÓN NUEVA										
NATURALEZA DEL ACUERDO:	CESIÓN										
DATOS DE LA PARTE CEDENTE											
<table><tr><th>Nombre</th><th>Fecha de ejecución</th></tr><tr><td>Indra Prakash</td><td>01/06/2007</td></tr><tr><td>Grant E. Dubois</td><td>01/06/2007</td></tr><tr><td>George A..King</td><td>01/06/2007</td></tr><tr><td>Mani Upreti</td><td>01/06/2007</td></tr></table>	Nombre	Fecha de ejecución	Indra Prakash	01/06/2007	Grant E. Dubois	01/06/2007	George A..King	01/06/2007	Mani Upreti	01/06/2007	
Nombre	Fecha de ejecución										
Indra Prakash	01/06/2007										
Grant E. Dubois	01/06/2007										
George A..King	01/06/2007										
Mani Upreti	01/06/2007										
DATOS DE LA PARTE QUE RECIBE											
<table><tr><td>Nombre:</td><td>The Coca-Cola Company</td></tr><tr><td>Dirección:</td><td>One Coca-Cola Plaza, NW</td></tr><tr><td>Ciudad:</td><td>Atlanta</td></tr><tr><td>Estado/País:</td><td>GEORGIA</td></tr><tr><td>Código Postal:</td><td>30313</td></tr></table>	Nombre:	The Coca-Cola Company	Dirección:	One Coca-Cola Plaza, NW	Ciudad:	Atlanta	Estado/País:	GEORGIA	Código Postal:	30313	
Nombre:	The Coca-Cola Company										
Dirección:	One Coca-Cola Plaza, NW										
Ciudad:	Atlanta										
Estado/País:	GEORGIA										
Código Postal:	30313										
NUMEROS DEL PROPIETARIO Total: 3											
<table><tr><th>Tipo de Propiedad</th><th>Número</th></tr><tr><td>Número de solicitud:</td><td>11751627</td></tr><tr><td>Número de la solicitud:</td><td>60805216</td></tr><tr><td>Número de la solicitud:</td><td>60889318</td></tr></table>	Tipo de Propiedad	Número	Número de solicitud:	11751627	Número de la solicitud:	60805216	Número de la solicitud:	60889318			
Tipo de Propiedad	Número										
Número de solicitud:	11751627										
Número de la solicitud:	60805216										
Número de la solicitud:	60889318										
DATOS DE CORRESPONDENCIA											
NUMERO DE FAX: (404) 853-8806											
La correspondencia se enviará por Correo de Estados Unidos cuando los intentos de hacerlo por fax no sean exitosos.											
Teléfono: (404)8538806											
Email: elizabeth.lester@sablaw.com											
Nombre de destinatario: Elizabeth A. Lester – Sutherland Asbill &											
Dirección línea 1: 999 Peachtree Street, NE											
Dirección Línea 4: Atlanta, GEORGIA 30309											
NUMERO DE EXPEDIENTE DEL ABOGADO:	25040-2776										
NOMBRE DEL REMITENTE:	Elizabeth A. Lester										

133

Anexos totales: 5
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Fuente=cesión#página3.tif
Fuente=cesión#página4.tif
Fuente=cesión#página5.tif

CESIÓN

CONSIDERANDO QUE, nosotros, **Indra Prakash**, ciudadana de los Estados Unidos de América, residente en 9750 Talisman Drive, Alpharetta, Georgia 30022; **Gran E. Dubois**, ciudadano de los Estados Unidos de América, residente en 215 Quincy Lane, Roswell, Georgia 30076; **George A. King**, ciudadano de los Estados Unidos de América, residente en 1755 Wildwood Road, Atlanta, Georgia 30306; y **Mani Upreti**, ciudadano de la India, residente en 1943 Rotherham Way, Dunwoody, Georgia 30338 (en adelante, "CEDENTES"), hemos inventado ciertas invenciones y mejoras divulgadas en una solicitud de patente titulada "**COMPOSICIÓN DE REBAUDIOSIDA A Y MÉTODO PARA PURIFICAR REBAUDIOSIDA A**", presentada en la Oficina de Marcas y Patentes de los Estados Unidos de América el 21 de mayo de 2007, con solicitud No. 11/751.627, la cual reivindica prioridad de la Solicitud Provisional de los estados Unidos No. 60/805.216, que fue presentada el 19 de junio de 2006 y de la Solicitud No. 60/889.318, que fue presentada el 12 de febrero de 2007 (en adelante, "SOLICITUDES"); y

CONSIDERANDO QUE, **The Coca-Cola Company**, una corporación del Estado de Delaware que tiene una oficina principal en One Coca-Cola Plaza, N. W., Atlanta, Georgia 30313 está deseosa de adquirir un interés en la misma;

AHORA, POR LO TANTO, por buena y valiosa contraprestación, el recibo y la suficiencia de la cual se reconoce por la presente, los CEDENTES por la presente vendemos, cedemos y transferimos al CESIONARIO el derecho e interés completo, exclusivo y total en y para dicha solicitud; en y para cualquier división, continuación, y reemisión de la misma, y en y para todas las invenciones y mejoras divulgadas y descritas en dichas SOLICITUDES DE PATENTE, preparatoria para obtener patente de Estados Unidos de la misma; y los CEDENTES por la presente solicitamos al Comisionado de Marcas y Patentes que emita cualquiera y todas las patentes de Estados Unidos que resulten de dichas SOLICITUDES DE PATENTE, o de una división, continuación, o reemisión de la misma, al

123

CESIONARIO, como el cesionario, para su interés y para el uso y beneficio único del CESIONARIO, y sus cesionarios y representantes legales;

Por la misma contraprestación, los CEDENTES, por la presente vendemos, cedemos, y transferimos al CESIONARIO el derecho, título e interés total, exclusivo y completo en y para cualquier solicitud extranjera o solicitud correspondiente a dichas SOLICITUDES DE PATENTE, en su totalidad o en parte, en países diferentes a Estados Unidos, en y para cualquier patente y derechos de protección similares concedidos sobre dichas solicitudes internacionales, y en y para el derecho a reivindicar cualquier derecho de prioridad aplicable que surja o se requiera para dichas solicitudes extranjeras bajo los términos de cualquier convención, tratado, estatuto, o regulación aplicable; dichas solicitudes extranjeras a ser presentadas y concedidas a nombre del CESIONARIO, o su designado hasta donde lo permita la ley aplicable.

Y, por la misma contraprestación, los CEDENTES acordamos firmar todos los documentos legales, ejecutar todas las solicitudes de divisiones, continuaciones, reemisiones y otras solicitudes, hacer todas las cesiones y juramentos, y generalmente hacer todo lo posible para ayudar al CESIONARIO, sus sucesores, cesionarios y nominados, para obtener y hacer valer dicha protección para todas dichas invenciones y mejoras en todos los países alrededor del mundo.

Fecha: 1 / 06 / 07

(Firma) _____

Indra Prakash

ESTADO DE Georgia

CONDADO DE Fulton

Ante mí, Notario Público en y para el Estado de Georgia, en este 1 de junio de 2007, personalmente compareció **Indra Prakash**, quien, debidamente jurada, firmó y declaró que la Cesión precedente como un acto libre.6

235

(SELLO)

Hay un sello que dice:

(Firma) _____

NOTARIO PÚBLICO

BRENDA PRIES

NOTARIO PÚBLICO

Mi comisión vence: 2 / 11 / 2010

MI COMISIÓN VENCE

EL 2 DE NOVIEMBRE DE 2010

CONDADO DEKALB, GA

Fecha: 1 / 06 / 07

(Firma) _____

Grant E. Dubois

ESTADO DE Georgia

CONDADO DE Fulton

Ante mí, Notario Público en y para el Estado de Georgia, en este 1 de junio de 2007, personalmente compareció **Grant E. Dubois**, quien, debidamente jurado, firmó y declaró que la Cesión precedente como un acto libre.

(SELLO)

Hay un sello que dice:

(Firma) _____

NOTARIO PÚBLICO

BRENDA PRIES

NOTARIO PÚBLICO

Mi comisión vence: 2 / 11 / 2010

MI COMISIÓN VENCE

EL 2 DE NOVIEMBRE DE 2010

CONDADO DEKALB, GA

263

Fecha: 1 / 11 / 06

(Firma) _____

George A. King

ESTADO DE Georgia

CONDADO DE Fulton

Ante mí, Notario Público en y para el Estado de Georgia, en este 1 de junio de 2007, personalmente compareció **George A. King**, quien, debidamente jurado, firmó y declaró que la Cesión precedente como un acto libre.

(SELLO)

Hay un sello que dice:

(Firma) _____

NOTARIO PÚBLICO

BRENDA PRIES

NOTARIO PÚBLICO

MI COMISIÓN VENCE

EL 2 DE NOVIEMBRE DE 2010

CONDADO DEKALB, GA

Mi comisión vence: 2 / 11 / 2010

825

Fecha: 1 / 06 / 07

(Firma) _____

Mani Upreti

ESTADO DE Georgia

CONDADO DE Fulton

Ante mí, Notario Público en y para el Estado de Georgia, en este 1 de junio de 2007, personalmente compareció **Mani Upreti**, quien, debidamente jurado, firmó y declaró que la Cesión precedente como un acto libre.

(SELLO)

Hay un sello que dice:

(Firma) _____

NOTARIO PÚBLICO

BRENDA PRIES

NOTARIO PÚBLICO

MI COMISIÓN VENCE

EL 2 DE NOVIEMBRE DE 2010

CONDADO DEKALB, GA

Mi comisión vence: 2 / 11 / 2010

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: United States of America

This public document

2. has been signed by M. K. Carter

3. acting in the capacity of Certifying Officer

4. bears the seal/stamp of U. S. Patent and Trademark Office

Certified

5. at Washington, D.C.

6. the sixteenth of December, 2008

7. by *Assistant Authentication Officer, United States Department of State*

8. No. 09008279-15

9. Seal/Stamp:

10. Signature:



Farnesia T. Crawford

A 7160438

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

December 05, 2008

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE
RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON
NOVEMBER 15, 2006.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office


M. K. CARTER

Certifying Officer



PATENT ASSIGNMENT

Electronic Version v1.1
 Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT
CONVEYING PARTY DATA	
Name	Execution Date
Indra Prakash	11/01/2006
Grant E. DuBois	11/01/2006
George A. King	11/01/2006
RECEIVING PARTY DATA	
Name:	The Coca-Cola Company
Street Address:	One Coca-Cola Plaza, NW
City:	Atlanta
State/Country:	GEORGIA
Postal Code:	30313
PROPERTY NUMBERS Total: 1	
Property Type	Number
Application Number:	60805216
CORRESPONDENCE DATA	
Fax Number:	(404)853-8806
<i>Correspondence will be sent via US Mail when the fax attempt is unsuccessful.</i>	
Phone:	404-853-8012
Email:	elizabeth.lester@sablaw.com
Correspondent Name:	Elizabeth A. Lester
Address Line 1:	999 Peachtree Street NE
Address Line 4:	Atlanta, GEORGIA 30313
ATTORNEY DOCKET NUMBER:	25040-1594
NAME OF SUBMITTER:	Elizabeth Lester
Total Attachments: 4 source=1594Assignment#page1.tif source=1594Assignment#page2.tif	

CH \$40.00 60805216

500179553

PATENT
REEL: 018521 FRAME: 0107

123

source=1594Assignment#page3.tif
source=1594Assignment#page4.tif

ASSIGNMENT

WHEREAS, we, **Indra Prakash**, a citizen of the United States of America, residing at 9750 Talisman Drive, Alpharetta, GA 30022; **Grant E. DuBois**, a citizen of the United States of America, residing at 215 Quincy Lane, Roswell, Georgia 30076; and **George A. King**, a citizen of the United States of America, residing at 1755 Wildwood Road, Atlanta, GA 30306 (hereinafter, "ASSIGNORS"), have invented certain inventions and improvements disclosed in a provisional patent application entitled "**REBAUDIOSIDE A COMPOSITION AND METHOD FOR PURIFYING REBAUDIOSIDE A**," filed in the United States Patent and Trademark Office on the 19th day of June, 2006, under Provisional Application No. 60/805,216; and

WHEREAS, **The Coca-Cola Company**, a corporation of the State of Delaware, having a principal place of business at One Coca-Cola Plaza, NW, Atlanta, GA 30313 (hereinafter, "ASSIGNEE"), is desirous of acquiring an interest in the same;

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, ASSIGNORS, by these presents do sell, assign and transfer unto ASSIGNEE the full, exclusive and entire right, title, and interest in and to said provisional application, and in and to all inventions and improvements disclosed and described in said provisional application, and in and to all U.S. non-provisional applications claiming benefit of said provisional application, including any continuations, divisionals, and reissues thereof, and all Letters Patents of the United States resulting from any of said applications;

For the same consideration, we, by these presents do sell, assign, and transfer to ASSIGNEE the full, exclusive, and entire right, title and interest in and to any foreign application or applications corresponding to said provisional application, in whole or in part, in countries other than the United States, in and to any Letters Patent and similar protective rights granted on said foreign applications, and in and to the right to claim any applicable priority rights arising from or required for said foreign applications under the terms of any applicable conventions, treaties, statutes, or regulations; said foreign applications to be filed and issued in the name of ASSIGNEE or its designee insofar as permitted by applicable law.

SEE

**Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"**
Attorney Docket No. 25040-1594
Page 2 of 4

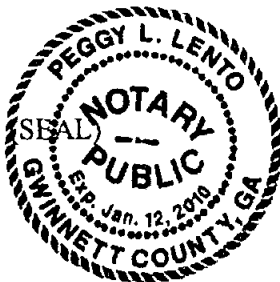
AND, for the same consideration, we agree to sign all lawful papers, execute all nonprovisional applications and other applications, make all assignments and rightful oaths, and generally do everything possible to aid ASSIGNEE its successors, assigns, and nominees, to obtain and enforce proper protection for all said inventions and improvements in all countries throughout the world.

Date: 11/1/06

Indra Prakash
Indra Prakash

STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 15 day of November, 2006, personally appeared **Indra Prakash**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.



Peggy L. Lento
NOTARY PUBLIC

My Commission Expires: 1-12-2010

2x3

Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"
Attorney Docket No. 25040-1594
Page 3 of 4

Date: 11-1-06

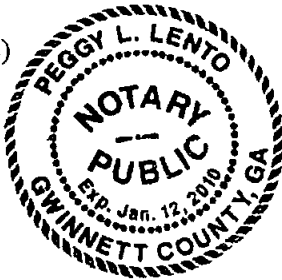
Grant E. DuBois
Grant E. DuBois

STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of November, 2006, personally appeared **Grant E. DuBois**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.

Peggy L. Lento
NOTARY PUBLIC

(SEAL)



My Commission Expires: 1-12-2010

Assignment "Rebaudioside A Composition And
Method for Purifying Rebaudioside A"
Attorney Docket No. 25040-1594
Page 4 of 4

Date: 11.01.06

George A. King
George A. King

STATE OF GEORGIA
COUNTY OF Fulton

Before me, a Notary Public in and for the State of Georgia, on this 1st day of November, 2006, personally appeared **George A. King**, who being duly sworn, signed and acknowledged the foregoing Assignment as his free act and deed.



Peggy L. Lento
NOTARY PUBLIC

My Commission Expires: 1-12-2010

5x5



3577

TRADUCCION AL ESPAÑOL del Documento de Cesión a **The Coca-Cola Company**, firmado por los Cedentes y el Cesionario.

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América
2. Este documento público
ha sido firmado por M. K. Carter
3. actuando en capacidad de Funcionario que Certifica
4. lleva el sello/timbre de la Oficina de Marcas y Patentes de Estados Unidos

Certificado

5. en Washington D.C.
6. el dieciséis de diciembre de 2008
7. por el Funcionario Asistente de Autenticación, Departamento de Estado de Estados Unidos
8. No. 09008279-15
9. Sello/timbre:
10. Firma:

(Firma)
Fernesia T. Crawford

LOS ESTADOS UNIDOS DE AMÉRICA

A TODO AQUEL A QUIEN PUEDA LLEGARLE LA PRESENTE:

DEPARTAMENTO DE COMERCIO DE ESTADOS UNIDOS
Oficina de Marcas y Patentes de Estados Unidos

Diciembre 5 de 2008

ESTE ES PARA CERTIFICAR QUE ANEXA SE ENCUENTRA UNA COPIA
VERDADERA DE LOS ARCHIVOS DE ESTA OFICINA DEL DOCUMENTO
REGISTRADO EL 15 DE NOVIEMBRE DE 2006.

Por autoridad del
Subsecretario de Comercio para la Propiedad Intelectual
y Director de la Oficina de Marcas y Patentes de Estados Unidos

(Firma)

M. K. CARTER

Funcionario que Certifica

18C

CESIÓN DE PATENTE

Versión electrónica v1.1

Versión de la hoja v1.1

TIPO DE PRESENTACIÓN:	CESIÓN NUEVA										
NATURALEZA DEL ACUERDO:	CESIÓN										
DATOS DE LA PARTE CEDENTE											
<table><tr><th>Nombre</th><th>Fecha de ejecución</th></tr><tr><td>Indra Prakash</td><td>01/11/2006</td></tr><tr><td>Grant E. Dubois</td><td>01/11/2006</td></tr><tr><td>George A. King</td><td>01/11/2006</td></tr></table>	Nombre	Fecha de ejecución	Indra Prakash	01/11/2006	Grant E. Dubois	01/11/2006	George A. King	01/11/2006			
Nombre	Fecha de ejecución										
Indra Prakash	01/11/2006										
Grant E. Dubois	01/11/2006										
George A. King	01/11/2006										
DATOS DE LA PARTE QUE RECIBE											
<table><tr><td>Nombre:</td><td>The Coca-Cola Company</td></tr><tr><td>Dirección:</td><td>One Coca-Cola Plaza, NW</td></tr><tr><td>Ciudad:</td><td>Atlanta</td></tr><tr><td>Estado/País:</td><td>GEORGIA</td></tr><tr><td>Código Postal:</td><td>30313</td></tr></table>	Nombre:	The Coca-Cola Company	Dirección:	One Coca-Cola Plaza, NW	Ciudad:	Atlanta	Estado/País:	GEORGIA	Código Postal:	30313	
Nombre:	The Coca-Cola Company										
Dirección:	One Coca-Cola Plaza, NW										
Ciudad:	Atlanta										
Estado/País:	GEORGIA										
Código Postal:	30313										
NUMEROS DEL PROPIETARIO Total: 1											
<table><tr><th>Tipo de Propiedad</th><th>Número</th></tr><tr><td>Número de solicitud:</td><td>60805216</td></tr></table>	Tipo de Propiedad	Número	Número de solicitud:	60805216							
Tipo de Propiedad	Número										
Número de solicitud:	60805216										
DATOS DE CORRESPONDENCIA											
NUMERO DE FAX: (404) 853-8806											
La correspondencia se enviará por Correo de Estados Unidos cuando los intentos de hacerlo por fax no sean exitosos.											
Teléfono:	(404)8538012										
Email:	elizabeth.lester@sablaw.com										
Nombre de destinatario:	Elizabeth A. Lester										
Dirección línea 1:	999 Peachtree Street, NE										
Dirección Línea 4:	Atlanta, GEORGIA 30313										
NUMERO DE EXPEDIENTE DEL ABOGADO:	25040-1594										
NOMBRE DEL REMITENTE:	Elizabeth Lester										

283

Anexos totales: 4

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Fuente=1594Cesión#página2.tif

Fuente=1594Cesión#página3.tif

Fuente=1594Cesión#página4.tif

CESIÓN

CONSIDERANDO QUE, nosotros, **Indra Prakash**, ciudadana de los Estados Unidos de América, residente en 9750 Talisman Drive, Alpharetta, Georgia 30022; **Gran E. Dubois**, ciudadano de los Estados Unidos de América, residente en 215 Quincy Lane, Roswell, Georgia 30076; y **George A. King**, ciudadano de los Estados Unidos de América, residente en 1755 Wildwood Road, Atlanta, Georgia 30306; (en adelante, "CEDENTES"), hemos inventado ciertas invenciones y mejoras divulgadas en una solicitud de patente titulada "**COMPOSICIÓN DE REBAUDIOSIDA A Y MÉTODO PARA PURIFICAR REBAUDIOSIDA A**", presentada en la Oficina de Marcas y Patentes de los Estados Unidos de América el 19 de junio de 2006, con solicitud provisional No. 60/805.216; y

CONSIDERANDO QUE, **The Coca-Cola Company**, una corporación del Estado de Delaware que tiene una oficina principal en One Coca-Cola Plaza, N. W., Atlanta, Georgia 30313 (en adelante "CESIONARIO") está deseosa de adquirir un interés en la misma;

AHORA, POR LO TANTO, por buena y valiosa contraprestación, el recibo y la suficiencia de la cual se reconoce por la presente, los CEDENTES por la presente vendemos, cedemos y transferimos al CESIONARIO el derecho e interés completo, exclusivo y total en y para dicha solicitud, en y para cualquier división, continuación, y reemisión de la misma, y en y para todas las invenciones y mejoras divulgadas y descritas en dichas SOLICITUDES DE PATENTE, preparatoria para obtener patente de Estados Unidos de la misma; y los CEDENTES por la presente solicitamos al Comisionado de Marcas y Patentes que emita cualquiera y todas las patentes de Estados Unidos que resulten de dichas SOLICITUDES DE PATENTE, o de una división, continuación, o reemisión de la misma, al CESIONARIO, como el cesionario, para su interés y para el uso y beneficio único del CESIONARIO, y sus cesionarios y representantes legales;

Por la misma contraprestación, los CEDENTES, por la presente vendemos, cedemos, y transferimos al CESIONARIO el derecho, título e interés total,

1283

exclusivo y completo en y para cualquier solicitud extranjera o solicitud correspondiente a dichas SOLICITUDES DE PATENTE, en su totalidad o en parte, en países diferentes a Estados Unidos, en y para cualquier patente y derechos de protección similares concedidos sobre dichas solicitudes internacionales, y en y para el derecho a reivindicar cualquier derecho de prioridad aplicable que surja o se requiera para dichas solicitudes extranjeras bajo los términos de cualquier convención, tratado, estatuto, o regulación aplicable; dichas solicitudes extranjeras a ser presentadas y concedidas a nombre del CESIONARIO, o su designado hasta donde lo permita la ley aplicable.

Y, por la misma contraprestación, los CEDENTES acordamos firmar todos los documentos legales, ejecutar todas las solicitudes de divisiones, continuaciones, reemisiones y otras solicitudes, hacer todas las cesiones y juramentos, y generalmente hacer todo lo posible para ayudar al CESIONARIO, sus sucesores, cesionarios y nominados, para obtener y hacer valer dicha protección para todas dichas invenciones y mejoras en todos los países alrededor del mundo.

Fecha: 1 / 11 / 06

(Firma) _____

Indra Prakash

ESTADO DE Georgia

CONDADO DE Fulton

Ante mí, Notario Público en y para el Estado de Georgia, en este 1 de noviembre de 2006, personalmente compareció **Indra Prakash**, quien, debidamente jurada, firmó y declaró que la Cesión precedente como un acto libre.

(SELLO)

Hay un sello que dice:

(Firma) _____

NOTARIO PÚBLICO

PEGGY L. LENTO

NOTARIO PÚBLICO
MI COMISIÓN VENCE
EL 12 DE ENERO DE 2010
CONDADO GWINNETT, GA

Mi comisión vence: 12 / 01 / 2010

523

Fecha: 1 / 11 / 06

(Firma) _____

Grant E. Dubois

ESTADO DE Georgia

CONDADO DE Fulton

Ante mí, Notario Público en y para el Estado de Georgia, en este 1 de noviembre de 2006, personalmente compareció **Grant E. Dubois**, quien, debidamente jurado, firmó y declaró que la Cesión precedente como un acto libre.

(SELLO)

Hay un sello que dice:

(Firma) _____

NOTARIO PÚBLICO

PEGGY L. LENTO

NOTARIO PÚBLICO

MI COMISIÓN VENCE

EL 12 DE ENERO DE 2010

CONDADO GWINNETT, GA

Mi comisión vence: 12 / 01 / 2010

Fecha: 1 / 11 / 2006

(Firma) _____

George A. King

ESTADO DE Georgia

CONDADO DE Fulton

Ante mí, Notario Público en y para el Estado de Georgia, en este 1 de noviembre de 2006, personalmente compareció **George A. King**, quien, debidamente jurado, firmó y declaró que la Cesión precedente como un acto libre.

(SELLO)

Hay un sello que dice:

(Firma) _____

NOTARIO PÚBLICO

PEGGY L. LENTO

NOTARIO PÚBLICO

MI COMISIÓN VENCE

EL 12 DE ENERO DE 2010

CONDADO GWINNETT, GA

Mi comisión vence: 12 / 01 / 2010

GEORGIA SUPERIOR COURT
CLERKS' COOPERATIVE AUTHORITY

Notary Division

1875 Century Boulevard, Suite 100

Atlanta, Georgia 30345

APOSTILLE
(Convention de La Haye du 5 Octobre 1961)

1. Country: UNITED STATES OF AMERICA

2. This public document

has been signed by TERESA MORRIS

3. acting in the capacity of

NOTARY PUBLIC, STATE OF GEORGIA

4. bears the seal/stamp of

TERESA MORRIS
NOTARY PUBLIC
FAYETTE COUNTY, GEORGIA

5. at ATLANTA, GEORGIA

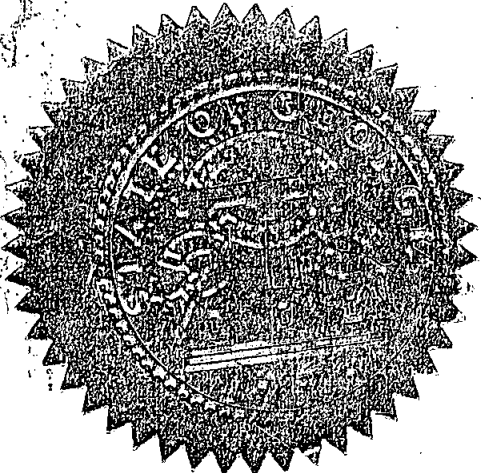
6. the 2ND DAY OF NOVEMBER, 2005

7. by GEORGIA SUPERIOR COURT CLERKS' COOPERATIVE AUTHORITY

8. No. I-137661

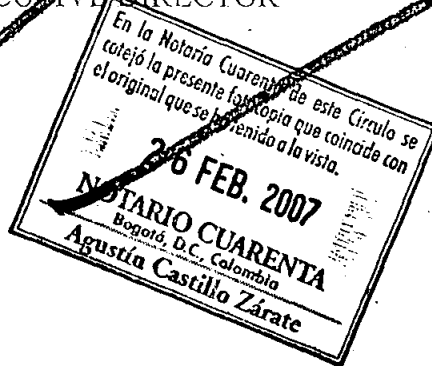
9. Seal/Stamp

10. Signature:



David R. Williams

DAVID R. WILLIAMS
EXECUTIVE DIRECTOR



NOTARY PUBLIC
(404) 327-6023

Brigard & Castro
BOGOTÁ - COLOMBIA

PODER

Otorgado
en.....

y

firmado

El
Suscrito.....

Hoy.....de.....de 20
0...

Firma.....

Nombre.....

Cargo.....

En.....calidad

De.....

Sociedad constituida de acuerdo con las leyes
de.....

con.....domicilio

Oficinas.....principales

Nombre(amos) a JUAN PABLO CADENA SARMIENTO y/o CARLOS H. PALACIO EASTMAN y/o HECTOR GOMEZ MEJIA, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales, lemas comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos, valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros) intereses, con todas las demás facultades legales necesarias.

Esté poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a JUAN PABLO CADENA SARMIENTO y/o CARLOS H. PALACIO EASTMAN y/o HECTOR GOMEZ MEJIA, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

POWER OF ATTORNEY

The
undersigned.....

Acting as Legal Representative

OF THE COCA-COLA COMPANY

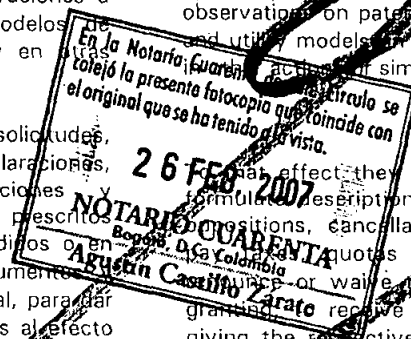
Company incorporated as per the laws of STATE OF DELAWARE
domiciled in One Coca-Cola Plaza, Atlanta, Georgia 30313,
Estados Unidos de América

With principal offices in ATLANTA, GEORGIA

Hereby appoints JUAN PABLO CADENA SARMIENTO and/or CARLOS H. PALACIO and/or HECTOR GOMEZ MEJIA, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names, slogans and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages; claims or observations on patent applications, models, industrial designs and utility models; and to take all the exercise of preventive measures and similar proceedings.

To that effect, they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoints JUAN PABLO CADENA SARMIENTO and/or CARLOS H. PALACIO EASTMAN and/or HECTOR GOMEZ MEJIA, domiciled in Carrera 7 No. 16-56 Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.



Granted and signed in Atlanta, Georgia

This 26th day of October of 2005

Signature

Name Steve Whaley

Title Vice President, General Tax Counsel & Assistant Treasurer

Hoy.....de.....de.....

compareció(eron) ante mí.....

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy.....de.....de.....

Notario Público (sello)

personalmente compareció ante mí.....

LEGALIZACION POR APOSTILLA ES REQUERIDA.

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él (ella) es.....

NOTARIAL CERTIFICATE (CORPORATION)

On this 26th day of October of 05

personally appeared before me

Steve Whaley

to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the Vice President

of The Coca-Cola Company

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del objeto social de la sociedad.

El suscrito Notario hace constar que.....

Estado de.....

con

fecha.....

y que quien confiere el presente poder es su representante.

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of Georgia

under date of 10/26/05

and that he (she) who grants the present power of is its Representative.

Teresa Morris

Public Notary (Seal)

Notario Público (sello)

CERTIFICADO NOTARIAL PERSONA NATURAL



163

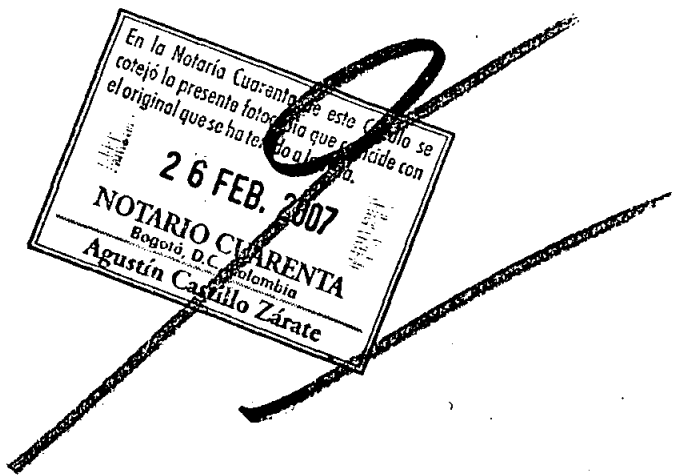
NOTARIAL CERTIFICATE
NATURAL PERSON

On _____ this _____ day
of _____ of _____,
personally _____ appeared _____ before
me _____

who is(are) known to me and who I attest executed the
foregoing document and he (they) declared he (they)
grant(s) the document for the uses and purposes
therein expressed.

Notary Public (Seal)

LEGALIZATION BY APOSTILLE IS REQUIRED.



225

TRADUCCION AL ESPAÑOL del Documento de Poder otorgado por THE
COCA-COLA COMPANY domiciliada en One Coca-Cola Plaza, Atlanta,
Georgia 30313, Estados Unidos de América.

AUTORIDAD COOPERATIVA DE FUNCIONARIOS
DE LA CORTE SUPERIOR DE GEORGIA

División de Notarial

1875 Century Boulevard , Suite 100

Atlanta, Georgia 30345

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. País: ESTADOS UNIDOS DE AMÉRICA
2. Este documento público
ha sido firmado por TERESA MORRIS
3. actuando en capacidad de NOTARIO PUBLICO, ESTADO DE
GEORGIA
4. lleva el sello/ timbre de TERESA MORRIS
NOTARIO PUBLICO
CONDADO DE FAYETTE, GEORGIA

CERTIFICADO

5. en ATLANTA, GEORGIA
6. el 2° DÍA DE NOVIEMBRE DE 2005
7. por LA AUTORIDAD COOPERATIVA DE FUNCIONARIOS DE LA
CORTE SUPERIOR DE GEORGIA
8. No. I-137661
9. Sello/timbre
10. Firma



(Firma)

DAVID R. WILLIAMS

DIRECTOR EJECUTIVO