

RAISBECK, LARA, RODRÍGUEZ & RUEDA
MIEMBROS DE LA FIRMA
BAKER & MCKENZIE

AVENIDA 82 N° 10 - 82, Piso 8
TELÉFONO: (57-1) 6341500
BOGOTÁ, D.C. COLOMBIA
WWW.BAKERINFO.COM
OFFICE.BOGOTA@BAKERNET.COM

41
A

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

SUPERINDUSTRIA Y COMERCIO
Radicación: 01050133 00000003 Folios: 3
Fecha (HMO): 2003-07-23 13:02:05
Tramite: 002 PATENTES A 1 REGISTRO/ 530 PETICION
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

Ref.: Expediente No. **01.050.133**

Solicitud de Patente de Invención Titulada:
"METODO DE CRISTALIZACION REACTIVA
PARA MEJORAR EL TAMAÑO DE
PARTICULA".

Solicitante: **PFIZER PRODUCTS INC.**

**SOLICITUD DE EXAMEN DE FONDO SEGÚN EL ARTICULO 44 DE LA
DECISION 486, GACETA No. 528**

ALVARO CORREA ORDOÑEZ, mayor de edad y vecino de Bogotá, D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado sustituto de la sociedad Pfizer Products Inc., respetuosamente me permito solicitar, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina de Naciones, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Adjunto recibo por el monto de \$ 335.000 pesos para cubrir la tasa correspondiente, según la Resolución 41687 del año 2002.

Atentamente,

ALVARO CORREA ORDOÑEZ
C.C. No. 19.143.366 de Usaquén
T.P. 20.281

Anexos: Sustitución de Poder
Recibo por \$ 335.000 pesos

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

Ante el Notario Once del Circuito de Bogotá de
Bogotá, compareció Alfonso

Barón Rodríguez

Quien exhibió la C.C. No. 89.43.366

expedida en Usaquén T.P. 10.88

y declaró que la firma y huella que aparecen en
el presente memorial son suyas y que el conte-
nido del mismo es cierto.

Memorial dirigido a interesado

Santafé de Bogotá, D.C.

23 JUL 2003

Firma del Notario

HUELLA

Autoriza la presente Diligencia

NOTARIO ONCE DEL CIRCUITO DE BOGOTÁ

REPÚBLICA DE COLOMBIA

NOTARIA 11 DEL CIRCULO DE
SANTAFÉ DE BOGOTÁ, D.C.

MANVARRO DE BAUTISTA

NOTARIA ONCE

RAISBECK, LARA, RODRÍGUEZ & RUEDA
MIEMBROS DE LA FIRMA
BAKER & MCKENZIE

AVENIDA 82 No. 10-62, 6° Piso
TELÉFONO: (57-1) 634-1500
BOGOTÁ, D.C. COLOMBIA
WWW.BAKERNET.COM
OFFICE.BOGOTA@BAKERNET.COM

42
f

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Solicitud colombiana de patente No. **01.050.133**

Solicitante: **PFIZER PRODUCTS INC.**
"METODO DE CRISTALIZACION REACTIVA
PARA MEJORAR EL TAMAÑO DE PARTICULA".

SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor y vecino de Bogotá. D.C., identificado como aparece al pie de mi firma, actuando en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad en el doctor **ALVARO CORREA ORDOÑEZ**, identificado con la Cédula de Ciudadanía número 79.143.366 de Usaquén y con la Tarjeta Profesional número 20.281, para que sea él quien en adelante, asuma el trámite de la presente solicitud.

El apoderado sustituto queda con las mismas facultades del principal.

Atentamente



CARLOS R OLARTE
C.C. No. 79.782.747 de Bogotá
T. P. No. 74.295 del Consejo Superior de la Judicatura

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**
Ante el Notario Once del Circulo de Santa Fe de
Bogotá, compareció [Firma]
Quién exhibió la C.C. No. 16717
expedida en [Firma] T.P. [Firma]
y declaró que la firma y huella que aparecen en
el presente memorial son suyas y que al con-
nido del mismo se interesa
Memorial dirigido a 15 JUL 2011
Santa Fe de Bogotá, D.C.
Firma del Declarante [Firma] **HUELLA**
Autorizó la anterior Diligencia.

REPUBLICA DE COLOMBIA
NOTARIA 11 DEL CIRCULO DE
SANTAFE DE BOGOTA, D.C.
MONICA Z. BAUTISTA N
NOTARIA ONCE(E)

43
52

SUPERINTENDENCIA Y COMERCIO
Radicacion : 01050133
Fecha (MM): 2003-07-23 13:02:45
Tramite : 002 PATENTES D 1 REGISTRO/ SDA PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 43,906
FECHA : JUNIO 24 DE 2003

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JULIAN ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	050-00110-6	13228244	24/06/2003	18,050,000.00

C O N C E P T O

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
	TOTAL :	\$ 335.000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 01-50133

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 528, DE
FECHA 30 DE MAYO DE 2003, EL TERMINO HABIL SEÑALADO POR LA LEY
EXPIRA EL 29 DE AGOSTO DE 2003.**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ **NO** X _____

45

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Álvaro Correa
Apoderado

Oficio N°
12248

REFERENCIA	Radicación	01 50133
	Trámite	002
	Evento	001
	Actuación	430
	Folios	009

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 01 50133, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 13-22
- . Ejemplos: folios 23-29
- . Capítulo reivindicatorio estudiado: 31-33
- . No se reivindica prioridad

Objeto de la invención

Según las reivindicaciones 1 a 19 de la presente solicitud, se refiere a un método para llevar a cabo de manera simultánea una reacción química y una cristalización controladas de un producto, empleando corrientes en chorro de fluido colisionantes que contienen reactivos capaces de producir el producto con un tamaño de partícula deseado.

Clasificación internacional de patentes B 01 D 9/02

Claridad de la solicitud

El artículo 30 de la decisión 486 establece que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

La expresión "velocidad lineal suficiente para conseguir micromezcladura de alta intensidad" de la reivindicación 1, contiene términos relativos (subrayados) que no son claros y dejan al lector en duda acerca del significado de las características a las cuales se refieren, haciendo del significado de dicha reivindicación poco claro. Hay que tener en cuenta que en la descripción se dice que es la manera de colisionar los reactivos los que son los responsables del crecimiento de los cristales de tamaño pequeño, por lo tanto es inevitable definir los parámetros del proceso que se pretende proteger (velocidad, intensidad de la micromezcla, temperatura y presión).

Los términos "compuesto químico", "intermedio reactivo", "disolvente" de la reivindicación 1 son muy amplios y pueden incluir compuestos que no se encuentran en la descripción.

La reivindicación 8 parece incompleta, pues solo se mencionan sales como acetato, clorhidrato, etc., pero no de qué compuestos activos.

Favor hacer las aclaraciones y correcciones del caso.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la presente solicitud - 22.08.01-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	US 5853891	"Haluros de plata de morfología o hábito de cristal alterado y método para producirlos"	29.13.98
2	US 5314506	"Método de cristalización para mejorar la estructura y el tamaño de los cristales"	24.05.94

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación del NIVEL INVENTIVO

El artículo 18 de la decisión 486 dispone *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

La patente US 5853891 enseña la posibilidad de producir cristalizaciones de manera simultánea con la reacción de dos reactantes los cuales son introducidos por corrientes a chorro en un cristalizador que presenta mezcla.

La patente US 5314506 muestra un proceso de cristalización de un compuesto químico utilizando chorros para crear corrientes de colisión antes la nucleación del producto. El producto tiene una estructura de cristal mejorada y controlada. Finalmente se mencionan ángulos y velocidades de inyección.

Teniendo en cuenta el objeto de la solicitud, el cual es proporcionar un método de producir cristalización simultáneamente con una reacción química mediante inyección, se aprecia que es una derivación evidente del estado de la técnica ya que los documentos citados enseñan procedimientos similares que tienen el mismo propósito.

Un técnico con sus conocimientos y usando cualquiera de los documentos citados llegaría a los procedimientos que se pretenden proteger.

Finalmente no se demuestran ventajas sorprendentes de los procedimientos de la presente solicitud en comparación con los del estado de la técnica.

Lo anterior hace que el documento citado pueda afectar el nivel inventivo de la presente solicitud.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US 5853691	1-19	Nivel Inventivo
2	US 5314506	1-19	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001


Álex Carmona Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

28 OCT. 2003

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO Número 1668	EXAMINADOR TÉCNICO Código 202024
---------------------------------	-------------------------------------

5748

United States Patent [19]
Doxsee

[11] Patent Number: 5,853,691
[45] Date of Patent: *Dec. 29, 1998

[54] SILVER HALIDES OF ALTERED CRYSTAL HABIT OR MORPHOLOGY AND METHODS FOR PRODUCING SAME
[75] Inventor: Kenneth M. Doxsee, Eugene, Oreg.
[73] Assignee: State of Oregon acting by and through the Oregon State Board of Higher Education on the behalf of the University of Oregon, Eugene, Oreg.
[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,545,394.

[21] Appl. No.: 695,784
[22] Filed: Aug. 12, 1996

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 104,863, Aug. 10, 1993, Pat. No. 5,545,394.
[51] Int. Cl.⁸ C01B 9/00; C01G 5/02
[52] U.S. Cl. 423/491; 23/300
[58] Field of Search 423/491; 23/295 R, 23/300

[56] References Cited

U.S. PATENT DOCUMENTS

4,308,091	12/1981	An	423/179
4,347,230	8/1982	Nicolau	429/491
4,436,664	3/1984	Gokel	260/330.6
4,474,963	10/1984	Gokel	549/352
4,687,844	8/1987	Gokel et al.	540/467
4,710,455	12/1987	Iguchi et al.	423/491
4,724,200	2/1988	Mankovsky	423/491
5,213,772	5/1993	Ichikawa et al.	423/491
5,258,275	11/1993	Arai et al.	430/253
5,320,822	6/1994	Ozai et al.	423/659
5,443,943	8/1995	Sanjowski	430/393
5,545,394	8/1996	Doxsee	423/659

OTHER PUBLICATIONS

Doxsee et al., "Complexation-Mediated Crystallization of Sodium Acetate Trihydrate Needles from Cyclohexane Solution," *J. Inclusion Phenom.* 9:327-336 (1990).

Doxsee et al., "Unusual Coordination Number and Geometry in a Potassium 18-Crown-6 Complex," *J. Am. Chem. Soc.* 114:5165-5171 (1992).
Bianconi et al., "Crystallization of an Inorganic Phase Controlled by a Polymer Matrix," *Nature* 349:315-317 (1991).
Nicolau, "Solution Growth of Sparingly Soluble Single Crystals from Soluble Complexes—I. General Introduction," *J. Crystal Growth* 48:45-50 (1980).
Nicolau, "Solution Growth of Sparingly Soluble Single Crystals from Soluble Complexes—II. Growth of α -HgI₂ Single Crystals from Iodomercurate Complexes," *J. Crystal Growth* 48:51-60 (1980).
Nicolau et al., "Solution Growth of Sparingly Soluble Single Crystals from Soluble Complexes—III. Growth of α -HgI₂ Single Crystals from Dimethylsulfoxide Complexes," *J. Crystal Growth* 48:61-73 (1980).
Boulin, et al., "Gel-Growth of Silver Acetate Crystals," *J. Crystal Growth* 6:290-292 (1970).
Armington, et al., "Recrystallization by Shifting the Equilibrium of Chemical Complexes—The Growth of Cinnabar," *J. Crystal Growth* 6:278-280 (1970).

Primary Examiner—Gary P. Straub
Attorney, Agent, or Firm—Klarquist Sparkman Campbell Leigh & Whinston, LLP

[57] ABSTRACT

Methods are disclosed in which first and second reactant salts and a complexing agent are added to a non-aqueous reaction solvent in which the complexing agent is soluble. The complexing agent is a crown ether or other cyclic or acyclic polydentate chelating agent that, in the reaction solvent, forms chelation complexes with at least one of the reactant salts. The reactant salts, which are substantially soluble and reactive with each other in water to form a first crystallite of silver halide, are present in the reaction solvent in relative amounts that are sufficient to form a desired amount of the silver halide in the reaction solvent. Reaction of the first and second reactant salts in the reaction solvent forms a second crystallite precipitate comprising crystals of silver halide having a different habit or morphology from silver halide crystals in the first crystallite that would otherwise be formable in water by reaction of similar amounts of the first and second reactant salts.

18 Claims, 6 Drawing Sheets



dissociate from the complexing agent. Release of the reactant-salt ion or molecule from the complexing-agent molecule to form the silver halide product must be energetically favorable.

Especially preferred complexing agents are any of various crown ethers (i.e., any of various cyclic polyethers in which the ether groups are connected by methylene or silicon linkages and the ether oxygen atoms serve as electron donors). Representative crown ethers include, but are not limited to, 12-crown-4, 15-crown-5, 18-crown-6, dicyclohexyl-18-crown-6, and dibenzo-18-crown-6. Each crown ether binds a particular range of cations, depending upon the size of the central cavity of the crown ether molecule. Other possible complexing agents are discussed in U.S. Pat. No. 5,545,394, incorporated herein by reference. Other cyclic and acyclic polydentate complexing agents can be used, including, but not limited to, crown ether analogs containing other donor atoms in addition to or in place of oxygen atoms, such as 1,4,7,10-tetraazacyclododecane ("cyclen"), 1,4,8,11-tetraazacyclotetradecane ("cyclam"), and 1,4,7,10,13,16-hexamethacyclooctadecane; and acyclic chelating agents such as tris[2-(2-methoxyethoxy)ethyl] amine, poly(ethylene glycols), and glymes.

The maximal amount of complexing agent to employ in a desired reaction system would be, for economic reasons, no greater than a stoichiometric amount relative to the amount of the corresponding reactant salt. Of course, if the complexing agent works "catalytically," substantially less than a stoichiometric amount would be required.

In any event, a person of ordinary skill in the relevant art would be familiar with various complexing agents and how to go about selecting an appropriate complexing agent for a particular reactant salt and reaction solvent. Many candidate complexing agents are commercially available and can be tested for efficacy in a given reaction by a simple test-tube experiment. I.e., bench-top experiments to test the efficacy of a particular complexing agent are within the skill of persons of ordinary skill in the relevant art.

It is also comprehended that many complexing agents, such as (but not limited to) crown ethers, can be made more soluble in certain hydrophobic solvents by chemically attaching lipophilic moieties to molecules of the agents.

As stated above, reactant salts for forming silver halides according to the present invention are normally soluble in water. Reaction solvents for use in reaction systems according to the present invention include any of various solvents that are less polar than water, particularly relatively non-polar organic solvents. Such reaction solvents include hydrophobic solvents and solvents that have some degree of hydrophilicity (normally less than water), and can comprise mixtures of pure solvents including mixtures with water.

Representative reaction solvents, not intended to be limiting in any way, include polar aprotic solvents such as dimethylsulfoxide (DMSO) and dimethylformamide (DMF); etheral solvents such as tetrahydrofuran (THF) and diethyl ether; alkanes, olefins, alkyl halides, alcohols, and ketones of up to 20 carbons; and aromatic, heteroaromatic, and aryl halide solvents of up to 20 carbons such as toluene, nitrobenzene, pyridine, and quinoline. These specific solvents, representing various classes and types of organic solvents, indicate that any of a wide variety of organic solvents can be utilized, and that useful reaction solvents are not limited to a particular class of solvents.

Since the reaction solvent is preferably a liquid under reaction conditions, this places a limit on the number of carbons, for example, molecules of the reaction solvent can

have. Solvent compounds having a greater number of carbon atoms (greater than about 20) tend either not to be liquids or to be too viscous under reaction conditions to be of practical utility.

Choosing a reaction solvent can be somewhat empirical. Basically, if a reactant salt cannot be made to dissolve in the reaction solvent, even after attempting to facilitate dissolution using any of various complexing agents, a different reaction solvent should be selected. Sometimes, difficulties with a reaction solvent can be solved by simply using a different complexing agent. If dissolution of the reactant salt is too slow, agitation can be helpful, including use of an ultrasonicator.

The reaction system can include a gel support. Representative gels that are relatively polar include, but are not limited to, poly(vinylacetate) (PVAc) and poly(vinylalcohol) (PVA). In the usual instance where the reaction solvent is non-polar, any of various non-polar gels can be used, including any of various solvent-swollen organic polymer gels such as, but not limited to, poly(ethylene) gel, poly(styrene) gel, and poly(vinylchloride) (PVC) gel. For example, dissolution of 7-9% (w/w) of poly(vinylchloride) in DMSO at elevated temperature (ca. 80° C.), followed by cooling to room temperature, affords a suitable solvent-swollen polymer gel. A comparable gel is obtained with ca. 18% (w/w) of poly(vinylchloride) in DMF. A gel can facilitate the formation of large crystals. Also, use of a gel can have particular utility in two-phase reactions (i.e., reactions involving one solution layered atop another wherein the reaction occurs at the layer interface) according to the present invention, wherein the gel can serve to slow the rate of reaction and can simplify setting up the phases prior to onset of the reaction.

The specific gelling agent to be used may be chosen on the basis of its ability to form a gel in the desired reaction solvent. The gelling agent may also be chosen in order to exploit its specific chemical properties (e.g., the ability to complex with ionic species or to interact with growing crystallites.)

Inducing formation of the silver halide product in a reaction system according to the present invention can be, and usually is, spontaneous. However, crystallization can be triggered by introducing a seed crystal or other nucleation aid to the system. Other methods of inducing crystal formation include thermal shock, physical shock, and methods that achieve at least localized supersaturation. "Double-jet precipitation" has also been used successfully, wherein first and second solutions of reactant salts are added simultaneously to a stirred crystallizer.

The products of reactions according to the present invention comprise crystals (i.e., the products are "crystallites") of silver halide. The crystallites can comprise an assemblage of individual silver halide crystals that are microscopic in size. Generally, the faster the reaction, the smaller the crystals of the product.

The silver halide crystallite products are not necessarily comprised of crystals larger than products of corresponding reactions performed according to the prior art. Rather, silver halide crystallites formed according to the present invention comprise crystals that exhibit an altered habit and/or morphology. In the case of reactions according to the present invention forming silver halide products consisting of smaller crystals, such crystallites can have unusual physical properties compared to crystallites consisting of larger crystals.

The product crystallite can comprise more than one silver halide compound. The crystallite can be a "mixed" silver

United States Patent [19]
Midler, Jr. et al.

[11] Patent Number: 5,314,506
[45] Date of Patent: May 24, 1994

[34] CRYSTALLIZATION METHOD TO
IMPROVE CRYSTAL STRUCTURE AND
SIZE

[75] Inventors: Michael Midler, Jr., East Brunswick;
Edward L. Paul, Chatham Township,
Morris County; Edwin F.
Whittington, Linden; Maurice
Futran, Westfield, all of N.J.; Paul D.
Lin, Concord, Mass.; Jongsyng Han,
Colonia; Shih-Hsieh Fan, Princeton
Junction, both of N.J.

[73] Assignee: Merck & Co., Inc., Rahway, N.J.

[21] Appl. No.: 793,764

[22] Filed: Nov. 18, 1991

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 706,682, Jan. 3, 1991,
abandoned, which is a continuation-in-part of Ser. No.
538,611, Jan. 15, 1990, abandoned.

[51] Int. Cl.³ B01D 9/02

[52] U.S. Cl. 23/295 R; 23/299;
423/639; 137/896; 239/421; 239/433; 366/173

[58] Field of Search 137/597, 896; 23/295 R,
23/293 R, 293 A, 293 S, 299; 241/39; 239/420,
421, 433; 366/172, 173, 176; 422/243; 423/639

[56] References Cited

U.S. PATENT DOCUMENTS

2,751,335 6/1956 Carver et al. 23/293 R
3,822,496 11/1971 Brilbauer et al. 208/35
4,367,912 2/1986 Levine 137/806
4,663,433 5/1987 Pyles et al. 328/496
4,783,008 11/1988 Ihauchi et al. 239/421
4,915,302 4/1990 Krus et al. 239/142
4,952,224 8/1990 Lilikon 62/534
5,011,293 4/1991 Reop et al. 366/173
5,074,671 12/1991 Ronocha et al. 366/172

FOREIGN PATENT DOCUMENTS

157562 10/1985 European Pat. Off. .

0044898A1 4/1990 European Pat. Off. .
393963 10/1990 European Pat. Off. .
3126634 1/1993 Fed. Rep. of Germany .

OTHER PUBLICATIONS

R. Pohorecki & J. Baldyga, The Use of a New Model of
Micromixing for Determination of Crystal Size in Pre-
cipitation, Chem. Eng. Sci. 38 79-83 vol. 38, No. 1 Jan.
1983.

J. Gerardo and N. S. Tavares, Mixing, Reaction and
Precipitation: Limits of Micromixing in an MSMFR
Crystallizer, Chem. Eng. Sci., vol. 40 No. 8 Aug. 1985.
A. Merzmann and M. Kind, Chemical Engineering As-
pects of Precipitation from Solution, Chem. Eng.
Technol., 11, pp. 264-276 (1988), Aug. 1994.

M. Midler, et al., Abstract, Annual Meeting American
Inst. Chem. Eng., San Francisco, Calif. (Nov. 3, 1989).

P. Lin, et al., (abstract) "The Use of Continuously Im-
pinging Jets to Control Crystallization and Particle Size
...", *Extended Abstracts, American Institute of Chemical
Engineers, 1990 Annual Meeting*, paper No. 66B, avail-
able to attendees Nov. 11, 1990, at Chicago, IL.

A. J. Mahajan, et al., (abstract) "Rapid Precipitation of
Amino Acids", *Extended Abstracts, American Institute of
Chemical Engineers, 1991 Annual Meeting*, paper No.
74a, available to attendees Nov. 17, 1991, at Los An-
geles, Calif.

Primary Examiner—Michael Lewis

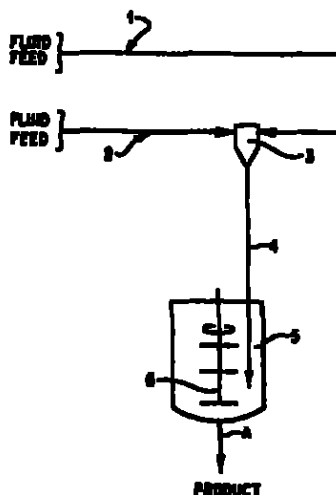
Assistant Examiner—Timothy C. Vancoy

Attorney, Agent, or Firm—Joseph F. DiPrima; Robert J.
North; Carol S. Quagliaro

[37] ABSTRACT

Impinging fluid jet streams are used in a continuous
crystallization process to achieve high intensity mi-
cromixing of fluids so as to form a homogeneous com-
position prior to the start of nucleation. This process
permits direct crystallization of high surface area par-
ticles of high purity and stability.

28 Claims, 4 Drawing Sheets



CRYSTALLIZATION METHOD TO IMPROVE CRYSTAL STRUCTURE AND SIZE

RELATED APPLICATION

This application is a continuation-in-part of co-pending U.S. application Ser. No. 706,682, filed Jun. 3, 1991, which itself is a continuation-in-part of U.S. application Ser. No. 07/338,611, filed on Jun. 13, 1990, and now abandoned.

BACKGROUND OF THE INVENTION

Crystallization from solution of pharmaceutically active compounds or their intermediates is the typical method of purification used in industry. The integrity of the crystal structure, or crystal habit, that is produced and the particle size of the end product are important considerations in the crystallization process.

High bioavailability and short dissolution time are desirable or often necessary attributes of the pharmaceutical end product. However, the direct crystallization of small sized, high surface area particles is usually accomplished in a high supersaturation environment which often results in material of low purity, high friability, and decreased stability due to poor crystal structure formation. Because the bonding forces in organic crystal lattices generate a much higher frequency of isomorphism than those found in highly ionic inorganic solids, "caking out" of supersaturated material is not uncommon, and such oils often solidify without structure.

Slow crystallization is a common technique used to increase product purity and produce a more stable crystal structure, but it is a process that decreases crystallizer productivity and produces large, low surface area particles that require subsequent high intensity milling. Currently, pharmaceutical compounds almost always require a post-crystallization milling step to increase particle surface area and thereby improve their bioavailability. However, high energy milling has drawbacks. Milling may result in yield loss, noise and dusting, as well as unwanted personnel exposure to highly potent pharmaceutical compounds. Also, stresses generated on crystal surfaces during milling can adversely affect labile compounds. Overall, the three most desirable end-product goals of high surface area, high chemical purity, and high stability cannot be optimized simultaneously using current crystallization technology without high energy milling.

One standard crystallization procedure involves contacting a supersaturated solution of the compound to be crystallized with an appropriate "anti-solvent" in a stirred vessel. Within the stirred vessel, the anti-solvent initiates primary nucleation which leads to crystal formation, sometimes with the help of seeding, and crystal digestion during an aging step. Mixing within the vessel can be achieved with a variety of agitators (e.g., Rushton or Pitched blade turbines, Intermix, etc.), and the process is done in a batchwise fashion.

When using current reverse addition technology for direct small particle crystallization, a concentration gradient can not be avoided during initial crystal formation because the introduction of feed solution to anti-solvent in the stirred vessel does not afford a thorough mixing of the two fluids prior to crystal formation. The existence of concentration gradients, and therefore a heterogeneous fluid environment at the point of initial crystal formation, impedes optimum crystal structure

formation and increases impurity entrainment. If a slow crystallization technique is employed, more thorough mixing of the fluids can be attained prior to crystal formation which will improve crystal structure and purity, but the crystals produced will be large and milling will be necessary to meet bioavailability requirements.

Another standard crystallization procedure employs temperature variation of a solution of the material to be crystallized in order to bring the solution to its supersaturation point, but this is a slow process that produces large crystals. Also, despite the elimination of a solvent gradient with this procedure, the resulting crystal characteristics of size, purity and stability are difficult to control and are inconsistent from batch to batch.

The novel process of this invention utilizes impinging jets to achieve high intensity micromixing in the crystallization process. High intensity micromixing is a well known technique where mixing-dependent reactions are involved. Feeding strategies as they relate to precipitation were addressed by Merzmann, A. and Kind, M., *Chemical Engineering Aspects of Precipitation from Solution*, Chem. Eng. Technol., V. 11, p. 264 (1988). Notable among other papers recently addressing the effect of micromixing in reaction processes are Garrido, J. and Tavera, N. S., *Mixing, Reaction and Precipitation: Limits of Micromixing in an MSMFR Crystallizer*, Chem. Eng. Sci., V. 40, p. 1483 (1985); Pohorecki, R. and Baldyga, J., *The Use of a New Model of Micromixing for Determination of Crystal Size in Precipitation*, Chem. Eng. Sci., V. 38, p. 79 (1983). However, the use of high intensity micromixing is not the norm in current crystallization technology where no chemical reaction is involved.

Impinging jets are used for micromixing routinely in reaction injection moulding (RIM) technology in the plastics industry but not for the purpose of causing crystallization. The use of an impinging jet device in a crystallization process to achieve intense micromixing is novel. Whether feed material is relatively pure or impure, the use of impinging jets results in crystal characteristics superior to those that result from standard crystallization methods.

Now with the present invention there is provided a method for crystallization of pharmaceutical compounds or their intermediates which directly produces high surface area end product crystals with greatly improved stability and purity and thereby eliminates the need for subsequent high intensity milling to meet bioavailability requirements. By removing the need for milling, the novel jet process avoids associated problems of noise and dusting, cuts yield loss, and saves the time and extra expense incurred during milling. It also removes an extra opportunity for personnel contact with a highly potent pharmaceutical agent, or for adverse effects on labile compounds. The small particle size attained with the jet process is consistent within a single run and as shown in Table I, results are reproducible between runs. Reproducibility is an attribute of this process that is not common to "reverse addition" methods typically used to produce small crystals.

The pure, high surface area particles that result from the jet process also display superior crystal structure when compared to particles formed via standard slow crystallization plus milling methods using the same quality and kind of feed compound. Improvements in crystal structure result in decreases in decomposition rate and therefore longer shelf-life for the crystallized

51
GA

3 where micromixing takes place. FIG. 5, shows another embodiment of this invention, wherein 2 jets are employed and the jetstreams impinge and micromix directly in the stirred vessel 13. As used herein, the terms stirred vessel and age vessel have the same meaning and are interchangeable.

The two fluids used in the novel process of this invention can be of different solvent composition, one fluid being a solution of the compound to be crystallized in a suitable solvent or combination of solvents ("feed solution"), and the other fluid being a suitable solvent or combination of solvents capable of initiating that compound's precipitation from solution ("anti-solvent"), chosen for its relatively low solvation property with respect to that compound. Such solvents and anti-solvents can include but are not limited to methanol, ethyl acetate, halogenated solvents such as methylene chloride, acetonitrile, acetic acid, hexanes, ethers, and water.

Or, the two fluids used in the process can both be solutions of the compound to be crystallized in the same suitable solvent or combination of solvents but each at a different temperature, and nucleation/precipitation can be initiated by instantaneous temperature reduction. The temperature and composition of each solution are chosen so that 1) no material will crystallize upstream of the impinging jets, and 2) sufficient supersaturation will be developed in the impinging jets to cause nucleation. Micromixing creates temperature and compositional uniformity throughout the mixture prior to the start of nucleation.

The fluids used in the process can also contain a small amount of a suitable surfactant which may alleviate agglomeration which might occur during the jet mix crystallization process. Thus, one, several or all of the fluids employed may contain a surfactant as less than 1% of its volume. The preferred amount of the surfactant is between 0.05% and 1% of the volume of the fluid. Since such a surfactant may be incorporated in the crystalline compound the surfactant should be chosen which will be innocuous to the eventual use of the crystalline compound. Suitable surfactants which may be included in the fluids employed in the process include but are not limited to Triton X-100, sodium dodecyl sulfate, Witconol-14F, Euthos D70-30C and the like.

The following is a list of compounds that have been successfully crystallized to meet particle size and purity specifications using the present invention: simvastatin, lovastatin (crude and pure), omeprazole, PROSCAR® ((3 α ,17 β)-(1,1-dimethylethyl)-3-oxo-4- Δ^5 -androst-1-ene-17-carboxamide), diltiazem maleate, 17 β -benzoyl-4- Δ^5 -androst-1-ene-3-one, 4"-epi-acetylmisino-evermectin B₁, [(trans-)-]-2-[3-methoxy-2-propoxy-5-(tetrahydro-5-(3,4,5-trimethoxyphenyl)-2-furanyl]phenyl]-sulfonyl]ethanol (DevLab, England). However, this is not an exhaustive list of all the compounds that can be used with the present invention.

After micromixing in a jet chamber, the material leaves the jet chamber as depicted in FIG. 1, travels into a stirred vessel 8 either directly or via a transfer line 4, and after an appropriate age time, the product suspension flows out of the vessel as indicated by arrow A. Another embodiment of this invention involves the micromixing of two impinging jetstreams directly in the stirred vessel without the use of a jet chamber or transfer line, as depicted in FIG. 5. For the crystallization of simvastatin, the preferred method is for two jetstreams to impinge directly in the stirred vessel. Once the mate-

rial leaves the stirred vessel, appropriate recovery techniques are used to isolate the product crystals. The material preferably flows through the system in a continuous process, although it is possible to hold up the process in a batchwise fashion at the stirred vessel-aging step given a vessel of sufficient volume.

As shown in FIG. 2 and FIG. 3, the jet chamber 3 is preferably cylindrical in shape and as shown in FIG. 2 the jet chamber 3 preferably has a floor 10 which slopes downward in a conical shape toward the floor's center which is open to a connecting transfer line 4 or directly into a stirred vessel or other appropriate container. The diameter and cylinder wall height of the chamber can vary according to scale needs.

Regardless of the number of jets used, the jet nozzles should be placed so that the fluid streams they emit will impinge, either inside the jet chamber or directly in the stirred vessel. The fluid jets must impinge to create an immediate high turbulence impact; converging or non-converging jets generally create insufficient turbulence to achieve the required micromixing. When two jets are used with a jet chamber, as shown in FIG. 2 and FIG. 3, the two jet nozzles 7 are preferably arranged so that they are substantially diametrically opposed to each other with their outlet tips directed to face each other; i.e., the two jet nozzles are at or close to a 180 degree angle to each other from an overhead view. Preferably, each jet outlet nozzle can have a slight downward angle from the horizontal of about 10 degrees to help the flowing material move down and out of the chamber.

Likewise, two jet nozzles placed directly inside the stirred vessel are preferably arranged so that they are substantially diametrically opposed to each other with their outlet tips directed to face each other. When the jet nozzles are so placed, each nozzle can have a slight upward or downward angle from the horizontal of from 0 degrees up to about 15 degrees, but preferably the two nozzles have just enough downward angle from the horizontal (ca. 13 degrees) to ensure that the fluid stream of one will not enter the outlet hole of the opposite nozzle.

One jet nozzle is used to transport one of the two fluids from an external source into the chamber and the other jet is used to similarly transport the other fluid. The distance between the nozzle tips inside the jet chamber or stirred vessel should be such that the hydrodynamic form of each fluid jet stream remains essentially intact up to the point of impingement. Therefore, the maximum distance between the nozzle tips will vary depending on the linear velocity of the fluids inside the jet nozzles. To obtain good results for generally non-viscous fluids, linear velocity in the jet nozzles should be at least about 5 meters/sec., more preferably above 10 meters/sec., and most preferably between about 20 to 25 meters/sec., although the upper limit of linear velocity is only limited by the practical difficulties involved in achieving it. Linear velocity and flow rate can both be controlled by various known methods, such as altering the diameter of the entry tube 6 and/or that of the nozzle outlet tip 9, and/or varying the strength of the external force that moves the fluid into and through the nozzle. Each jet apparatus can be manipulated independently to attain a desired final fluid composition ratio. When the desired flow ratio of one jet to the other differs from unity, preferably the difference is compensated for by appropriate sizing of the entry tubes. For example, if a 4:1 volumetric ratio of feed solution to anti-solvent is desired, the entry tube delivering feed

52
67

The solution was allowed to cool to room temperature then cooled in an ice bath to 5° C. while agitation was continued. The solid was then filtered, washed with water and dried. The crystals were cube-like particles; approximately 95% of the particles were smaller than 3 microns.

What is claimed is:

1. A process for crystallization of an organic pharmaceutical compound comprising contacting one or more jet streams of a feed solution of the organic pharmaceutical compound with one or more jet streams of an anti-solvent, said jet streams impinging to create high turbulence at their point of impact, and each jet stream having sufficient linear velocity to achieve high intensity micromixing of the feed solution and the anti-solvent prior to nucleation, followed by nucleation and the direct production of small crystals, at least 95% of said crystals having a diameter equal to or less than 25 microns.

2. The process of claim 1 wherein at least one of the jet streams comprises a surfactant.

3. The process of claim 1 wherein the pharmaceutical compound is selected from the group consisting of simvastatin, lovastatin, ((3 α , 17 β)-(1,1-dimethylethyl)-3-oxo-4- Δ -androst-1-ene-17-carboxamide), diltiazem maleate, 17 β -benzoyl-4- Δ - Δ -androst-1-ene-3-one, 4"-epi-acetylamino-avermectin B₁ and [trans(-)]-2-[[3-methoxy-2-propoxy-5-(tetrahydro-5-(3,4,5-trimethoxyphenyl)-2-furanyl]phenyl)sulfonyl]ethanol.

4. The process of claim 1 wherein each jet stream is independently at a temperature in the range of about 24° C. to 70° C.

5. The process of claim 1 wherein substantially all of said crystals have a diameter equal to or less than 20 microns.

6. A process for crystallization of an organic pharmaceutical compound comprising contacting one or more jet streams of a first feed solution of the organic pharmaceutical compound with one or more jet streams of a second feed solution of the organic pharmaceutical compound, said jet streams impinging to create high turbulence at their point of impact, and each jet stream having sufficient linear velocity to achieve high intensity micromixing of the first and second feed solutions prior to nucleation followed by nucleation and the direct production of small crystals, at least 95% of said crystals having a diameter equal to or less than 25 microns.

7. The process of claim 6 wherein the pharmaceutical compound is selected from the group consisting of simvastatin, lovastatin, ((3 α , 17 β)-(1,1-dimethylethyl)-3-oxo-4- Δ -androst-1-ene-17-carboxamide), diltiazem maleate, 17 β -benzoyl-4- Δ - Δ -androst-1-ene-3-one, 4"-epi-acetylamino-avermectin B₁ and [trans(-)]-2-[[3-methoxy-2-propoxy-5-(tetrahydro-5-(3,4,5-trimethoxyphenyl)-2-furanyl]phenyl)sulfonyl]ethanol.

8. The process of claim 6 wherein two jet streams are used and the two jet streams are substantially diametrically opposed to each other, and the hydrodynamic form of each jet stream remains essentially intact up to the point of impingement.

9. The process of claim 6 wherein at least one of the jet streams comprises a surfactant.

10. The process of claim 6 wherein substantially all of said crystals have a diameter equal to or less than 20 microns.

11. A process for crystallization of an organic pharmaceutical compound comprising contacting two opposing jet streams, one jet stream comprising a feed

solution of the organic pharmaceutical compound and the other jet stream comprising an anti-solvent, said opposing jet streams impinging to create high turbulence at their point of impact, and each jet stream having sufficient linear velocity to achieve high intensity micromixing of the feed solution and the anti-solvent prior to nucleation, followed by nucleation and the direct production of small crystals, at least 95% of said crystals having a diameter equal to or less than 25 microns.

12. The process of claim 11 wherein the linear velocity of the jet streams is at least about 3 meters/sec.

13. The process of claim 12 wherein the linear velocity is greater than 10 meters/sec.

14. The process of claim 13 wherein the linear velocity is between about 20-25 meters/sec.

15. The process of claim 14 wherein the compound to be crystallized is simvastatin, and the process is conducted in a temperature range of about 55-70° C.

16. The process of claim 15 wherein the feed solution is comprised of simvastatin dissolved in 100% methanol, the anti-solvent is comprised of 100% water, and a 41:59 volumetric ratio of feed solution:anti-solvent is used.

17. The process of claim 15 wherein the temperature is between 60-70° C.

18. The process of claim 15 wherein the compound to be crystallized is ((3 α , 17 β)-(1,1-dimethylethyl)-3-oxo-4- Δ -androst-1-ene-17-carboxamide and the process is conducted at room temperature.

19. The process of claim 18 wherein the feed solution is comprised of ((3 α , 17 β)-(1,1-dimethylethyl)-3-oxo-4- Δ -androst-1-ene-17-carboxamide dissolved in a 60:40 volumetric ratio of glacial acetic acid:water, the anti-solvent is comprised of 100% water, and a 1:5.5 volumetric ratio of feed solution:anti-solvent is used.

20. The process of claim 13 wherein the compound to be crystallized is lovastatin, and the process is conducted in a temperature range of about 40-55° C.

21. The process of claim 20 wherein the feed solution is comprised of lovastatin dissolved in a 90:10 volumetric ratio of methanol:water, the anti-solvent is comprised of 100% water, and about a 2.6:1 volumetric ratio of feed solution to anti-solvent is used.

22. The process of claim 13 wherein the compound to be crystallized is omeprazole and the process is conducted in temperature range of about 30° to 42° C.

23. The process of claim 23 wherein at least one of the fluids comprises a surfactant.

24. The process of claim 11 wherein at least one of the jet streams comprises a surfactant.

25. The process of claim 11 wherein the organic pharmaceutical compound is selected from the group consisting of simvastatin, lovastatin, ((3 α , 17 β)-(1,1-dimethylethyl)-3-oxo-4- Δ -androst-1-ene-17-carboxamide), diltiazem maleate, 17 β -benzoyl-4- Δ - Δ -androst-1-ene-3-one, 4"-epi-acetylamino-avermectin B₁ and [trans(-)]-2-[[3-methoxy-2-propoxy-5-(tetrahydro-5-(3,4,5-trimethoxyphenyl)-2-furanyl]phenyl)sulfonyl]ethanol.

26. The process of claim 11 wherein each jet stream is independently at a temperature in the range of about 25° C. to 70° C.

27. The process of claim 11 wherein substantially all of said crystals have a diameter equal to or less than 20 microns.

28. The process of claim 1 wherein the pharmaceutical compound is omeprazole and at least one of the fluids comprises a surfactant.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 1-80133

EDICTO No. 4476

**LA SECRETARÍA GENERAL AD-HOC
HACE SABER:**

Que esta Superintendencia profirió Resolución No. 4804 de 26-FEB-2007. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "METODO DE CRISTALIZACION REACTIVA PARA MEJORAR EL TAMAÑO DE PARTICULA".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Álvaro Correa Ordoñez, o a quien haga sus veces, en su calidad de apoderado de Pfizer Products Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFIQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los

26 FEB 2007

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIRO PABLO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:00 a.m. de hoy.

Secretaría General Ad-Hoc 13-MAR-2007 Este edicto se desflja hoy 27-MAR-2007 a las 4:30 p.m.
Secretaría General Ad-Hoc
EDICTO No. 4476