65

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-077560- -00004-0000 Fec: 2006-04-25 16:00:52
Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII Eve 379 FASENACIONALII
Act 329 CTOINFORMACION Folios: 5

FORMULARIO ÚNICO DE CORRECIONES Y MODIFICACIONES
2000-10

1 **SOLICITUD DE:**

[ ] Corrección de Error Material [X] Modificación a una Solicitud.

2 **SOLICITANTE**

Nombre: **STRAKAN INTERNATIONAL LIMITED**
Dirección: 5th Floor, The Penthouse, Washington Mall 1, Church Street
Teléfono:
E-mail
Domicilio: Hamilton, Bermuda

IDENTIFICACIÓN
C.C [ ] NIT [ ]
C.E. [ ] Otro [ ]
Número _____

3 **REPRESENTANTE O APODERADO**

Nombre: **GERMAN CASTILLO GRAU**
Dirección: Carrera 13 No. 37-43 Piso 12
Teléfono: 285 74 60 Fax: 285 92 67
E-mail info@castillograu.com

IDENTIFICACIÓN
C.C [X] NIT [ ]
C.E. [ ] Otro [ ]
Número 17.017.671 de Bogotá T.P. 2.978 del C.S.J.

4 **Número de Expediente**
05 77.560

5 **Descripción de la corrección o modificación solicitada** **MODIFICACION** de nombre de solicitante
por TRANSFERENCIA de
De: STRAKAN LIMITED
A: STRAKAN INTERNATIONAL LIMITED

6 **Comprobante de pago N°** 06-37,535 **Fecha** 25/04/2006

7 **Anexos:**

[X] Comprobante de pago de la tasa
[X] Poderes, si fuere el caso **copia auténtica**
[ ] Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas.
[X] documento que respalda la modificación **copia auténtica**

8

NOMBRE GERMAN CASTILLO GRAU **FIRMA**
C.C 17.017.671 de Bogotá T.P. 2978 del C.S.J.

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

COLOMBIA 66 67

Castillo Grau & Associates
Law Offices
P.O. Box 251473
Bogotá, Colombia

FOR PATENTS AND TRADEMARKS IN

COLOMBIA

PODER GENERAL

(1) STRAKAN INTERNATIONAL LIMITED

domiciliado en (2) 5[th] Floor, The Penthouse, Washington Mall 1, Church Street, Hamilton, Bermuda

nombra al Dr. Germán Castillo Grau y/o Adriana Castillo Gibsone y/o Luis Felipe Castillo Gibsone ....

con oficinas en la Carrera 13 No. 37-43, Piso 12 en Bogotá, D.C., Colombia como sus representantes con poder especial amplio y *suficiente*, para *recabar de las oficinas y* autoridades Colombianas, administrativas, judiciales o de policía, en primera o segunda instancia, la Obtención de Patentes de Invención, Registro de Marcas, de Diseños Industriales, de Nombres y Enseñas Comerciales, lo mismo que traspasos, extensiones, renovaciones, cambios de nombre y domicilio, registro de licencias de explotación y registro de licencias de uso referentes a tales actuaciones, a cuyo efecto les faculta para dar ante dichas autoridades todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, apelaciones y reclamos, solicitar la aplicación de medidas cautelares, aceptar en nuestro nombre y representación la Cesión de derechos de invención y de patente de invención que se nos haga por cualquier persona, abonar todos los impuestos cuotas y pagos determinados por la ley, recibir todos los documentos y valores dando el descargo respectivo, llenar cualesquiera otros requisitos, desistir, y tomar en fin todas las medidas que creyeren conducentes al resguardo de nuestros intereses y en caso de presentarse oposiciones para que intervengan como demandantes o como demandados, con todas las demás facultades legales necesarias. Este poder comprende además las facultades de recibir, desistir, transigir, comprometer, sustituir, revocar sustituciones, recibir notificaciones y nombrar apoderados judiciales ó extra-judiciales

Esta Notaría Veintiséis del Círculo de Bogotá, hago constar que esta copia coincide con original que se ha presentado Bogotá D.C. - Colombia

Dado y firmado en (4) 20 ABR 2006 ....

....

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

Firma/Signature ....

Corporate Seal to be Affixed

GENERAL POWER OF ATTORNEY

(1) STRAKAN INTERNATIONAL LIMITED

domiciled in (2) 5[th] Floor, The Penthouse, Washington Mall 1, Church Street, Hamilton, Bermuda

hereby appoint Dr. Germán Castillo Grau and/or Adriana Castillo-Gibsone and/or Luis Felipe Castillo-Gibsone ....

with offices at Carrera 13 No. 37-43, 12[th] Floor in Bogotá, Colombia as our representatives with special ample and sufficient power to obtain from *the offices* and Colombian authorities, administrative, judicial and police, in first or in second instance, Patents of Invention, registration of Trade or Service Marks, Industrial Designs, of Commercial Names and Ensigns, as well as assignments, extensions, renewals, changes of names and addresses, registration of *licences of exploitation and licences of use* referring to said actions who are empowered to take before said authorities all of the necessary steps for the purposes indicated, to file applications, to formulate descriptions, corrections, protests, declarations, appeals and claims, apply for precautionary measures, to *accept on our behalf and representation the* assignment of rights on invention and titles of invention that may be given to us by any person, to pay all taxes, quotas and payments prescribed by law, to receive all the documents and proceeds giving the respective acquiescence or receipt, to fulfill any other requisites *to desist and take in fact any other* measures that may be deemed conductive to the safeguard of our interests, and in case oppositions are presented to intervene as plaintiff or defendant, with all necessary legal faculties. This power includes the faculties to receive, desist, compromise, transact, substitute it in all or in part, to revoke *substitutions, to* receive notifications and to appoint judicial or extra-judicial attorneys.

Galashiels, UK 10th March 2006

Given and signed in (4)

....

Andrew McLean Bird

....

261354

DECLARACION NOTARIAL
(Individual)

A los .....días del mes de .....de 2005 compareció personalmente ante mí, Notario Público el/la señor(a)

.....

A quien(es) doy fé de conocer y me consta que es(son) la(s) persona(s) descrita(s) y firmante(s) del documento que precede, declarando ante mí que otorga(n) el mismo para los fines y propósitos que en él se expresan.

El Notario Público

.....

(Sociedades)

El infrascrito Notario certifica: que la firma que antecede y dice .....

.....

es auténtica; que el signatario desempeña el cargo de

.....

de **STRAKAN INTERNATIONAL LIMITED**

que tiene facultad para otorgar este poder; y que dicha compañía está domiciliada en Hamilton, Bermuda

y actualmente existe y está organizada de acuerdo a las leyes de

.....

Todos los hechos anteriores le constan por haber examinado los documentos respectivos y de todo ello da fe..

Dado y firmado en .....

.....

Como Notario Veintiséis del Circulo de Bogotá, hago constar que esta copia coincide con original que se ha presentado

Bogotá D.C. - Colombia.

20 ABR 2006

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

El Notario Público

(Con Apostilla)

NOTARIAL CERTIFICATE
(Individuals)

On this 10th day of March of 2006 personally appeared before me, a Notary Public, ...JAMES IAN COGLE.....
70 HIGH STREET, GALASHIELS
to me known, and known to me be the person(s) described in and who executed the foregoing document, and he(they) duly acknowledged to me that he(they) executed same for the uses and purposes therein expressed.

Notary Public

.....

(Corporations)

The undersigned Notary Public certifies: that

The preceeding signature reading ....Andrew McLean

.....

is authentic; that the signor at present fills the post of Director

.....

of **STRAKAN INTERNATIONAL LIMITED**

and that he/~~she~~ is empowered to grant this power; and that said company is domiciled in Hamilton, Bermuda

and actually exists and is organized in accordance with the laws of Bermuda

All the foregoing facts are known to the Notary due to his/her having examined the respective documents to which he/she, the Notary, attests.

Granted and signed in.....Galashiels, Scotland.....

Notary Public

(With Apostille)

67 8 68

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by / a été signé par: **James Ian Collie**

3. Acting in the capacity of / agissant en qualité de: **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de: **The Said Notary Public**

Certified/Attesté

5. at London/à Londres

6. the/le **12 April 2006**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G987785**

9. Stamp: / timbre:

10. Signature: **L. Groves**

LG

Como Notario Veintiséis del Circulo de Bogotá, hago constar que esta copia coincide con el original que se me presentado
Bogotá D.C. - Colombia
20 ABR 2006
GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

EN BLANCO
NOTARIA VEINTISEIS

COLOMBIA
68

68

CASTILLO GRAU & ASSOCIATES
Law Offices
P.O. Box 251473
Bogotá, Colombia

PODER CON CESION

El (los) infrascrito(s)

STRAKAN LIMITED

domiciliado(s) en Buckholm Mill, Buckholm Mill Brae, Galashiels, Reino Unido

titular de la Solicitud de Patente

GRANISETRON TRANSDERMICO Expediente No. 05 77.560

declara por el presente que ha cedido a

STRAKAN INTERNATIONAL LIMITED

domiciliado(a) en 5th Floor, The Penthouse, Washington Mall 1, Church Street, Hamilton, Bermuda
la(s) referida(s) solicitud de patente con todos los derechos y prerrogativas correspondientes, sin excepción ni limitación alguna, pudiendo por consiguiente, de hoy en adelante, el cesionario considerarse como único dueño de dicha(s) patente para usarla(s) y disponer de ella(s) como mejor convenga a sus intereses sin que haya lugar a reclamación ulterior alguna por parte del cedente o sus causahabientes en ningún caso ni en ningún tiempo.
El Cesionario por el presente acepta la cesión y confiere poder al Dr. GERMAN CASTILLO GRAU y/o ADRIANA CASTILLO GIBSONE y/o LUIS FELIPE CASTILLO GIBSONE domiciliados en la Carrera 13 No. 37-43 Piso 12 en Bogotá, como sus representantes y para que lo representen en las gestiones y para que lo representen en las gestiones judiciales o administrativas a que haya lugar para perfeccionar la presente cesión con facultad para recibir, efectuar renovaciones, registros de marcas, nuevas transferencias, cambios de nombre y domicilio, recibir notificaciones y nombrar apoderados judiciales y extrajudiciales.

Firmado en Galashiels, UK

El Cedente, 15th March 2006
The Assignor

Director

POWER WITH ASSIGNMENT

The Undersigned,

STRAKAN LIMITED

domiciled in Buckholm Mill, Buckholm Mill Brae, Galashiels, United Kingdom

proprietor of the Colombian Patent Application

TRANSDERMAL GRANISETRON No. 05 77.560

declares by this document that assignment has been made of all rights and titles with any *exception or limitation to*

STRAKAN INTERNATIONAL LIMITED

domiciled in 5th Floor, The Penthouse, Washington Mall 1, Church Street, Hamilton, *Bermuda*
of said Patent Application, the assignee being able to be considered therefore as the sole owner of said patent to use the same and to dispose of same to his best interest without any further claim in the matter on behalf of the *assignor in any case or at any time.*
The assignee, by means of this document accepts the assignment and hereby appoints Dr. GERMAN CASTILLO GRAU and/or ADRIANA CASTILLO GISONE and/or LUIS FELIPE CASTILLO GIBSONE domiciled at Carrera 13 *No. 37-43 12th Floor in Bogotá as our* representatives and as attorneys with special and sufficient power to represent the assignee in the judicial or administrative negotiations which may arise from the present assignment, with faculty to receive, withdraw, settle disputes and *with full powers of substitution, to carry* out renewals, registration of trademarks, new assignments, changes of name and domicile, to receive notifications and to appoint judicial or extrajudicial attorneys.

Signed in Galashiels, UK

15th March 2006

El Cesionario
The Assignee

Director

Como Notario Veintisiete del Circuito de Bogotá, hago constar que esta copia coincide con el original que se ha presentado
Bogotá D.C. - Colombia.
20 ABR 2006
GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISIETE

NOTE: The signatures must be attested by a Notary Public. A notarial declaration has to be added about the legal existence of the concern and the right to act for same of the persons authorizing this document, which must be finally legalized by Apostille.

261085

EL CEDENTE

El infrascrito Notario Público certifica que: la firma que antecede y dice

es auténtica; que el firmante desempeña actualmente el cargo de

de **STRAKAN LIMITED**

que tiene facultad para otorgar este documento; y que dicha compañía está domiciliada en Galashiels, Reino Unido

y actualmente existe y está organizada de acuerdo con las leyes de

Todos los hechos anteriores le constan por haber examinado los documentos respectivos, y de todo ello da fe.

Dado y firmado en

EL NOTARIO PUBLICO

THE ASSIGNOR

The Undersigned Notary Public certifies: that the preceeding signature reading

Andrew McLean

is authentic; that the signor at present fills the post of Director

of **STRAKAN LIMITED**

and that he/she is empowered to grant this document; and that said company is domiciled in Galashiels, United Kingdom

and actually exists and is organized in accordance with the laws of

All the foregoing facts are known to the Notary due to his having examined the respective documents to which he/she, the Notary, attests.

Granted and signed in Galashiels, Scotland

THE NOTARY PUBLIC

EL CESIONARIO

El infrascrito Notario Público certifica que: la firma que antecede y dice

es auténtica; que el firmante desempeña actualmente el cargo de

de **STRAKAN INTERNATIONAL LIMITED**

que tiene facultad para otorgar este documento; y que dicha compañía está domiciliada en Hamilton, Bermuda

y actualmente existe y está organizada de acuerdo con las leyes de

Todos los hechos anteriores le constan por haber examinado los documentos respectivos, y de todo ello da fe.

Dado y firmado en

EL NOTARIO PUBLICO

THE ASSIGNEE

The Undersigned Notary Public certifies: that the preceeding signature reading

Andrew McLean

is authentic; that the signor at present fills the post of Director

of **STRAKAN INTERNATIONAL LIMITED**

and that he/she is empowered to grant this document; and that said company is domiciled in Hamilton, Bermuda

and actually exists and is organized under the laws of

All the foregoing facts are known to the Notary due to his having examined the respective documents to which he/she, the Notary, attests.

Granted and signed in Galashiels, Scotland

THE NOTARY PUBLIC

Como Notario Veintiséis del Círculo de Bogotá, hago constar que esta copia coincide con original que se ha presentado Bogotá D.C. - Colombia.

20 ABR 2006

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

NOTE: Both certifications must be legalized by Apostille.

69 70

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by **James Ian Collie**
   a été signé par

3. Acting in the capacity of **Notary Public**
   agissant en qualité de

4. Bears the seal/stamp of **The Said Notary Public**
   est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres

6. the/le **12 April 2006**

7. by *Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs* /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G987781**

9. Stamp:
   timbre:

10. Signature: **L. Groves**

LG

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

Consulado Notario Veintiseis del Circulo de Bogotá. Hago constar que esta copia coincide con el original que se ha presentado
Bogotá D.C. - Colombia.
20 ABR 2006
GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

EN BLANCO
NOTARIA VEINTISEIS

70 874

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-077660- -00004-0000 Fec: 2006-04-25 16:00:52
Dep: 2020 NUEVCREACIONES
Tra: 11 PATENTEIYII Eve 379 FASENACIONALII
Act 329 CTOINFORMACION Folios: 6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 31,535
FECHA : ABRIL 25 DE 2006

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	37207249	25/04/2006	211,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	95,000.00
		TOTAL : $	95,000.00

SON: NOVENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

71

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio ~~78~~

2020
Bogotá D.C.,

Doctor(a)
CASTILLO GRAU GERMAN
Apoderado(a) y/o Representante de
STRAKAN LIMITED

REFERENCIA	Radicación No.	05 77560
	Solicitud internacional	GB2004/000403
	Fecha inicio fase nacional	05/09/2005
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	2170
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el *expediente indicado en* la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 12 DIC. 2005

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa10

72 72

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-077560

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **575** DE

FECHA **30** DE **ABRIL DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **31** DE **JULIO** DEL **2007**

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 _____

23

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
SISTEMA DE TRAMITES-CONSULTA DE TRÁMITES*

Martes 19 de Febrero de 2008

|< < > >|

Datos del Trámite (PENDIENTE)

Radicación: Año: 2005 * Número: 77560 * Ctrl: * Cons Rad: 5 * Secu Even: 0 *

Tipo Trámite: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II *

Tipo Evento: 379. FASE NACIONAL INCLUIDO CAPITULO II *

Tipo Actuación: 539. PETICION DE EXAMEN *

Dependencia Origen: *

Dependencia Destino: 2020. DIVISION DE NUEVAS CREACIONES *

Solicitante/Destinatario: GERMAN CASTILLO GRAU * Tipo: Contenida

Identificación: CC - CEDULA DE CIUDADANIA - Número: 17017671.0

Dirección: CARRERA 13 NO. 37-43 PISO 12 BOGOTA D.C. COLOMBIA

Tipo de Radicación: EN - ENTRADA * Folios: 2

Fecha de Radicación: Dia: 7 - Mes: Septiembre - Año: 2007 - 09:59:46 Entrega: VENTANILLA

Guía: fecha:

Observaciones:

Otros Datos

[Documentos][Recibos]

Nueva Consulta

[Cerrar Sesión

Registro :6 / 7

Información adicional en la Oficina de Sistemas

Año	Número	Ctrl	Cons Rad	Sec Eve	Trámite	Evento	Actuación	Tipo	Fecha	Solicitante	Asignacion/ Estado-Correspondencia		
5	77560		0	0	PCT-PATENTE DE INVENCION CAPITULOS I Y II	FASE NACIONAL INCLUIDO CAPITULO II	PRESENTACION	EN	2005-08-05 16:03:22	GERMAN CASTILLO GRAU			
5	77560		1	0	PCT-PATENTE DE INVENCION CAPITULOS I Y II	FASE NACIONAL INCLUIDO CAPITULO II	REQUERIMIENTO DE INFORMACION	SA	2005-10-06 12:18:17	PARA MIGRACION TRAMITES SOLICITANTE DESTINATARIO NO IDENTIFICADO			
5	77560		2	0	PCT-PATENTE DE INVENCION CAPITULOS I Y II	FASE NACIONAL INCLUIDO CAPITULO II	SOLICITUD PRORROGA	EN	2005-12-05 16:03:05	GERMAN CASTILLO GRAU			
5	77560		3	0	PCT-PATENTE DE INVENCION CAPITULOS I Y II	FASE NACIONAL INCLUIDO CAPITULO II	REPUESTA A REQUERIMIENTO DE INFORMACION	EN	2006-02-07 16:46:03	GERMAN CASTILLO GRAU			
					PCT-	FASE							

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 044 684 A2

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
18.10.2000 Bulletin 2000/42

(51) Int. Cl.⁷: A61K 9/70

(21) Application number: 00107843.5

(22) Date of filing: 12.04.2000

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 13.04.1999 JP 10590199

(71) Applicant:
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- Hori, Mitsuhiko,
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Ibaraki-shi, Osaka 567-8680 (JP)

(74) Representative:
von Kreisler, Alek, Dipl.-Chem. et al
Patentanwälte,
von Kreisler-Selting-Werner,
Bahnhofsvorplatz 1 (Deichmannhaus)
50667 Köln (DE)

(54) Percutaneously absorbable preparation

(57) A percutaneously absorptive preparation is provided, which includes a drug reservoir layer, a drug reservoir layer-forming film, a cloth layer, an adhesive layer and optionally an impermeable support, wherein the drug reservoir layer is enclosed in the drug reservoir layer-forming film or enclosed by the drug reservoir layer-forming film and the support formed on the drug reservoir layer-forming film, the drug reservoir layer contains a drug except 2-tert-butylamino-1-(2-chloro-4-hydroxyphenyl)ethan-1-ol and a pharmacologically acceptable salt thereof, and the cloth layer and the adhesive layer are successively laminated on either side of the drug reservoir layer-forming film or on the side opposite from the support layer. The preparation of the present invention inhibits separation of the drug reservoir layer-forming film from the adhesive layer, glue remainder on the skin after peeling off, and deformation of the drug reservoir layer-forming film due to the solvent in the drug reservoir layer. In addition, the preparation of the present invention is superior in the percutaneous absorption of a drug.

EP 1 044 684 A2

Description

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to a percutaneously absorptive preparation for transdermally administering a drug except 2-tert-butylamino-1-(2-chloro-4-hydroxyphenyl)ethan-1-ol and a pharmacologically acceptable salt thereof. More particularly, the present invention relates to a practical reservoir type percutaneously absorptive preparation that achieves superior percutaneous absorption when applied to the skin surface, with the aid of a cloth layer formed between a drug reservoir layer-forming film and an adhesive layer.

BACKGROUND OF THE INVENTION

[0002] In recent years, percutaneous administration of various drugs has been actively studied and developed in an attempt to prolong duration of the effect and to reduce side effects. Due to the barrier function of the skin that lowers the skin permeability, however, it is extremely difficult to have the necessary amount of a drug absorbed from the skin upon application to a practical area of the skin.

[0003] Generally, percutaneously absorptive preparations mainly consist of monolithic type preparation having two layers of a support and a drug-containing adhesive layer. Because the drug is contained in the adhesive layer, a drug having a lower solubility in the adhesive remains mostly undissolved but exists in a crystalline state. In the course of transfer of the drug into the skin, a drug in a dissolved state can migrate into the skin quickly, but a drug in a crystalline state requires an additional step of dissolution in an adhesive. This step becomes a rate-limiting factor and reduces drug release from the preparation to consequently prevent absorption of a sufficient amount of the drug by the skin. The easiest method to improve this state is to enlarge the area of application or thicken the adhesive layer. Such method is not always effective, because the method in turn causes increased feeling of discomfort during application or longer distance of diffusion for the drug.

[0004] When a drug is to be more efficiently administered percutaneously, a method for increasing drug absorption typically includes (1) increasing solubility of the drug in the preparation, which is achieved by either using a specific adhesive or adding a solubilizer, thereby to enhance drug release from the preparation, or (2) improving skin permeability by the addition of a percutaneous absorption promoter.

[0005] The above-mentioned monolithic type preparation containing a drug in the adhesive is subject to various limitations when the above method is applied. For example, the solubilizer or percutaneous absorption promoter may not be compatible with the adhesive, or these may be volatilized during heating process. Therefore, a sufficient amount to achieve a desired effect may be too much to be contained in the adhesive. In addition, the adhesive is required to have a higher cohesive force to retain a component, particularly a liquid component, containing a solubilizer and/or a percutaneous absorption promoter. When the adhesive contains a carboxylic group, hydroxyl group or amino group, the adhesive can be crosslinked using a crosslinking agent to achieve higher adhesion. When the above-mentioned liquid component contains a compound having the aforementioned functional group reactive with the crosslinking agent, however, the functional group preferentially reacts with the agent. Consequently, the crosslinking reaction of the adhesive is inhibited, with the result that the liquid component cannot be retained in the adhesive and a desired efficacy cannot be afforded.

[0006] Then, the present inventors took note of a reservoir type percutaneously absorptive preparation wherein a drug is sealed in a drug reservoir layer which is located in a drug reservoir layer-forming film or enclosed by a drug reservoir layer-forming film and an impermeable support laminated on the drug reservoir layer-forming film, and an adhesive layer is laminated on the drug reservoir layer-forming film.

[0007] The above-mentioned reservoir type preparation comprising a drug reservoir layer containing a drug and a solubilizer shows a weak adhesion between an adhesive layer and a drug reservoir layer-forming film due to a large amount of the liquid component contained in the drug reservoir layer. Consequently, the preparation is associated with a possibility that the drug reservoir layer-forming film may come off during use or when peeling off, leaving the adhesive layer. It frequently happens that the adhesive remains on the skin (i.e., glue remainder) upon peeling off of the preparation. When the drug reservoir layer-forming film is swellable with solubilizer, the preparation itself may deform.

[0008] It is therefore an object of the present invention to provide a percutaneously absorptive preparation superior in percutaneous absorption of the drug, which is capable of inhibiting a glue remainder on the skin upon peeling off and inhibiting swelling or deformation of a drug reservoir layer-forming film by a solvent of a drug contained in a drug reservoir layer.

SUMMARY OF THE INVENTION

[0009] Such object can be achieved by the present invention described in the following. The present invention is

[0021] The cloth layer may be laminated on a porous film. The cloth layer in the present invention encompasses such a laminate. The porous film preferably is one usable as the above-mentioned drug reservoir layer-forming film, or one having air permeability (Gurley method) of not more than 9000 sec/100 cc. The laminate is used in such a manner that the adhesive layer is in contact with the cloth.

[0022] The cloth layer has a superior anchor effect that allows for strong adhesion to the adhesive layer. This has a consequence that, even if a solubilizer causes marked plasticization of adhesive, the drug reservoir layer-forming film does not come off during application or upon peeling off, leaving the adhesive layer, and a glue remainder on the skin surface is inhibited upon peeling off. The cloth layer prevents swelling and deformation of the drug reservoir layer-forming film containing a large amount of the liquid component. Even if the drug reservoir layer-forming film is swellable with the solubilizer to be used, the presence of a cloth layer prevents deformation of the preparation of the present invention.

[0023] The drug reservoir layer completely seals a drug other than 2-tert-butylamino-1-(2-chloro-4-hydroxyphenyl)ethan-1-ol and pharmacologically acceptable salts thereof. This drug may be in the form of a pharmacologically acceptable salt or a prodrug.

[0024] The drug to be sealed in the drug reservoir layer may be any and is exemplified by corticosteroides, analgesic antiphlogistic, somnifacient sedative agent, tranquilizer, antihypertensive, hypotensive diuretic, antibiotic, anesthetic, antimicrobial, antifungal agent, vitamin agent, coronary vasodilator, antihistamine, cough medicine, sex hormone agent, antidepressant, cerebral circulation improver, antiemetic, antitumor agent, biological drug and the like. In particular, the drug preferably has a solubility of not less than 1 wt% in a solubilizer to be mentioned later.

[0025] The composition to be sealed in the drug reservoir layer has a drug content that is subject to change depending on the kind of the drug and the like. It is generally preferably 0.5 - 40 wt%. When it is less than 0.5 wt%, the therapeutic effect is insufficient and the content exceeding 40 wt% is unpreferable from the aspect of drug utilization.

[0026] The drug reservoir layer preferably additionally seals a solubilizer and/or a percutaneous absorption promoter.

[0027] The mixing ratio of the solubilizer and the drug can vary depending on the object of the preparation, the drug to be sealed and the like. The proportion of the drug is generally preferably 0.1 - 200 parts by weight, more preferably 1 - 100 parts by weight, per 100 parts by weight of the solubilizer.

[0028] The mixing ratio of the percutaneous absorption promoter and the drug can vary depending on the object of the preparation, the drug to be sealed and the like. The proportion of the drug is generally preferably 0.5 - 2000 parts by weight, more preferably 1 - 1000 parts by weight, per 100 parts by weight of the percutaneous absorption promoter.

[0029] When the drug reservoir layer seals a solubilizer and a percutaneous absorption promoter, the mixing ratio of the two is preferably 3 - 200 parts of the percutaneous absorption promoter by weight per 100 parts by weight of the solubilizer. When it is less than 3 parts by weight, the adhesive cannot contain a sufficient amount of the percutaneous absorption promoter, which in turn results in a failure to achieve a desired promoting effect. When it exceeds 200 parts by weight, the relative amount of the solubilizer in the drug reservoir layer decreases, undesirably lowering the solubility of the drug.

[0030] The solubilizer is added to increase solubility of the drug. The dissolved drug permeates the skin preferably with the aid of the percutaneous absorption promoter. Therefore, the solubilizer preferably dissolves the drug and is miscible with the percutaneous absorption promoter to be mentioned later. Examples of the solubilizer include lower alcohol such as ethyl alcohol and the like, polyhydric alcohol such as ethylene glycol, glycerol and the like, dimethyl sulfoxide, dimethylacetamide, dimethylformamide, N-methyl-2-pyrrolidone, dimethyllaurylamide, dodecylpyrrolidone, isosorbitol, liquid paraffin, various liquid surfactants, mineral oil, lanolin, ethyl acetate, crotamiton, water and the like. Preferable solubilizer may be lower alcohol having 1 to 4 carbon atoms. The alcohol having 1 to 4 carbon atoms is exemplified by methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, isobutyl alcohol and tert-butyl alcohol.

[0031] The percutaneous absorption promoter may be glycol such as ethylene glycol and the like, fats and oils such as olive oil, squalene and the like, polar solvent such as dimethyl sulfoxide, dimethylformamide and the like, surfactant such as sodium lauryl sulfate, sorbitan fatty acid ester and the like, long chain fatty acid such as oleic acid and the like, and the like. From the aspect of increased percutaneous absorption of the drug, compatibility with the above-mentioned solubilizer and the like, at least one kind selected from esters of fatty acid having 12 to 18 carbon atoms, diesters of dicarboxylic acid having 6 to 10 carbon atoms and glycerol esters of fatty acid having 8 to 10 carbon atoms is preferably used.

[0032] As the fatty acid ester, an alkyl ester of aliphatic monocarboxylic acid having 12 to 18 carbon atoms such as lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid and the like, and alcohol having 1 to 10 carbon atoms such as methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, isobutyl alcohol, pentyl alcohol, hexyl alcohol, heptyl alcohol, octyl alcohol, nonyl alcohol, isononyl alcohol and the like may be used.

[0033] The diester of dicarboxylic acid is preferably dialkyl esters of aliphatic dicarboxylic acid having 6 to 10 carbon atoms, such as diester of adipic acid or sebacic acid and alcohol having 1 to 10 carbon atoms.

[0034] The glycerol ester of fatty acid is exemplified by glycerol ester of fatty acid having 8 to 10 carbon atoms, such

as glyceryl monocaprylate, glyceryl monocaprate, tricaprylin and the like.

[0035] For an improved manipulability of the composition to be sealed in the drug reservoir layer during production, glycerol, propylene glycol, polyethylene glycol, poly (vinylpyrrolidone), hydroxypropylcellulose and the like may be added to increase viscosity.

[0036] When the drug is in the form of a salt, a pH adjusting agent is preferably contained in the drug reservoir layer and/or adhesive layer. By adding a basic pH adjusting agent, such as sodium hydroxide, triethanolamine, triisopropanolamine, diisopropanolamine, monoisopropanolamine, sodium caprylate, potassium hydroxide and the like, or an acidic pH adjusting agent, such as citric acid, lactic acid, glyconic acid, succinic acid, tartaric acid, lactic acid, maleic acid and the like, the drug in the form of a salt can be liberated. As a result, the drug can be converted to a drug in the form of a base or an acid capable of higher percutaneous absorption. The content of the pH adjusting agent is such an amount as is necessary for neutralizing the acid or base attached to the drug in the form of a base or an acid.

[0037] When the content of the pH adjusting agent is less than this level, a base or an acid is generated in a less amount. The percutaneous absorption may become somewhat inferior, but the stability of the drug in the preparation becomes superior. When the content is higher, the adhesive layer becomes basic or acidic, and may induce irritation to the skin when applied.

[0038] The amount of the composition to be sealed in the drug reservoir layer is preferably not more than 50 $\mu L/cm^2$. When it exceeds 50 $\mu L/cm^2$, it may happen that the composition that cannot be retained in the drug reservoir layer or the composition that was transferred from the drug reservoir layer into the adhesive layer cannot be retained in the adhesive. It has a consequence of separation of the adhesive component (blooming) or marked plasticization of the adhesive, which in turn may cause a glue remainder on the skin surface upon peeling off.

[0039] The adhesive layer and/or drug reservoir layer may contain, where necessary, in addition to the above-mentioned pH adjusting agent and percutaneous absorption promoter, various known additives such as solubilizer, stabilizer represented by antioxidant (e.g., ascorbic acid, tocopherol, dibutylhydroxytoluene and the like), plasticizer (e.g., glycerol, propylene glycol, polyethylene glycol and the like), filler (e.g., titanium oxide, zinc oxide, water-containing silicon dioxide and the like), and the like.

[0040] The adhesive layer of the percutaneously absorptive preparation may cover the entire surface of a cloth layer, or may cover only an appropriate width on the periphery of the cloth layer forming a frame-like shape.

[0041] The polymer to be used for the adhesive layer is a pressure sensitive adhesive polymer that shows adhesive property at normal temperature. Preferably, one compatible with the aforementioned solubilizer-percutaneous absorption promoter mixture is used. Preferable examples of such adhesive include acrylic adhesive and rubber adhesive.

[0042] Examples of the acrylic adhesive include homopolymer such as alkyl acrylate and alkyl methacrylate, and copolymers thereof. The alkyl of the alkyl acrylate and alkyl methacrylate means linear or branched chain alkyl having 1 to 18 carbon atoms, which is specifically methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, isooctyl, 2-ethylhexyl, nonyl, isononyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl and the like. Preferred is linear or branched chain alkyl having 4 to 12 carbon atoms. The acrylic adhesive to be used in the present invention may be a copolymer of the aforementioned alkyl acrylate and/or alkyl methacrylate with one or more kinds of the monomers mentioned below.

[0043] The monomer is exemplified by those having carboxylic group (e.g., acrylic acid, itaconic acid, maleic acid, maleic anhydride), those having sulfonic acid group (e.g., styrenesulfonic acid, allylsulfonic acid, sulfopropyl acrylate, acryloyloxynaphthalenesulfonic acid, acrylamidomethylpropanesulfonic acid), hydroxy lower alkyl acrylate (e.g., hydroxymethyl acrylate, hydroxyethyl acrylate, hydroxypropyl acrylate, hydroxybutyl acrylate), acrylamide, acrylamide derivative (e.g., dimethylacrylamide, N-butylacrylamide, N-methylolacrylamide, N-methylolpropaneacrylamide), aminoalkyl acrylate (e.g., aminoethyl acrylate), alkylaminoalkyl acrylate (e.g., dimethylaminoethyl acrylate, tert-butylaminoethyl acrylate), alkoxyalkyl acrylate (e.g., methoxyethyl acrylate, ethoxyethyl acrylate), tetrahydrofurfuryl acrylate, ester of acrylic acid and methoxydiethylene glycol, ester of acrylic acid and methoxypolyethylene glycol, ester of acrylic acid and methoxypolypropylene glycol, hydroxy lower alkyl methacrylate (e.g., hydroxymethyl methacrylate, hydroxyethyl methacrylate, hydroxypropyl methacrylate, hydroxybutyl methacrylate), methacrylamide, methacrylamide derivative (e.g., dimethylmethacrylamide, N-butylmethacrylamide, N-methylolmethacrylamide, N-methylolpropane methacrylamide), aminoalkyl methacrylate (e.g., aminoethyl methacrylate), alkylaminoalkyl methacrylate (e.g., dimethylaminoethyl methacrylate, tert-butyl aminoethyl methacrylate), alkoxyalkyl methacrylate (e.g., methoxyethyl methacrylate, ethoxyethyl methacrylate), tetrahydrofurfuryl methacrylate, ester of methacrylic acid and methoxydiethylene glycol, ester of methacrylic acid and methoxypolyethylene glycol, ester of methacrylic acid and methoxypolypropylene glycol, methacrylonitrile, acrylonitrile, vinyl acetate, vinyl propionate, vinylpyrrolidone, methylvinylpyrrolidone, vinyl pyridine, vinylpiperidone, vinylpyrimidine, vinylpiperazine, vinylpyrazine, vinylpyrrole, vinylimidazole, vinylcaprolactam, vinyloxazole, vinylmorpholine, styrene and the like.

[0044] When a copolymer of alkyl acrylate and/or alkyl methacrylate with the above-mentioned monomers is used as the acrylic adhesive, 30 - 99.5 wt%, preferably 50 - 90 wt% of the alkyl acrylate and/or alkyl methacrylate and 0.5 - 70 wt%, preferably 10 - 50 wt%, of the above-mentioned monomer are preferably copolymerized.

Preparation of adhesive solution A

[0057] 2-Ethylhexyl acrylate (95 parts) and acrylic acid (5 parts) were polymerized in ethyl acetate under an inert gas atmosphere to give an acrylic adhesive solution A.

Preparation of adhesive solution B

[0058] High molecular weight polyisobutylene (50 parts, viscosity-average molecular weight 2,100,000, VISTANEX MML-140, manufactured by Exxon Chemicals Japan LTD.), medium molecular weight polyisobutylene (30 parts, viscosity-average molecular weight 60,000, HIMOL 6H, manufactured by NIPPON PETROCHEMICALS CO., LTD.) and alicyclic petroleum resin (20 parts, softening point 100°C, Arkon P-100, manufactured by ARAKAWA CHEMICAL INDUSTRIES LTD.) were dissolved in hexane to give a rubber adhesive solution B.

Example 1

[0059] To the adhesive solution A was added and mixed a polyisocyanate compound (CORONATE HL, manufactured by NIPPON POLYURETHANE INDUSTRY CO., LTD., solid content 0.15% in adhesive). The mixture was applied onto a release liner (75 μm thick polyester film after peeling off treatment) to a thickness after drying of 40 μm and dried. A polyester nonwoven fabric (basic weight 8 g/m^2) was laminated thereon and a 50 μm thick ethylene - vinyl acetate copolymer film (vinyl acetate content 14%) was heat melt adhered. A support (a laminate of aluminum-deposited polyester film and polyethylene) was heat sealed therewith leaving a drug reservoir layer solution inlet in the size of inner diameter 20 mm, seal width 4 mm, and cut along the periphery of the heat sealed part.

[0060] A drug reservoir layer solution (50 μL, containing an ethyl alcohol-isopropyl myristate mixture (mixing ratio 7:3) and ketoprofen at a concentration of 10%) was injected from the inlet and the inlet was completely heat sealed to give the percutaneously absorptive preparation of the present invention.

Example 2

[0061] In the same manner as in Example 1 except that the drug reservoir layer solution contained an ethyl alcohol-isopropyl myristate-glyceryl monocaprylate mixture (mixing ratio 7:2:1) and ketoprofen at a concentration of 10%, the percutaneously absorptive preparation of the present invention was obtained.

Example 3

[0062] In the same manner as in Example 1 except that the drug reservoir layer solution contained an ethyl alcohol-diethyl sebacate mixture (mixing ratio 7:3) and ketoprofen at a concentration of 10%, the percutaneously absorptive preparation of the present invention was obtained.

Example 4

[0063] In the same manner as in Example 1 except that isopropyl myristate was added to the adhesive solution B in a proportion of 40% and the drug reservoir layer solution contained an isopropyl alcohol-isopropyl myristate mixture (mixing ratio 6:4) and metoprolol at a concentration of 10%, the percutaneously absorptive preparation of the present invention was obtained.

Example 5

[0064] In the same manner as in Example 4 except that the ethylene-vinyl acetate copolymer had a vinyl acetate content of 5% and the drug reservoir layer solution contained an ethyl alcohol-isopropyl myristate mixture (mixing ratio 6:4) and metoprolol at a concentration of 10%, the percutaneously absorptive preparation of the present invention was obtained.

Example 6

[0065] In the same manner as in Example 4 except that the ethylene-vinyl acetate copolymer had a vinyl acetate content of 33% and the drug reservoir layer solution contained an ethyl alcohol-isopropyl myristate mixture (mixing ratio 6:4) and metoprolol at a concentration of 10%, the percutaneously absorptive preparation of the present invention was obtained.

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[54] **COMPOSITION FOR THE TRANSDERMAL DELIVERY OF LERISETRON**

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[52] **U.S. Cl.** **514/254**; *424/449*

[58] **Field of Search** 514/254; 424/449

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[57] ***ABSTRACT***

The present invention provides a transdermal drug delivery composition comprising:

(a) a copolymer of one or more (meth)acrylate monomers being selected from the group consisting of alkyl acrylates containing 4 to 12 carbon atoms in the alkyl group and alkyl *methacrylates containing* 4 to 12 carbon atoms in the alkyl group and one or more hydrophilic monomers being copolymerizable with said (meth)acrylate monomers, and

(b) a therapeutically effective amount of lerisetron. The transdermal drug delivery composition is used to make a transdermal drug delivery device for the delivery of lerisetron.

21 Claims, No Drawings

release liners include conventional release liners comprising a known sheet material such as a polyester web, polyethylene web, or a polystyrene web, or a polyethylene-coated paper coated with a suitable fluoropolymer or silicone based coating. Preferred release liners include 1-5PESTR(P2)-164P, 1-5PESTR(MATTE)-164Z from DCP-Lohja Inc or ScotchPak™ 1022 from 3M, St. Paul, Minn.

The coated release liner is then dried and laminated onto a backing using conventional methods. The backing can be occlusive, non-occlusive or a breathable film as desired. The backing is flexible such that it conforms to the skin. It can be any of the conventional materials for pressure sensitive adhesive tapes, such as polyethylene, particularly low density polyethylene, linear low density polyethylene, high density polyethylene, randomly-oriented nylon fibers, polypropylene, ethylene-vinylacetate copolymer, polyurethane, rayon and the like. Backings that are layered, such as polyethylene-aluminum-polyethylene composites are also suitable. The backing should be substantially non-reactive with the ingredients of the composition. Particularly preferred backings are COTRAN™ 9726, COTRAN™ 9720, and CoTran™ 9722 all available from 3M.

The transdermal delivery devices can be made in the form of an article such as a tape, a patch, a sheet, a dressing or any other form known to those skilled in the art. Generally, the device will be in the form of a patch of a size suitable to deliver a preselected amount of lerisetron through the skin. Generally, the device will have a surface area of about 10 cm^2 to about 140 cm^2 and preferably about 20 cm^2 to about 80 cm^2.

A transdermal drug delivery composition of the invention can be used to treat any condition capable of treatment with lerisetron and in particular, the prevention or treatment of nausea and emesis. The composition can be placed on the skin and allowed to remain for a time sufficient to achieve or maintain the intended therapeutic effect. The time that constitutes a sufficient time can be selected by those skilled in the art with consideration of the flux rate of the device of the invention and of the condition being treated.

The examples set forth below are intended to illustrate the invention, and not to be limiting in any way.

EXAMPLES

In Vitro Skin Penetration Test Method

The skin penetration data given in the examples below was obtained using the following test method. A static diffusion cell (Franz-cell type) is used. Hairless mouse skin (female hairless mice, 3-4 weeks old) or human skin (obtained from surgery) is used. The skin is mounted epidermal side up between the upper and the lower portion of the cell, which are held together by means of a ball joint clamp.

The portion of the cell below the mounted skin is completely filled with receptor fluid ["HEPES" (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]) buffered Hanks balanced salt solution, pH 7.2, supplemented with 4 ml of antibiotics (A 7292 obtained from Sigma) and 15-volume-% ethanol (extra pure grade, 96%) per liter] such that the receptor fluid is in contact with the skin. The receptor fluid is stirred using a magnetic stir bar. The sampling port is covered except when in use.

When a transdermal delivery device is evaluated, the release liner is removed from a 1.55 cm^2 patch and the patch is applied to the skin and pressed to cause uniform contact with the skin. The skin is then placed across the orifice of the lower portion of the diffusion cell. The diffusion cell is assembled and the lower portion is filled with receptor fluid.

The cell is then placed in a constant temperature (32±1.5° C.) and humidity (45±10% relative humidity) chamber. The receptor fluid is stirred by means of a magnetic stirrer throughout the experiment to assure a uniform sample and a reduced diffusion barrier on the dermal side of the skin. The entire volume of receptor fluid is withdrawn at specified time intervals (2, 4, 6, 8, and 24 hours) and immediately replaced with fresh receptor fluid. The withdrawn receptor fluid is analyzed for drug content using conventional high performance liquid chromatography. The cumulative amount of drug penetrating the skin and the flux rate are calculated.

Stability Test Method

Transdermal drug delivery devices (10 cm^2 patches) were sealed in pouches (BAREX™/aluminum/polyester or BAREX™/aluminum/paper laminates) and stored at 25° C./60% relative humidity and 40° C./75% relative humidity.

The patches were analyzed for their drug content before storage and after 2 and 4 weeks storage time. The drug content was determined by removing the liner from the patches. The backing and coating were extracted using 40.0 ml of ethyl acetate. The sample was shaken for approximately 2 hr. A portion (2.0 ml) of the ethyl acetate solution was pipetted into a 50.0 ml volumetric flask and diluted to mark with mobile phase (a solution containing acetonitrile and 0.01M triethylamine in water in the ratio of 60:40 (vol-%) having a pH of about 6.5). An aliquot of the solution was transferred into a tube and centrifuged at 4300 rpm for 10 minutes. The sample was placed in a vial and injected into an HPLC equipped with a Spherisorb™ C8 column. Quantification was performed by external standard methodology (peak area) using a UV-detector working at 282 nm.

The abbreviations listed below are used in the examples.

IOA: isooctyl acrylate

NVP: N-vinyl-2-pyrrolidone

HEA: 2-hydroxyethyl acrylate

IPM: isopropyl myristate

PG: propylene glycol

OA: oleic acid

LA: lauric acid

ELVACITE™: polymethylmethacrylate macromonomer available from ICI Acrylics

DCP-Lohja 164Z: release liner 1-5PESTR(MATTE)-164Z release liner available from

DCP-Lohja Inc.

Preparation of the Copolymers

The inherent viscosity values which are reported below were measured by conventional means using a Canon-Fenske #50 viscometer in a water bath controlled at 27° C. to measure the flow time of 10 millimeters of the polymer solution (0.15 g of polymer per deciliter of ethyl acetate). The test procedure and apparatus are described in detail in *Textbook of Polymer Science*, F. W. Billmeyer, Wiley Interscience, Second Edition (1971), pages 84 and 85.

Preparation of Isooctyl Acrylate/N-Vinyl-2-pyrrolidone/Elvacite™ 1020 (77/20/3) Copolymer

A flask equipped with an agitator, condenser, nitrogen inlet tube and an addition funnel was charged with isooctyl acrylate (134.75 g), N-vinyl-2-pyrrolidone (35.0 g) and Elvacite™ 1020 (5.25 g) premixed in a mixture of ethyl acetate (236.25 g) and methanol (26.25 g). The mixture was heated to 60° C. with medium agitation and purged with nitrogen to remove oxygen. 2,2'-Azobis-(2-methylbutyronitrile) (0.26 g, Wako™ V-59) was added to initiate reaction. The reaction temperature was maintained at 57° C.

and the reaction was run for about 24 hours. After termination of the reaction additional ethyl acetate (90 g) and methanol (10 g) were added. The inherent viscosity was 1.4 dl/g.

Preparation of Isooctyl Acrylate/2-Hydroxyethyl acrylate/Elvacite™ 1020 (59/39/2) Copolymer

This copolymer was prepared using a procedure similar to the one described above for isooctyl acrylate/N-vinyl-2-pyrrolidone/Elvacite™ 1020. The inherent viscosity of the polymer in ethyl acetate was 0.69 dl/g.

Preparation of Isooctyl acrylate/2-Hydroxyethyl acrylate/N-vinyl-2-pyrrolidone (89/2/9) Copolymer

A flask equipped with an agitator, condenser, nitrogen inlet tube and an addition funnel was charged with isooctyl acrylate (155.75 g), N-vinyl-2-pyrrolidone (15.75 g) and hydroxyethyl acrylate (3.50 g) premixed in a mixture of ethyl acetate (249.38 g) and methanol (13.13 g). 2,2'-Azobis-(2-methyl-butyronitrile) (0.26 g, Wako™ V-59) was added to initiate reaction. The mixture was purged with nitrogen to remove oxygen. The mixture was agitated and heated to 57° C. and the reaction was run for about 24 hours at this temperature. After termination of the reaction additional ethyl acetate (178.13 g) and methanol (9.38 g) were added. The inherent viscosity was 1.27 dl/g.

EXAMPLE 1

To 48.74 g of a solution containing 39% by weight of IOA/HEA/Elvacite 59/39/2 in ethyl acetate there were added 0.68 g OA, 6.12 g PG and a solution of 6.29 g of lerisetron in 8.2 g of methanol. Intensive mixing provided a homogeneous coating solution.

The solution was coated onto a release liner (DCP-Lohja 164Z) and oven dried for 20 minutes at 60° C. The dried coating was then laminated to a CoTran™ 9720 backing. The resulting devices had a drug loading of 2.37 mg lerisetron per 1 cm^2.

EXAMPLE 2

To 69.13 g of a solution containing 28% by weight of IOA/NVP/Elvacite 77/20/3 in ethyl acetate there were added, 0.53 g LA, 10.07 g PG and a solution of 2.21 g lerisetron in 6.23 g methanol. Intensive mixing provided a homogeneous coating solution.

The solution was coated onto a release liner (DCP-Lohja 164Z) and oven dried for 20 minutes at 60° C. The dried coating was then laminated to a CoTran™ 9720 backing. The resulting devices had a drug loading of 0.48 mg lerisetron per 1 cm^2.

EXAMPLE 3

To 37.73 g of a solution containing 28% by weight of IOA/NVP/Elvacite 77/20/3 in ethyl acetate there were added 0.45 g LA, 4.08 g 1,3-butandiol and a solution of 1.60 g lerisetron in 3.4 g methanol. Intensive mixing provided a homogeneous coating solution.

The solution was coated onto a release liner (DCP-Lohja 164Z) and oven dried for 20 minutes at 60° C. The dried coating was then laminated to a CoTran™ 9720 backing. The resulting devices had a drug loading of 0.75 mg lerisetron per 1 cm^2.

EXAMPLE 4

To 34.50 g of a solution containing 39% by weight of IOA/HEA/Elvacite 59/39/2 in ethyl acetate there was added a solution of 2.19 g lerisetron in 4.67 g methanol. Intensive mixing provided a homogeneous coating solution.

The solution was coated onto a release liner (DCP-Lohja 164Z) and oven dried for 20 minutes at 60° C. The dried coating was then laminated to a CoTran™ 9720 backing. The resulting devices had a drug loading of 1.47 mg lerisetron per 1 cm^2.

EXAMPLE 5

To 35.70 g of a solution containing 28% by weight of IOA/NVP/HEA 89/9/2 in ethyl acetate there were added 0.65 g LA, 5.85 g PG and a solution of 1.64 g lerisetron in 3.20 g methanol. Intensive mixing provided a homogeneous coating solution.

The solution was coated onto a release liner (DCP-Lohja 164Z) and oven dried for 20 minutes at 60° C. The dried coating was then laminated to a CoTran™ 9720 backing. The resulting devices had a drug loading of 0.66 mg lerisetron per 1 cm^2.

EXAMPLE 6

To 67.48 g of a solution containing 29% by weight of IOA/NVP/Elvacite 77/20/3 in ethyl acetate there were added 0.55 g of 4.3% by weight of 1,4 -diazabicyclo[2.2.2]octane in ethyl acetate, 0.50 g LA, 9.50 g PG and a solution of 2.20 g lerisetron in 6.01 g methanol. Intensive mixing provided a homogeneous coating solution.

The solution was coated onto a release liner (ScotchPak™ 1022) and oven dried for 20 minutes at 60° C. The dried coating was then laminated to a CoTran™ 9722 backing. The resulting devices had a drug loading of 0.69 mg lerisetron per 1 cm^2.

EXAMPLE 7

To 68.20 g of a solution containing 28% by weight of IOA/NVP/Elvacite 77/20/3 in ethyl acetate there were added 0.55 g of 4.3% by weight of 1,4-diazabicyclo[2.2.2]octane in ethyl acetate, 5.76 g IPM and a solution of 1.50 g lerisetron in 5.44 g methanol. Intensive mixing provided a homogeneous coating solution.

The solution was coated onto a release liner (ScotchPak™ 1022) and oven dried for 20 minutes at 60° C. The dried coating was then laminated to a CoTran™ 9722 backing. The resulting devices had a drug loading of 0.62 mg lerisetron per 1 cm^2.

EXAMPLE 8

To 67.92 g of a solution containing 28% by weight of IOA/NVP/Elvacite 77/20/3 in ethyl acetate there were added 0.55 g of 4.3% by weight of 1,4-diazabicyclo[2.2.2]octane in ethyl acetate, 10.24 g PG and a solution of 2.22 g lerisetron in 6.02 g methanol. Intensive mixing provided a homogeneous coating solution.

The solution was coated onto a release liner (ScotchPak™ 1022) and oven dried for 20 minutes at 60° C. The dried coating was then laminated to a CoTran™ 9722 backing. The resulting devices had a drug loading of 0.68 mg lerisetron per 1 cm^2.

EXAMPLE 9

To 29.98 g of a solution containing 24% by weight of IOA/NVP/Elvacite 77/20/3 in ethyl acetate there were added 0.09 g LA, 3.34 g PG and a solution of 0.80 g lerisetron in 1.87 g methanol. Intensive mixing provided a homogeneous coating solution.

The solution was coated onto a release liner (DCP-Lohja 164P) and oven dried for 20 minutes at 60° C. The dried

coating was then laminated to a CoTran™ 9726 backing. The resulting devices had a drug loading of 0.66 mg lerisetron per 1 cm².

EXAMPLE 10

To 30.13 g of a solution containing 24% by weight of IOA/NVP/Elvacite 77/20/3 in ethyl acetate there were added 0.67 g OA, 2.68 g PG and a solution of 0.68 g lerisetron in 1.60 g methanol. Intensive mixing provided a homogeneous coating solution.

The solution was coated onto a release liner (DCP-Lohja 164P) and oven dried for 20 minutes at 60° C. The dried coating was then laminated to a CoTran™ 9720 backing. The resulting devices had a drug loading of 0.74 mg lerisetron per 1 cm².

The transdermal drug delivery devices prepared in Examples 1–10 were tested using the skin penetration test method described above. The results are shown in Table 1 below where each entry is the average of four independent determinations.

TABLE 1

Skin Penetration

Example	Copolymer	Enhancers[1] (wt-%)	Coating Weight (mg/cm²)	Drug loading (mg/cm²)	Flux Rate (μg/cm²/24 hr)
1	IOA/HEA/ELV 59/39/2	20% PG 2% OA	11.9	2.37	61
2	IOA/NVP/ELV 77/20/3	32% PG 2% LA	6.8	0.48	132
3	IOA/NVP/ELV 77/20/3	25% 1,3-Butandiol 3% LA	7.5	0.75	328
4	IOA/HEA/ELV 59/39/2	—	7.0	1.47	65
5	IOA/NVP/HEA 89/9/2	32% PG 4% LA	7.4	0.66	178
6	IOA/NVP/ELV 77/20/3	30% PG 2% LA	9.8	0.69	199
7	IOA/NVP/ELV 77/20/3	22% IPM	11.0	0.62	129
8	IOA/NVP/ELV 77/20/3	32% PG	9.6	0.68	131
9	IOA/NVP/ELV 77/20/3	29% PG 1% LA	9.4	0.66	177
10	IOA/NVP/ELV 77/20/3	24% PG 6% OA	12.3	0.74	272

[1]weight % of enhancer based on the total weight of solids

The transdermal drug delivery devices prepared in Examples 6, 9 and 10 were tested for stability using the test method described above. The results are shown in Table 2 below.

TABLE 2

Stability Data

Example No.	Drug content after 2 weeks*	Drug content after 4 weeks*
6	101.2	99.9
9	102.1	102.7
10	96.2	99.5

*Drug content is reported as the percentage remaining of the original drug loading; the accuracy of the data is +/−2 to 3%.

What is claimed is:

1. A transdermal drug delivery composition comprising:

(a) a copolymer of one or more (meth)acrylate monomers being selected from the group consisting of alkyl acrylates containing 4 to 12 carbon atoms in the alkyl group and alkyl methacrylates containing 4 to 12 carbon atoms in the alkyl group and one or more hydrophilic monomers being copolymerizable with said (meth)acrylate monomers, and

(b) a therapeutically effective amount of lerisetron.

2. A transdermal drug delivery composition of claim 1 further comprising a penetration enhancer.

3. A transdermal drug delivery composition of claim 2 wherein said penetration enhancer is selected from the group consisting of alkane polyols, fatty acids, fatty acid esters, fatty alcohols, and C_5–C_{18} alkyl esters of a carboxylic acid, and mixtures thereof.

4. A transdermal drug delivery composition of claim 3 wherein the alkane polyol is propylene glycol and the fatty acid is oleic acid or lauric acid.

5. A transdermal drug delivery composition of claim 2 wherein the enhancer is present in an amount of from about 10 to about 50 percent by weight based on the total weight of the composition.

6. A transdermal drug delivery composition of claim 5 wherein the enhancer is present in an amount of from about 20 to about 35 percent by weight based on the total weight of the composition.

7. A transdermal drug delivery composition of claim 1 wherein the lerisetron is present in an amount of from about 2 to about 20 percent by weight based on the total weight of the composition.

8. A transdermal drug delivery composition of claim 7 wherein the lerisetron is present in an amount of from about 5 to about 10 percent by weight based on the total weight of the composition.

9. A transdermal drug delivery composition of claim 1 wherein the lerisetron is dissolved in the composition.

10. A transdermal drug delivery composition of claim 1 wherein the acrylate monomer is selected from the group consisting of isooctyl acrylate, 2-ethylhexyl acrylate, cyclohexyl acrylate and n-butyl acrylate, and mixtures thereof.

11. A transdermal drug delivery composition of claim 10 wherein the acrylate monomer is isooctyl acrylate.

12. A transdermal drug delivery composition of claim 1 wherein the hydrophilic monomer is selected from the group consisting of 2-hydroxyethyl acrylate, N-vinyl-2-pyrrolidone, acrylic acid, and mixtures thereof.

13. A transdermal drug delivery composition of claim 1 wherein the hydrophilic monomer is N-vinyl-2-pyrrolidone.

14. A transdermal drug delivery composition of claim 1 wherein the copolymer further comprises one or more substantially linear macromonomers copolymerizable with the (meth)acrylate and hydrophilic monomers.

15. A transdermal drug delivery composition of claim 14 wherein the macromonomer is selected from the group consisting of polymethylmethacrylate, styrene/acrylonitrile, polyether and polystyrene macromonomers.

16. A transdermal drug delivery composition of claim 15 wherein the macromonomer is polymethylmethacrylate.

17. A transdermal drug delivery composition of claim 14 wherein the copolymer comprises from about 55 to 90 percent by weight of (meth)acrylate monomers, from about 7 to about 40 percent by weight of hydrophilic monomers, and from about 1 to about 7 percent by weight of macromonomers based on the total weight of the copolymer.

18. A device for the transdermal delivery of lerisetron comprising a backing having a composition adhered to one surface of the backing, said composition comprising

(a) a copolymer of one or more (meth)acrylate monomers being selected from the group consisting of alkyl acrylates containing 4 to 12 carbon atoms in the alkyl group and alkyl methacrylates containing 4 to 12 carbon atoms in the alkyl group and one or more hydrophilic monomers being copolymerizable with said (meth)acrylate monomers, and

(b) a therapeutically effective amount of lerisetron.

19. A method of transdermal delivery of lerisetron to a mammal comprising the steps of:

(a) providing a composition according to claim 1;

(b) placing the composition on the skin of a mammal; and

(c) allowing the composition to remain on the skin for a time sufficient to allow lerisetron to penetrate the skin of the mammal.

20. A method of treating in a mammal a condition capable of treatment by lerisetron comprising the steps of:

(a) providing a composition according to claim 1;

(b) placing the composition on the skin of a mammal; and

(c) allowing the composition to remain on the skin for a time sufficient to establish or maintain a therapeutically effective blood level of lerisetron in the mammal.

21. A method of preventing and/or treating nausea and emesis in a mammal comprising the steps of:

(a) providing a composition according to claim 1;

(b) placing the composition on the skin of a mammal; and

(c) allowing the composition to remain on the skin for a time sufficient to establish or maintain a therapeutically effective blood level of lerisetron in the mammal.

* * * * *

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Published

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(54) Title: TRANSDERMAL DRUG DELIVERY DEVICE FOR THE DELIVERY OF TROPISETRON OR GRANISETRON

(57) Abstract

The present invention discloses a transdermal drug delivery device comprising on a backing an adhesive layer, said adhesive layer comprising: (a) a copolymer of one or more A monomers and one or more B monomers, said A monomers being selected from the group consisting of alkylacrylates containing 4 to 12 carbon atoms in the alkyl group and alkylmethacrylates containing 4 to 12 carbon atoms in the alkyl group and said (B) monomers being hydrophilic monomers copolymerizable with said (A) monomers, and (b) a therapeutically effective amount of a drug selected from the group consisting of tropisetron and granisetron. The transdermal drug delivery device is suitable for the treatment of emesis and/or nausea or for the prevention of emesis and/or nausea. Further provided are pressure sensitive skin adhesives containing tropisetron or granisetron.

Still further, the present invention provides a transdermal drug delivery device as defined above for the treatment of emesis and/or nausea or for the prevention of emesis and/or nausea and the use of the pressure sensitive skin adhesive in the manufacture of a transdermal drug delivery device for use in the treatment or prevention of emesis or for use in the treatment or prevention of nausea.

4. Detailed description of the invention.

In accordance with the present invention it was found that the adhesive layer should include an acrylate or methacryate polymer that also includes a hydrophilic comonomer. It is believed that the latter comonomer provides the necessary solubility of the drug in the adhesive layer.

Hydrophilic B monomers in connection with the present invention are typically monomers that have a tendency to bind or absorb water and are preferably monomers of which a homopolymer shows a tendency to swell or dissolve in water. Examples of B monomers include N-vinyl-2-pyrrolidone, vinylimidazoles, 2-hydroxyethylacrylate, mono acrylates of poly(alkyleneoxide) alkyl ether, mono methacrylates of poly(alkyleneoxide) alkyl ether, acrylamides, methacrylamides, N-vinyl valerolactam, N-vinyl caprolactam, vinyl acetate, tetra-alkylammonium containing monomers such as (meth)acryloxyethyl trimethylammonium chloride, (meth)acryloxyethyl triethylammonium chloride, (meth)acrylamido-ethyl trimethyl ammonium chloride and aminogroup containing monomers such as dimethylaminoethyl(meth)acrylate, diethylamino(meth)acrylate, morpholino-ethyl(meth)acrylate, piperidino-ethyl(meth)acrylate, piperidino-ethyl-(meth)acrylamide, dimethylamino-ethyl(meth)acrylamide and diethylamino-ethyl(meth)acrylamide. Particularly preferred is N-vinyl-2-pyrrolidone.

Preferably, the B monomer is free of nucleophilic groups, in particular those that are capable of reaction with ester functions in the copolymer. While not intending to be bound by any theory, it is believed that such nucleophilic groups might react with ester functions in the copolymer leading to cross-linking of the adhesive layer and accordingly reducing the storage stability of the transdermal drug delivery device. Presumably, such reaction would be catalysed by the drugs which are fairly strong bases. For example, tropisetron has a pK_a of about 9.5. Preferably, the B monomer is free of nucleophilic

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Stability test method

Drug containing patch formulations (10 cm^2 patches) were sealed in BAREX pouches and stored at the following two conditions:

25°C / 60 % relative humidity and 40°C / 75 % relative humidity

The patches were checked for their drug content before storage and after 2 and 4 weeks storage time. The drug content was determined by removing the liner from the patches and placing the remaining patch in a jar with a methanol/ethyl acetate mixture. Upon stirring over night the adhesive coating dissolved in the solvent mixture. After filtration of the solution an aliquot was taken and analysed for the drug content.

List of abbreviations:

IOA: iso-octylacrylate

NVP: N-vinyl-2-pyrrolidone

HEA: hydroxyethyl acrylate

IPM: isopropyl myristate

ELVACITE™: polymethylmethacrylate macromer available from ICI Acrylics

Preparation of the copolymers used in the examples.

Preparation of isooctyl acrylate/N-vinylpyrrolidone (91/9) copolymer

A flask equipped with an agitator, condensor, nitrogen inlet tube and an addition funnel is charged with isooctyl acrylate (91.0 g), N-vinylpyrrolidone (9.0 g) and ethylacetate (85 g). The mixture is heated to 60°C with medium agitation and purged with nitrogen to remove oxygen. 2,2'-Azobis-(2-methyl-butyronitrile) (0.1 g, Wako™ V-59) premixed in ethyl acetate (3.0 g) is added to initiate reaction. The reaction temperature is maintained at 60°C. Ethyl acetate (1.5 g) is added to the polymer solution every 30 minutes until the conversion of isooctyl acrylate to polymer reaches a minimum of 95%, typically 20-30 hours. An additional charge of 2,2'-azobis-(2-methyl-butyronitrile) (0.1 g) premixed with ethyl acetate is added after 5 hours and 9 hours

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tropisetron per 10 cm². Samples of these devices with a size of 1.55 cm² were tested with respect to the drug release/penetration characteristics through human cadaver skin (HCS). The cumulative amounts released after 24 hours was 112.90 µg/cm. This corresponds to 18.82 % of the initial drug loading.

EXAMPLE 6

To 50.45 g of adhesive solution (IOA/NVP/ELVACITE™ 1020 (77/20/3); 28.1% solid content) 0.84 g of tropisetron, 3.91 g IPM and 5.09 g methanol were added. The solution was stirred at room temperature until all tropisetron was dissolved. The coating solution was coated onto a release liner (SCOTCHPAK™ 1022) at a wet thickness of 650µm and oven dried for 20 minutes at 60°C. The dried coatings were then laminated with SCOTCHPAK™ 1109 backing. The resulting device had a drug loading of 5.3 mg tropisetron per 10 cm². Samples of these devices with a size of 1.55 cm² were tested with respect to the drug release/penetration characteristics through human cadaver skin (HCS). The cumulative amount released after 24 hours was 88.0 µg/cm² for the system with SCOTCHPAK™ 1109. This corresponds to 16.6 % of the initial drug loading.

EXAMPLE 7

To 287.51 g of adhesive solution (IOA/HEA/ELVACITE™ 1020 (59/39/2); 39.2% solid content) 8.77 g of tropisetron, 31.77 g IPM and 30.0 g methanol were added. The solution was stirred at room temperature until all tropisetron was dissolved. The coating solution was coated onto a release liner (Daubert 164P) at a wet thickness of 400µm and oven dried for 20 minutes at 60°C. The dried coatings were then laminated with SCOTCHPAK™ 1109 backing. The resulting device had a drug loading of 5.7 mg tropisetron per 10 cm². Samples of these devices with a size of 1.55 cm² were tested with respect to the drug release/penetration characteristics through human cadaver skin (HCS). The cumulative amount released after 24 hours was 159.6 µg/cm² for the system with SCOTCHPAK™ 1109. This corresponds to 28.0% of the initial drug loading.

Stability testing of this formulation revealed a crosslinking of the drug-in-adhesive matrix and a decrease in the drug content of more than 10% within 4 weeks of storage.

CLAIMS

1. A transdermal drug delivery device comprising on a backing an adhesive layer, said adhesive layer comprising:

(a) a copolymer of one or more A monomers and one or more B monomers, said A monomers being selected from the group consisting of alkylacrylates containing 4 to 12 carbon atoms in the alkyl group and alkylmethacrylates containing 4 to 12 carbon atoms in the alkyl group and said B monomers being hydrophilic monomers copolymerizable with said A monomers, and

(b) a therapeutically effective amount of a drug selected from the group consisting of tropisetron and granisetron.

2. A transdermal drug delivery device according to claim 1 wherein said B monomers are free of nucleophilic groups selected from the group consisting of hydroxy, thiol, primary amino groups, secondary amino groups and acid groups.

3. A transdermal drug delivery device according to claim 1 wherein said B monomers are selected from the group consisting of N-vinyl-2-pyrrolidone, vinylimidazoles, mono acrylates of poly(alkyleneoxide) alkyl ether, mono methacrylates of poly(alkyleneoxide) alkyl ether, acrylamides, N-vinyl valerolactam, N-vinyl caprolactam, vinyl acetate, tetra-alkylammonium containing monomers and tertiary amino group containing monomers.

4. A transdermal drug delivery device according to any of claims 1 to 3 wherein said copolymer is a copolymer of one or more A monomers and one or more B monomers and a macromer copolymerizable with the A and B monomers and said macromer having a weight average molecular weight between 500 and 500000.

5. A transdermal drug delivery device according to claim 4 wherein said macromer is selected from the group consisting of polymethylmethacrylate macromer, polymethylacrylate macromer, polystyrene macromer and polystyrene-acrylonitrile macromer.

6. A transdermal drug delivery device according to claim 4 wherein said copolymer comprises between 1 and 7% by weight of units derived from said macromer.

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(54) Title: TRANSDERMAL PRESSURE SENSITIVE ADHESIVE DRUG DELIVERY SYSTEM AND PRESSURE SENSITIVE ADHESIVE USED THEREIN

(57) Abstract

A graft copolymer pressure sensitive adhesive is provided comprised of a backbone polymer having a polymeric moiety grafted thereto. The copolymer comprises at least one A monomer consisting of a monomeric (meth)acrylic acid ester of a non-tertiary alcohol, optionally at least one B monomer, optionally at least one polymeric graft moiety C having a T_g greater than 20 °C, and a macromeric graft moiety D containing repeat hydrophilic units. The adhesive may be used with advantage in a transdermal drug delivery system in homogeneous admixture with a pharmacologically active agent.

progestin) present in the drug delivery system to crystallize within the system. This permits the active agent to remain effective over the entire period of time of delivery to the patient through the drug delivery device. The presence of the graft moieties enhances the ability of the adhesive system to retain its structural integrity and adhesive character during the period of use of the drug delivery device. More specifically, the presence of a graft macromeric moiety containing hydrophilic repeat units enhances the compatibility of any drug flux enhancer with the graft copolymer.

The pharmacologically active agent to be administered by use of the transdermal drug delivery means is employed in a conventional manner. Suitable active agents include those that are compatible with the administration system of the present invention and exhibit the expected benefit upon percutaneous administration. Such active agents include, without limitation, antibiotics, antipyretics, analgesics, anti-inflammatory drugs, antihistaminics, psychotropic drugs, coronary vasodilators, antiarrhythmics, antihypertensives, chemotherapeutic drugs, anticancer agents, antiemetics, vitamins, antispasmodics, antitussives, antifungal drugs, steroids, etc. Exemplary of the most commonly transdermally-administered active agents are clonidine, estrodiol, nicotine, nitroglycerine and scopolamine, each commercially available in transdermal devices. See U.S. Patent No. 5,372,819, herein incorporated by reference, for a more detailed discussion of suitable percutaneous administered active agents.

WHAT IS CLAIMED IS:

1. A normally tacky graft copolymer pressure sensitive adhesive comprised of a backbone polymer having a polymeric moiety grafted thereto, comprising the reaction product of:

(1) at least one A monomer consisting of a monomeric acrylic or methacrylic acid ester of a non-tertiary alcohol, said alcohol having from 1 to 30 carbon atoms, wherein at least about 30 percent by weight of said A monomer consists of a monomeric acrylic or methacrylic acid ester of a non-tertiary alcohol having at least 12 carbon atoms, and said at least one A monomer exhibiting an average number of carbon atoms in the alcohol portion of the total acrylic or methacrylic acid esters of at least 10,

(2) at least one optional B monomer,

(3) an optional polymeric graft moiety C having a T_g greater than 20°C, and

(4) a graft macromer D containing repeat hydrophilic units.

2. A pressure sensitive adhesive drug delivery composition for use in the transdermal administration of a pharmacologically active agent comprised of a homogeneous admixture of a hydrophilic macromer reinforced copolymer and a pharmacologically active agent, said copolymer comprising the reaction product of:

(1) at least one A monomer consisting of a monomeric acrylic or methacrylic acid ester of a non-tertiary alcohol, said alcohol having from 1 to 30 carbon atoms, wherein at least about 30 percent by weight of said A monomer consists of a

monomeric acrylic or methacrylic acid ester of a non-tertiary alcohol having at least 12 carbon atoms, and said at least one A monomer exhibiting an average number of carbon atoms in the alcohol portion of the total acrylic or methacrylic acid esters of at least 10,

(2) optionally at least one B monomer,

(3) optionally a polymeric graft moiety C having a T_g greater than 20°C, and

(4) a graft macromer D containing hydrophilic repeat units.

3. A transdermal delivery system for administering a pharmacologically active agent comprising a flexible backing material impermeable to said active agent and a pressure sensitive adhesive layer on at least a portion of said backing layer in homogeneous admixture with said active agent, said pressure sensitive adhesive comprising a graft macromer reinforced copolymer formed by the reaction of:

(1) at least one A monomer consisting of a monomeric acrylic or methacrylic acid ester of a non-tertiary alcohol, said alcohol having from 1 to 30 carbon atoms, wherein at least about 30 percent by weight of said A monomer consists of a monomeric acrylic or methacrylic acid ester of a non-tertiary alcohol having at least 12 carbon atoms, and said at least one A monomer exhibiting an average number of carbon atoms in the alcohol portion of the total acrylic or methacrylic acid esters of at least 10,

(2) optionally at least one B monomer,

(3) optionally a polymeric graft moiety C having a T_g greater than 20°C, and

(4) a graft macromer D containing hydrophilic repeat units.

4. The product of any one of claims 1-3 wherein said graft moiety C is a polymerized monoalkenyl-substituted aromatic hydrocarbon.

5. The product of claim 4 wherein said polymerized monoalkenyl-substituted aromatic hydrocarbon comprises polystyrene.

6. The product of any one of claims 1-3 wherein said at least one A monomer comprises an ester of acrylic or methacrylic acid with a non-tertiary alcohol selected from the group consisting of 1-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-1-butanol, 1-methyl-1-pentanol, 2-methyl-1-pentanol, 3-methyl-1-pentanol, 2-ethyl-1-butanol, 3,5,5-trimethyl-1-hexanol, 3-heptanol, 2-octanol, 1-decanol, and 1-dodecanol.

7. The product of any one of claims 1-3 wherein the A monomer is present in the copolymer in an amount within the range of from about 20 to 80 percent by weight.

8. The product of any one of claims 1-3 wherein the B monomer is present in the copolymer in an amount within the range of from about 3 to 30 percent by weight.

9. The product of any one of claims 1-3 wherein the D macromer is present in the copolymer

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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ASUNTO	*Radicación*	*05077560*
	Trámite	002
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	Actuación	430
	Oficio	No. 4504
	Folios	*025*

Patente de Invención [X] Patente de Modelo de Utilidad [ ]

Vía Nacional [ ]

Vía PCT (fase nacional) [X] Cap.I [ ] Cap. II [X]

No. Sol. Internacional PCT/GB2004/000403
Fecha de Presentación Internacional 5-02-2004

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. ***Documentos estudiados:***

1.1. Descripción: (Folios: 4 a 35) como se radicó inicialmente.

1.2. Reivindicaciones: 1 a 29 (Folios: 36 a 39) como se radicó *inicialmente.*

1.3. Prioridad: 05/02/2003, GB 0302662.2..

2. **Análisis de la Prioridad:**

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. **Objeto de la invención:**

La presente solicitud se titula: "Granisetrón transdérmico".

El objeto de la presente solicitud se refiere a parches transdérmicos comprendiendo granisetrón, a usos de los mismos y a métodos para su preparación.

Según la descripción, las náuseas y vómitos son frecuentemente los síntomas más debilitantes y desalentadores de las medicaciones administradas a pacientes con cáncer. Los efectos secundarios de vómito no sonsolo desagradables debido a la condición, per se, pueden conducir a seria deshidratación y *aun mala nutrición.*

La quimioterapia citotóxica se piensa que libera serotonina de ciertas células del intestino delgado. La serotonina liberada puede estimular los nervios aferentes vagales a través de los receptores 5HT3, estimulando así el reflejo de vómito. De *acuerdo con lo anterior, se asume* que los medicamentos antagonísticos del receptor 5HT3, tales como ondansetrón, granisetrón y tropisetrón, ejercen sus efectos al bloquear serotonina, tanto periféricamente, en terminales nerviosas vagales como centralmenete, en la zona de accionamiento *del quimiorreceptor.*

Los antieméticos antagonísticos del receptor 5HT3 se administran actualmente de manera intravenosa, oral o rectal. La administración intravenosa puede realizarse solamente bajo supervisión médica y causa incomodidad del paciente significativa, *tal como rojez y quemadura en* el sitio de inyección. Los problemas se agravan en medicina pediátrica, pertenecientes al desagrado de los niños por las agujas y siempre existen preocupaciones con respecto a las lesiones por adhesión de la aguja.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 28 (folios: 36 a 39): Un parche adhesivo adecuado para la *administración transdérmica* de granisetrón.

Reivindicación 29 (folio: 39): Un método para el tratamiento de una condición asociada con actividad *del receptor 5HT3 en un paciente en necesidad del mismo.*

El problema planteado en esta solicitud es la necesidad del sistema de suministro de medicamento no oral capaz de mantener los niveles de plasma constantes de agentes antieméticos durante periodos extendidos de tiempo.

La solución propuesta por la presente solicitud consiste en un parche adhesivo adecuado para administración transdérmica de granisetrón.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 9/07, 31/439.

4. **De la solicitud de Patente**

4.1. Reivindicaciones *(artículo 30 D 486)*

De acuerdo con lo revelado en el capítulo reivindicatorio, las reivindicaciones 15 a 22 (folios: 37 y 38) que se relacionan con un parche transdérmico de granisetrón, está caracterizado por un método de tratamiento, lo cual no son claras debido a que estas reivindicaciones se deben caracterizar por sus componentes.

5. **Excepciones de Patentabilidad** *(artículo 20 D486 literal a)-d))*

De acuerdo con lo anterior, la(s) reivindicación(es): 15 a 22 y 29 (folios: 37 a 39), que *se refiere(n) a un método de tratamiento, no es (son)* patentable(s) porque se encuentran dentro de las excepciones de patentabilidad.

6. **Análisis de la(s) Oposición(es):** *(artículo 43 D. 486)*

No se presentaron oposiciones al objeto reivindicado.

7. **Determinación del Estado de la Técnica:**

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud *prioritaria 5-02-2003.*

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	EP 1044684	Percutaneuosly absorbable preparation	18 de octubre de 2000
D2	US 6136807	Composition for the transdermal delivery of lerisetron	24 de octubre de 2000
D3	WO 98/53815	Transdermal drug delivery device for the delivery of tropisetron or granisetron	3 de diciembre de 1998
D4	WO 98/37111	Transdermal pressure sensitive adhesive drug delivery system and pressure sensitive adhesive used therein	27 de agosto de *1998*

8. Análisis de patentabilidad (artículo 14 D486)

8.1. Nivel inventivo *(artículo18 D486)*

La presente Solicitud de Patente reivindica lo siguiente: Un parche adhesivo adecuado para la administración transdérmica de granisetrón, en donde el adhesivo es un adhesivo acrílico conteniendo porciones de *hidroxilo no ácido, una cantidad* fisiológicamente efectiva de granisetrón cargándose en el adhesivo.

La anterioridad EP 1044684 (folios: 74 a 78) se relaciona con una preparación absorbible via percutánea que tiene una capa adhesiva conformada por polímeros de acrílato y metacrilato, como *por ejemplo: acrilato de hidroximetilo*, acrilato de hidroxietilo, acrilato de hidroxipropilo, acrilato de hidroxibutilo, metacrilato de hidroximetilo, metacrilato de hidroxietilo, metacrilato de hidroxipropilo, metacrilato de hidroxibutilo. Este tipo de preparación sirve para administrar diferentes tipos de fármacos incluidos los antieméticos.

El documento US 6136807 (folios: 79 a 83) se refiere a una composición para liberación transdérmica de lerisetrón que comprende un copolímero de uno o más monómeros de metacrilato, como por ejemplo acrílatos de *alquilo que contienen 4 a* 12 carbonos en el grupo alquilo y metacrilatos de alquilo también con 4 a 12

carbonos en el grupo alquilo, y también comprende una cantidad efectiva de lerisetrón.

La anterioridad WO 98/53815 (folios: 84 a 88) menciona una forma de liberación transdérmica de tropisetrón o granisetrón, que comprende una capa adhesiva compuesta por copolímeros de uno o más monómeros A y uno o más monómeros B, entre los cuales están el acrilato de 2-hidroxietilo (HEA) y mono acrilatos de poli(alquilenóxido)-alquil-éter. En este documento se observa la preparación del parche adhesivo cuyo principio activo es el tropisetrón.

El documento WO 98/37111 (folios: 89 a 93) menciona formas transdérmicas para liberación de fármacos como por ejemplo antieméticos; el sistema de liberación transdérmico comprende al menos un monómero A que consiste de un éster de ácido acrílico o metacrílico, un monómero B y una unidad polimérica C.

Estos documentos revelan la existencia y amplio uso de formas transdérmicas tipo parches transdérmicos que emplean como adhesivo un polimero derivado acrílico como por ejemplo metacrilatos y acrilatos de hidroxipropilo, hidroxietilo e hidroximetilo, para la liberación de antieméticos tipo granisetrón o fármacos que también son antagonistas de $5HT_3$ como el tropisetrón.

El problema técnico planteado en esta solicitud: la necesidad del sistema de suministro de medicamento no oral capaz de mantener los niveles de plasma constantes de agentes antieméticos durante periodos extendidos de tiempo, se habia resuelto previamente mediante parches o preparaciones transdérmicas ya conocidos(as). Por esta razón se considera que los componentes de los parches transdérmicos reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia.

La reivindicación 1 a 14, 23 a 28 de esta solicitud no menciona una caracteristica que conceda un efecto inesperado o especial a los parches transdérmicos, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia.

Además, puesto que D1, D2, D3, D4 divulgaban previamente parches transdérmicos (folios: 74 a 93), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto de esta solicitud parches transdérmicos de granisetrón; de manera que para una persona medianamente versada en la materia sería obvio emplear estos documentos. Por lo cual puede no haber Nivel Inventivo.

9. **Conclusión:**

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	**Documento N°**	**Reivindicaciones afectadas**	***Requisito que afecta***
D1	EP 1044684	1 a 14, 23 a 28	Nivel Inventivo
D2	US 6136807	1 a 14, 23 a 28	Nivel Inventivo
D3	WO 98/53815	1 a 14, 23 a 28	Nivel Inventivo
D4	WO 98/37111	1 a 14, 23 a 28	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 quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 17 ABR. 2009

CONCEPTO TÉCNICO No. 1122	***EXAMINADOR TÉCNICO*** Código No. 202005