Industria y Comercio

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03059764 00000004 Folios: 106
Fecha (AMD): 2005-02-07 17:23:10
Tramite : 011 PCT-PATENT 379 FASE NAC1 400 OPOSICION
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

247

FORMULARIO UNICO DE OPOSICION

① OPOSICION A

- [x] Patente de Invencion
- [ ] Patente de Modelo de Utilidad
- [ ] Diseno Industrial
- [ ] Esquema de Trazado para Circuitos Integrados.
- [ ] Marcas de Productos o Servicios
- [ ] Marca Colectiva
- [ ] Marca de Certificacion
- [ ] Lema Comercial

② SOLICITUD PUBLICADA

Número del expediente 03-059764
Solicitante SHERING AKTIENGESELLSCHAFT
Apoderado GUSTAVO HOLLMAN RESTREPO
Titulo de la nueva creacion o denominación del signo "COMPOSICIONES DE COMPLEJOS DE ESTRÓGENO-CICLODEXTRINA"
Gaceta 546

③ OPOSICIÓN PRESENTADA POR

SOLICITANTE

Nombre GYNOPHARM LTDA
Dirección CALLE 90 No 78b-201
Nacionalidad o Domicilio COLOMBIA
Lugar de Constitucion BARRANQUILLA
Teléfono 371 99 00 Fax 373 08 11
E mail

IDENTIFICACIÓN
CC [ ] NIT [x]
CE [ ] Otro [ ]
Cual
Número 890 106 527-5

REPRESENTANTE O APODERADO

Nombre LUIS FERNANDO RINCÓN
Dirección CALLE 119ª No 53 99
Teléfono 613 34 18 Fax 24 47 87
E mail negocios@optimum-co com

IDENTIFICACIÓN
CC [x] NIT [ ]
CE [ ] Otro [ ]
Cual
Numero 79 532 186 TP 113438

④ FUNDAMENTOS DE LA OPOSICIÓN

Art 14, 16, 18, 20 y 30 de la Decision 486 de la CAN

Causal No cumple con los requisitos de patentabilidad

Signo opositor

Justificacion

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos"

2000 F04

⑤ **Comprobante de pago No** _____ **Fecha** _____

248

⑥ **ANEXOS**

- [x] Comprobante de pago de la tasa
- [x] Poderes si fuere el caso
- [x] Pruebas de los fundamentos de la oposicion
- [ ] Documentos que acrediten el legitimo interes si fuere el caso
- [x] Documento que acredita la existencia y representación legal de las partes cuando sean personas jurídicas

⑦

NOMBRE LUIS FERNANDO RINCÓN CUELLAR

FIRMA

C C 79 532 186 **TP** 113438

Instrucciones para el diligenciamiento de este formulario ver reverso de esta pagina

Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

F S D

Referencia	Expediente N° **03-059764**
Asunto	Oposicion a la solicitud de patente de Invencion titulada **"COMPOSICIONES DE COMPLEJOS DE ESTROGENO-CICLODEXTRINA"**
Solicitante	**SCHERING AKTIENGESELLSCHAFT**
Opositora	**GYNOPHARM LTDA**

Publicada en la Gaceta de la Propiedad Industrial
N° 546 del 30 de Noviembre de 2004

Yo, **Luis Fernando Poncón Cuellar**, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condicion de apoderado de la sociedad GYNOPHARM LTDA, conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invencion titulada **"COMPOSICIONES DE COMPLEJOS DE ESTROGENO-CICLODEXTRINA"**, solicitada por **SCHERING AKTIENGESELLSCHAFT**, y pido a Usted declarar fundada esta oposicion y en consecuencia negar el registro de la patente solicitada

Calle 119 A N° 53-09 I (571) 6 13 34 18 – 6 13 33 74 – Fax (571) 6 14 47 87
E mail mail@optimum-co.com www.optimum-co.com
Bogotá Colombia

3

1 INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el articulo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del termino estipulado por la ley, manifiesto el legitimo interes de nuestra representada debido a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizara mas adelante y de ser concedida atentaria directamente a la comercialización que mi representada pretende con la presentacion farmacéutica elaborada con base en Etinilestradiol + Drosprenona Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del tramite administrativo que se surte en esta Superintendencia

2. FUNDAMENTOS DE HECHOS

2 1 La solicitud objeto de la presente oposición fue presentada en Colombia el 15 de Julio de 2003 reivindicando prioridad bajo EP00610135 6 del 20/12/2000 y US00/2 6 484 del 20/12/2000, cuya fecha de inicio en la fase nacional fue el 20 de Julio de 2003 con publicación internacional Nº WO0249675 del 27 de Junio de 2002 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial Nº 546, del 30 de Noviembre de 2004, bajo el numero de publicacion NP 596 (página 356)

2 2 La solicitud colombiana Nº 03-059764 objeto de la presente oposicion, comprende segun sus cláusulas, una composicion que comprende un complejo entre un estrogeno y una ciclodextrina en una preparación granulada en donde dicha preparacion granulada contiene polivinilpirrolidona, que se encuentra en una concentración de a lo sumo 2% p/p, y opcionalmente uno o más excipientes, composicion que tiene

una estabilidad tal que dicho estrógeno se encuentra en una cantidad de al menos 85% p/p con relación al contenido inicial de dicho estrógeno despues de un almacenamiento por 12 meses a 40° C y 75% de humedad relativa (RH) donde el estrogeno se selecciona del grupo que consiste en etinilestradiol (EE) estradiol, sulfamatos de estradiol, valerato de estradiol, benzoato de estradiol, estrona y sulfato de estrona, o mezcla de los mismos, donde el estrogeno se selecciona del grupo que consiste en etinilestradiol (EE), sulfamatos de estradiol, valerato de estradiol, benzoato de estradiol estrona y sulfato de estrona, o mezcla de los mismos

2 3 En primera instancia las reivindicaciones referidas al uso no son objeto de patentabilidad a la luz de la norma vigente en Colombia La Decisión 486 de la CAN, en el articulo 14 consagra que *"Los países miembros otorgaran patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnologia, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"* Como tal, los usos no estan contemplados como objeto de proteccion, solo los productos o procedimientos Adicionalmente, el uso referido en la presente solicitud no tiene aplicación industrial, porque primero no se obtiene un producto o proceso a partir del mismo, y, segundo no es reproducible o repetible a escala industrial

2 4 Ese mismo articulo aplicable de la Decision 486 de la CAN, se refiere a que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran el siguiente documento que afectan la novedad y el nivel inventivo de la presente solicitud

5

- D1 EP0349091 3 de Enero de 1990
- D2 US4727064 2 de Febrero de 1988
- D3 EP0579435 19 de Enero de 1994
- D4 WO0021570 20 de abril de 2000
- D5 US5798338 25 de Agosto de 1998

2.5 Segun el documento D1 en sus reivindicaciones y ejemplos, se revela una composicion farmaceutica igual a la pretendida en la presente solicitud, que contiene estradiol y/o progesterona y dimetil-beta-ciclodextrina Segun la descripcion, algunos preservativos pueden ser adicionados a la composición, similar a lo reivindicado Igualmente, este documento D1 relaciona un complejo entre un estrógeno y una ciclodextrina Por lo tanto la presente solicitud a la luz del documento D1, carece del requisito de NOVEDAD, dado que lo que pretende ya se encontraba publicado mucho antes de la radicacion de la prioridad de la solicitud Colombiana

2.6 El documento D2 define en las reivindicaciones las mejoras de la solubilidad en composiciones farmacéuticas, mezclandolos con ciclodextrina Segun se afirma, el enfoque es modificar la ciclodextrina para mejorar las propiedades farmaceuticas (Véase, columna 1, líneas 26 a 36), mismo objeto pretendido en la presente solicitud Las composiciones para el uso en la invencion del documento D2 son por ejemplo hormonas sexuales, como el estradiol, progesterona y testosterona (Vease ejemplo 4, tablas 2 y 3) Las composiciones se prepararon para disolver dichas composiciones en un 50% (p/p) de la solución de ciclodextrina Igualmente, este documento D2 relaciona un complejo entre un estrógeno y una ciclodextrina De esta manera, la

NOVEDAD de l[illegible]nte solicitud objeto de oposicion, se ve afectada sustancialmente a los ojos del documento D2

27 Por su parte el [illegible]mento D3 relaciona igulamente un metodo para mejorar la conjuga[illegible]n de una droga con ciclodextrina, comprendiendo la suma de un polimero Segun varios ejemplos expuestos, esta anterioridad revel[illegible] composiciones que comprenden varias sustancias además de hidroxipropil-beta-ciclodextrina y polimeros CMC y PVP De nuevo, un co[illegible]nto anterior relaciona un complejo entre un estrógeno y una [illegible]clodextrina Así las cosas, este documento D3 afecta la NOVEDAD de l[illegible]esente solicitud

28 El documento D4 relaciona composiciones que comprenden al menos un gestagen, tal como el etinilestradiol y ciclodextrina tal como beta-ciclodextrina La descripción de D4 define claramente que ciertos suplementos, normalmente presentes preparaciones farmaceuticas, reducen la estabilidad del gestagen Para resolver dicha inestabilidad, en D4 se propone una mezcla de un gestagen con ciclodextrina, igual alo expuesto en l[illegible]presente solicitud El metodo descrito segun D4, comprende una [illegible]granulacion La conjugación del gestagen con beta-ciclodextrina aumentó la estabilidad de geslagen notablemente tal y como se obser[illegible]el ejemplo Por lo tanto, se damuestra que el desarrollo mostrado en la presente solicitud, no es NOVEDOSO con base en este documento D4

29 El documento D[illegible]cribe un metodo y composiciones farmaceuticas para reducir la degradación por oxidacion del 17 alfa - el etinilestradiol comprendiendo una combinando de estradiol con una cantidad eficaz de ciclodextrina Particularmente se describen medicamentos sólidos que contienen hormonas sexuales esteroideas, que se caracterizan

porque contiene ... l ...tos de ciclodextrina en polvo de estos principios activos Las compo...iciones para el uso en la invención del documento D5 son por ejemplo hormonas sexuales, como el estradiol (Vease columna 1, linea ... 4 ... reivindicaciones) Asi las cosas, este documento D5 relaciona un ... complejo entre un estrogeno tal como un estradiol y una ciclodextri... ...ual a lo pretendido en la solicitud objeto de proteccion Por lo tanto este documento D5 afecta la NOVEDAD de la presente solicitud

2 10 Ahora bien, a partir de dichas anterioridades D1 a D5 es también posible deduci... q... cualquier persona versada en la materia puede combinar los ... proporcionados y conformar una composicion que comprende un complejo entre un estrógeno y una ciclodextrina en una preparacion granulada en las proporciones indicadas De hecho, como se demost... ...tas, el combinar un estrogeno con ciclodextrina ya es ampliamente conocido en la técnica, por lo tanto, debe ser claro para un experto que ... ...ar a presentaciones granulares o proporciones alternativas o com... ...aciones de opcionalmente uno o más excipientes, es posible deri... ...de dicho arte anterior Así las cosas, estos documentos combinados, afectarian de manera directa el requisito de ALTURA INVENTIV de la presente solicitud objeto de oposicion

2 11 En consecuencia ... ...acuerdo a lo descrito anteriormente, se deriva que la solicitud ... lombiana 03-059764 no puede pretender un monopolio por parte ... toda vez que lo que pretende no cumple con los tres requisitos ... ...os para su protección

2 12 Que por consiguiente ... respecto a la solicitud pretendida se tiene que

2 12 1 <u>CARECE DE NOVEDAD</u> segun la decisión 486 de la Comunidad Andina de Nacio... Artículo 16 - "*Una invención se considerara*

nueva cuando no esta comprendida en el estado de la tecnica El estado de la técnica comprendera todo lo que haya sido accesible al público por una descripcion escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentacion de la solicitud de patente o, en su caso de la prioridad reconocida" A la fecha de prioridad, 20 de diciembre de 2000, ya era conocido, pues como se demostró era parte del arte anterior un complejo entre un estrogeno y una ciclodextrina, con base en D1, D2, D3, D4 y D5

2 12 2 **CARENCIA DE ALTURA INVENTIVA.** Según la Decision 486 de la Comunidad Andina de Naciones, Articulo 18 - *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invencion no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la tecnica"* A la fecha de prioridad, 20 de diciembre de 2000 a partir de los documentos D1, D2, D3, D4 y D5 en combinacion es posible derivar de manera evidente un complejo entre un estrógeno y una ciclodextrina en una preparación granulada en las proporciones indicadas

2 12 3 **CARENCIA DE APLICACIÓN INDUSTRIAL.** La Decisión 486 de la CAN consagra en su articulo 14 lo siguiente *"Los países miembros otorgaran patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial* Como primeros usos no están contemplados como objeto de protección solo los productos o procedimientos Adicionalmente, el uso referido en la presente solicitud no tiene aplicacion industrial,

porque primero t v obtiene un producto o proceso a partir del mismo, y, egun lo t s reproducible o repetible a escala industrial

2 13 Dado lo anterior es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decision 486 de la Comunidad Andina de Naciones, Articulo 14 La solicitud pretendida no cumple con los tres requisitos de patentabilidad

2 14. Por consiguiente, de concederle el registro solicitado se induciria al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486

2.15 Por todo lo anteriormente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada "**COMPOSICIONES DE COMPLEJOS DE ESTROGENO CICLODEXTRINA**", solicitada por **SCHERING AKTIENGESELLSCHAFT**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 546 del 30 de Noviembre de 2004 en la página 356, bajo el NP 596

3 PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como pruebas en el asunto los siguientes

- D1 EP0349067 3 Enero de 1990
- D2 US4727064 2 de Febrero de 1988
- D3 EP0579463 1 de Enero de 1994
- D4 WO0021515 20 de abril de 2000
- D5 US5798345 25 de Agosto de 1998

4 FUNDAMENTO DE DERECHO

Fundamento esta oposición en las normas legales siguientes

4 1 Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena

4 2 En las demas normas concordantes

5 ANEXOS

Para los efectos correspondientes anexo al presente, aquellas referenciadas en el capítulo de pruebas, a saber los siguientes documentos

5 1 Recibo de pago expedido por el Fondo Especial de esa Superintendencia en el cual consta que se ha pagado el valor correspondiente a la tasa por tramitacion de esta oposicion

5 2 Copia de la oposición para el traslado al solicitante

5 3 Poder para actuar en nombre de mi representada

5 4 Documento que acredita la existencia y representación legal de la empresa

(NOTIFICACIONES

Para efectos de n t ficaciones que por disposición del artículo 50 del Decreto 01 de 1984 deb r su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaria de su Despacho o en mis oficinas de abogado situadas en la calle 119ª Nº 53-99 de esta ciudad de Bogota

Señora Jefe,

LUIS FERNANDO RINCÓN CUELLAR
C C 79'532 186 de Bogotá
T P A. 113 438 del C S. de la J

259

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03059764 00000004 Folios: 106
Fecha (MMD) 2005-02-07 17 23:10
Tramite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT 800176089-2

RECIBO OFICIAL DE CAJA 05 - 8,945
FECHA FEBRERO 7 DE 2005

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
LAB PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	37689246	27/01/2005	470,000 00
LAB PROCAPS	CONSIGNACIÓN	BANCO POPULAR	050-00110-6	37689247	27/01/2005	235,000 00
LAB PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	37689248	27/01/2005	710,000 00

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

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	30005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	235,000 00
		TOTAL $	235,000 00

SON DOSCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

PODER ESPECIAL

Yo **LUIS PALACIOS ARAGÓN,** mayor de edad y vecino de la ciudad de Barranquilla (Colombia) identificado como aparece al pie de mi firma quien en el presente documento actua en calidad de Representante Legal de la sociedad **GYNOPHARM LTDA.,** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla ,Colombia por el presente documento otorgo a **LUIS FERNANDO RINCON CUELLAR,** abogado titulado identificado como aparece al pie de su firma con tarjeta profesional No 113438 expedida por el Consejo Superior de la Judicatura, poder especial amplio y suficiente para formular oposiciones u observaciones a la solicitud de patente No 03-059 764 de titulo ***"COMPOSICIONES DE COMPLEJOS DE ESTROGENO - CICLODEXTRINA"*** publicada en la gaceta No 546 del 30 Noviembre de 2004 numero de publicación 596

Nuestro apoderado queda facultado de manera expresa para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición incluyendo sin limitación preparar y presentar solicitudes hacer declaraciones pagar tasas contribuciones e impuestos recabar los titulos o certificados Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder con todas las facultades generales y especificas que fuera requerido para ella

De la misma manera además de las facultades que le confiere la naturaleza del presente mandato se encuentran facultados para recibir desistir transigir sustituir y reasumir el presente poder incoar acciones interponer recursos y demás facultades conferidas por la ley

Dado y Firmado en Barranquilla (Colombia) a los 25 días del mes de enero de 2005

GYNOPHARM LTDA.
LUIS PALACIOS ARAGÓN
C C No 3[illegible].788
Representante Legal

Acepto:

LUIS FERNANDO RINCÓN CUÉLLAR
C C No. 79.532.186
T P 113438

DILIGENCIA DE RECONOCIMIENTO

Ante el Notario Tercero de Barranquilla
se presentó Carlos Alberto Palacio Posada
identificado con C.C. 3192688 de Bogotá
y declaró que el contenido del documento
anterior es cierto y suya la firma que lo refrenda
Barranquilla 26 ENE 2005

ANTONIO L. G...

DILIGENCIA DE RECONOCIMIENTO
PRESENTACION PERSONAL

Ante el Notario Once del Circulo de Santafé de
Bogotá compareció [redacted]
Quién exhibió la C C No [redacted]
expedida en [redacted] T P [redacted]
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 [redacted]

Santafé de Bogotá, D.C. 07 FEB 2005

Firma del Contribuyente

HUELLA

Autorizó la anterior Diligencia

NOTARIO ONCE DEL CIRCULO DE SANTAFE DE BOG...

...BLICA DE COLOMBIA
...ARIA ... DEL CIRCULO DE
...ANTAFE DE BOGOTA D C

... NAVARRO DE BAUTISTA
NOTARIA ONCE

No 8782807

261

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
17**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS

GYNOPHARM S A ----------

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Publica Nro 3551 del 17 de Dic/bre de 1,997,
t rgada en la Notaria 3a de Barranquilla ----------
inscrita en esta Camara de Comercio, el 18 de Dic/bre de 1,997 bajo
l No 72,965 del libro respectivo, fue constituida la sociedad
an nima denominada GYNOPHARM S A ----------

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras
y/ documentos privados

Numero	mm/dd/aaaa	Notaria	No Ins o Reg	mm/dd/aaaa
532	3/25/1999	Notaria 3a de Barranquilla	80,373	4/13/1999

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad
se rige por las siguientes disposiciones ----------
DENOMINACION O RAZON SOCIAL ----------
GYNOPHARM S A ----------
DOMICILIO PRINCIPAL BARRANQUILLA ----------
Nit No 802,006,279-4----------
MATRICULA MERCANTIL 245,470 ----------

C E R T I F I C A

Direccion para notificaciones judiciales
CL 80 # 78B -201
de la ciudad de BARRANQUILLA

C E R T I F I C A

DURACION El termino de duracion de la sociedad se fijo en CINCUENTA
(50) anos, contados desde el 16 de Dic/bre del ano 1,997 ---------

C E R T I F I C A

OBJETO SOCIAL a) La fabricacion de capsulas y otro productos simi-
lares a partir de materiales tales como gelatinas u otros de distin-
ta naturaleza, que puedan ser utilizados como envases o recipientes

********** C O N T I N U A **********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS

GYNOPHARM S A ----------

de productos y sustancias quimicas, farmaceuticas y cosmeticas, para us y consumo humano y veterinario b) La investigacion, desarr ll y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal c) La compra y venta de meterias primas , insumos y productos intermedi s necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, asi como la comercializacion interna y externa de los productos terminados d) La compra, venta, imp rtacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relaci - nadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S A , asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial g) Adquirir, operar, administrar y explotar, a cualquier titulo,empresas o establecimient s dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmetic s En desarrollo de su objeto principal, la sociedad podra t - mar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades, tomar dinero en prestamo,financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objet , celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operacioes, girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravamenes sobre bienes muebles e inmuebles, designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor pr - tecci n de sus intereses corporativos o lo de sus socios ----------

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Accion
AUTORIZADO		
$******4,000,000,000 00	4,000,000 00	1,000 00
SUSCRITO		
$******2,672,646,000 00	2,672,646 00	1,000 00
PAGADO		
$******2,672,646,000 00	2,672,646 00	1,000 00

********** C O N T I N U A **********

CAMARA DE COMERCIO DE BARRANQUILLA

********** Pag 02
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
****
CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS

GYNOPHARM S A ----------

C E R T I F I C A

ADMINISTRACION Seran funciones de la junta directiva, entre otras Aut rizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US$50 000 oo), liquidados a la tasa de cambi representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion Las demas que le sean propias y no esten atribuidas a otro rgano social y las que le correspondan en virtud de la ley la s ciedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarroll del objeto social, de conformidad con lo previsto en las leyes y en l s presentes estatutos Aprobar y celebrar en nombre de la sociedad tod acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US$50 000 oo), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion celebracion del acto Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravamenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion, o las demas funciones que le correspondan como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente accidentales, sin que sea necesario para ello acreditar la ausencia del principal ----------

C E R T I F I C A

Que por Escritura Publica Nro 3551 del 17 de Dic/bre de 1,997, t rgada en la Notaria 3a de Barranquilla ----------
cuya parte pertinente se inscribio en esta Camara de Comercio, el 18 de Dic/bre de 1,997 bajo el No 72,965 del libro respectivo, fueron hechos los siguientes nombramientos ----------

J U N T A D I R E C T I V A

	Principales	Suplentes
1	Minski Gontovnik Ruben	Minski Gontovnik Meyer
2	Minski Minski Abraham	Minski Gontovnik Jose
3	Weinstein Manieu Alejandro	Weinstein Crenovich Alejandr
4	Nicolas Weinstein Manieu	Alejandro Aycardi

********** C O N T I N U A **********

16

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS

GYNOPHARM S A ----------

C E R T I F I C A

Que segun Acta No 2 del 13 de Enero de 1,998, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad ------
GYNOPHARM S A ----------
cuya parte pertinente se inscribio en esta Camara de Comercio, el 20 de Enero de 1,998 bajo el No 73,393 del libro respectivo, fuer n hechos los siguientes nombramientos ----------

Cargo	Nombre	Identificacion
Revis r Fiscal Ppal	Barros Cerra William Alberto	C *****8,715,941=
Suplente del Revisor Fiscal	Duarte Diaz David	C ****73,115,965=

C E R T I F I C A

Que segun Acta No 18 del 30 de Octubre de 2,003, correspondiente a la Junta Directiva en Barranquilla de la sociedad ----------
GYNOPHARM S A ----------
cuya parte pertinente se inscribio en esta Camara de Comercio, el 6 de Nov/bre de 2,003 bajo el No 107,783 del libro respectivo, fueron hechos los siguientes nombramientos ----------

Cargo	Nombre	Identificacion
Gerente General	Palacios Aragon Luis Alberto	E *******319,788=
Suplente del Gerente General	Castellanos Martinez Jorge Alfredo	C ****19,460,089=

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2 000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2 000 baj el N 1 872 del libro repectivo, consta que el senor RUBEN MINSKI GONTOVNIK C C No 7 463 982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S A , otorga Poder Especial, Ampli y Suficienta a KAREN JENNIFER FIGUEROA GARCIA C C No 32 - 732 070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM S A , en el giro normal de sus negocios y operaciones sociales -----

C E R T I F I C A

Que p r escritura publica No 522 del 16 de Febrero de 1 998,ot rgada en la Notaria Segunda de Barranquilla, inscrita en esta Camara de Comercio el 9 de Marzo de 1 998 bajo los Numeros 1 348 y 1 349 de l s libros respectivos, el senor MARIO LOMBANA GARZON C C No 19 - 358 058, quien actua en su condicion de Gerente General de la sociedad GYNOPHARM S A , otorga Poder Especial a los senores WALTER TANAKA TATEKAWA C C No 16 251 923, para que en nombre y representacion de GYNOPHARM S A , suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi

********** C O N T I N U A **********

como para que responda todo tipo de requerimientos o solicitudes de inf rmacion de las autoridades tributarias, aduaneras y cambiarias, en las ordenes distrital, departamental y nacional, y JOSEFINA DEL CARMEN MIELES BUELVAS C C No 33 138 497, para que represente a GYNOPHARM S A , ante todo tipo de autoridades administrativas y judiciales en asuntos de naturaleza aduanera, cambiaria, fiscal tales como contestar e interponer demandas y requerimientos, comparecer en juicio, pedir la practica de pruebas, recibir notificaciones, interponer recursos, ejercer la accion de tutela, transigir, conciliar, recibir en nombre de la sociedad, desistir, sustituir, y reasumir este mandato Para la celebracion de cualquier acuerdo conciliat ri o transaccional judicial o extrajudicial,cualquiera que sea su cuantia, la apoderada debera aportar la autorizacion escrita del representante legal de la sociedad La apoderada podra presentar solicitudes de devolucion y/o compensacion de impuestos y rentas reciba los pagos por devoluciones ----------

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2 000, inscrito en esta Camara de Comercio el 12 de junio del 2 002, baj el 2 164 del libro respectivo,consta que el senor JORGE CASTELLANOS MARTINEZ,identificado con C C No 19 460 089,actuando como repr sentante legal de la sociedad GYNOPHARM S A, otorga Poder Especial Amplı y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadania No 32 732 070 de Barranquilla, mediante d cument privado de octubre 10/2000, inscrito en la Camara de Comerci de Barranquilla bajo el No 1 872 del libro respectivo, para que en representacion de GYNOFARM S A, suscriba las declaraciones cambiarias a los que esta obligada GYNOFARM S A en el giro ordinario de sus negocios y operaciones sociales ----------

C E R T I F I C A

463 982, actuando como Presidente y represen-tante legal de la sociedad GYNOPHARM S A , otorga Poder Especial, Amplio y Suficienta a KAREN JENNIFER FIGUEROA GARCIA C C No 32 -732 070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARS A , en el giro normal de sus negcios y operaciones sociales ---

C E R T I F I C A

Que en esta Camara de Comercio no aparecen inscripciones posteri res de d cumentos referentes a reforma, disolucion, liquidacion o nombramientos de representantes legales de la expresada sociedad ------

********** C O N T I N U A **********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS

GYNOPHARM S A ----------

C E R T I F I C A

Que su ultima Renovacion fue el 31 de Marzo de 2,004 ----------

La informacion sobre embargos de establecimientos se suministra en Certificados de Matricula, la de contratos sujetos a registro, en Certificados Especiales

NO CAUSA IMPUESTO DE TIMBRE

EL SECRETARIO
MARIBEL REYES OVIEDO

ANEXO 1

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

(11) Publication number 0 349 091 A1

265

(12) EUROPEAN PATENT APPLICATION

(21) Application number 89201731.0

(22) Date of filing 30.06.89

(51) Int. Cl.4 A61K 31/715 , A61K 9/06 , C08B 37/00

(30) Priority 01.07.88 NL 8801670

(43) Date of publication of application 03.01.90 Bulletin 90/01

(84) Designated Contracting States DE FR GB NL

(71) Applicant: Hermens, Walter Adrianus Josephus Johannes
Thorbeckestraat 80
NL-6136 DD Sittard(NL)

Applicant: Merkus, Franciscus Wilhelmus Henricus Maria
Mozartlaan 7
NL-3723 JL Bilthoven(NL)

(72) Inventor: Hermens, Walter Adrianus Josephus Johannes
Thorbeckestraat 80
NL-6136 DD Sittard(NL)
Inventor: Merkus, Franciscus Wilhelmus Henricus Maria
Mozartlaan 7
NL-3723 JL Bilthoven(NL)

(74) Representative: Smulders, Theodorus A.H.J., Ir et al
Vereenigde Octrooibureaux Nieuwe Parklaan 107
NL-2587 BP 's-Gravenhage(NL)

(54) Pharmaceutical composition.

(57) Pharmaceutical compositions having a formulation and form suitable for nasal administration and containing 17β-oestradiol and/or progesterone. According to the invention the composition also contains dimethyl β-cyclodextrin.

EP 0 349 091 A1

Pharmaceutical composition.

This invention relates to a pharmaceutical composition having a formulation and form suitable for nasal administration, and containing a sex hormone selected from 17β-oestradiol progesterone, and combinations thereof

17β-oestradiol is the most active natural human oestrogen The oral administration of 17β-oestradiol is accompanied by a considerable conversion into the less active hormone estrone and subsequently into other metabolites This conversion takes place during the absorption from the intestine and transport through the liver (first pass). This requires high dosages to achieve the effects desired as compared with parenteral administration Progesterone, too, which is the most important natural human progestagen has a very limited activity after oral administration by reason of the metabolism in the gastro-intestinal trac and the first-pass effect of the liver

By reason of this limited oral effectiveness of the natural female sex hormones synthetic derivatives have replaced the natural hormones in virtually all cases

The synthetic derivatives however have an adverse stimulating effect on the protein synthesis of the liver (possibly promoting thrombosis) and exhibit a diabetogenic effect, in contrast to the natural sex hormones

For the above reasons, there is an urgent need of suitable, non-oral compositions and dosage forms of the natural female sex hormones

Rigg et al J Clin.Endocrinol Metab 45 1977 pp 1281-1284, have investigated the intravaginal and intranasal administration of 17β-oestradiol in the form of a suspension in a physiological saline solution Intranasal administration proved to be unsuitable

In US patent 4 383,993, however, intranasal administration is yet proposed for both progesterone and 17β-oestradiol and esters thereof It describes a composition for intranasal administration comprising a solution of the sex hormones in an isotonic saline containing a surfactant, such as Tween 80 as a solubilizer This publication shows that the sex hormones in question can be absorbed nasally In which connection it is doubtless of importance that the hormones are offered to the nasal mucosa in a dissolved form On account of the apolar character of the natural sex hormones, particular measures must be taken to realize the desired dissolved form such as the use of Tween 80 or other adjuvants as solubilizers.

Adjuvants suitable for use as solubilizers, however are often unsuitable for the nasal mucosa and/or have an insufficient solubility increasing effect. In the first case, a chronic therapy with such a composition is undesirable. In the second case the concentration of the natural hormone in the composition is too low so that the dosage volume must become too high to bring about an effective therapy

It is an object of the present invention to provide a composition suitable for the nasal administration of 17β-oestradiol progesterone or mixtures thereof which ensures an effective absorption of the hormones but avoids the above disadvantages of known compositions

This object is realized, in accordance with the present invention, by providing a pharmaceutical composition of the above type which is characterized in that it also contains dimethyl-β-cyclodextrin

For that matter dimethyl-β-cyclodextrin is known per se from German patent application 3 118,218. In it, it is proposed for dimethyl-β-cyclodextrin to be used for the preparation of aqueous solutions of poorly soluble biologically active, organic compounds such as various vitamins steroids, prostanoids, local anaesthetics, etc The combination of such substances, which include for example progesterone with dimethyl-β-cyclodextrin results in the formation of intercalation complexes which are soluble in water Generally speaking, that publication describes pharmaceutical compositions for oral or parenteral administration Concretely however, the publication does show infusion and injection solutions of various biologically active compounds, but pharmaceutical compositions with a formulation and form suitable for nasal administration are neither mentioned nor illustrated let alone such pharmaceutical compositions specifically containing a sex hormone selected from 17β-oestradiol progesterone and combinations thereof

The ideas laid down in the German patent application have not found practical application, as will become apparent from the following publications which point in a different direction

In European patent application 0 149,197 attention is directed to major drawbacks reported to be involved in the use of dimethyl-β-cyclodextrin Specifically the application refers in this connection to a hemolytic effect and an irritant effect on mucosa and eyes, a higher acute intravenous toxicity than non-substituted β-cyclodextrin and practical problems in connection with sterilization Indeed the publication recommends using a partially etherified β-cyclodextrin containing hydroxyalkyl groups.

For that matter the objections raised in European patent application 0 149 197 against the use of

267

dimethyl-β-cyclodextrins have not been noted with pharmaceutical compositions according to the present invention Evidently the concentrations to be used are so low that no trace of irritation of mucosa is found Tests for the in-vitro examination of the effect of compositions according to this invention on the ciliary movement of human nasal ciliary epithelium showed that, unlike Tween 80 containing compositions as disclosed in US patent 4,383,993 they do not stop ciliary movement and are not harmful (see Fig 1)

In addition it is surprising that the pharmaceutical compositions according to the invention result in a biological availability substantially equal to that achieved with intravenous administration In fact, US patent 4,596,795 teaches that the use of the dimethyl-β-cyclodextrin in sex hormone compositions for sublingual and buccal administration have virtually no effect on the absorption of the sex hormones, unlike poly-β-cyclodextrin and hydroxypropyl-β-cyclodextrin That publication too, therefore teaches away from the use of dimethyl-β-cyclodextrin.

The invention accordingly relates to pharmaceutical compositions for the nasal administration of the natural female sex hormones 17β-oestradiol and progesterone with an increased absorption of the hormones referred to by combination with the adjuvant dimethyl-β-cyclodextrin. Examples of dosage forms of 17β-oestradiol and/or progesterone suitable for nasal administration are solutions suspensions, gels and ointments. The dosage forms containing the hormones referred to either separately or in combination can be used, for example in treating or preventing postmenopausal conditions such as vasomotor symptoms and osteoporosis.

The word progesterone as used herein, means pregn-4-ene-3,20-dione, and comprises both progesterone obtained from natural sources and synthetic progesterone

The word 17β-oestradiol as used herein means estral-1,3,5(10)-triene-3 17β-diol and includes both 17β-oestradiol obtained from a natural source and that obtained synthetically

According to the present invention it was surprisingly found that 17β-oestradiol and progesterone in combination with dimethyl-β-cyclodextrin can be nasally administered with a biological availability substantially equal to that of intravenous administration

The following study was undertaken to study the biological availability of 17β-oestradiol after nasal administration as compared with intravenous administration Female rabbits (New Zealanders) with an average weight of about 4 kg were used To suppress a stemutatory reflex during nasal administration the rabbits were lightly sedated with 0.2 ml Hypnorm® (i v) The nasal administration (50 µl unilaterally, 1 cm from the nostril) was effected by means of a small flexible polythene hose fixed to a syringe I v administration (100 µl) was in the aural vene Venous blood samples were taken from the aural vena at regular intervals to 2 hours after administration The two nasal formulations, the I v formulation and the control vehicle were tested in 5 rabbits The composition of the nasal formulations was as follows a 0 2% 17β-oestradiol suspension in Sol benzalkonn et hypromellosi FNA and a 0 2% 17β-oestradiol solution with 2% dimethyl β-cyclodextrin in Sol benzalkonii et hypromellosi FNA. The I v formulation was a 0 1% 17β oestradiol solution with 1% dimethyl β-cyclodextrin in physiological saline. The control vehicle (placebo) was Sol benzalkonii et hypromellosi FNA The 17β-oestradiol serel levels were analyzed by an RIA method (Pharmacia) The results are summarized in Table 1 and Figs. 2 and 3

$$\text{Calculation \% AUC} \frac{AUC_{Fi,Kj}}{AUC_{Fiv,Kj}} \times 100\%$$

$$\text{Calculation \% F} \frac{AUC_{Fi,Kj} - AUC_{Fc,Kj}}{AUC_{Fiv,Kj} - AUC_{Fc,Kj}} \times 100\%$$

Fi = formul 1-4
Fiv= intravenous
Fc = placebo
Kj = rabbit 1-5

This study shows that, after nasal administration 17β-oestradiol is rapidly and substantially completely taken up in the systemic circulation without intestinal or first-pass metabolism

The following study was done to determine the bioavailability of progesterone after nasal administration relative to intravenous administration Male Wistar rats weighing 175-225 gram were anaesthetized with Hypnorm® (0 1 ml/100 g) intramuscularly In order to facilitate nasal administration and to prevent perorel absorption the trachea was canulated and the oesophagus was tied to this canula. Animals were kept lying on their back on thermostated rugs (37 C) during the experiment. Nasal formulations were instilled

unilaterally through the nares using PVC-tubing affixed to a microliter syringe The composition of the nasal formulations was as follows. a 1% progesterone suspension in Sol benzalkonil FNA and 1% progesterone solution with 8.5% dimethyl-β-cyclodextrin in Sol benzalkonil FNA. The intravenous formulation via a femoral vein (20 µl corresponding to 200 µg progesterone) had the same composition as the nasal progesterone/dimethyl-β-cyclodextrin solution The control (placebo) was Sol Benzalkonil FNA. Blood samples were taken from a canulated femoral artery at regular time intervals. Progesterone serum levels were measured using a Coat a count® radioimmunoassay kit form DPC (Laboratorium Service The Netherlands) in this rat model nasal administration of the described progesterone/dimethyl-β-cyclodextrin solution (20 µl corresponding to 200 µg progesterone) showed an absolute bioavailability of 58.5% ± 15 7% (n = 5) relative to the intravenous injection whereas the progesterone suspension (20 µl corresponding to 200 progesterone) showed an absolute bioavailability of only 18.5% ± 13 4% (n = 4) Nasal administration of the progesterone/dimethyl-β-cyclodextrin solution gives a significantly higher progesterone absorption than the progesterone suspension ($p<0.05$).

A nasal formulation of 0.2% 17β-oestradiol in solution with 2% dimethyl-β-cyclodestrin was given to women (n = 6) with estrogen deficiency due to bilateral ovariectomy The formulation was administered as a nasal spray in a daily dose of 0 68 mg 17β-oestradiol divided in 2 nasal gifts. Serum 17β-oestradiol levels 10 min after nasal administration of 0.34 mg 17β-oestradiol with this formulation were in the order of 3 nmol/l This demonstrates a rapid and good absorption of 17β-oestradiol from the described formulation Clinical results were also encouraging The patients decided to continue with the nasal formulation instead of oral estrogen substitution

The composition for nasal administration according to the present invention may be of solid, semi-solid or liquid form Preferably it is an aqueous solution In the case of a liquid form, the concentration of 17β-oestradiol preferably ranges between 0.01% and 5% w/v and most preferably between 0 1% and 0 5% w/v The concentration of progesterone preferably ranges from 0.05% to 5% w/v and most preferably from 0 1% to 1% w/v The concentration of dimethyl-β cyclodextrin preferably ranges from 0 1% to 20% w/v and most preferably from 1% to 10% w/v

The molar ratio of sex hormone to dimethyl β-cyclodextrin preferably ranges from 1:8 to 4:1 and most preferably from 1.2 to 2:1

The pH of the composition can be adjusted by adding an acid base or buffer solution during preparation The pH preferably ranges from 6 to 8.

Preservatives such as benzalkonium chloride can be added to the composition Swelling agents such as cellulose derivatives can be incorporated in the composition to form nasal gels

The solution can be autoclaved or sterilized by means of 0 2 µm membrane filtration

The nasal compositions according to the invention have the following advantages.

1 The natural female sex hormones are rapidly and virtually completely absorbed into the systemic circulation through the nasal mucosa, without intestinal metabolism or liver first-pass effect.

2 The administration of the compositions is highly patient-friendly which is especially important in long-term therapy

3 Dimethyl-β-cyclodextrin is tasteless, odourless, low-toxic and little irritating to the nasal mucous membrane in the concentrations used in the composition and accordingly is safe in long-term use

4. The composition has no significant effect on ciliary movement in vitro which is important, because an inhibition of ciliary movement affects the nasal defence mechanism

The compositions according to the present invention can be prepared by dissolving 17β-oestradiol and/or progesterone together with dimethyl-β-cyclodextrin in 96% alcohol followed by evaporation at 40°C under an N_2 stream The dry residue can be dissolved in an aqueous medium such as Sol Benzalkonil FNA, whereafter for example sodium chloride can be added to achieve isotony

Examples of typical compositions for the nasal administration of female sex hormones according to the present invention

1 100 mg 17β-oestradiol was combined with 0.86g dimethyl β-cyclodextrin and 0 45 g sodium chloride The total volume was made up to 50 ml with Solutio benzalkonil FNA (containing 0 01% benzalkonium chloride and 0 1% sodium edetate)

2 250 mg progesterone was combined with 2.12 g dimethyl-β-cyclodextrin and 0.45 g sodium chloride The total volume was made up to 50 ml with Solutio benzalkonil FNA (containing 0 01% benzalkonium chloride and 0 1% sodium edetate)

3. 100 mg 17β-oestradiol and 250 mg progesterone were combined with 3.10 g dimethyl-β-cyclodextrin and 0.45 g sodium chloride The total volume was made up to 50 ml with Solutio benzalkonil FNA (containing 0.01% benzalkonium chloride and 0 1% sodium edetate)

4 100 mg 17β-oestradiol was combined with 0 98 g dimethyl-β-cyclodextrin and 0.45 g sodium

269

chloride The total volume was made up to 50 ml with Solutio benzalkonii et hypromellosi FNA (containing 0.01% benzalkonium chloride and 0 1% sodium edetate and 1% methylhydroxypropyl cellulose 4000 mPa.s)

A suitable dose of the above compositions can be 0 05 ml to 0.2 ml for a single dose and 0.05 ml to 0.8 ml per 24 hours

The compositions according to the invention are not limited to the above examples. The scope of the invention is only determined by the claims

BIOLOGICAL AVAILABILITY (F) in %							
	K_1	K_2	K_3	K_4	K_5	average	B.d
O	0	0	0	0	0	0	
+	100	100	100	100	100	100	
●	146	88	115	33	91	94,6	41,6
▲	47	17	16	9	37	25,2	16

O control (placebo), nasal ● 17β-oestradiol, nasal as a solution with dimethyl-β-cyclodextrin (2%) ▲ 17β-oestradiol nasal as a suspension + 17b-oestradiol intravenous as a solution with dimethyl-β-cyclodextrin (1%).

Description of the drawings

Fig 1 shows the effect of 17β-oestradiol compositions on the nasal ciliary frequency in vitro ▲ 17β-oestradiol (0.01%) in polysorbate 80 (2%) according to US patent 4,383 993, O 17β-oestradiol (0 1%) in dimethyl-β-cyclodextrin (1%) ● Locke Ringer (control) ciliary tissue washed in Locke Ringer

Fig 2 shows the average serum concentration-time curves of 17β-oestradiol in rabbits (n=5) after nasal and I v administration. O control (placebo) nasal ● 100 µg 17β-oestradiol nasal as a solution with dimethyl-β-cyclodextrin (2%) ▲ 100 µg 17β-oestradiol nasal, as a suspension, + 100 µg 17β-oestradiol intravenous, as a solution with dimethyl-β-cyclodextrin (1%)

Fig 3 shows the surfaces (AUCs) under the serum concentration-time curves after nasal and i v administration of 17β-oestradiol Left axis. absolute (ng.min/ml) Right axis: relative to I v (=100%) O control (placebo) nasal ● 17β-oestradiol nasal as a solution with dimethyl-β-cyclodextrin (2%), ▲ 17β-oestradiol nasal as a suspension + 17β-oestradiol intravenous as a solution with dimethyl-β-cyclodextrin (1%).

Claims

1 A pharmaceutical composition having a formulation and form suitable for nasal administration and containing a sex hormone selected from 17β-oestradiol, progesterone and combinations thereof characterized in that it also contains dimethyl-β-cyclodextrin

2. A pharmaceutical composition as claimed in claim 1 characterized by containing 0.25-6 moles of dimethyl-β-cyclodextrin per mole of sex hormone

3 A pharmaceutical composition as claimed in claim 1 characterized by containing 0.5-2 moles of dimethyl-β-cyclodextrin per mole of sex hormone

4. A pharmaceutical composition as claimed in any of the preceding claims characterized by further containing a preservative, such as benzalkonium chloride, an isotonicity agent, such as sodium chloride a complexing agent, such as sodium edetate and/or a swelling agent such as methylhydroxypropyl cellulose

5. A pharmaceutical composition as claimed in any of the preceding claims characterized in that it has the form of an aqueous solution containing 0 01-5% (w/v), preferably 0 1-0.5% (w/v) 17β-oestradiol and/or 0.05-5% (w/v) preferably 0 1 1% (w/v) progesterone in combination with 0 1 20% (w/v) preferably 1-10% (w/v) dimethyl-β-cyclodextrin

FIG 1

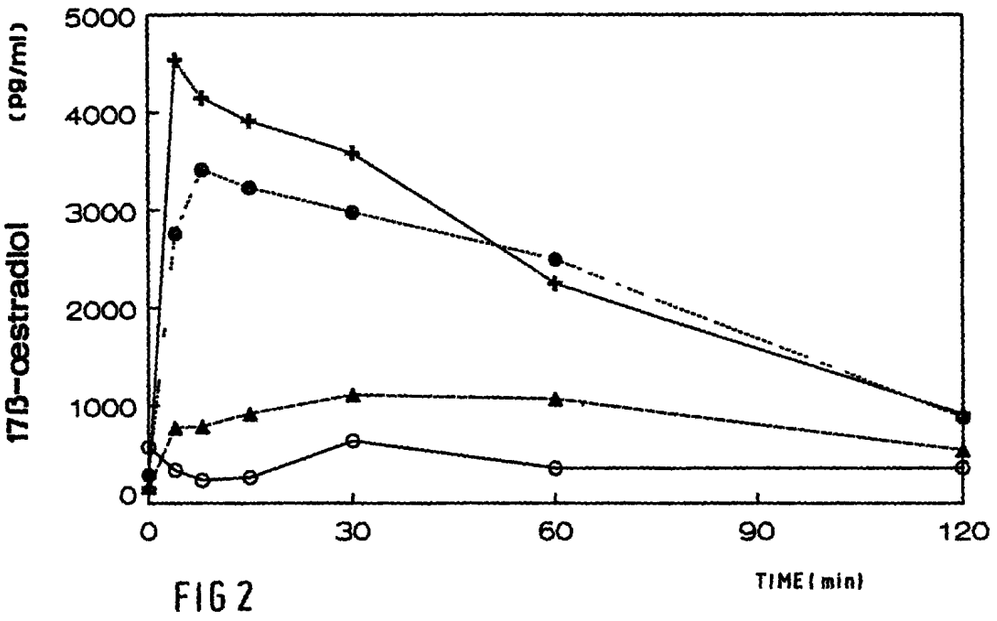


FIG 2

EP 0 348 081 A1

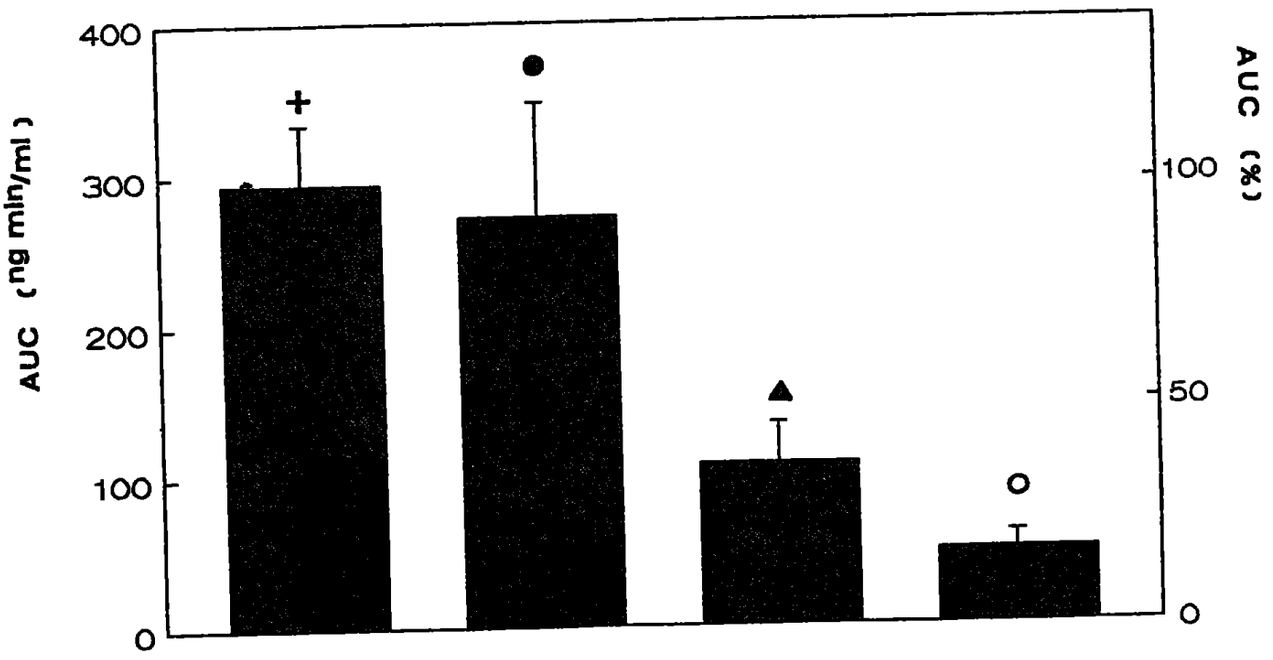


FIG 3

EP 0 349 091 A1

ANEXO 2

United States Patent [19]

Pitha

[11] **Patent Number: 4,727,064**

[45] **Date of Patent: Feb 23, 1988**

[54] **PHARMACEUTICAL PREPARATIONS CONTAINING CYCLODEXTRIN DERIVATIVES**

[75] Inventor: **Josef Pitha, Baltimore, Md.**

[73] Assignee: **The United States of America as represented by the Department of Health and Human Services, Washington, D C.**

[21] Appl. No. **738,749**

[22] Filed. **May 29, 1985**

Related U.S. Application Data

[63] Continuation-in-part of Ser No. 603 839, Apr 25, 1984, Pat. No. 4,596,795

[51] Int. Cl.[4] ... A61K 31/70; C08B 37/16

[52] U.S. Cl. ... 514/58; 106/210; 536/103 514/965; 514/971

[58] Field of Search ... 536/103, 106/210; 514/58, 971 965

[56] **References Cited**

U S. PATENT DOCUMENTS

2 827,452	3/1958	Schlenk et al.	514/58
3 420,788	1/1969	Solms	536/103
3,453,257	7/1969	Parmerter et al.	536/103
3,453,259	7/1969	Parmerter et al.	536/103
3,459,731	8/1969	Gramera et al	536/103
4,380,626	4/1983	Szejtli et al	536/103
4,383,992	5/1983	Lipari	514/174
4,524,068	6/1985	Szejtli et al.	514/58
4,555,504	11/1985	Jones	536/103
4,596,795	6/1986	Pitha	514/58

FOREIGN PATENT DOCUMENTS

57 130914	8/1982	Japan	
1453801	10/1976	United Kingdom	536/103
2104907	3/1983	United Kingdom	536/103

OTHER PUBLICATIONS

Fenyvesi et al Water-Soluble Cyclodextrin Polymers-

ing I. Int Symposium on Cyclodextrins, p. 345 (Budapest, 1981)

Maeno, Liquid Crystal Element and Its Use, Chem Abstracts, 87 144000u (1977)

Kyowa Hakko Kogyo Co., Inclusion Compound of Medroxyprogesterone and B-Cyclodextrin, Chem Abstracts, 98 8163z (1982).

Uekama et al., Inclusion Complexation of Steroid Hormones with Cyclodextrins Chem. Abstracts. 96 149046j (1982).

J Szejth, 'Cyclodextrins and Their Inclusion Complexes' Akademiai Kiado Budapest, 1982, pp. 204–232

J Pitha, L. Szente and J Szejth Molecular Encapsulation of Drugs by Cyclodextrins and Congeners in *Controlled Drug Deliver* S D Bruck, ed., CRC Press, 1983, pp. 125–148.

M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer–Verlag, Berlin, 1978 pp 29–32

E. Fenyvesi et al, *Chem. P' m. Bull.* 32.665 1984

E. Fenyvesi et al, *Che' n. Bull.* 32-670, 1984.

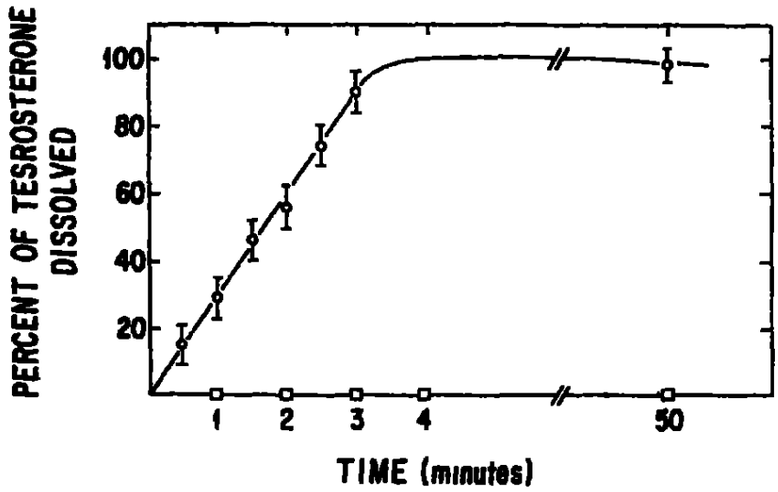
Primary Examiner—Ronald W Griffin

Attorney, Agent, or Firm—John S. Roberts, Jr

[57] **ABSTRACT**

The invention comprises pharmaceutical preparations consisting generally of a drug with a substantially low water solubility and an amorphous, water-soluble cyclodextrin-based mixtures. In these preparations a stable amorphous state can be achieved. This improves the dissolution properties of the drug and hence its absorption by the body The required cyclodextrin-based mixtures were prepared from α-, β-, or γ-cyclodextrin which were rendered amorphous through non-selective alkylation. The alkylation agents suitable for that purposes are exemplified by propylene oxide glycidol iodoacetamide, chloroacetate, or 2-diethylammoethyl chloride; their reactions with cyclodextrins were performed in a manner to yield mixtures containing many components, a circumstance which effectively prevents crystallization processes within the above pharmaceutical preparation.

28 Claims, 2 Drawing Figures



28

FIG. 1A

FIG. 1B

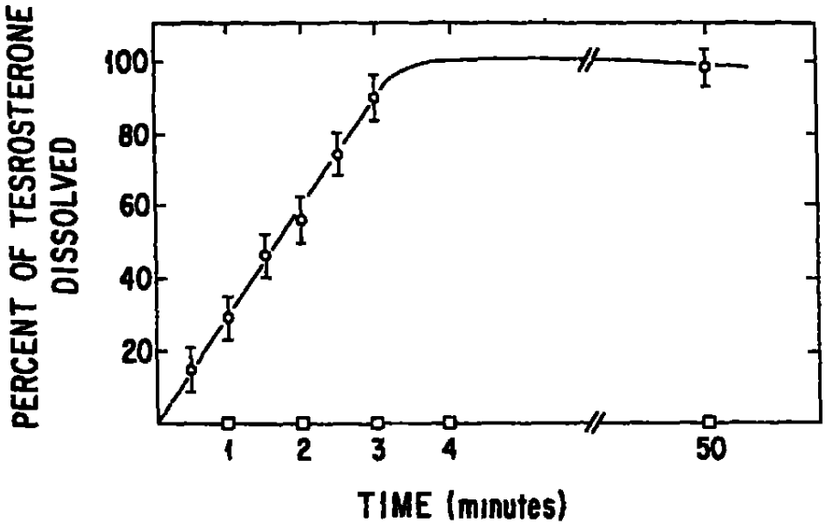

PERCENT OF TESROSTERONE DISSOLVED
100
80
60
40
20
1
2
3
4
50
TIME (minutes)

FIG. 2

PHARMACEUTICAL PREPARATIONS CONTAINING CYCLODEXTRIN DERIVATIVES

This application is a continuation-in-part of pending Ser No 603,839 filed April 25, 1984, now U S. Pat. No 4,596,795

This invention comprises pharmaceutical preparations consisting generally of a drug with a substantially low water solubility and an amorphous, water-soluble cyclodextrin-based mixtures. In these preparations a stable amorphous state can be achieved and that improves the dissolution properties of the drug and hence its absorption by the body The required cyclodextrin based mixtures were prepared from α, β-, or γ cyclodextrin which were rendered amorphous through non-selective alkylation. The alkylation agents suitable for that purpose are exemplified by propylene oxide, glycidol iodoacetamide, chloroacetate, or 2-diethylaminoethylchloride; their reactions with cyclodextrins were performed in a manner to yield mixtures containing many components, a circumstance which effectively prevents crystallization processes within the above pharmaceutical preparation.

This method of improvement of pharmaceutical preparation comprises the addition of crystalline drugs with substantialy low solubility to compounds which have the following characteristics. (a) are water-soluble cyclodextrins, (b) have the ability to form inclusion complexes with the drugs in question, (c) are intrinsically amorphous and substantially decrease the tendency of the drug to crystallize. The above addition results in an improved solubility of the drug composition in question and more efficient absorption of the drug by the body

The parent cyclodextrins are converted by alkylation with, e.g., epoxides or organic halides into mixtures of substituted cyclodextrins. These mixtures of cyclodextrin derivatives, after separation from contaminating products of self-condensation of epoxides or halides, are used as such, i.e., without separation into the individual cyclodextrin derivatives. Use of such water-soluble mixtures of cyclodextrin derivatives in pharmaceutical preparations enables stabilization of the amorphous state and leads to better absorption of drugs by a body

BACKGROUND OF THE INVENTION

This invention is directed to the method of conversion of drug compositions which themselves are crystalline and of low water-solubility into intrinsically amorphous complexes which have improved pharmaceutical properties. This conversion is achieved by inclusion of the above drug compositions into water-soluble, multi component mixtures of cyclodextrin derivatives. More particularly, the invention is related to copending application Ser No. 603 839 which concerned cyclodextrins and sex hormones.

MATERIAL INFORMATION DISCLOSURE

Cyclodextrins are cyclic oligomers of glucose; these compounds form inclusion complexes with any drug whose molecule can fit into the lipophile-seeking cavities of the cyclodextrin molecule. Cyclodextrins are crystalline and so are their complexes with drugs, and these complexes have somewhat improved water solubilities compared to the drugs themselves. The latter improvements are the subject of reviews and of numerous patents (J Szejtli, 'Cyclodextrins and Their Inclusion Complexes," Akademiai Kiado, Budapest, 1982, pp. 204–232 J Pitha, L. Szente, and J Szejtli, "Molecular Encapsulation of Drugs by Cyclodextrins and Congeners," *In Controlled Drug Deliver* S. D Bruck, ed. CRC Press Inc., Boca Raton, FL, 1983, pp. 125–148)

Chemical modifications of cyclodextrins have been widely performed, with a few exceptions nevertheless the aim was preparation of another individual crystalline compound (M L. Bender and M. Komiyama, "Cyclodextrin Chemistry Springer-Verlag, Berlin, 1978, pp. 29–32). Condensation reactions of cyclodextrins with various epoxides or organic halides yielding compounds which are principally similar to those presently used have been known (1) electroneutral, soluble cyclodextrin derivatives were described by Parmerter et al, U S Pat. No. 3,453,259, July 1969- Gramera et al U S. Pat No 3 459,731 Aug. 1969- (2) cationic, soluble cyclodextrin derivatives were described by Parmerter et al, U S. Pat. No. 3,453,257 July 1969 and (3) insoluble, crosslinked cyclodextrins were described by Solms, U.S. Pat. No. 3,420,788, Jan 1969 The above mixtures have not been used to obtain amorphous and water-soluble pharmaceutical preparations. Water-insoluble (crosslinked) polymers of β-cyclodextrins were previously tested as tableting additives (E. Fenyvesi, et al, *Chem. Pharm. Bull.* 32:665 1984; E. Fenyvesi, et al, *Chem. Pharm. Bull.* 32:670, 1984). Furthermore, crosslinked α-cyclodextrin was previously used in the preparation of sustained-release formulation of penicillin (Japanese Kokai Tokkyo Koho Patent No. 82-130914).

SUMMARY OF THE INVENTION

Dissolution properties of drugs may be improved by their conversion to an amorphous state or by complexation with cyclodextrins. The present invention combines these two improvements described is the preparation and use of mixtures of cyclodextrin derivatives which are intrinsically amorphous, water-soluble, and capable of forming inclusion complexes with drugs These cyclodextrin mixtures effectively solubilize lipophilic drugs into aqueous media The solutions of these cyclodextrin mixtures are non-irritating topically and in difference to the solutions of cyclodextrins themselves do not support microbial growth. Thus, these compounds are well suited as additives/solubilizers in topical preparations. The solutions of the above cyclodextrin mixtures furthermore have very low toxicity, both systemic and local, when applied parenterally Thus, they are well suited as additives for parenteral preparations. Furthermore, when solutions of these cyclodextrin mixtures are saturated with drugs and then evaporated or freeze-dried, solids are obtained which dissolve easily and completely and are stable for an extended period of time. These solids can be either directly tableted to yield products well suited for oral or buccal administration or processed into suppositories

The cyclodextrin additives may be utilized in weight percent of usually about 40–60% of the drug solution composition and may be utilized from about 5–95% of the drug solution composition. Actual working models of the cyclodextrin derivatives are set out in Table 1 which shows some of the preferred as 40–50% of the drug solution composition.

TABLE 1

Solubilization of Various Drugs

Drug	Solubility in water (mg/ml)	Solubility in solubilizer solution: Solubilizer[1] (conc. in water)	Solubility (mg/ml)
acetaminophen	11	hydroxypropyl-β-cyclodextrin (50%)	67.0
apomorphine	20	hydroxypropyl-β-cyclodextrin (50%)	116.0
butylated hydroxytoluene	insoluble	hydroxypropyl-α-cyclodextrin (40%)	0.3
butylated hydroxytoluene	insoluble	hydroxypropyl-β-cyclodextrin (40%)	3.0
butylated hydroxytoluene	insoluble	hydroxypropyl-γ-cyclodextrin (40%)	0.2
chlorthalidone	0.12	hydroxypropyl-β-cyclodextrin (50%)	10.5
cholecalciferol	<0.23	hydroxypropyl-β-cyclodextrin (50%)	10.0
dexamethasone	0.1	hydroxypropyl-β-cyclodextrin (50%)	24.0
dienestrol	<0.15	hydroxypropyl-β-cyclodextrin (50%)	1.3
digoxin	0.07[2]	hydroxypropyl-β-cyclodextrin (50%)	45.0
diphenylhydantoin	0.03[2]	hydroxypropyl-β-cyclodextrin (50%)	1 7
estradiol	<1 6	hydroxypropyl-β-cyclodextrin (40%)	28.0
estradiol	<1.6	carboxamidomethyl-β-cyclodextrin (50%)	25.0
estradiol	<1 6	carboxymethyl-β-cyclodextrin (50%)	10.0
estriol	<1 3	hydroxypropyl-β-cyclodextrin (50%)	41.0
ethinylestradiol-3-methyl ether	<1 5	hydroxypropyl-β-cyclodextrin (50%)	27.0
ethisterone	<0.2	hydroxypropyl-β-cyclodextrin (50%)	0.5
furosemide	0.07[2]	hydroxypropyl-β-cyclodextrin (50%)	1 7
hydroflumethiazide	0.3	hydroxypropyl-β-cyclodextrin (50%)	9 3
indomethacin	0.02[2]	hydroxypropyl-β-cyclodextrin (50%)	4.2
isoniazid phosphate	30	hydroxypropyl-β-cyclodextrin (50%)	95.0
17-methyltestosterone	<0.17	hydroxypropyl-β-cyclodextrin (50%)	39.0
nitroglycerin	1 25	hydroxypropyl-α-cyclodextrin (40%)	8.7
nitroglycerin	1.25	hydroxypropyl-β-cyclodextrin[1] (40%)	10.4
nitroglycerin	1 25	hydroxypropyl-γ-cyclodextrin (40%)	9.8
norethindrone	2.5	hydroxypropyl-β-cyclodextrin (50%)	6.8
oviban	13	hydroxypropyl-β-cyclodextrin (50%)	80.0
oxprenolol	127	hydroxypropyl-β-cyclodextrin (50%)	238.0
progesterone	0.015[3]	hydroxypropyl-β-cyclodextrin (40%)	34.0
retinal	<0.07	hydroxypropyl-β-cyclodextrin (40%)	2.6
retinoic acid, all trans	<0.07	hydroxypropyl-β-cyclodextrin (40%)	0.8
retinoic acid, choline salt of all trans		hydroxypropyl-β-cyclodextrin (40%)	18.8
retinoic acid, ethanolamine salt of all trans		hydroxypropyl-β-cyclodextrin (40%) and ethanolamine (1%)	28.4
retinoic acid, sodium salt of all trans		hydroxypropyl-β-cyclodextrin (40%)	1.6
retinol	<0.10	hydroxypropyl-β-cyclodextrin (40%)	5.5
spironolactone	0.03[2]	hydroxypropyl-β-cyclodextrin (40%)	42.0
sulpiride	<0.21	hydroxypropyl-β-cyclodextrin (50%)	10.0
testosterone	0.026[3]	hydroxypropyl-β-cyclodextrin (40%)	38.0
testosterone	0.026[3]	carboxamidomethyl-β-cyclodextrin (50%)	24.0
testosterone	0.026[3]	carboxymethyl-β-cyclodextrin (50%)	30.0
theophylline	8.3	hydroxypropyl-β-cyclodextrin (50%)	11.0
acyclovir	insoluble	hydroxypropyl-β-cyclodextrin (50%)	2.5
clonidine hydrochloride		hydroxypropyl-β-cyclodextrin (50%)	83.0
testosterone	0.026[3]	dihydroxypropyl-β-cyclodextrin (40%)	25.0

[1]Degree of substitution of solubilizers used: hydroxypropyl-β-cyclodextrin and homologs, 6-7; diethylaminoethyl-β-cyclodextrin, 3.5; carboxymethyl-β-cyclodextrin, 4; carboxamidomethyl-β-cyclodextrin, 3.
[2]Data from K. Uekama, Pharmacology International, 61–65 (1983).
[3]Data from J. Brotherton, Sex Hormone Pharmacology Academic Press, New York (1976), p. 36.

DESCRIPTION OF THE FIGURES

FIGS. 1(A and B) shows the activity of derivatives of cyclodextrins on the forearm with a band-aid patch showing lack of topical irritation. On the left is a photograph of the forearm with band-aid patches wetted with isotonic solutions in water of AL16 (carboxamidomethyl-β-cyclodextrin), AL11 (carboxymethyl-β-cyclodextrin), M146 (hydroxypropyl-β-cyclodextrin), and SzA59/2 (diethylaminoethyl β-cyclodextrin). On the right is the forearm after band-aids were removed after 18 hours of exposure

FIG 2 shows the dissolution of testosterone from a tablet made from testosterone/hydroxypropyl-β cyclodextrin complex (—●—) or from a tablet made from testosterone-microcrystalline cellulose (—□—).

PREPARATION OF CYCLODEXTRIN MIXTURES

Suitability of cyclodextrins as pharmaceutical additives/solubilizers can be considerably improved if these are converted to mixtures of derivatives which are highly soluble and retain the capacity to form inclusion complexes with drugs. Such mixtures may be prepared by alkylation reactions which lack chemoselectivity and stereoselectivity and introduce hydrophilic substituents. In the examples are shown such alkylations.

Tables 1–3 below show solubility or dissolution of various compounds under option of cyclodextrin derivatives.

Systemic and Local Toxicity of Cyclodextrin Derivatives

The lack of topical irritation of the above cyclodextrin derivatives was tested by wetting a band-aid with their isotonic solutions and by application of that band aid to the forearm for about 18 hours. The representative results can be seen in FIG 1.

The lack of parenteral toxicity of the above cyclodextrin derivatives was tested by intraperitoneal injection into mice; the following results were obtained.

(a) Two different preparations of hydroxypropyl β-cyclodextrin were tested The first preparation (degree

32

of substitution 6), m doses of 10 g/kg, was without lethal effects (4 animals). The second preparation (degree of substitution 8), at 6.3 g/kg, resulted m 2 deaths (after 4 days) and 1 surviving animal, at 3 2 g/kg all 4 animals survived.

(b) Diethylammoethyl-β-cyclodextrin at 4.7 g/kg—1 death (after 4 hrs) and 2 surviving animals, at 2.4 g/kg all 3 animals survived

(c) Carboxymethyl-β-cyclodextrin at 3.8 g/kg—no deaths, 3 surviving animals.

(d) Carboxamidomethyl-β-cyclodextrin at 6 9 g/kg—2 deaths, 1 surviving animal, at 3 5 g/kg all 4 animals survived.

The lack of oral toxicity of hydroxypropyl-β-cyclodextrin in mice was documented in patent application Ser No 603,839 filed April 25, 1984, by Pitha.

Dissolution Effects of Cyclodextrin Derivatives

Effectiveness of cyclodextrin derivatives in assisting dissolution of drugs is satisfactory if (a) a substantial part of the drug molecule can be fitted into the hydrophobic cavity of the cyclodextrin molecule, and (b) the same part of the drug molecule is hydrophobic Since thee principles were established previously (see Material Information Disclosure section), the present efforts have been directed to dividing drugs into categories according to their steric bulk and documenting the usefulness of the present method for a few representatives of every category

Improved Absorption of Drugs from the Preparations Described Above

The principal improvement of absorption of a drug by a body accompanying the conversion of a drug from a crystalline state into an amorphous state is generally recognized.

TABLE 2

Solubilities of Steroids (mg/ml) in 50% Aqueous Solutions of Hydroxypropyl-β-cyclodextrin Samples With Different Degrees of Substitution (d.s.)

	d.s. 4.7	d.s. 5.7	d.s. 7.0	d.s. 14
Estradiol	30	39	26	18
Progesterone	30	44	35	23
Testosterone	56	62	40	23

TABLE 3

Solubilities of Steroids (mg/ml) in 50% Aqueous Solutions of Substituted Cyclodextrins

	Carboxamido-β-cyclodextrin	Diethyl-aminoethyl-β-cyclodextrin	Carboxymethyl β-cyclodextrin
Estradiol	28	6	14
Progesterone	38	18	14
Testosterone	24	9	24

EXAMPLE 1

Preparation of hydroxypropyl-β-cyclodextrin

Sodium hydroxide (105 7 g, 2.64 moles) was dissolved in 750 ml of distilled water and to this solution was added β-cyclodextrin (346.4 g of commercial preparation containing 13.4% of water; i.e., 300 g of anhydrous compound corresponding to 0.264 moles). Suspension was stirred at 60° C until all γ-cyclodextrin was dissolved. Thereafter solution was cooled to room temperature and reflux condenser, filled with dry ice-acetone mixture, was attached. Then propylene oxide (redistilled, 185 ml, i.e. 153.5 g corresponding to 2 64 moles) was added, in fast manner but with necessary cautions, to the stirred solution. After addition of propylene oxide, the solution was stirred overnight at room temperature Thereafter the alkaline solution was neutralized by concentrated hydrochloric acid and evaporated in vacuo to the consistency of thick syrup The syrup was dissolved in ethanol (1 5 L) and left standing to precipitate sodium chloride which was subsequently filtered off The ethanolic solution was evaporated in vacuo and the rest was dissolved in water The solution was enclosed in dialysis tubing and dialyzed for 2–3 hours against water The dialyzed solution was then clarified by centrifugation and freeze-dried. The resulting white powder (282 g) contained 5.2% water (measured by weight loss), 0.65% of inorganic residue (by ashing), and 0.87% of chloride (elementary analysis) Upon prolonged standing water content increased to 7–8% but appearance of the compound (white powder) was not changed By prolonged trituration of this powder with acetone, the products of self-condensation of propylene oxide, which contaminate the desired hydroxypropyl- β-cyclodextrin, can be removed The degree of substitution of the cyclodextrin moiety achieved in the above reaction was about 7 by variation of the amounts of reagents the substitution degrees were manipulated. Further or alternative purification of hydroxypropyl-β-cyclodextrin consisted in the preparation of clear solutions of the raw material in water or ethanol and addition of large volumes of a nonpolar solvent (e.g., acetone) which precipitated the desired solid hydroxypropyl β-cyclodextrin, whereas highly substituted cyclodextrins and products of self-condensation of propylene oxide remained in the solution from which they can be recovered by evaporation, leaving oily liquid In a representative experiment, precipitation yielded 81% of the desired solid hydroxypropyl β cyclodextrin (degree of substitution 7 by nuclear magnetic resonance and 8.02 by mass spectroscopy) and 18% of oily liquid containing also hydroxypropyl-β-cyclodextrin (degree of substitution 16 by nuclear magnetic resonance and 11 3 by mass spectrometry). When condensation of propylene oxide with γ-cyclodextrin was performed with a high ratio of the former to the latter, products were precipitable by cyclohexane but not by acetone and were semi-solid liquids (degree of substitution 14 by nuclear magnetic resonance)

EXAMPLE 2

Related preparations. O-alkylation of cyclodextrins with epoxides

Basically the same conditions as above were used also for condensation of α- or γ-cyclodextrins with propylene oxide; degrees of substitution achieved (by nuclear magnetic resonance) were close to those described above.

EXAMPLE 3

Related preparations O-alkylation of cyclodextrins with organic halides.

The procedures analogous to those above were also used for condensation of β-cyclodextrin with the following hydrophilic alkylating agents (a) diethylammoethylchloride-hydrochloride yielding diethylammoethyl- β-cyclodextrin, the degree of substitution in the product was about 3 5 (calculated from nitrogen content), (b) chloroacetic acid yielding carboxymethyl-β-cyclodextrin; the degree of substitution in the product was about 4 (calculated from sodium content) (c) iodoacetamide yielding carboxamidomethyl β

cyclodextrin, the degree of substitution in the product was about 3 (calculated from nitrogen content)

EXAMPLE 4

The solutions of solubilizer in water were saturated by stirring with excess of drug at room temperature for about 24 hours. The resulting suspensions were clarified either by filtration through a sintered glass filter or by centrifugation. Concentration of hormones in clarified solutions was measured spectrophotometrically Representative results are given in Table I, ante. In these experiments drugs were solubilized with cyclodextrin derivatives with constant degrees of substitution and which are given in the footnote to Table 1 In Table 2 are the results on the solubilization of sex hormones with hydroxypropyl-β-cyclodextrin samples of different degrees of substitution. It is apparent that samples of hydroxypropyl-β-cyclodextrin with medium degrees of substitution (5–7) are more effective solubilizers than those of higher degrees of substitution. It should be noted that while the former derivatives are solid and suitable for tableting purposes, the latter are semisolids or liquids. The results on the solubilization of sex hormones by cyclodextrin derivatives containing carboxamido or diethylaminoethyl or carboxymethyl substituents are summarized in Table 3 It is apparent that the carboxamido methyl derivative is a relatively potent solubilizer; nevertheless, comparison with the results in Table 2 show that the potency of hydroxypropyl containing derivatives has not been surpassed

EXAMPLE 5

The above solutions of drugs in cyclodextrin derivatives were stable when kept at room temperature for several months and no microbial growth on the solutions was observed When freeze-dried, the solutions which were prepared using solid derivatives of cyclodextrins again yielded non-hygroscopic, stable powders which were found suitable for tableting by direct compression. The tablets prepared in such a manner again dissolved completely in water as documented by Example 6.

EXAMPLE 6

Using a die of 0 9 cm diameter and a force of 3000 pounds weight exerted in a single-station hand-operated unit, the tablets were made directly from the freeze-dried solutions of drugs prepared as described above. In one such experment tablets weighing about 130 mg and containing 10 mg of testosterone in complexed form were made. These tablets were stored for up to 16 months at room temperature in a well-closed glass container without any deterioration and were thereafter tested for dissolution properties. In the dissolution experiments a tablet was submerged in a basket made out of stainless steel mesh in a bath of water, at 20 C and sink conditions. As noted in FIG 2, the complexed testosterone tablets dissolved completely with 4 minutes, whereas similar tablets prepared from testosterone and microcrystalline cellulose did not release practically any testosterone into the aqueous phase.

Definitions

The term "mixture of substituted amorphous cyclodextrins" is directed towards where there is more than one cyclodextrin and where there is more than one degree of substitution which will vary from a preferred range of about 3 to about 7

I claim

1 A method of producing a stabilizing amorphous complex of a drug and a mixture of cyclodextrins which comprises the steps of

1 Dissolving an intrinsically amorphous mixture of cyclodextrin deratives which are water soluble and capable of forming inclusion complexes with drugs in water; and

2 Solubilzing lipophilic drugs into the aqueous media to form a solution and form a solublized drug/cyclodextrin complex.

2. A method of claim 1 wherein the solubilized complex is subjected to freeze-dried or evaporation to provide a solid cyclodextrin/drug complex in powder form

3. A method of claim 1 wherein cyclodextrins used are substituted by at least one of the following substituents. hydroalkyl, carboxamide, diethylaminoethyl carboxymethyl and carboxyamidomethyl.

4. A method of claim 1 wherein the drug is a hormone

5. A method of claim 4 wherein the drug is testosterone, an estrogen, or a progesterone.

6. A composition of matter which contains an amorphous complex of cylodextrin and a drug.

7 A composition of matter of claim 6 wherein the drug is a hormone.

8. A composition of claim 6 wherein the drug is at least one of testosterone, progesterone, and an estrogenic drug.

9. A composition of matter of claim 6 in solid form

10. A composition of matter of claim 9 which is a tablet.

11 A composition of matter of claim 6 which is in a liquid or semi liquid form.

12 A composition of matter for use in the process of claim 1 containing a mixture of substituted cyclodextrin derivatives in amorphous form

13. A composition of matter of claim 6 wherein the drug is a vitamin.

14. A composition of matter of claim 6 wherein the drug is a salt of retinoic acid

15. A composition of matter of claim 6 wherein the drug is a steroid

16. A composition of matter of claim 6 wherein the drug is a spironolactone.

17 A composition of matter of claim 6 wherein the drug is an antiviral agent.

18 A composition of matter of claim 17 wherein the antiviral agent is acylovir

19 A composition of matter of claim 6 wherein the drug is a diuretic.

20. A composition of matter of claim 19 wherein the diuretic is chlorthalidone

21 A composition of matter of claim 6 wherein the drug is an anticoagulant.

22. A composition of matter of claim 21 wherein the anticoagulant is dicumerol.

23. A composition of matter of claim 6 wherein the drug is an anticonvulsant

24. A composition of matter of claim 23 wherein the drug is diphenylhydantoin.

25 A composition of matter of claim 6 wherein the drug is an antiinflammatory agent.

26. A composition of matter of claim 25 wherein the antiinflammatory agent is ipronaxzd.

27 A composition of matter of claim 16 wherein the drug is oxyprenolol.

28 A composition of matter in solid or semi-solid form comprising at least one of testosterone, progesterone, and estradiol as an inclusion complex with poly β cylodextin and/or hydroxypropyl β-cyclodextrin adapted for adminstration by buccal route

* * * * *

ANEXO 3

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

(11) Publication number 0 579 435 A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number 93305280 5

(51) Int. Cl 5 A61K 47/48

(22) Date of filing 06.07 93

(30) Priority 14.07 92 US 912853

(43) Date of publication of application
19.01 94 Bulletin 94/03

(84) Designated Contracting States
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(71) Applicant Loftsson Thorsteinn
Sorlaskjol 44
IS-101 Reykjavik (IS)

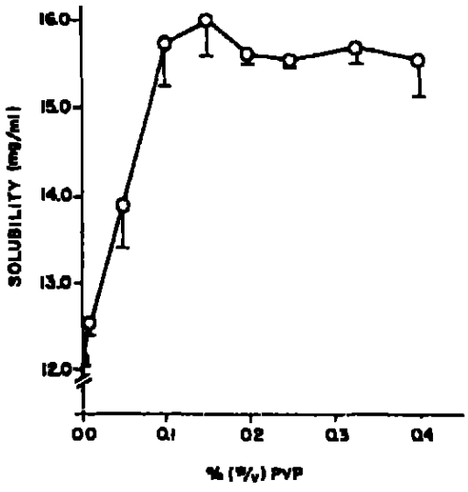
(72) Inventor Loftsson, Thorsteinn
Sorlaskjol 44
IS-101 Reykjavik (IS)

(74) Representative Pendlebury, Anthony et al
PAGE, WHITE & FARRER 54 Doughty Street
London WC1N 2LS (GB)

(54) Cyclodextrin complexation.

(57) The invention provides a method for enhancing the complexation of a cyclodextrin with a lipophilic and/or water-labile drug comprising combining from about 0 1 to about 70% (weight/volume) of a cyclodextrin and from about 0.001 to about 5% (weight/volume) of a pharmaceutically acceptable pharmacologically inactive water-soluble polymer in an aqueous medium the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours before during and/or after the drug is added optionally followed by removal of water Related methods co-complexes of drug/cyclodextrin/polymer pharmaceutical compositions and cyclodextrin/polymer complexing agents are also provided Analogous methods co-complexes and compositions in which the drug is replaced with a food additive cosmetic additive or agrochemical are also described

FIG.1



EP 0 579 435 A1

283

Field of the Invention

The present invention relates to the use of certain polymers in the preparation of cyclodextrin-drug complexes as a means for increasing the solubilizing and stabilizing effects of cyclodextrin derivatives on drugs and complexation therewith Pharmaceutical compositions comprising complexes prepared according to these methods are characterized by fast and efficient drug release The invention further relates to polymer/cyclodextrin complexing agents Still further the invention relates to use of the polymers to increase the solubilizing and stabilizing effects of cyclodextrins on food additives agrochemicals and chemicals used in cosmetics and complexation therewith

Background of the Invention

Formulation of pharmaceutical dosage forms is frequently hampered by the poor aqueous solubility and stability of the drugs, which in turn can severely limit their therapeutic application Also the slow dissolution of solid state drug formulations and the side-effects of some drugs result from their poor aqueous solubility Drug degradation products, formed in the pharmaceutical dosage forms can also result in severe side effects. Increasing drug solubility and stability through appropriate formulation can thus, lead to increased therapeutic efficiency of the drug Various methods have been used to increase the solubility and stability of drugs such as the use of organic solvents, emulsions liposomes and micelles adjustments of pH and the dielectric constant of the solvent system chemical modifications and complexation of the drugs with appropriate complexing agents e g cyclodextrins Similar approaches have been taken to increase the solubility and stability of food additives agrochemicals and cosmetic additives

Cyclodextrins were first isolated by Villiers in 1891 as a digest of *Bacillus amylobacter* on potato starch [see A. Villiers Sur la fermentation de la fécule par l action du ferment butyrique *C R Acad Sci* 112 536-538 (1891)], but the foundations of cyclodextrin chemistry were laid down by Schardinger in the period 1903-1911 [see for example F Schardinger Uber thermophile Bacterien aus verschiedenen Speisen und Milch sowie über einige Umsetzungsproducte derselben in kohlenhydrathaltigen Nährlösungen darunter krystallisierte Polysaccharide (Dextrine) aus Stärke Z *Unters Nahr Genußm* 6 865-880 (1903)] and much of the older literature refers to cyclodextrins as Schardinger's dextrins Until 1970 only small amounts of cyclodextrins could be produced in the laboratory and the high production cost prevented the usage of cyclodextrins in industry In recent years, dramatic improvements in cyclodextrin production and purification have been achieved and the cyclodextrins have become much cheaper This has made industrial application of cyclodextrins possible

Cyclodextrins are cyclic oligosaccharides with hydroxyl groups on the outer surface and a void cavity in the center Their outer surface is hydrophilic, and therefore they are usually soluble in water but the cavity has a lipophilic character The most common cyclodextrins are α-cyclodextrin β-cyclodextrin and γ-cyclodextrin consisting of 6 7 and 8 α 1 4-linked glucose units, respectively The number of these units determines the size of the cavity

Cyclodextrins are capable of forming inclusion complexes with a wide variety of hydrophobic molecules by taking up a whole molecule or some part of it, into the cavity The stability of the complex formed depends on how well the guest molecule fits into the cyclodextrin cavity Common cyclodextrin derivatives are formed by alkylation (e g methyl- and ethyl β-cyclodextrin) or hydroxyalkylation of the hydroxyl groups (e g hydroxypropyl- and hydroxyethyl derivatives of α- β- and γ-cyclodextrin) or by substituting the primary hydroxyl groups with saccharides (e.g glucosyl- and maltosyl-β-cyclodextrin). Hydroxypropyl-β-cyclodextrin and its preparation by propylene oxide addition to β-cyclodextrin and hydroxyethyl-β-cyclodextrin and its preparation by ethylene oxide addition to β-cyclodextrin were described in a patent of Gramera *et al.* (United States Patent No. 3,459 731 issued August 1969) over 20 years ago For a comprehensive review of cyclodextrins see *Cyclodextrins and their Industrial uses*, editor Dominique Duchêne Editions de Santé Paris 1987 For a more recent overview see J Szejtli Cyclodextrins in drug formulations. Part I *Pharm Techn Int.* 3(2) 15-22 (1991), and J Szejtli Cyclodextrins in drug formulations. Part II *Pharm. Techn Int.* 3*(3)* 16-24 (1991)

Numerous reports have been published with respect to the solubilizing effects of cyclodextrins The general procedure described in these reports for preparing aqueous cyclodextrin solutions containing various drugs is as follows An excess amount of the drug is added to an aqueous cyclodextrin solution and the suspension formed is agitated for up to one week at room temperature Then the suspension is filtered or centrifuged to form a clear drug-cyclodextrin complex solution For the preparation of solid formulations of the drug-cyclodextrin complex, the water is removed from the aqueous drug-cyclodextrin complex solution by evaporation in a rotation evaporator in a spray dryer or by lyophilization. Pitha (Josef Pitha Administration of sex hormones in the form of hydrophilic cyclodextrin derivatives United States Patent No. 4,596 795 issued June

34

284

24 1986) describes inclusion complexes of sex hormones, particularly testosterone progesterone and estradiol with specific cyclodextrins preferably hydroxypropyl β-cyclodextrin and poly β-cyclodextrin The complexes enable the sex hormones to be successfully delivered to the systemic circulation via the sublingual or buccal route In another patent (Josef Pitha Pharmaceutical preparations containing cyclodextrin derivatives United States Patent No 4 727 064 issued February 23 1988) Pitha describes formulations of a number of drugs with various cyclodextrin derivatives mainly hydroxypropyl-β-cyclodextrin but also hydroxypropyl-γ-cyclodextrin In a series of patents (N.S Bodor Improvements in redox systems for brain-targeted drug delivery United States Patent No 5,002 935 issued March 26 1991 N S Bodor Pharmaceutical formulations for parenteral use United States Patent No 4 983,586 issued January 8 1991 N S Bodor Redox systems for brain-targeted drug delivery United States Patent No. 5 017 566 issued May 21 1991 and N S. Bodor Pharmaceutical formulations for parenteral use United States Patent No 5 024 998 issued June 18 1991) Bodor describes formulations of a number of drugs with hydroxypropyl hydroxyethyl, glucosyl maltosyl and maltotriosyl derivatives of β- and γ-cyclodextrin Also, Brauns and Müller (U Brauns and B W W Müller Pharmazeutische Präparate von in Wasser schwerlöslichen oder instabilen Arzneistoffen und Verfahren zu ihrer Herstellung European Patent No. 0 149 197 B1 dated March 21 1990) have described formulations of drugs with various β-cyclodextrin derivatives mainly hydroxypropyl β-cyclodextrin The solubilizing and stabilizing effects of hydroxypropyl β-cyclodextrin on drugs have been reviewed by T Loftsson M E Brewster H Derendorf and N Bodor 2-Hydroxypropyl-β-cyclodextrin Properties and usage in pharmaceutical formulations. *Pharm Ztg Wiss.* 4/136 5-10 (1991)

Methods of preparing drug-cyclodextrin complexes have been described by Hirayama and Uekama [F Hirayama and K Uekama Methods of investigating and preparing inclusion compounds In D Duchêne (editor) Cyclodextrins and their industrial uses Editions de Santé Paris, 1987 pp 133-172] In solution the drug-cyclodextrin complexes are prepared by the simple method described above and the complexation evaluated by determination of stability constants by a solubility method a kinetic method a spectroscopic method or some other analytical method On a laboratory scale solid drug-cyclodextrin complexes are usually formed by lyophilization of drug-cyclodextrin complex solution but on an industrial scale other methods are also used such as the kneading method spray-drying coprecipitation neutralization and grinding methods In none of these methods are water-soluble pharmaceutical polymers or other polymers in general used for enhancing the drug-cyclodextrin complexation

There are few samples of formation of drug-cyclodextrin complexes by heating Thus Hassan *et al. Int J Pharm* 58 19-24 (1990) prepared a famotidine-β-cyclodextrin complex by adding the drug to aqueous β-cyclodextrin solution heating the mixture under reflux for 1 hour and then stirring it at room temperature for 5 days The solution which formed was concentrated by evaporation under vacuum and the precipitate which formed was filtered and dried under vacuum at 50°C. In a series of articles, Nakai *et al* describe how they make cyclodextrin inclusion complexes by heating ground mixtures of physical mixtures to 80 to 130°C in sealed containers See Nakai *et al Chem Pharm Bull* 35(11) 4809-4815 (1987) Nakai *et al Chem Pharm Bull* 37(4) 1055-1058 (1989) Nakai *et al Chem Pharm Bull* 38(3) 728-732 (1990) Nakai *et al Chem Pharm Bull* 38(5) 1345-1348 (1990) and Nakai *et al Chem Pharm. Bull.* 39(6), 1532 1535 (1991) Finally, Schmidt and Maier [E Schmidt and H G Maier Thermostabile Bindung von Aromastoffen an Starke Teil 2 Bindung von Menthol durch Autoklavieren, *Starch/Stärke* 39(8) 203-207 (1987)] describe formation of thermostable binding of menthol to various types of starches including β-cyclodextrin by autoclaving In none of the above mentioned articles are starches or other polymers used to enhance complexation of drugs by cyclodextrins

Due to the negative enthalpy of cyclodextrin complexation the solubility enhancement of drugs by aqueous cyclodextrin solutions is generally larger at low temperature than at high temperature [T Loftsson and N Bodor Effects of 2 hydroxypropyl β-cyclodextrin on the aqueous solubility of drugs and transdermal delivery of 17β-estradiol *Acta Pharm Nord* 1(4) 185-193 (1989)] Also additives such as sodium chloride buffer salts surfactants and organic solvents (e g ethanol) usually reduce the solubilizing effects of cyclodextrins

Summary and Objects of the Invention

One object of the present invention is to provide a method for enhancing the complexation of cyclodextrins with lipophilic and/or water labile drugs, food additives, cosmetic additives and agrochemicals.

Another object of the invention is to provide a method for increasing the solubilizing and stabilizing effects of cyclodextrins on drugs which are insoluble or sparingly soluble or unstable in water and on food additives cosmetic additives and agrochemicals which are insoluble or sparingly soluble or unstable in water

Another object of the invention is to provide novel co-complexes of drugs cyclodextrins and selected polymers and of food additives, cosmetic additives and agrochemicals with cyclodextrins and selected polymers

Yet another object of the invention is to provide pharmaceutical compositions comprising novel drug com-

3/8

285

plexes as well as analogous food cosmetic and agricultural compositions.

Still another object of the invention is to provide a novel complexing agent for use in solubilizing and/or stabilizing a lipophilic and/or water labile drug food additive cosmetic additive or agrochemical

In accord with these and other objects the present invention provides the following

(1) A method for enhancing the complexation of a cyclodextrin with a lipophilic and/or water labile drug comprising combining from about 0 1 to about 70% (weight/volume) of cyclodextrin and from about 0 001 to about 5% (weight/volume) preferably from about 0 01 to about 0.5% (weight/volume) of a pharmaceutically acceptable pharmacologically inactive water-soluble polymer with a lipophilic and/or water labile drug in an aqueous medium to form a drug complex the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added and the aqueous medium being maintained at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours before during and/or after the drug is added optionally followed by removal of water

(2) A method for solubilizing and/or stabilizing a lipophilic and/or water labile drug in an aqueous medium comprising complexing the drug in an aqueous medium with from about 0 1 to about 70% (weight/volume) of cyclodextrin and from about 0 001 to about 5% (weight/volume) preferably from about 0 01 to about 0 5% (weight/volume) of a pharmaceutically acceptable pharmacologically inactive water-soluble polymer the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added and the aqueous medium being maintained at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours before, during and/or after the drug is added

(3) A co-complex of a lipophilic and/or water labile drug with a cyclodextrin and a pharmaceutically acceptable pharmacologically inactive water-soluble polymer the ratio by weight of cyclodextrin to polymer being from about 4 1 to about 50 000 1 preferably from about 100 1 to about 10 000 1

(4) A pharmaceutical composition comprising

(a) a drug complex prepared by complexing in an aqueous medium a lipophilic and/or water-labile drug with from about 0 1 to about 70% (weight/volume) of cyclodextrin in the presence of from about 0.001 to about 5% (weight/volume), preferably from about 0 01 to about 0 5% weight/volume of a pharmaceutically acceptable pharmacologically inactive water-soluble polymer, the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added and the aqueous medium being maintained at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours before, during and/or after the drug is added optionally followed by removal of water and

(b) a non-toxic, pharmaceutically acceptable carrier therefor

(5) A pharmaceutical composition comprising

(a) a co-complex of a lipophilic and/or water-labile drug with a cyclodextrin and a pharmaceutically acceptable pharmacologically inactive water-soluble polymer the ratio by weight of cyclodextrin to polymer being from about 4 1 to about 50 000 1 preferably from about 100 1 to about 10 000 1 and

(b) a non-toxic, pharmaceutically acceptable carrier therefor and

(6) A complexing agent for use in solubilizing and/or stabilizing a lipophilic and/or water-labile drug comprising a cyclodextrin and a pharmaceutically acceptable pharmacologically inactive water soluble polymer, the ratio by weight of cyclodextrin to polymer being from about 4 1 to about 50 000 1 preferably from about 100 1 to about 10 000 1 said complexing agent being formed by heating the cyclodextrin and polymer in an aqueous medium at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours.

The present invention further provides methods and compositions analogous to those listed above in which the lipophilic and/or water-soluble drug is replaced by a lipophilic and/or water-soluble food additive cosmetic additive or agrochemical

Brief Description of the Drawings

Other objects and advantages of the present invention will be apparent from the following detailed description and accompanying drawings in which

Fig 1 is a plot of the solubilization of hydrocortisone in mg/ml in aqueous 10% HPβCD (2 hydroxypropyl-β-cyclodextrin) MS 0.6 solution containing varying amounts of PVP (polyvinylpyrrolidone)

Fig 2 is a series of plots depicting the dissolution profile of hydrocortisone from tablets containing hydrocortisone-HPβCD complex Δ, 0% (w/v) CMC ♦ 0 1% (w/v) CMC o 0.25% (w/v) CMC and

Fig 3 is a pair of plots illustrating the effect of 1% (w/v) acetazolamide eye drop solution on the intraocular pressure (IOP) of normotensive conscious, albino rabbits wherein the right eye received the drug (O) and the left eye was the control (□)

3/4

286

Detailed Description of the Invention and Preferred Embodiments

Here and throughout this description the following definitions are applicable

The term "lipophilic" is used herein to describe drugs (or food additives or cosmetic additives or agrochemicals) which are lipid-soluble and hydrophobic, i e which are insoluble or sparingly soluble in water

The term "water labile" is used herein to describe drugs (or food additives or cosmetic additives or agrochemicals) which are unstable in water

Cyclodextrins for use in the present invention include the natural cyclodextrins and their derivatives including the alkylated and hydroxyalkylated derivatives and the branched cyclodextrins. Cyclodextrins and their derivatives which have been previously described as useful for complexation with drugs are of particular interest herein In addition to α- β- and γ-cyclodextrins the ether and mixed ether derivatives and those derivatives bearing sugar residues are of special interest Especially useful herein are the hydroxyethyl hydroxypropyl (including 2 and 3-hydroxypropyl) and dihydroxypropyl ethers their corresponding mixed ethers and further mixed ethers with methyl or ethyl groups, such as methylhydroxyethyl ethyl-hydroxyethyl and ethylhydroxypropyl ethers of α- β- and γ-cyclodextrin and the maltosyl glucosyl and maltotriosyl derivatives of α β- and γ-cyclodextrin which may contain one or more sugar residues e g. glucosyl or diglucosyl maltosyl or dimaltosyl as well as various mixtures thereof e g a mixture of maltosyl and dimaltosyl derivatives Specific cyclodextrin derivatives for use herein include hydroxypropyl β-cyclodextrin hydroxyethyl-β-cyclodextrin hydroxypropyl-γ-cyclodextrin hydroxyethyl-γ-cyclodextrin dihydroxypropyl β-cyclodextrin glucosyl-α cyclodextrin glucosyl β-cyclodextrin diglucosyl-β-cyclodextrin maltosyl-α-cyclodextrin maltosyl-β-cyclodextrin maltosyl-γ-cyclodextrin maltotriosyl-β-cyclodextrin maltotriosyl-γ-cyclodextrin and dimaltosyl-β-cyclodextrin and mixtures thereof such as maltosyl-β-cyclodextrin/dimaltosyl-β-cyclodextrin as well as methyl-β-cyclodextrin Procedures for preparing such cyclodextrin derivatives are well-known for example from Bodor United States Patent No 5,024 998 dated June 18 1991 and references cited therein Particularly preferred cyclodextrins for use in the present invention are hydroxypropyl hydroxyethyl, dihydroxypropyl glucosyl and maltosyl derivatives of α , β- and γ-cyclodextrin and their mixtures especially those having a molar degree of substitution of from about 0.05 to about 10. The expression "molar degree of substitution" is used in the same sense as employed in Brauns and Müller European Patent No 0149197 B1

Suitable polymers for use herein are those which are soluble in water are acceptable for use in pharmaceuticals and are pharmacologically inactive Such polymers are well-known excipients commonly used in the field of pharmaceutical formulations [See for example *Remington's Pharmaceutical Sciences* 18th edition Alfonso R Gennaro (editor) Mack Publishing Company Easton PA, 1990 pp 291 294 Alfred Martin James Swarbrick and Arthur Commarata *Physical Pharmacy Physical Chemical Principles in Pharmaceutical Sciences*, 3rd edition Lea & Febinger Philadelphia PA, 1983 pp 592-638 A.T Florence and D Attwood Physicochemical Principles of Pharmacy 2nd edition MacMillan Press, London 1988 pp 281-334] Suitable polymers include water-soluble natural polymers water-soluble semi-synthetic polymers (such as the water-soluble derivatives of cellulose) and water-soluble synthetic polymers The natural polymers include polysaccharides such as inulin pectins, algin derivatives (e g sodium alginate) and agar and polypeptides such as casein and gelatin The semi-synthetic polymers include cellulose derivatives such as methylcellulose hydroxyethyl cellulose hydroxypropyl cellulose their mixed ethers such as hydroxypropyl methylcellulose and other mixed ethers such as hydroxyethyl ethylcellulose and hydroxypropyl ethylcellulose hydroxypropyl methylcellulose phthalate and carboxymethylcellulose and its salts especially sodium carboxymethylcellulose The synthetic polymers include polyoxyethylene derivatives (polyethylene glycols) and polyvinyl derivatives (polyvinyl alcohol polyvinylpyrrolidone and polystyrene sulfonate) and various copolymers of acrylic acid (e g carbomer) Other natural semi-synthetic and synthetic polymers not named here which meet the criteria of water solubility pharmaceutical acceptability and pharmacological inactivity are likewise considered to be within the ambit of the present invention Particularly preferred polymers for use herein are sodium carboxymethylcellulose hydroxypropyl methylcellulose and polyvinylpyrrolidone

Water-soluble polymers for use with drugs herein as pointed out above need to be pharmaceutically acceptable and pharmacologically inactive Generally speaking such water-soluble polymers will also be acceptable for use with food additives cosmetic additives and agrochemicals (agricultural chemicals), since the most stringent requirements are usually placed on pharmaceuticals, particularly for parenteral use Conversely however a polymer which is not pharmaceutically acceptable could for example nevertheless be agriculturally acceptable particularly for non-crop applications such a polymer is intended for use herein in compositions with those non-drug materials e g agrochemicals which do not require pharmaceutical acceptability Similarly the water soluble polymers for use with food and cosmetic additives need only be acceptable for use in foods and cosmetics

As lipophilic and/or water labile food additives which are contemplated for use in the methods and com-

40

positions of the present invention there can be mentioned by way of example flavoring agents, preservatives antioxidants sweetening agents and coloring agents Illustrative of such additives are flavors such as vanillin aromatic flavoring oils such as lemon oil cinnamon oil oil of anise oil of bitter almond or benzaldehyde oil of clove oil of orange oil of peppermint, garlic oil onion oil and menthol sweeteners such as aspartame and saccharin colors such as methyl yellow as well as natural colors preservatives such as methylparaben propylparaben chlorbutol benzoic acid and salicylic acid and antioxidants such as butylated hydroxyanisol

In the case of cosmetic additives contemplated for use in the methods and compositions of this invention many of the same classes of ingredients (including some of the same specific ingredients) noted above as food additives are intended Illustrative classes of cosmetic additives include preservatives antioxidants aromatic oils (fragrances) coloring agents and vitamins (also noted as drugs herein) Specific additives of interest for cosmetics include fragrant aromatic oils such as lavender oil pine oil oil of geranium, oil of rose, oil of sweet bay oil of lemon, oil of lemon grass preservatives such as camphor and vitamins such as vitamin D_2 (cholecalciferol) vitamin D_3, vitamin A and vitamin E

With regard to agrochemicals those contemplated for use in the methods and compositions of this invention include pesticides (including for example insecticides and nematocides) fungicides herbicides and plant growth regulators Illustrative of such agrochemicals are pesticides such as pentachlorophenol, mevinphos piperonyl butoxide hydroprene methoprene and kinoprene· fungicides such as 4-chloro-3-methylbenzothiazolone and pyrrolnitrin and herbicides such as pentachlorophenol and 2 6-dichlorobenzonitrile

It is well-known that a number of food and cosmetic additives, particularly flavors fragrances and colors, as well as agrochemicals (pesticides herbicides insecticides and fungicides) can be complexed with cyclodextrin Such materials exhibit significantly increased complexation and water solubility however when used in the methods and compositions of the present invention

Among the lipophilic and/or water-labile drugs which are contemplated for use in the methods and compositions of the present invention there can be mentioned antineoplastics (anticancer/antitumor agents) sedatives anti-inflammatory steroids (glucocorticoids) tranquilizers anticonvulsants, antivirals antihistammics, vitamins/nutritional factors emetics anticoagulants cardiotonics (including cardiac glycosides) diuretics nonsteroidal analgesic and/or anti-inflammatory agents (NSAID s) androgens estrogens anabolic agents vasodilators antidepressants antipsychotics hypnotics, antifungals progestins antiprotozoals anthelmintics, anesthetics vasoconstrictors hypoglycemics antibacterials/antibiotics and anti-infectives platelet inhibitors muscle relaxants antiemetics, radiodiagnostics antispasmodics antiarrythmics, carbonic anhydrase inhibitors gastrointestinal agents (including H_2-antagonists and other anti-ulcer agents) antihypertensives serotonin antagonists, narcotic antagonists, narcotic agonists, mixed narcotic agonists-antagonists pharmacologically active proteins such as peptide hormones enzymes antibodies and other biologically produced substances anti-Parkinsonism/dopaminergic agents and drugs for treating Alzheimer's disease

It is now well known that lipophilic and/or water-labile drugs which complex with cyclodextrin have the required shape and size to fit at least partially into the cavity of the hydrated cyclodextrin molecule· see for example, Brauns and Müller European Patent No 0149197 B1 Drugs whose water solubility can be improved by complexation with cyclodextrins exhibit significantly increased complexation and water solubility when treated in accord with the present invention

Specific drugs contemplated for use in the methods and compositions of the present invention include antineoplastics such as chlorambucil lomustine melphalan methotrexate hexamethylmelamine teniposide etoposide semustine (methyl CCNU) fazarabine (Ara-AC) mercaptopurine tubulazole carmofur carmustine amsacrine doxorubicin bruceantin diaziquone dideminin B echinomycin and PCNU anti-inflammatory steroids such as betamethasone, fludrocortisone, dexamethasone cortisone hydrocortisone triamcinolone triamcinolone acetonide prednisone and prednisolone estrogens such as 17β estradiol 17α-ethynylestradiol (ethynylestradiol) ethynylestradiol 3-methyl ether estrone mestranol and estriol progestins such as dimethisterone norethindrone norethindrone acetate, norgestrel norethynodrel ethisterone, medroxyprogesterone acetate and progesterone anticonvulsants such as phenytoin (diphenylhydantoin) and carbamazepine barbiturates such as pentobarbital phenobarbital and secobarbital variously useful as hypnotics, anticonvulsants and sedatives antivirals such as vidarabine and virazole (also known as ribavirin) vitamins/nutritional factors such as retinol (vitamin A) vitamin A-acetate, cholecalciferol and retinal as well as other fat-soluble vitamins such as the E D and K vitamins β-blockers such as timolol and atenolol, propranolol and nadolol emetics such as apomorphine; diuretics such as chlorthalidone furosemide and other sulfonamide-type diuretics and spironolactone an aldosterone antagonist type diuretic anticoagulants such as dicumarol cardiotonics such as digoxin and digitoxin non-steroidal analgesics and/or anti-inflammatory agents such as aspirin ibuprofen indomethacin piroxicam sulindac and flurbiprofen androgens such as 17-methyltestosterone and testosterone· mineral corticoids such as desoxycorticosterone; steroidal hypnotics/anesthetics such as alfaxalone ane-

bolic agents such as fluoxymesterone and methanstenolone antidepressants such as sulpiride antibiotics such as ampicillin and penicillin G anti-infectives such as benzalkonium chloride cetylpyridinium chloride and chlorhexidine coronary vasodilators such as nitroglycerin flunarizine lidoflazine and mioflazine hypnotics such as etomidate carbonic anhydrase inhibitors such as acetazolamide chlorzolamide ethoxzolamine methazolamide L 671 152 and MK-927 antifungals such as imidazole-type antifungals e.g econazole clotrimazole oxiconazole bifonazole metronidazole (metronidazole benzoate) fenticonazole miconazole sulconazole tioconazole isoconazole butoconazole ketoconazole doconazole parconazole orconazole valconazole and lombazole and triazole-type antifungals. e g terconazole and itraconazole antiprotozoals such as imidazole type antiprotozoals, e.g metronidazole ornidazole carnidazole ipronidazole tinidazole and nimorazole and benzimidazole-type antifungals e g flubendazole H_2-antagonists including those of the imidazole-type e.g burimamide metiamide cimetidine and oxmetidine imidazole-type antineoplastics such as tubulazole, a microtubule inhibitor antihelmintic agents including those of the benzimidazole-type, for example thiabendazole oxibendazole cambendazole fenbendazole flubendazole albendazole and oxfendazole, antihistaminics, including benzimidazoles such as astemizole piperidines such as levocabastine and piperazines such as flunarizine oxatomide and cinnarizine antipsychotics including those of the piperidine-type such as fluspirilene pimozide and penfluridole gastrointestinal agents including piperidine derivatives such as loperamide and cisapride serotonin antagonists for example those of the piperidine type such as ketanserin ritanserin and altanserin and those of the piperazine-type such as mianserin (also an antihistaminic) anesthetics such as lidocaine hypoglycemics such as acetohexamide anti-emetics such as dimenhydrinate antibacterials such as co-trimoxazole dopaminergic agents such as L-DOPA, anti-Alzheimer's agents such as THA famotidine an anti-ulcer agent/H_2-antagonist; benzodiazepines for example chlordiazepoxide diazepam medazepam, oxazepam lorazepam flunitrazepam estazolam, flurazepam loprazolam lormetazepam nitrazepam quazepam temazepam and triazolam, variously useful as sedatives hypnotics anticonvulsants, tranquilizers and muscle relaxants, and prostaglandins for example PGE s such as PGE_1 (alprostadil) a vasodilator and PGI_2 (prostacyclin or epoprostenol) a platelet inhibitor

In one particularly preferred aspect of the present invention the drug contemplated for use herein is a carbonic anhydrase inhibitor especially acetazolamide

In another preferred aspect of the invention the drug contemplated for use herein is a steroid particularly an anti-inflammatory steroid (glucocorticoid) or a steroidal estrogen progestin anabolic agent, androgen anesthetic/hypnotic or diuretic/aldosterone antagonist

In another preferred aspect of the invention the drug contemplated for use herein is a benzodiazepine sedative or an anti-infective agent.

In yet another preferred aspect of the invention the drug contemplated for use herein is the reduced dihydropyridine form of a dihydropyridine ⇌ pyridinium salt redox system for brain-targeted drug delivery

With respect to the redox system for brain-targeted drug delivery the following definitions are applicable

The term "lipoidal" is intended to designate a redox moiety which is lipid-soluble or lipophilic.

The terms "redox carrier system" and "redox analog system" are intended to designate two different approaches to targeting drugs to the brain using a dihydropyridine ⇌ pyridinium salt system; compounds representing either of these approaches are contemplated for use in the present invention.

The redox carrier system provides for brain-targeted drug delivery by means of carrier-drugs which in their reduced form which is the form intended for administration can be represented by the formula

[D-DHC]

wherein [D] is a centrally acting drug species and [DHC] is the reduced blooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine ⇌ pyridinium salt redox carrier In their oxidized form which is the form "locked" in the brain from which the active drug is ultimately released the carrier drugs can be represented by the formula

$[D\text{-}QC]^+ X^-$

wherein X^- is the anion of a non-toxic pharmaceutically acceptable acid [D] is a centrally acting drug species and $(QC)^+$ is the hydrophilic, ionic pyridinium salt form of a dihydropyridine ⇌ pyridinium salt redox carrier The various redox approaches are now well-known having been described in many patents and literature articles the originator of the redox technology Nicholas S Bodor has also described the use of cyclodextrin derivatives in conjunction with the reduced dihydropyridine forms of the redox systems e g In Bodor United States Patents No 4 983,586 5,002 935 5,017 566 and 5,024 998. While the redox systems for use herein can be any of those defined in the Bodor patents, those in which the centrally acting drug species and redox carriers are indicated in the Bodor patents as being preferred are likewise preferred for use herein Thus preferred redox carrier compounds of the formula [D DHC] are those in which [D] the centrally acting drug species is a dopaminergic agent, an androgenic agent, an anticonvulsant, an anxiolytic agent a neurotransmitter an antibiotic or antibacterial agent, an antidepressant, an antiviral agent, an anticancer or antitumor agent an anti-

inflammatory agent, an estrogen or a progestin particularly when the centrally acting drug species is dopamine testosterone phenytoin GABA, valproic acid tyrosine methicillin oxacillin benzylpenicillin cloxacillin dicloxacillin desipramine acyclovir trifluorothymidine zidovudine hydroxy-CCNU chlorambucil tryptamine dexamethasone hydrocortisone ethinyl estradiol norethindrone, estradiol ethisterone norgestrel estrone estradiol 3-methyl ether estradiol benzoate norethynodrel mestranol indomethacin naproxen FENU HENU or 5-FU Especially preferred redox carrier compounds of the formula [D-DHC] are

1 methyl-3-{(N-{β-[3 4-bis(pivalyloxy)phenyl]ethyl}carbamoyl}} 1,4 dihydropyridine 1 methyl 3-[N [[β-[3,4 bis(isobutyryloxy)phenyl]-ethyl]]carbamoyl 1 4-dihydropyridine and N-{β [3 4-bis(pivalyloxy)-phenyl] ethyl}aminocarbonyloxymethyl 1,4-dihydro-1-methyl 3-pyridinecarboxylate which are dopamine derivatives,

17β-[(1,4-dihydro-1 methyl-3-pyridinylcarbonyl)oxy]androst-4-en-3-one and 17β-[[(3"-carbamoyl 1 4 dihydropyridinyl)acetyl]oxy}androst-4-en-3-one which are testosterone derivatives

5 5-diphenyl-3-[(1-methyl 1 ,4 -dihydropyridin-3 yl)carbonyloxymethyl]-2,4-imidazolidinedione 3-[(3 -carbamoyl 1 4 -dihydropyridin-1 -yl)acetyloxymethyl]-5 5-diphenyl-2 4-imidazolidinedione and 3-[3 (3'-carbamoyl-1" 4"-dihydropyridin-1 yl)propionyloxymethyl]-5 5-diphenyl 2,4-imidazolidinediones which are phenytoin derivatives

1 methyl-3-N [3-(benzyloxycarbonyl)propyl]carbamoyl-1,4-dihydropyridine and 1 methyl 3-{N [(3 cyclohexylcarbonyl)propyl]}-carbamoyl 1 4-dihydropyridine which are GABA derivatives

1-methyl-3-[2' (2" propyl)pentanoyloxy]ethylcarbamoyl-1 4-dihydropyridine 1 methyl 3-[2'-(2" propyl)pentanoyloxy]ethoxycarbonyl-1 4-dihydropyridine and 1-[2 -(2 propyl)pentanoyloxy]ethyl 3-carboxamide-1,4-dihydropyridine, which are valproic acid derivatives,

1-methyl-3-{N-[(1 -ethoxycarbonyl)-2 -(4"-pivaloyloxyphenyl)ethyl]}-carbamoyl-1 4-dihydropyridine and 1-methyl 3-{N-[(1 -ethoxycarbonyl) 2' (4 -isobutyryloxyphenyl)ethyl]}carbamoyl 1,4-dihydropyridine which are tyrosine derivatives

[[(1 4-dihydro-1-methyl-3-pyridinyl)carbonyl]oxy]methyl [2S-(2α, 5α 6β)]-3 3-dimethyl-7-oxo-6-[(2 6-dimethoxy)benzamido]-4-thia-1-azabicyclo[3 2 0]heptane-2 carboxylate [[(1 4 dihydro-1 methyl 3 pyridinyl)carbonyl]oxy]methyl [2S-(2α,5α,6β)]-3,3dimethyl-6-(5-methyl-3-phenyl-4-isoxazolecarboxamido-7-oxo-4-thia-1 azabicyclo[3 2 0]heptane 2-carboxylate [[(1,4-dihydro-1-methyl 3-pyridinyl)carbonyl]oxy]methyl [2S-(2α 5α 6β)]-3 3dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1 azabicyclo-[3 2.0]heptane-2-carboxylate, [[(1 4-dihydro-1 methyl 3-pyridinyl)carbonyl]-oxy]methyl [2S (2α,5α,6β)]-6-[3-(2-chlorophenyl)-5-methyl 4-isoxazolecarboxamido]-3 3-dimethyl-7 oxo-4-thia-1-azabicyclo[3 2 0]heptane-2-carboxylate and [[(1 4-dihydro-1-methyl-3-pyridinyl)carbonyl]oxy]methyl [2S-(2α,5α,6β)]-6-[3- (2 6-dichlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3 3-dimethyl-7 oxo-4-thia 1 azabicyclo[3.2 0]heptane-2 carboxylate which are derivatives of methicillin oxacillin benzylpenicillin cloxacillin and dicloxacillin respectively

[(N [3-(10 11-dihydro-5H-dibenz(b f)azepin-5-yl)]propyl-N methylamino}carbonyloxy]methyl 1 4-dihydro-1-methyl-3 pyridinecarboxylate and [1-{N-[3-(10 11-dihydro-5H-dibenz[b,f]azepin-5-yl)]propyl N-methylamino)carbonyloxy]ethyl 1 4-dihydro-1-methyl-3-pyridinecarboxylate which are derivatives of desipramine

1-methyl 3-[[2-(9-guanylmethoxy)ethoxy]carbonyl}-1 4-dihydropyridine, which is a derivative of acyclovir

3 -(1 4-dihydro-1-methyl 3-pyridinylcarbonyl)-5' pivaloyltrifluoro-thymidine which is a derivative of trifluorothymidine

3 azido-3 deoxy-5' (1 methyl-1,4-dihydro-3-pyridinyl)-carbonyl]thymidine which is a derivative of zidovudine (AZT)

N-(2 chloroethyl)-N -[4-(1,4-dihydro-1-methyl-3-pyridinecarbonyloxy)-cyclohexyl] N-nitrosourea N-(2-fluoroethyl) N'-[2-(1,4-dihydro-1 methyl 3 pyridinecarbonyloxy)ethyl]-N-nitrosoureas and N-(2 chloroethyl) N [2 (1 4-dihydro-1 methyl-3-pyridinecarbonyloxy)ethyl]-N-nitrosourea which are derivatives of hydroxy-CCNU FENU and HENU respectively

1-methyl-3-[(N-[2-[4-({4-[bis(2-chloroethyl)]amino}phenyl)-butanoyloxy]ethyl})carbamoyl]-1,4-dihydropyridine 1 methyl 3-(N-[4-[4-(4-[[bis(2-chloroethyl)]amino]phenyl)butanoyloxy]cyclohexyl}carbamoyl)-1,4-dihydropyridine 1 methyl 3-[(N-{2 [4 ({4 bis(2 chloroethyl)]amino} phenyl)butanoyloxy]propyl})carbamoyl]-1,4-dihydropyridine 1 methyl-3-[(N-{2 phenyl-2-({4 [bis(2-chloroethyl)]amino}phenyl)butanoyloxy]}ethyl)-carbamoyl]-1,4-dihydropyridine and 1-methyl-3-[N-({1 [4(4-[[bis(2-chloroethyl)]amino)phenyl)butanoyloxy]cyclohexyl)methyl)carbamoyl]-1,4-dihydropyridine which are derivatives of chlorambucil

1-methyl-3-N [2-(3-indolyl)ethyl]carbamoyl 1 4-dihydropyridine which is a derivative of tryptamine

9-fluoro-11β,17-dihydroxy-16α-methyl-21-[[(1-methyl-1 4-dihydropyridin 3 yl)carbonyl]oxy]pregna 1 4-diene-3,20-dione and 11β 17 dihydroxy-21-[[(1-methyl 1 4-dihydropyridin-3-yl)carbonyl]oxy}pregn-4-ene-3 20-dione which are derivatives of dexamethasone and hydrocortisone respectively

3-hydroxy- 17,β-[(1 methyl 1,4dihydropyridin-3-yl)carbonyl]oxyestra 1 3,5(10) triene which is an estradiol derivative

LB

3-hydroxy-17β-[[1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}-19-nor 17α-pregna-1 3,5(10)-trien-20-yne, 3-[(1 methyl 1,4-dihydro-3-pyridinyl)carbonyloxy]estra-1 3,5(10)-trien-17-one 17β-[(1-methyl-1 4 dihydro-3-pyridinyl)carbonyloxy]estra-1 3,5(10)-trien-3-ol 3-methyl ether 3 17β-bis-[[(1-methyl 1,4-dihydropyridin 3-yl)carbonyl]oxy}estra-1 3,5(10)-triene 3-(phenylcarbonyloxy)-17β-[[(1 methyl 1,4-dihydropyridin 3-yl)carbonyl]oxy}estra-1 3 5(10)-triene and 3-methoxy 17β-[[1-methyl 1 4- dihydropyridin-3-yl)carbonyl]oxy) 19-nor 17α pregna-1 3,5(10)-trien-20-yne which are derivatives of ethinyl estradiol estrone estradiol 3-methyl ether estradiol, estradiol benzoate and mestranol respectively

17β-[[(1-methyl-1 4 dihydropyridin 3-yl)carbonyl]oxy}-19-norpregn 4-en 20-yn-3-one 17β-[[(1 methyl 1 4-dihydropyridin-3-yl)carbonyl]oxy}pregn-4-en 20-yn-3-one 13-ethyl 17β-[[(1 methyl-1 4-dihydropyridin-3-yl)carbonyl]oxy}-18 19-dinorpregn-4-en-20-yn-3-one and 17β [[(1-methyl 1 4-dihydropyridin-3-yl)carbonyl]oxy}-19-norpregn-5(10)-en-20-yn-3-one which are derivatives of norethindrone ethisterone norgestrel and norethynodrel respectively

1 methyl-3-[N-(2-[1 (p-chlorobenzoyl)-5-methoxy-2 methyl-3-indolyl]acetoxy]ethyl)carbamoyl]-1,4-dihydropyridine and 1-methyl-3-[N-[2 (6-methoxy-α-methyl 2 naphthalenylacetoxy)ethyl]carbamoyl-1 4-dihydropyridine, which are derivatives of indomethacin and naproxen respectively and

3-(1 4-dihydro- 1-methyl-3 pyridinylcarbonyloxymethyl)-5-fluorouracil and 1 (1,4-dihydro-1 methyl 3-pyridinecarbonyloxymethyl)-5-fluorouracil which are derivatives of 5-FU (5-fluorouracil)

In the discussion that follows the particulars of the present invention are discussed with respect to drugs It is to be understood however that except where the discussion focuses on matters which are obviously unique to drugs (such as bioavailability) the particulars are the same when a food additive cosmetic additive or agrochemical is used instead of a drug herein

Quite surprisingly it has now been found that is possible to increase the effects of cyclodextrin complexation by adding small amounts of water-soluble pharmaceutically acceptable pharmacologically inactive polymers to aqueous cyclodextrin/drug solutions and then heating the solutions for some time Typically the polymer is dissolved in an aqueous solution of the cyclodextrin or both polymer and cyclodextrin are dissolved in water and then the drug is added The cyclodextrin concentration can range from about 0 1 to 70% w/v and the polymer concentration from about 0 001 to about 5% w/v preferably from about 0.01 to about 0 5% w/v in the original solution The polymer cyclodextrin weight ratio can range from about 1 4 to about 1 50,000 but is usually from about 1 100 to about 1 10 000 that is 1 part of polymer to 100 to 10 000 parts of cyclodextrin and is even more preferably from about 1 500-5 000 I e 1 part of polymer to from 500 to 5 000 parts of cyclodextrin Since maximum complexation is ordinarily desired the drug is usually added in excess The drug may be dissolved in the cyclodextrin/polymer solution before during and/or after the cyclodextrin solution has been kept at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours. Optionally the polymer and cyclodextrin can be combined in aqueous solution with heating at the temperature and for the time indicated in the preceding sentence and dried (preferably lyophilized) to give a cyclodextrin/polymer combination complexing agent That complexing agent can subsequently be combined in aqueous solution with the drug with or without heating for the time and at the temperature indicated above Whatever the manner of preparing the drug/cyclodextrin/polymer aqueous solution said solution can optionally be dried in accord with methods which are known per se Depending on the drug employed acid or base may be added to the cyclodextrin/polymer/drug solution during preparation

As will be apparent from the Examples hereinafter one can readily determine the concentration at which a given water-soluble polymer exerts a maximum solubilizing/stabilizing/complexing effect on a given drug and a given cyclodextrin in aqueous medium It is generally disadvantageous to use a significant amount of polymer in excess of that needed to achieve the maximum effect. Excess polymer can actually decrease the desired solubilizing/stabilizing/complexing effect, and can tend to increase the viscosity of the aqueous medium in which complexation occurs. The amount of polymer used should be sufficient to enhance stabilization/solubilization/complexation but insufficient to cause a significant increase in viscosity upon heating Increase in viscosity to a gel-like or near gel-like stage should be avoided when carrying out the stabilization/solubilization/complexation processes of the invention Obviously, once the process has been completed the resultant mixture can be made more viscous if desired in the pharmaceutical or other compositions provided by the present invention

Aqueous solutions of cyclodextrins and polymers prepared in accord with the present invention have a greater solubilizing and stabilizing effect on lipophilic and/or water labile drugs than cyclodextrin solutions made by simply dissolving cyclodextrins in water or aqueous buffer solutions The water soluble pharmaceutical polymers increase the solubilizing effect of the cyclodextrins and thus make it possible to reduce the amount of cyclodextrin which will be present in the pharmaceutical composition ultimately administered Aqueous cyclodextrin drug formulations containing water soluble pharmaceutical polymers are characterized by fast and efficient drug release which can result in a more rapid onset of the desired therapeutic response and

44

better total bioavailability of the drugs Solid pharmaceutical preparations, made, for example by removal of water from the above-mentioned aqueous cyclodextrin-polymer-drug solutions for example by lyophilization are characterized by faster and more efficient dissolution of drugs compared to the dissolution of drugs from solid cyclodextrin preparations without polymers This can lead to hastening the onset of the therapeutic response and can also increase the total bioavailability of drugs from solid pharmaceutical preparations

It appears that the water-soluble polymers used in accord with the present invention alter the hydration of the cyclodextrin molecules and thus their three-dimensional structure in aqueous solutions Heating accelerates this process. It also appears that the polymer participates directly in the drug complex formation acting as a co-complexing agent with the cyclodextrin S H.S Leung J R. Robinson and V H L. Lee ["Parenteral Products" Chapter 10 in *Controlled Drug Delivery Fundamentals* and *Applications*, second edition J R Robinson and V H L Lee editors Marcel Dekker Inc New York 1987 pp 433-480] in a review of studies from the 1950's and early 1960's, point out that the role of plasma protein and tissue binding in prolonging drug action is well-known and that the same result can be achieved by forming a dissociable complex of a drug with macromolecules such as methylcellulose carboxymethylcellulose and polyvinylpyrrolidone **Table 1** and **Table 6** hereinbelow show that aqueous polymer solutions (S_2) solubilize drugs to a greater extent than pure water (S_1) This can be attributed to complexation of the drug with the polymer Thus, the polymers and the cyclodextrins both form soluble complexes with various drug molecules and can be used to increase the aqueous solubility of the drugs However when polymer and cyclodextrin are mixed together in accord with the present invention one obtains greater drug solubility enhancement than when the polymer and cyclodextrin are used separately Indeed the combination effect is more than simply additive, it is synergistic. This is indicative of the formation of a new type of complex between the drug and the polymer-cyclodextrin The cyclodextrin can thus be considered to be the complexing agent, the polymer a co-complexing agent and the drug complex not simply a drug/cyclodextrin complex but a drug/cyclodextrin/ polymer co-complex

Pharmaceutical compositions utilizing the drug/cyclodextrin/polymer products prepared in accord with the present invention can be used to treat a variety of conditions depending upon the pharmacological nature of the drug selected for administration The compositions contain a pharmacologically/ therapeutically effective amount of the selected drug and the amounts/ratios of selected cyclodextrin and selected polymer noted hereinabove together with a non-toxic, pharmaceutically-acceptable carrier For example if the selected drug is an anti-inflammatory agent, a pharmacologically effective amount thereof will be an amount sufficient to elicit an anti-inflammatory response Selection of the cyclodextrin and the polymer in the compositions will depend upon the nature of the drug and the contemplated route of administration Virtually any route of administration by which a selected drug can be used can be employed for the instant compositions including but not limited to parenteral oral and topical (including ophthalmic) routes. Polymers and cyclodextrins as defined herein will be selected according to the contemplated route of administration since some may be acceptable for certain routes of administration and not for others. For example a hydroxyalkylated cyclodextrin such as hydroxypropyl β-cyclodextrin rather than an alkylated cyclodextrin would be selected for intravenous use because of toxicity considerations Similarly only some of the polymers disclosed herein may be suitable for intravenous use as is indeed well-known in the art.

In the case of parenteral formulations intended for example for intramuscular subcutaneous intra-ocular or intravenous administration the pharmaceutical composition of drug/cyclodextrin/polymer will be in the form of an aqueous solution which is acceptable for parenteral administration I e which is sterile and pyrogen free and has been prepared in accord with accepted pharmaceutical procedures, for example as described in *Remington's Pharmaceutical Sciences*, seventeenth edition ed Alfonso R Gennaro Mack Publishing Company Easton PA (1985) pp 1518-1552. The aqueous sterile injection solutions may further contain antioxidants buffers bacteriostats, isotonicity adjusters and like additions acceptable for parenteral formulations Various unit dose and multidose containers e g sealed ampules and vials, may be used as is well known in the art The essential ingredients of the sterile parenteral formulation I e the drug(s) water and selected cyclodextrin(s) and polymer(s) may be presented in a variety of ways just so long as the solution ultimately administered to the patient contains the appropriate amounts of the essential ingredients Thus for example the drug/cyclodextrin/polymer/ water formulation may be presented in a unit dose or multidose container ready for injection As another example a concentrated solution of drug/cyclodextrin/polymer/water may be presented in a separate container from a diluting liquid (water or cyclodextrin/water) designed so that the contents can be combined to give a formulation containing appropriate amounts for injection As another alternative the drug or a drug/cyclodextrin/polymer combination may be provided in a freeze-dried condition in one container while a separate container contains diluting liquid (water or cyclodextrin/water depending on the amount of cyclodextrin in the other container) again designed so that the contents can be combined to give a formulation containing the appropriate amounts of the essential ingredients As yet another alternative the cyclodextrin/polymer may be provided in a freeze-dried condition in one container the drug in another and the di

luting liquid in yet another container In any event the contents of each container will be sterile

For oral administration the pharmaceutical compositions may be in the form of any well-known oral dosage form e g tablets caplets, capsules pills powders, solutions gels and the like. Orally acceptable carrier materials including excipients binders and disintegrators are well-known in the art Moreover the usual buffers, coloring agents flavoring agents and sweetening agents can be added if necessary or if desired Tablets and caplets may also be coated with the usual coating materials.

In addition to oral dosage forms which are intended to be swallowed the present invention contemplates oral dosage forms which are intended for usage only in the oral cavity typically mouthwashes, and those which are intended for buccal and/or sublingual administration (such as lozenges)

For rectal or vaginal administration suppositories may be suitable appropriate carriers for which are well known Similarly for topical use well-known topically acceptable carriers/vehicles can be employed to form creams gels ointments and the like Appropriate carriers for use in nasal dosage forms (solutions, gels ointments and the like) are similarly well known

In the case of ophthalmic compositions the carrier must be a non-toxic, ophthalmically acceptable carrier Suitable ophthalmic carriers will be apparent to those skilled in the art of ophthalmic formulations. Obviously the choice of suitable carriers will depend on the exact nature of the particular dosage form desired, e g whether the drug/cyclodextrin/polymer complex is to be formulated into an ophthalmic solution or suspension (typically for use as eye drops) an ophthalmic ointment or cream or an ophthalmic gel Preferred dosage forms are solutions which contain a major amount of water in addition to the active ingredient. Minor amounts of other ingredients such as pH adjusters (e g a base such as NaOH) emulsifiers or dispersing agents buffering agents preservatives wetting agents and jelling agents may also be present. Most preferably the ophthalmic composition is a sterile isotonic, buffered aqueous solution

Especially preferred pharmaceutical compositions provided by the present invention include ophthalmic formulations (e g eyedrops) containing a carbonic anhydrase inhibitor such as acetazolamide oral formulations such as mouthwashes or buccal tablets containing an anti-inflammatory steroid, e g hydrocortisone, dexamethasone or triamcinolone acetonide oral formulations such as sublingual tablets containing a benzodiazepam such as flunitrazepam for treatment of insomnia, and sublingual tablets comprising an estrogen progestin or androgen (such as 17β-estradiol for treatment of post menopeusal symptoms in women) or an anti-infective agent (e g benzalkonium chloride)

Generally speaking the therapeutic dosage ranges for administration of drugs in the pharmaceutical formulations described herein will be the same as or less than (in some instances, substantially less than) those characteristically used for administration of the drug *per se* (or in the case of the carrier-drugs of the parent drug species *per se*). Naturally such therapeutic dosage ranges will vary with the size and species of the patient, the condition for which the formulation is administered the route of administration employed and the like The quantity of given dosage form needed to deliver the desired dose of active ingredients will of course depend upon the concentration of the drug in the pharmaceutical formulation

In a similar manner to the pharmaceutical compositions described above compositions comprising the non-drug/cyclodextrin/polymer products prepared according to the present invention will be formulated in accord with their intended use A non-toxic pharmaceutically acceptable carrier as used in the instant pharmaceutical compositions will normally meet or exceed the requirements for use in cosmetics agrochemicals and even in foods Such a carrier is therefore eminently well suited for cosmetic, food and agricultural applications as well Yet other carriers can be used for these other applications, however just so long as they are acceptable for use in foods or cosmetics or agrochemicals as the case may be Thus, for example an agriculturally acceptable carrier will be used with an agrochemical/cyclodextrin/polymer product, which will itself be present in an effective amount, i e a herbicidally effective amount when the agrochemical is a herbicide a pesticidally effective amount when the agrochemical is a pesticide a fungicidally effective amount when the agrochemical is a fungicide and so forth Appropriate carrier materials for use with food additives or cosmetic additives or agrochemicals in addition to non toxic pharmaceutically acceptable carriers will be apparent to those skilled in the food cosmetic and agrochemical arts.

In order to further illustrate the present invention and the advantages thereof the following specific examples are given it being understood that same are intended only as illustrative and in no way limitative of the invention

Example 1

Solubilities (S) of various drugs in four different solvents, i.e (a) water (S_1) (b) aqueous 0 25% (w/v) sodium carboxymethylcellulose solution (CMC) (S_2) (c) aqueous solution of 10% (w/v) 2 hydroxypropyl β-cyclodextrin (HPβCD) of molar substitution (MS) = 0 6 (S_3) and (d) aqueous solution containing both 0.25% (w/v) CMC and

46

10% (w/v) HPβCD MS = 0 6 (S_4) were determined by adding an excess amount of the drug to be tested to the solvents and heating the suspensions formed in sealed containers to 120°C The suspensions were kept at this temperature for 20 minutes and then allowed to equilibrate for 3 days at room temperature (approximately 23°C) After equilibration aliquots were filtered through 0 45 µm membrane filters diluted with a mixture of methanol and water (7 3 v/v) and analyzed by an high pressure liquid chromatographic (HPLC) method The results set forth in Table 1 show that the solubilizing effect of HPβCD was increased by 4 to 57% (S_4/S_3 = 1 04 to 1 57) when 0 25% CMC was present in the solution

Table 1

The effect of CMC on the solubilization of various drugs in aqueous HPβCD solutions

Drug	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_4/S_3
Acetazolamide	0 70	0 84	2 52	3 11	1 23
Alprazolam	0 07	0 18	1 28	1 55	1 21
Carbamazepine	0 11	0 20	7 00	9 20	1 31
Clonimazole	0 00	0 00	1 20	1 40	1 17
Dexamethasone	0 26	0 33	8 43	8 75	1 04
Diazepam	0 69	0 81	9 14	9 70	1 06
Econazole	0 57	0 60	4 86	7 41	1 52
17β-Estradiol	0 01	0 17	5 10	5 35	1 05
Ethoxyzolamide	0 04	0 07	1 19	1 66	1 39
Hydrocortisone	0 36	1 10	12 88	17 02	1 32
Miconazole	0 04	0 06	1 98	2 50	1 26
Oxazepam	0 03	0 04	0 90	1 42	1 57

Table 1 – continued

Drug	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_4/S_3
Prednisolone	0 38	0 53	13 60	15 30	1 13
Progesterone	0 00	0 00	4 03	6 11	1 52
Sulfamethoxazole	0 36	0 69	10 01	12 60	1 26
Temazepam	0 60	0 65	3 01	3 48	1 16
Triamcinolone acetonide	0 03	0 07	2 09	2 58	1 23

EP 0 579 435 A1

Example 2

The effect of increasing CMC concentration on the solubility of three drugs in aqueous 10% (w/v) HPβCD NS = 0 9 solution was also determined under the same condition as in Example 1 The results are shown in Table 2.

Table 2

The effect of increasing CMC concentration on solubulization

Drug	0.00% CMC (w/v)	0.10% CMC (w/v)	0 25% CMC (w/v)	0.50% CMC (w/v)
Acetazolamide	2 52	3 60	3 21	3 75
Hydrocortisone	12 88	15 97	15 78	18 70
Oxazepam	0 90	1 49	1 31	1 88

Example 3

The effect of heating on the solubilization of hydrocortisone in aqueous solution containing 10% (w/v)

HPβCD MS = 0 6 and 0.25% (w/v) CMC was investigated as follows An excess amount of hydrocortisone was added to the solution and the suspension which was formed was heated to 120°C in a sealed container The suspension was kept at this temperature for (a) 20 (b) 40 (c) 60 and (d) 80 minutes At each time point an aliquot of the suspension was removed and allowed to equilibrate for 3 days at room temperature (approximately 23°C) After equilibration each aliquot was filtered through a 0.45 µm membrane filter, diluted with a mixture of methanol and water (7 3 v/v) and analyzed by HPLC The results in Table 3 show that the solubilizing effect of the HPβCD-CMC mixture increases with increasing duration of heating

Example 4

Part A

The effect of polyvinylpyrrolidone (PVP) of molecular weight 360 000 on drug-cyclodextrin complexation

Table 3

The effect of heating on the solubilization of hydrocortisone. The solubility of hydrocortisone in aqueous 10% (w/v) HPβCD - 0 25% (w/v) CMC solution at room temperature

	Duration of Heating (Minutes)			
	20	40	60	80
Solubility (mg/ml)	17 02	17 02	19 86	25 92

was investigated by determining the phase-solubility diagrams of hydrocortisone in aqueous 2-hydroxypropyl β-cyclodextrin (HPβCD) of molar substitution (MS) 0 6 solutions and calculating the stability constant (K_c) for the complex from the slope and the solubility (S_o) of hydrocortisone in water ($1x10^{-3}$ mol/liter)

$$K_c = \text{slope} \times (S_o x(1-\text{slope}))^{-1}$$

An excess amount of the drug was added to water containing from 0 to 0 7% (w/v) PVP and varying amounts of HPβCD The suspensions which formed were heated in sealed containers to 120°C and kept at that temperature for 22 minutes After equilibration for at least three days at room temperature (approximately 22°C), aliquots of the suspensions were removed from the containers and each aliquot was filtered through a 0 45 µm membrane filter and analyzed by HPLC The solubility of the drug was determined at least three times at each HPβCD and PVP concentration and the slope of the phase-solubility diagram was determined by linear regression of the mean solubility versus HPβCD concentration values in mole per liter The correlation coefficient (corr) was calculated for each linear regression The results are shown in Table A below

Table A

The effect of PVP on the stability constant of the hydrocortisone-HPβCD MS 0 6 complex at room temperature (approx 22°C)

PVP Concentration (% w/v)	Slope	Corr	Kc (liter/mol)
0	0 502	0 988	1010
0 01	0 528	0 972	1120
0 025	0 532	0 994	1140
0 05	0 544	0 977	1190
0 1	0 591	0 999	1450
0 15	0 577	0 999	1360
0 2	0 548	0 999	1210
0 3	0 535	0 995	1150
0 4	0 537	0 996	1160
0 5	0 544	0 998	1190
0 6	0 561	1 000	1280
0 7	0 543	0 999	1190

The results in Table A show that it was possible to obtain over 40% increase (at 0 1% PVP concentration) in K_c by addition of PVP The increase was concentration dependent and decreased somewhat upon further addition of PVP

Part B

Comparable results were obtained when the effect of PVP on the solubilization of hydrocortisone by HPβCD MS 0.6 was investigated The solubility of hydrocortisone was determined in aqueous 10% (w/v)

HPβCD MS 0 6 solutions containing from 0 to 0.4% (w/v) PVP (molecular weight 360,000) An excess amount of hydrocortisone was added to the aqueous 10% HPβCD solutions and the suspensions which formed were heated in sealed containers to 120°C and kept at that temperature for 22 minutes After equilibration for at least three days at room temperature (approximately 22°C), aliquots of the suspensions were removed from the containers and each aliquot was filtered through a 0.45 µm membrane filter and analyzed by HPLC The solubility of the drug was determined at least three times at each PVP concentration and the results are shown in Fig 1 (the mean values of three experiments ± the standard error of the mean)

Fig 1 shows that a maximum solubilization of hydrocortisone in aqueous 10% (w/v) HPβCD MS 0 6 solution was obtained when 0 1 to 0 15% (w/v) PVP was present in the solution and that the solubilization at the maximum was about 32% compared to aqueous 10% (w/v) HPβCD MS 0 6 solution containing no PVP Similar results were obtained when other water-soluble polymers e g carboxymethylcellulose and hydroxypropyl methylcellulose were added to aqueous cyclodextrin solutions Generally a maximum solubilization was obtained when the polymer concentration was above 0 003% (w/v) but below 0 1 % but this was dependent on the type of polymer added to the aqueous cyclodextrin solution the chain length (or the molecular weight) of the polymer and the cyclodextrin concentration in the aqueous solution

The maximum effect is obtained at a very low polymer concentration before the polymer has any real effect on the viscosity of the solution For example the viscosity of a solution containing 10% or less PVP is essentially the same as that of water *(Handbook of Pharmaceutical Excipients* American Pharmaceutical Association and the Pharmaceutical Society of Great Britain Washington 1986 pp 234 239) Also this increased solubilization (i.e complexation) is a stable condition The increased drug solubility frequently observed in viscous aqueous solutions that is formation of supersaturated drug solution is an unstable condition which usually returns to a stable condition (under precipitation of the drug) within a few hours from its formation (Uekama et al *J Incl Phenomena* 1 309-312 1984) Thus this increased complexation in the presence of a very small amount of a water soluble polymer is not directly related to increased viscosity of the aqueous solution

Example 5

Solubilities (S) of three drugs in four different solvents I e (a) water (S_1) (b) aqueous 0.25 % (w/v) sodium carboxymethylcellulose solution (CMC) (S_2) (c) aqueous solution of 10% (w/v) hydroxyethyl-β-cyclodextrin (HEβCD) of molar substitution (MS) = 0 6 (S_3) and (d) aqueous solution containing both 0 25% (w/v) CMC and 10% (w/v) HEβCD MS = 0 6 (S_4) were determined as in Example 1 The results in Table 4 show that the solubilizing effect of HEβCD was increased by 32 to 53% (S_4/S_3 = 1 32 to 1 53) when 0 25% (w/v) CMC was present in the solution

Example 6

Solubilities (S) of hydrocortisone in four different solvents i e (a) water (S_1) (b) aqueous 0 25% (w/v) hydroxypropyl methylcellulose solution (HPMC) (S2) (c) aqueous solution of 5% (w/v) 2-hydroxypropyl α β- or γ-cyclodextrin (HPαCD HPβCD or HPγCD) of molar substitution (MS) = 0 6, 0 9 and 0 6 respectively (S3) and (d) aqueous solution containing both 0 25% (w/v) HPMC and 5% (w/v) HPαCD HPβCD or HPγCD (S_4) were determined as in Example 1 The results in Table 5 show that the solubilizing effect of the cyclodextrin derivative was increased by 10 to 50% (S_4 /S_3 = 1 1 to 1 5) when 0 25% HPMC was present in the solution

Table 4

The effect of CMC on the solubilization of drugs in aqueous HEβCD solutions

Drug	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_4/S_3
Hydrocortisone	0 36	1 10	17 51	26 81	1 53
Miconazole	0 04	0 06	2 51	3 31	1 32
Sulfamethoxazole	0 36	0 69	7 07	9 81	1 39

Table 5

The effect of HPMC on the solubilization of hydrocortisone in aqueous cyclodextrin solutions

Cyclodextrin	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_4/S_3
HPαCD MS = 0 6	0 4	1 4	2 4	3 6	1 5
HPβCD MS = 0 9	0 4	1 4	6 7	7 7	1 2
HPγCD MS = 0 6	0 4	1 4	7 7	8 7	1 1

Example 7

Solubilities (S) of three drugs in four different solvents i e (a) water (S_1), (b) aqueous 0.25% (w/v) polyvinylpyrrolidone solution (PVP) (S_2) (c) aqueous solution of 10% (w/v) hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0 7 (S_3) and (d) aqueous solution containing both 0.25% (w/v) PVP and 10% (w/v) HPβCD MS = 0 7 (S_4), was determined as in Example 1 The results in Table 6 show that the solubilizing effect of HPβCD was increased by 27 to 129% (S_4/S_3 = 1 27 to 2 29) when 0.25% (w/v) PVP was present in the solution

Example 6

Table 6

The effect of PVP on the solubilization of drugs in aqueous HPβCD solutions

Drug	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_4/S_3
Acetazolamide	0 70	1 05	2 80	3 66	1 31
Carbamazepine	0 11	0 31	6 43	7 50	1 17
Clotrimazole	0 00	0 00	1 20	1 80	1 50
Dexamethasone	0 26	0 33	7 53	8 00	1 06
Econazole	0 57	0 64	5 22	5 65	1 08
17β-Estradiol	0 01	-	5 10	9 50	1 86
Ethoxyzolamide	0 04	0 06	1 36	2 72	2 00
Miconazole	0 04	0 20	2 36	3 40	1 44
Progesterone	0 00	0 00	4 76	5 71	1 20
Oxazepam	0 03	0 04	0 90	1 14	1 27
Trimethoprim	0 82	1 35	2 83	6 47	2 29
Sulfamethoxazole	0 36	0 86	5 71	8 92	1 56

Solubilities (S) of various drugs in eight different solvents i e (a) water (S_1) (b) aqueous 10% (v/v) ethanol solution (S_2) (c) aqueous 0.25% (w/v) sodium carboxymethyl-cellulose solution (CMC) (S_3) (d) aqueous solution containing both 10% (v/v) ethanol and 0.25% (w/v) CMC (S_4) (e) aqueous solution of 10% (w/v) 2-hydroxypropyl β-cyclodextrin (HPβCD) of molar substitution (MS) = 0 6 (S_4) (f) aqueous solution containing both 10% (v/v) ethanol and 10% (w/v) HPβCD MS = 0 6 (S_4) (g) aqueous solution containing both 0 25% (w/v) CMC and 10% (w/v) HPβCD MS = 0 6 (S_4) and (h) aqueous solution containing 10% (v/v) ethanol 0 25% (w/v) CMC and 10% (w/v) HPβCD MS = 0 6 (S_4) were determined as in Example 1 The results in Table 7 show that CMC

is also able to increase the solubilizing effect of HPβCD in aqueous ethanolic solutions.

Table 7

The effect of ethanol and CMC on the solubilizing effect of HPβCD in aqueous solutions

	Solubility (mg/ml)							
Drug	S_1	S_2	S_3	S_4	S_5	S_6	S_7	S_8
Acetazolamide	0 70	1 11	0 84	0 75	2 52	2 19	3 11	2 50
Hydrocortisone	0 36	0 83	1 10	1 53	12 88	10 91	20 64	13 27
Miconazole	0 04	0 31	0 06	-	1 98	2 22	2 50	12 55

Example 9

The permeability through a semi-permeable membrane was investigated. Semipermeable cellophane membrane was placed in a Franz diffusion cell containing 10 ml aqueous 5% (w/v) HPβCD solution as the receptor phase. The donor phase consisted of a suspension of approximately 3% (w/v) hydrocortisone in (a) aqueous 10% (w/v) hydroxypropyl-β-cyclodextrin (HPβCD) solution and (b) aqueous solution containing both 10%

(w/v) HPβCD and 0 25% (w/v) carboxymethyl-cellulose (CMC) prepared as described in Example 1 and 2 ml of the donor phase applied to the membrane surface (area 3 1 cm²) The assembled diffusion cells were kept at room temperature (22±1°C) and samples (30 µl) were removed from the donor phase every 10 minutes up to 2 hours and analyzed immediately by HPLC The results shown in Table 8 clearly indicate that hydrocortisone is released faster from a suspension containing CMC than from suspension containing no CMC

Table 8

The solubility (S) and the flux (F) of hydrocortisone through a semi-permeable cellophane membrane from hydrocortisone suspensions in HPβCD vehicles

Vehicle composition	S (mg/ml)	F (µg/cm²/minute)
Aqueous (10%) (w/v) HPβCD solution	14 96	3 02
Aqueous solution containing 10% (w/v) HPβCD and 0 25% (w/v) CMC	19 23	5 36

Example 10

The effect of carboxymethylcellulose (CMC) on the release of hydrocortisone from tablets containing hydrocortisone-HPβCD complex was investigated

The freeze-dried hydrocortisone HPβCD complex was prepared by adding an excess of hydrocortisone to aqueous solution containing 50% (w/w) (about 58 % w/v) HPβCD and 0 0 1 or 0 25% (w/v) CMC and heating the hydrocortisone suspensions formed for 20 minutes at 120°C After equilibration for 3 days at room temperature the suspensions were filtered through 0 45 µm membrane filters the filtrates were lyophilized and the solid which formed was ground with a mortar and pestle The amount of hydrocortisone incorporated into the HPβCD complex was determined by HPLC

Individual disks of 200 mg hydrocortisone-HPβCD complex were compressed in a hydraulic press under vacuum and a force of $1x10^4$ kg for 1 5 minutes using a 13 mm (diameter) IR potassium bromide pellet punch The disks had a cross-sectional area of 1 33 cm^2 Each disk contained approximately 27 mg of hydrocortisone

The dissolution studies were carried out using a USP XXII described paddle apparatus for dissolution rate determination The release rate was determined at 37±1°C and 100 rpm by adding one tablet to 900 ml of water Samples were withdrawn at various time intervals filtered through 0 45 membrane filters and analyzed by HPLC

The results in Fig 2 show that hydrocortisone dissolves significantly faster from tablets containing hydrocortisone HPβCD complex prepared in the presence of CMC than from tablets prepared in the absence of CMC The results shown in Fig 2 are the average of four experiments The dissolution tests were started at time zero Three minutes later 66.3% of the hydrocortisone had dissolved from tablets containing hydrocortisone-HPβCD complex formed without the addition of CMC, 74 2% of the hydrocortisone had dissolved from tablets containing hydrocortisone-HPβCD complex formed with the addition of 0 1% (w/v) CMC and 81 0% of the hydrocortisone had dissolved from tablets containing hydrocortisone-HPβCD complex formed with the addition of 0 25% (w/v) CMC

Example 11

Eye drops containing a carbonic anhydrase inhibitor acetazolamide were prepared the following way Hydroxypropyl methylcellulose (HPMC) 0 25% (w/v) was dissolved in distilled water and hydroxypropyl-β-cyclodextrin MS = 0 6 20% (w/v) benzalkonium chloride [0 02% (w/v)] and the sodium salt of ethylenediaminetetraacetic acid [EDTA, 0 1% (w/v)] were then dissolved in the aqueous HPMC solution Finally acetazolamide 1% (w/v) was added to this solution and dissolved by heating in an autoclave (120°C for 20 min). The eye drop solution which formed was allowed to equilibrate at room temperature for one week

The topical activity of the carbonic anhydrase inhibitor eye drop solution was evaluated in conscious white New Zealand rabbits of either sex (2.5 to 3 5 kg) The intraocular pressure was recorded by a pneumatic tonometer without local anaesthesia. The eye drop solution (0 1 ml) was placed on the cornea of the right eye (the left eye was used as control) and the intraocular pressure was recorded at various time intervals (Fig 3)

Example 12

Hydrocortisone mouthwash was prepared in the following way HPβCD MS = 0 6 (3 5% (w/v)) peppermint oil (0 05% (w/v)), ethanol (12% (v/v)) CMC (0 5% (w/v)), benzalkonium chloride (0 02% (w/v)) and the sodium salt of ethylenediaminetetraacetic acid (0 1% (w/v)) were dissolved in water and the solution was heated in a sealed container in an autoclave (120°C for 20 minutes) After equilibration to room temperature hydrocortisone (0.3% (w/v)) was dissolved in the cyclodextrin solution

The topical activity of the hydrocortisone mouthwash solution was evaluated as follows Patients were selected on the basis of severe ulceration, causing considerable pain discomfort inconvenience with work and the like Normally the patients had unsuccessfully tried numerous other remedies such as gentian violet, chlorhexidine silver nitrate hydrocortisone and triamcinolone from a variety of sources Each patient washed his/her mouth with 5-10 ml of the hydrocortisone mouthwash three to four times a day and the results were evaluated after treatment for two weeks The results are shown in Table 9

Table 9

Clinical results of treatment of patients with hydrocortisone mouthwash

	Number of patients				
Disease	**Total**	**Worse**	**No Change**	**Improved**	**Relapsed***
Lichen Planus	17	1	2	14	1
Recurrent oral ulceration	6	0	0	6	1
Miscellaneous autoimmune disease	8	0	2	6	1

*Relapse, of those which showed improvement, within 6 months after end of treatment

Quantitative analysis

The quantitative determinations of the individual drugs were performed on a reversed-phase high performance liquid chromatographic (HPLC) component system consisting of a Milton Roy ConstaMetric 3200 solvent delivery system, a Rheodyne 7125 injector a Spectro Monitor 3200 uv/vis variable wavelength detector and a LiChrosorb®RP-18 5µ (125 x 4mm) column. For other conditions see Table 10. The quantitative determination of econazole was done spectrophotometrically (Perkin-Elmer 550SE uv/vis spectrophotometer) at wavelength 226nm. Solvent ratios indicated refer to parts by volume

Table 10

Conditions of quantitative drug determination by HPLC

Drug	Mobile phase	Flow rate (ml/min)	Wave length (nm)	Retention time (min)
Acetazolamide	Acetonitrile, acetic acid, water (10 2 88) containing 0.015% 1-octanesulfonate	1 5	263	4 0
Alprazolam	Methanol, water (70 30)	1 5	254	2 8
Butylated hydroxyanisole	Methanol, water (70 30)	1 5	285	3 6
Camphor	Methanol, water (70 30)	1 5	200	3 2
Chlorbutol	Acetonitrile, water (60 40)	1 5	205	2 0
Dexamethasone	Acetonitrile, tetrahydrofuran, water (30 5 65)	1 5	254	4 0
Diazepam	Methanol, water (75 25)	1 5	226	4 0
Ethoxyzolamide	Acetonitrile, water (35 65) containing 0 1% 1-hexanesulfonate	1 0	254	3 2
Hydrocortisone	Acetonitrile, tetrahydrofuran, water (30 1 69)	1 5	254	2 6
Methylparaben	Acetonitrile, water (36 64)	1 5	260	4 4
Methylyellow	Acetonitrile, water (78 22)	1 5	205	5 2

EP 0 579 435 A1

Table 10 -- continued

Drug	Mobile phase	Flow rate (ml/min)	Wave length (nm)	Retention time (min)
Miconazole	Methanol, 0 01M aqueous potassium phosphate solution (pH=4 5) (90:10)	1 5	272	2 6
Oxazepam	Methanol, tetrahydrofuran, water (55 2 43)	1 5	226	2 8
Pentachlorophenol	Acetonitrile, tetrahydrofuran, water (78 3 19)	1 5	248	2 4
Prednisolone	Acetonitrile, acetic acid, water (17 0 5 82 5)	1 5	242	4 0
Propylparaben	Acetonitrile, water (40 60)	1 5	260	5 2
Salicylic acid	Methanol, acetic acid, water (35 1 64)	1 5	300	4 8
Sulfamethoxazole	Acetonitrile, acetic acid, water (30 1 69)	1 5	253	2 4
Temazepam	Methanol, water (70 30)	1 5	275	2 8
Triamcinolone acetonide	Acetonitrile, water (42 58)	1 5	254	2 8
Trimetoprim	Methanol, acetic acid, water (39 1 60) containing 0 005M 1-pentasulfonate	1 5	287	2 4
Vanillin	Methanol, water (70 30)	1 5	275	2 4

Example 13

To aqueous solutions containing 20% (w/v) 2-hydroxypropyl-β- cyclodextrin (HPβCD) of molar substitution (MS) = 0 6 were added 0 25% (w/v) polyvinylpyrrolidone (PVP), 0.25% (w/v) sodium carboxymethylcellulose (CMC) or 0 25% (w/v) hydroxypropyl methylcellulose (HPMC) The resultant solutions were heated in sealed containers to 120°C and maintained at that temperature for 30 minutes, then were lyophilized The solids thus obtained were ground with a mortar and pestle

The solid cyclodextrin/polymer products were reconstituted with water to afford solutions containing 9 88%

(w/v) HPβCD and 0 12% (w/v) PVP 0.12% (w/v) or CMC 0 12% (w/v) HPMC The solubilities (S) of three drugs in these solutions and in an aqueous solution containing 10% (w/v) HPβCD without added polymer were then determined as follows

An excess amount of each drug was added to each of the four cyclodextrin solutions and the solutions were sonicated in an ultrasonic bath for 3 hours then allowed to equilibrate for 60 hours at room temperature (23°C) After equilibration aliquots were filtered through 0 45mm membrane filters diluted with a mixture of methanol and water and analyzed by an HPLC method The results are set forth in **Table 11** below where S_1 is the solubility in aqueous solution containing 10% (w/v) HPβCD S_2 is the solubility in aqueous solution containing 9 88% (w/v) HPβCD and 0 12% (w/v) PVP; S_3 is the solubility in aqueous solution containing 9.88% (w/v) HPβCD and 0 12% (w/v) CMC and S_4 is the solubility in aqueous solution containing 9 88% (w/v) HPβCD and 0 12% (w/v) HPMC The results show that a solid polymer/cyclodextrin product can be prepared which has enhanced complexing abilities and that the drug itself need not be heated to achieve enhancement. Nevertheless it is expected that a greater increase in solubility would be observed at higher polymer concentrations [e g 0 25% (w/v)] and/or if the solutions were heated after addition of the drug However by separate preparation of the cyclodextrin/polymer complexing agent as illustrated here one can readily avoid heating drugs which are unstable at elevated temperature

aqueous solution of 10% (w/v) 2-hydroxypropyl β-cyclodextrin (HPβCD) of molar substitution (MS) = 0 6 (S_6) f) aqueous solutions containing both 0.25% (w/v) CMC and 10% (w/v) HPβCD MS = 0 6 (S_6) g) aqueous solutions containing both 0 25% (w/v) PVP and 10% (w/v) HPβCD MS = 0 6 (S_7) and h) aqueous solutions containing both 0 25% (w/v) HPMC and 10% (w/v) HPβCD MS = 0 6 (S_8) An excess amount of the compound to be tested was added to each solvent and the suspensions which formed were heated in sealed containers to 120°C The solubility of salicylic acid was determined in acidic (HCl) solution The suspensions were kept at this temperature for 20 minutes and then allowed to equilibrate for 3 days at room temperature (approximately 23°C) After equilibration aliquots were filtered through 0.45 µm membrane filters diluted with a mixture of methanol and water (7 3) and analyzed by a high pressure liquid chromatographic (HPLC) method The results in Table 12 show that the solubilizing effect of HPβCD was increased by 2 to 134% (solubility ratio of 1 02 to 2 34) when 0 25% polymer (CMC PVP or HPMC) was present in the solution

Table 12

The effect of polymers on the solubilization of various compounds in aqueous HPβCD solutions The solubility ratios (the solubility in HPβCD solution containing the polymer divided by the solubility in HPβCD solution containing no polymer) are shown in parentheses

Compound	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_5 (mg/ml)	S_6 (mg/ml)	S_7 (mg/ml)	S_8 (mg/ml)
Butylated hydroxyanisole	0 40	0 40	1 24	0 28	13 9	14 3 (1 03)	15 8 (1 14)	15 5 (1 12)
Camphor	1 84	2 01	2 20	1 92	12 7	13 8 (1 09)	13 7 (1 08)	13 3 (1 05)
Chlorbutol	8 11	8 41	8 41	8 15	28 6	29 3 (1 02)	-	29 9 (1 05)
Cholecalciferol	NO	NO	NO	NO	0 61	0 72 (1 18)	0 76 (1 25)	0 69 (1 14)
Methylparaben	3 16	3 16	3 40	3 16	8 46	-	10 5 (1 24)	11 4 (1 35)
Methylyellow	$6\ 4x10^{-4}$	$8\ 5x10^{-4}$	$8\ 5x10^{-4}$	$7\ 5x10^{-4}$	0 23	0 24 (1 04)	0 24 (1 04)	0 25 (1 09)
Pentachlorophenol	0 02	0 06	0 03	0 03	0 61	0 99 (1 62)	1 43 (2 34)	-

EP 0 579 435 A1

Table 12 – continued

Compound	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_5 (mg/ml)	S_6 (mg/ml)	S_7 (mg/ml)	S_8 (mg/ml)
Propylparaben	0 19	0 33	0 29	0 29	8 28	8 90 (1 07)	9 00 (1 09)	8 85 (1 07)
Salicylic acid	-	-	-	-	3 71	4 23 (1 14)	4 07 (1 10)	3 92 (1 06)
Vanillin	13 9	13 7	11 5	17 1	25 0	27 3 (1 09)	-	26 5 (1 06)

- Not tested

NO No solubility could be observed, the solubility was below the detection limits

Example 15

The effect of polyvinylpyrrolidone (PVP) on transdermal delivery of hydrocortisone from aqueous 2 hydroxypropyl β-cyclodextrin of molar substitution 0 6 (HPβCD MS 0 6) was investigated in vitro Female hairless mice were sacrificed by cervical dislocation The whole dorsal skin was removed and placed carefully in a Franz

diffusion cell containing 10 ml aqueous 5% (w/v) HPβCD MS 0 6 as the receptor phase The donor phase consisted of a saturated hydrocortisone solution in (a) aqueous 8% (w/v) HPβCD MS 0 6 solution and (b) aqueous solution containing both 6% (w/v) HPβCD MS 0 6 and 0 25% (w/v) PVP prepared as described in Example 1 [The amounts of cyclodextrin and polymer were selected such that solutions (a) and (b) achieved equivalent solubilizing of the drug] 2 Ml of the donor phase was applied to the skin surface (area 3.1 cm^2) The diffusion cells were kept at constant temperature circulating 37°C water from a constant temperature water bath and samples (500 µm) were removed at various time intervals up to three days from the donor phase and analyzed by HPLC The results in Table 13 clearly show that transdermal delivery of hydrocortisone was over two times faster from the PVP-containing sample

Table 13

The concentration of a saturated solution (C) and the flux (F) of hydrocortisone through hairless mouse skin from HPβCS MS 0 6 containing vehicles Each experiment was repeated 4 times and the results are the mean ± standard deviation

Vehicle composition	C (mg/ml)	F (µm/cm^2/h)
Aqueous 8% (w/v) HPβCD MS 0 6 solution	10 9	0 075±0 023
Aqueous solution containing both 6% (w/v) HPβCD MS 0 6 and 0 25% (w/v) PVP	10 6	0 158±0 035

Example 16

Solubilities (S) of hydrocortisone in aqueous solutions containing four different cyclodextrins (CDs) i e hydroxyethyl-β-cyclodextrin (HEβCD) with molar substitution (MS) 0 6 methyl β-cyclodextrin (MβCD) with degree of substitution 1 8 monosubstituted glucosyl-α cyclodextrin (Glucosyl αCD) monosubstituted glucosyl β-cyclodextrin (Glucosyl-βCD) monosubstituted maltosyl-α cyclodextrin (Maltosyl-αCD) or monosubstituted maltosyl-β- cyclodextrin (Maltosyl-βCD) with and without 0 25% (w/v) polymer i e sodium carboxymethylcellulose (CMC) polyvinylyrrolidone (PVP) or hydroxypropyl methylcellulose (HMC). were determined as in Example 1 The results in Table 14 show that the polymers increased the solubilizing effect of the CD derivatives by 8 to 100% (S_{cp}/S_{cc} = 1 08 to 2.00) when 0 25% polymer was present in the solution

68

Table 14

The effect of polymers on the solubilization of hydrocortisone in aqueous CD solutions

Cyclodextrin	Polymer	S_{co} [a] (mg/ml)	S_{cp} [b] (mg/ml)	S_{cp}/S_{co} [c]
HEβCD	CMC	17 5	26 8	1 53
MβCD	CMC	18 6	20 1	1 08
MβCD	PVP	18 6	20 2	1 09
MβCD	HMC	18 6	21 8	1 17
Glucosyl-αCD	CMC	2 7	5 4	2 00
Glucosyl-αCD	PVP	2 7	3 6	1 33
Glucosyl-αCD	HMC	2 7	5 4	2 00
Glucosyl-βCD	CMC	17 0	20 2	1 19
Glucosyl-βCD	PVP	17 0	22 2	1 31
Maltosyl-αCD	CMC	4 1	6 1	1 49
Maltosyl-βCD	CMC	10 4	18 3	1 76
Maltosyl-βCD	PVP	10 4	19 5	1 88
Maltosyl-βCD	HMC	10 4	17 9	1 72

[a] = Solubility in aqueous 10% (w/v) CD solution
[b] = Solubility in aqueous solution containing both 0 25% (w/v) of the given polymer and 10% (w/v) CD
[c] = The solubility ratio

Example 17

The effect of polyvinylpyrrolidone (PVP) on the enthalpy (ΔH) and the entropy (ΔS) of the stability constant (K_c) of the drug-cyclodextrin complex was determined The phase-solubility diagrams of hydrocortisone 17β-estradiol and acetazolamide in aqueous 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) 0 6 or aqueous 2-hydroxypropyl-α-cyclodextrin (HPαCD) MS 0.6 solutions containing from 0 to 0 5% (w/v) PVP were determined and the stability constant (K_c) was calculated for the complex from the slope (see Example 4)

An excess amount of the drug was added to water containing 0 0 1 0 25 or 0 5% (w/v) PVP and various amounts of HPβCD or HPαCD The suspensions which formed were heated in sealed containers to 120°C and kept at that temperature for 22 minutes After equilibration for at least seven days at 6 20 30 40 and 50°C aliquots of the suspensions were removed from the containers and each aliquot was filtered through a 0 45 µm membrane filter and analyzed by HPLC K_c was calculated at each temperature and ΔH and ΔS were calculated as described in A. Martin J Swarbrick and A Cammarata *Physical Pharmacy The Physical Chemical Principles in the Pharmaceutical Sciences*, Third Edition Lea & Febiger Philadelphia 1983, Chapter 13, pp 314-348

The results are shown in Tables 15-18 below

Table 15

The effect of PVP on ΔH and ΔS for the stability constant (K_c) of the acetazolamide-HPβCD MS 0 6 complex

PVP concentration (% w/v)	ΔH (kJ mol^{-1})	ΔS (J $mol^{-1}K^{-1}$)
0 00	-18 4	-26 0
0 10	-25 8	-49 6
0 25	-24 8	-46 2
0 50	-25 8	-49 8

Table 16

The effect of PVP on ΔH and ΔS for the stability constant (K_c) of the hydrocortisone-HPαCD MS 0 6 complex

PVP concentration (% w/v)	ΔH (kJ mol^{-1})	ΔS (J $mol^{-1}K^{-1}$)
0 00	-32 1	-70 2
0 10	-39 3	-94 5
0 25	-48 4	-124 2
0 50	-35 7	-81 9

Table 17

The effect of PVP on ΔH and ΔS for the stability constant (K_c) of the hydrocortisone-HPβCD MS 0 6 complex

PVP concentration (% w/v)	ΔH (kJ mol^{-1})	ΔS (J $mol^{-1}K^{-1}$)
0 00	-20 4	-6 2
0 10	-41 0	-68 6
0 25	-36 5	-56 4
0 50	-38 8	-64 9

Table 18

The effect of PVP on ΔH and ΔS for the stability constant (K_c) of the 17β-estradiol-HPβCD MS 0 6 complex

PVP concentration (% w/v)	ΔH (kJ mol^{-1})	ΔS (J $mol^{-1}K^{-1}$)
0 00	-71 1	-151
0 10	-75 3	-166
0 25	-89 5	-213
0 50	-81 2	185

It has been shown that ΔH and ΔS generally become more negative as the stability constant for molecular complexation increases (A Martin J Swarbrick and A Cammarata *Physical Pharmacy The Physical Chemical Principles in the Pharmaceutical Sciences* Third Edition Lea & Febiger Philadelphia, 1983 Chapter 13 pp 314-348) As the binding between the drug and the cyclodextrin becomes stronger ΔH would be expected to have a larger negative value Apparently PVP increases the structural restraint of the complex in the aqueous solution leading to a larger negative ΔS value These thermodynamic changes indicate that the water soluble PVP polymer participates directly in the complex formation

While the invention has been described in terms of various preferred embodiments the skilled artisan will appreciate that various modifications substitutions omissions and changes may be made without departing from the spirit thereof Accordingly it is intended that the scope of the present invention be limited solely by the scope of the following claims including equivalents thereof

Claims

1 A method for enhancing the complexation of cyclodextrin with a lipophilic and/or water labile drug said method comprising combining from about 0 1 to about 70% (weight/volume) of cyclodextrin and from about 0 001 to about 5% (weight/volume) of a pharmaceutically acceptable pharmacologically inactive water-soluble polymer in an aqueous medium the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours before during and/or after the drug is added optionally followed by removal of water

2. A method for enhancing the complexation of cyclodextrin with a lipophilic and/or water labile cosmetic additive food additive or agrochemical said method comprising combining from about 0 1 to about 70% (weight/volume) of cyclodextrin and from about 0 001 to about 5% (weight/volume) of a water-soluble polymer acceptable for use in cosmetics, foods or agricultural compositions in an aqueous medium, the polymer and cyclodextrin being dissolved in the aqueous medium before the cosmetic additive food additive or agrochemical is added the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours before during and/or after the cosmetic additive food additive or agrochemical is added optionally followed by removal of water

3 A method for solubilizing and/or stabilizing a lipophilic and/or water labile drug in an aqueous medium said method comprising complexing said drug in an aqueous medium comprising from about 0 1 to about 70% (weight/volume) of cyclodextrin and from about 0 001 to about 5% (weight/volume) of a pharmaceutically acceptable pharmacologically inactive water-soluble polymer the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours before during and/or after the drug is added

4. A method for solubilizing and/or stabilizing a lipophilic and/or water-labile cosmetic additive food additive or agrochemical in an aqueous medium said method comprising complexing said cosmetic additive food additive or agrochemical in an aqueous medium comprising from about 0 1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to about 5% (weight/volume) of a water-soluble polymer acceptable for use in cosmetics foods or agricultural compositions the polymer and cyclodextrin being dissolved in the aqueous medium before the cosmetic additive food additive or agrochemical is added the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours before during and/or after the drug is added

5 A co-complex of a lipophilic and/or water labile drug cosmetic additive food additive or agrochemical with a cyclodextrin and a pharmaceutically acceptable, pharmacologically inactive water soluble polymer the ratio by weight of cyclodextrin to polymer being from about 4 1 to about 50 000 1 preferably from about 100·1 to about 10 000·1

6. A pharmaceutical composition comprising
(a) a drug complex prepared by complexing a lipophilic and/or water-labile drug with cyclodextrin in an aqueous medium comprising from about 0 1 to about 70% (weight/volume) of cyclodextrin and from about 0 001 to about 5% (weight/volume) of a pharmaceutically acceptable pharmacologically inactive water-soluble polymer, the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added, the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours before during and/or after the drug is added optionally followed by removal of water; and
(b) a non-toxic, pharmaceutically acceptable carrier therefor

7 A food or cosmetic composition comprising
(a) a complex of a food additive or cosmetic additive prepared by complexing a lipophilic and/or water labile cosmetic additive or food additive with cyclodextrin in an aqueous medium comprising from about 0 1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to about 5% (weight/volume) of a water-soluble polymer acceptable for use in cosmetics or foods the polymer and cyclodextrin being dissolved in the aqueous medium before the cosmetic additive or food additive is added the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about

150°C for a period of from about 0 1 to about 100 hours before during and/or after the cosmetic additive or food additive is added optionally followed by removal of water and
(b) a non-toxic carrier acceptable for use in cosmetics or foods

8. An agricultural composition comprising
(a) an agrochemical complex prepared by complexing a lipophilic and/or water-labile agrochemical with cyclodextrin in an aqueous medium comprising from about 0 1 to about 70% (weight/volume) of cyclodextrin and from about 0 001 to 5% (weight/volume) of an agriculturally acceptable water soluble polymer, the polymer and cyclodextrin being dissolved in the aqueous medium before the agrochemical is added the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours before during and/or after the agrochemical is added optionally followed by removal of water and
(b) a non-toxic agriculturally acceptable carrier therefor

9 A composition comprising
(a) a co-complex of a lipophilic and/or water-labile drug cosmetic additive food additive or agrochemical with a cyclodextrin and a pharmaceutically acceptable, pharmacologically inactive water soluble polymer the ratio by weight of cyclodextrin to polymer being from about 4 1 to about 50,000 1 preferably from about 100 1 to 10 000.1 and
(b) a non-toxic, pharmaceutically acceptable carrier therefor

10. A complexing agent for use in solubilizing and/or stabilizing a lipophilic and/or water-labile drug cosmetic additive food additive or agrochemical said complexing agent comprising a cyclodextrin and a pharmaceutically acceptable pharmacologically inactive water soluble polymer the ratio by weight of cyclodextrin to polymer being from about 4 1 to about 50,000 1 preferably from about 100 1 to 10 000 1 said complexing agent being formed by heating the cyclodextrin and polymer in an aqueous medium at from about 30 to about 150°C for a period of from about 0 1 to about 100 hours

11 A method according to any one of Claims 1 to 4 or a composition according to any one of Claims 6 to 9 wherein the amount of water-soluble polymer is from about 0 01 to about 0 5% (weight/volume)

12. A method co-complex, composition or complexing agent according to any one of the preceding claims wherein the cyclodextrin comprises at least one member selected from the group consisting of hydroxypropyl hydroxyethyl dihydroxypropyl, glucosyl and maltosyl derivatives of α,β-and γ-cyclodextrin especially when the cyclodextrin has a molar degree of substitution of from about 0 05 to about 10

13 A method co-complex composition or complexing agent according to any one of the preceding claims, wherein the water soluble polymer is a cellulose derivative a natural polysaccharide or polypeptide, or a synthetic polymer which is a polyvinyl polymer or a copolymer of acrylic acid

14. A method co-complex, composition or complexing agent according to Claim 13, wherein the cellulose derivative is methylcellulose hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose hydroxyethyl methylcellulose hydroxypropyl ethylcellulose hydroxyethyl ethyl cellulose or sodium carboxymethylcellulose wherein the polysaccharide is inulin pectin sodium, alginate or agar wherein the polypeptide is casein or gelatin wherein the polyvinyl polymer is polyvinyl alcohol polyvinylpyrrolidone or polystyrene sulfonate or wherein the copolymer of acrylic acid is carbomer

15. A method co-complex composition or complexing agent according to Claim 13 wherein the water soluble polymer is hydroxypropyl methylcellulose sodium carboxymethylcellulose or polyvinylpyrrolidone

16. A method according to Claim 1 or 3, a co-complex according to Claim 5 or a composition according to Claim 6 or 9 wherein the drug is a carbonic anhydrase inhibitor β-adrenergic blocking agent, steroid sedative tranquilizer anticonvulsant, antidepressant, antipsychotic, hypnotic, muscle relaxant, antispasmodic, anticoagulant, cardiotonic, vasodilator vasoconstrictor platelet inhibitor anti-arrhythmic, antihypertensive antifungal antiprotozoal antibacterial antibiotic, anti-infective antiviral antihelmintic antineoplastic vitamin emetic, antiemetic diuretic, non-steroidal analgesic or anti-inflammatory agent, anesthetic, hypoglycemic, radiodiagnostic, antihistaminic, serotonin antagonist, H2 antagonist, narcotic antagonist, narcotic agonist, mixed narcotic agonist-antagonist, pharmacologically active protein dopaminergic/anti-Parkinsonism agent or agent for treating Alzheimer's disease

17 A method co-complex or composition according to Claim 16 wherein the steroid is an androgen estrogen progestin diuretic anabolic agent, anesthetic or glucocorticoid

18. A method, co-complex or composition according to Claim 16 wherein the drug is acetazolamide chlorzolamide ethoxzolamide methazolamide timolol atenolol carbamazepine phenytoin ketoconazole itraconazole metronidazole benzoate flubendazole co-trimoxazole miconazole carmustine chlorambucil doxorubicin lomustine melphalan methotrexate dicumarol nitroglycerin flunarizine, alprostadil prostacyclin digitoxin digoxin aspirin apomorphine famotidine furosemide flubiprofen ibuprofen indomethacin piroxicam, lidocaine, sulindac, pentobarbital phenobarbital secobarbital chlordiazepoxide diazepam medazepam oxazepam lorazepam flunitrazepam estazolam, flurazepam loprazolam lormetazepam nitrazepam quazepam, temazepam or triazolam

19. A method co-complex or composition according to Claim 17 wherein the drug is hydrocortisone dexamethasone prednisolone 17β-estradiol 17α-ethinylestradiol ethinylestradiol 3-methyl ether estriol norethindrone norethindrone acetate norgestrel ethisterone methoxyprogesterone acetate progesterone 17-methyltestosterone triamcinolone triamcinolone acetonide testosterone spironolactone or alfaxalone

20 A method according to Claim 1 or 3, a co-complex according to Claim 5 or a composition according to Claim 6 or 9, wherein the drug is the reduced biooxidizable blood-brain barrier penetrating lipoidal dihydropyridine form of a dihydropyridine ⇌ pyridinium salt redox system for brain-targeted drug delivery preferably wherein the dihydropyridine form is a compound of the formula

[D-DHC]

wherein [D] is a centrally acting drug species and [DHC] is the reduced biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine ⇌ pyridinium salt redox carrier especially when the centrally acting drug species is dopamine testosterone phenytoin GABA, valproic acid tyrosine methicillin oxacillin benzylpenicillin cloxacillin, dicloxacillin desipramine acyclovir trifluorothymidine zidovudine hydroxy-CCNU, chlorambucil tryptamine dexamethasone hydrocortisone, ethinyl estradiol norethindrone estradiol ethisterone norgestrel estrone estradiol 3-methyl ether estradiol benzoate norethynodrel mestranol indomethacin naproxen FENU HENU or 5-FU

21 A method co-complex or composition according to any one of Claims 16-20, wherein the cyclodextrin is as defined in Claim 12 and the polymer is as defined in any one of Claims 13 to 15, especially when the cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin the polymer is hydroxypropyl methylcellulose sodium carboxymethylcellulose or polyvinylpyrrolidone and the drug is a carbonic anhydrase inhibitor or a steroid

22 A composition according to Claim 6, 9 or 11 wherein all ingredients are ophthalmically acceptable and wherein the drug is a carbonic anhydrase inhibitor or a steroid the polymer is hydroxypropyl methylcellulose sodium carboxymethylcellulose or polyvinylpyrrolidone and the cyclodextrin is hydroxypropyl β-cyclodextrin or hydroxypropyl-γ-cyclodextrin

23. A composition according to Claim 6 9 or 11 wherein all ingredients are acceptable for use in a mouthwash and wherein the drug is a steroid the polymer is hydroxypropyl methylcellulose sodium carboxymethylcellulose or polyvinylpyrrolidone and the cyclodextrin is hydroxypropyl β-cyclodextrin or hydroxypropyl-γ-cyclodextrin

24. A method according to Claim 2 or 4 a co-complex according to Claim 5 or a composition according to Claim 7 8 or 9 wherein the food or cosmetic additive is a flavoring agent or fragrance preservative antioxidant, sweetening agent, coloring agent or vitamin or wherein the agrochemical is a fungicide herbicide or plant growth regulator or an insecticide nematocide or other pesticide.

Fig. 1

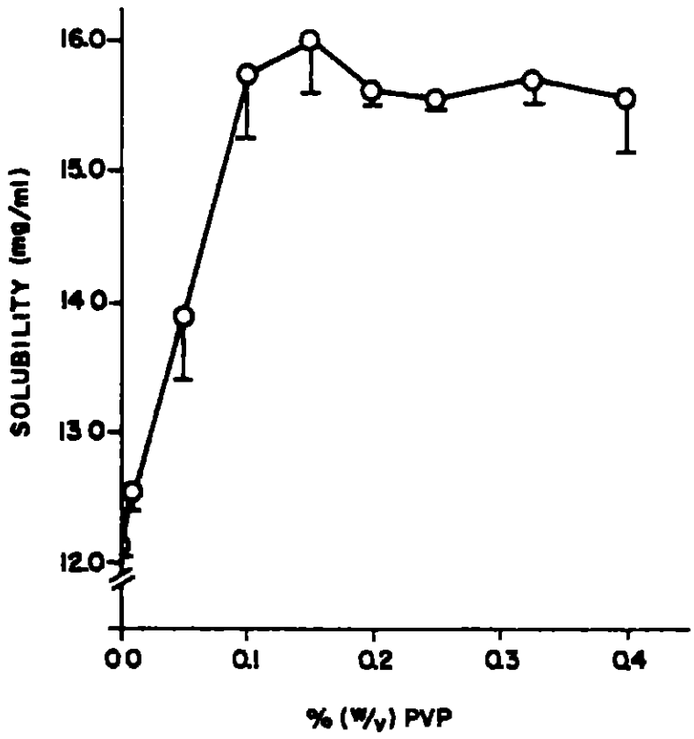


Fig. 2

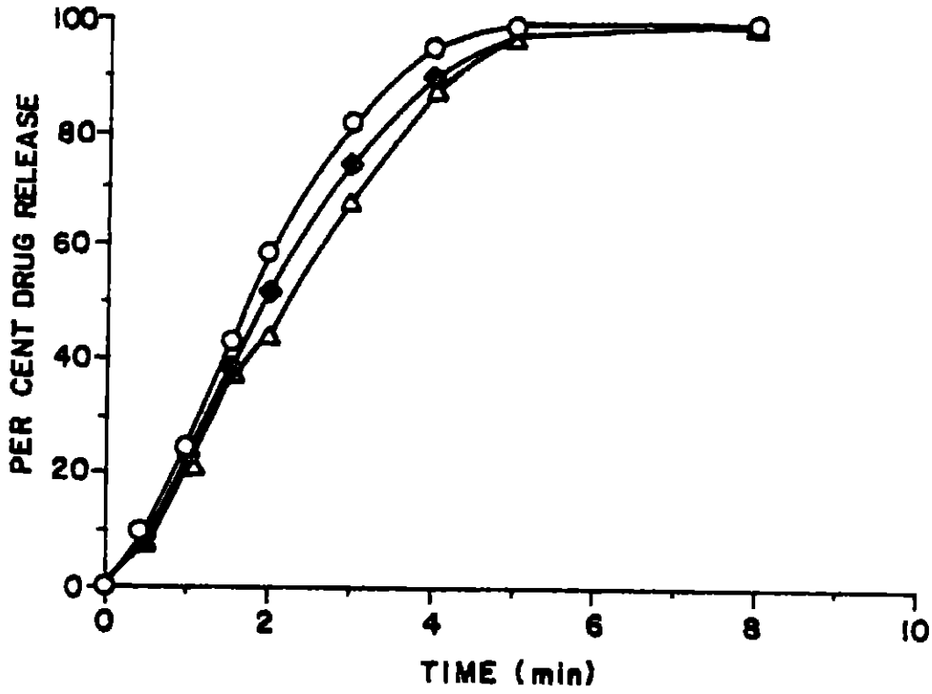
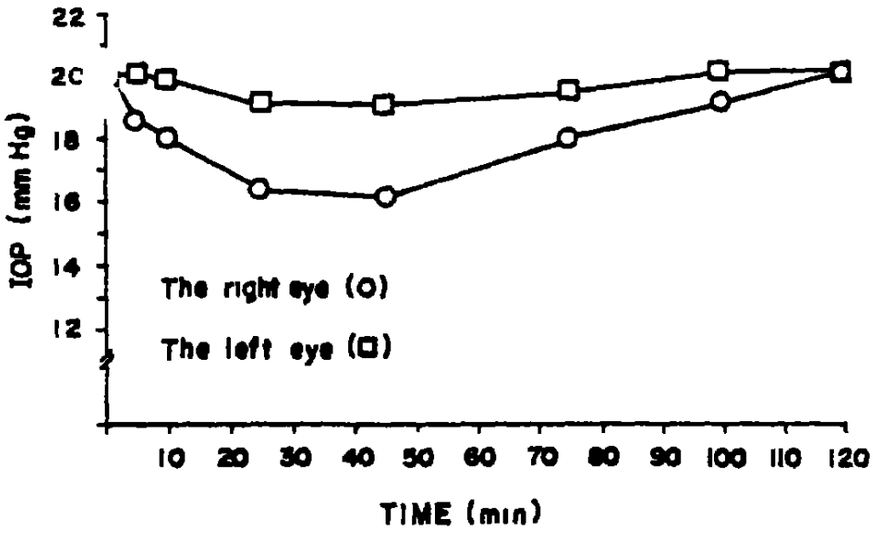


Fig. 3


22
20
18
16
14
12
IOP (mm Hg)
The right eye (O)
The left eye (□)
10 20 30 40 50 60 70 80 90 100 110 120
TIME (min)

ANEXO 4

325

PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro

INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 7
A61K 47/48, 31/57

A1

(11) Internationale Veröffentlichungsnummer **WO 00/21570**

(43) Internationales Veröffentlichungsdatum 20 April 2000 (20.04.00)

(21) Internationales Aktenzeichen PCT/EP99/07711

(22) Internationales Anmeldedatum 13 Oktober 1999 (13.10.99)

(30) Prioritätsdaten
198 48 303 14 Oktober 1998 (14.10.98) DE

(71) Anmelder *(für alle Bestimmungsstaaten ausser US)*: SCHERING AKTIENGESELLSCHAFT [DE/DE] Müllerstrasse 178 D-13342 Berlin (DE).

(72) Erfinder, und
(75) Erfinder/Anmelder *(nur für US)*: HÖFFRT Peter [DE/DE] Ordensmeistorstrasse 49A D-12099 Berlin (DE) BACKENSFELD Thomas [DE/DE] Eddastrasse 39A D-13127 Berlin (DE)

(81) Bestimmungsstaaten AE, AL, AM AT AU AZ, BA BB BG, BR BY CA, CH, CN CU CZ, DK EE, ES FI, GB GD GE, GH GM HR HU, ID IL IN IS JP KE, KG KP KR KZ, LC LK, LR LS LT LU LV MD MG MK MN MW MX NO, NZ, PL, PT, RO RU SD, SE, SG SI SK SL, TJ TM TR TT UA UG US UZ, VN YU ZA ZW eurasisches Patent (AM AZ, BY KG KZ, MD RU TJ TM) europäisches Patent (AT BE, CH CY, DE, DK ES FI FR GB GR IE, IT LU MC, NL, PT SE)

Veröffentlicht
Mit internationalem Recherchenbericht
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist Veröffentlichung wird wiederholt falls Änderungen eintreffen

(54) Title COMBINATION OF GESTAGENS AND SUGARS

(54) Bezeichnung KOMBINATION AUS NORPREGNAN DERIVATEN UND CYCLODEXTRIN

(57) Abstract

The invention relates to a combination of at least one gestagen and a β-cyclodextrin or an γ-cyclodextrin or the derivatives of said cyclodextrins obtained by etherification or esterification of the free alcohol functions of cyclodextrin wherein the gestagen is a bridged 4,17-C_2-steroid The gestagen is preferably (21S)-21-hydroxy-21-methyl-14 17-ethano-19-norpregna-4,9 15-triene-3,20-dion). The cyclodextrin is preferably β-cyclodextrin Said combination is used as medicament in the treatment of climacteric complaints and fertility control

(57) Zusammenfassung

Die Erfindung betrifft eine Kombination aus mindestens einem Gestagen und einem β-Cyclodextrin oder γ-Cyclodextrin oder Derivaten dieser Cyclodextrine, die durch Verätherung oder Veresterung freier alkoholischer Funktionen der Cyclodextrine erhalten werden wobei das Gestagen ein 14 17-C_2-überbrücktes Steroid ist Bevorzugt ist das Gestagen (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9 15-triene-3 20-dion) Bevorzugt ist ein β-Cyclodextrin Die Kombination wird als Arzneimittel zur Behandlung von klimakterischen Beschwerden und zur Fertilitätskontrolle eingesetzt

KOMBINATION AUS NORPREGNAN DERIVATEN UND CYCLODEXTRIN

Die Erfindung betrifft eine Kombination aus mindestens einem Gestagen und einem Zucker Der Zucker stabilisiert das Gestagen dahingehend daß die Acyloinumlagerung in der Seitenkette an den Atomen C_{20} und C_{21} sowie oxidative Zersetzung verhindert wird Weiterhin umfaßt die Erfindung auch die Verwendung der Kombination als Arzneimittel und Verfahren zur Herstellung von Kombinationen

Stand der Technik

Aus der WO 96 / 02277 (Anmeldetag 10 Juli 1996) sind Komplexe aus steroidalen Sexualhormonen und Cyclodextrin bekannt Allein der Komplex aus 17α-Ethinylestradiol und ß-Cyclodextrin wird konkret beschrieben

In der Publikation WO 96/20209 mit Anmeldetag vom 4 Juli 1996 werden allgemein Gestagene beschrieben Dabei wird insbesondere auch ein (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4 9 15-triene-3 20-dion erwähnt Gestagene werden zur Behandlung von klimakterischen Beschwerden eingesetzt Auch läßt sich die Fertilität mit diesen Gestagenen kontrollieren

Gestagene mit einer α-Hydroxyketonstruktur in der Seitenkette unterliegen bei Lagerung einer Acyloinumlagerung Dabei treten sterische Varianten auf Diese Umlagerung wird durch viele pharmazeutische Hilfsstoffe (z.B Lactose Magnesiumstearat) beschleunigt

Darüber hinaus treten Oxidationsreaktionen in verschiedenen Molekülpositionen auf

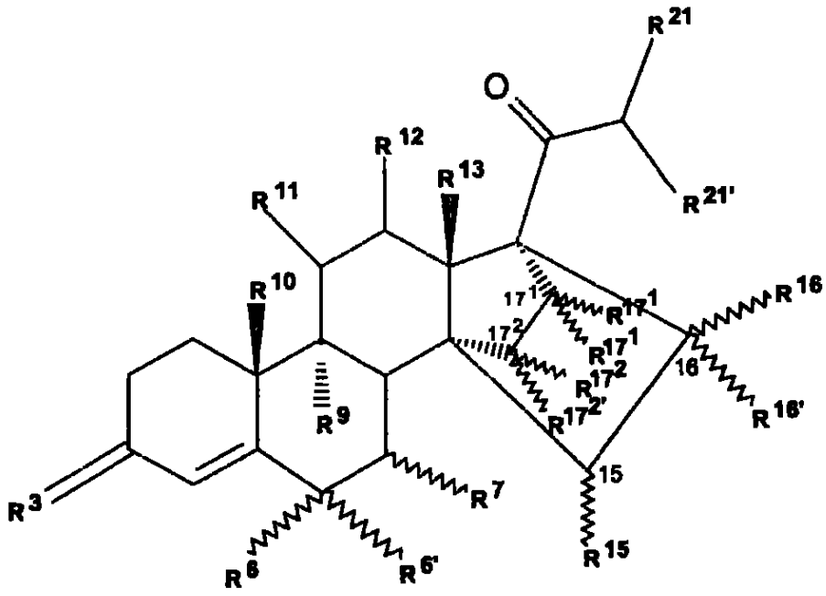
Aufgabe und Losung

Es stellt sich somit die Aufgabe Gestagene, insbesondere (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4 9 15-triene-3 20-dion gegen Zersetzung durch Acyloinumlagerung oder Oxidation zu schützen, ohne die pharmakologische Verträglichkeit und pharmazeutische Bearbeitung negativ zu beeinträchtigen

Die Aufgabe wird gelöst durch eine Kombination aus mindestens einem Gestagen und einem ß – Cyclodextrin oder ɣ - Cyclodextrin oder Derivaten dieser Cyclodextrine die

durch Veretherung oder Veresterung freier alkoholischer Funktionen der Cyclodextrine erhalten werden,

wobei die Gestagene 14 17-C_2 - überbrückte Steroide sind die zur Gruppe der Formel I zählen



(I)

worin

R^3 für ein Sauerstoffatom die Hydroxyiminogruppe oder zwei Wasserstoffatome

R^6 für ein Wasserstoff- Fluor- Chlor- oder Bromatom oder für einen α- oder β-ständigen C_1-C_4-Alkylrest, wobei dann $R^{6'}$ und R^7 Wasserstoffatome darstellen oder aber

$R^{6'}$ für ein Wasserstoff- Fluor-, Chlor- oder Bromatom oder für einen C_1-C_4-Alkylrest wobei dann R^6 und R^7 eine gemeinsame zusätzliche Bindung darstellen

R^7 für einen α- oder β-ständigen C_1-C_4-Alkylrest wobei dann R^6 und $R^{6'}$ Wasserstoffatome darstellen oder aber

R^6 und R^7 gemeinsam für eine α- oder β-ständige Methylengruppe und $R^{6'}$ für ein Wasserstoffatom oder

R^6 und $R^{6'}$ gemeinsam für eine Ethylen- oder Methylengruppe und R^7 fur ein Wasserstoffatom

R^9 und R^{10} jeweils für ein Wasserstoffatom oder eine gemeinsame Bindung,

R^{11} und R^{12} jeweils für ein Wasserstoffatom oder eine gemeinsame Bindung

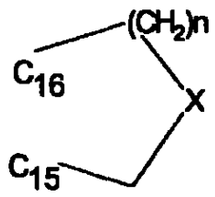
R^{13} für eine Methyl oder Ethylgruppe

R^{15} für ein Wasserstoffatom oder einen C_1-C_3-Alkylrest,

R^{16} und $R^{16'}$ unabhängig voneinander fur ein Wasserstoffatom einen C_1-C_3-Alkylrest oder einen C_2-C_4-Alkenylrest oder gemeinsam für eine C_1-C_3-Alkylidengruppe

R^{15} und R^{16} für eine gemeinsame Bindung sowie R^{16} fur ein Wasserstoffatom oder einen C_1-C_3-Alkylrest oder

R^{15} und R^{16} gemeinsam für einen Ring der Teilformel



worin n = 1 und 2 und X eine Methylengruppe oder ein Sauerstoffatom bedeuten sowie

$R^{16'}$ für ein Wasserstoffatom

R^{171} für ein Wasserstoffatom oder einen C_1-C_3-Alkylrest

R^{172} für ein Wasserstoffatom einen C_1-C_3-Alkylrest oder einen C_2-C_4-Alkenylrest

$R^{171'}$ und $R^{172'}$ jeweils für ein Wasserstoffatom oder für eine gemeinsame Bindung

R^{21} für ein Wasserstoffatom oder einen C_1 C_3-Alkylrest,

$R^{21'}$ für ein Wasserstoffatom einen C_1-C_3-Alkylrest oder eine Hydroxygruppe stehen

Die Schlangenlinien /\/\/\ in den allgemeinen Formeln der vorliegenden Erfindung bedeuten daß der betreffende Substituent sich in der α- oder β-Position an dem entsprechenden Kohlenstoffatom befinden kann

82

Bei den vorstehend als mögliche Substituenten genannten C_1-C_3-Alkylgruppen kann es sich um eine Methyl- Ethyl n-Propyl- oder i-Propyl- und bei den C_1-C_4-Alkylgruppen zusätzlich um eine n-Butyl- i-Butyl- oder tert -Butylgruppe handeln Eine Methyl- oder Ethylgruppe ist in allen Fällen bevorzugt

Im Falle des C_2-C_4-Alkenylrestes für R^{16} $R^{16'}$ und/oder R^{172} handelt es sich um einen Vinyl- Allyl- oder But 3-enylrest der Vinylrest ist bevorzugt.

Spezielle Gestagene

Bevorzugt gemäß vorliegender Erfindung sind Kombinationen aus mindestens einem Gestagen und einem ß – Cyclodextrin oder γ - Cyclodextrin oder Derivaten dieser Cyclodextrine die durch Veretherung oder Veresterung freier alkoholischer Funktionen der Cyclodextrine erhalten werden

wobei die Gestagene zur Gruppe der Formel I zählen

in der

R^3 für ein Sauerstoffatom oder zwei Wasserstoffatome, und/oder

R^6 für ein Wasserstoffatom oder für einen α- oder β-ständigen C_1-C_4-Alkylrest

wenn R^6 und R^7 Wasserstoffatome darstellen, oder aber

$R^{6'}$ für ein Wasserstoff- Chlor- oder Bromatom oder für einen C_1-C_4-Alkylrest,

wenn $R^{6'}$ und R^7 eine gemeinsame zusätzliche Bindung darstellen

und/oder

R^{16} und $R^{16'}$ jeweils für ein Wasserstoffatom jeweils für eine Methylgruppe oder der eine dieser beiden Substituenten für eine C_1-C_4-Alkyl- oder eine Vinylgruppe und der andere dieser beiden Substituenten für ein Wasserstoffatom stehen, oder

beide gemeinsam eine C1-C3-Alkenylgruppe bilden

und/oder

R^{171} und R^{172} unabhängig voneinander für ein Wasserstoffatom oder eine Methylgruppe

und/oder

$R^{171'}$ und $R^{172'}$ jeweils für ein Wasserstoffatom oder eine gemeinsame Bindung

und/oder

R^{21} für ein Wasserstoffatom oder einen C_1-C_3-Alkylrest sowie $R^{21'}$ für ein Wasserstoffatom oder eine Hydroxygruppe

stehen

sowie die anderen Substituenten alle die in Formel (I) angegebenen Bedeutungen haben können

Mehr bevorzugt sind Kombinationen aus mindestens einem Gestagen und einem ß – Cyclodextrin oder γ - Cyclodextrin oder Derivaten dieser Cyclodextrine die durch Verätherung oder Veresterung freier alkoholischer Funktionen der Cyclodextrine erhalten werden,

wobei das Gestagen zur Gruppe der folgenden Substanzen zählen

14 17-Ethano-19-norpregna-4 9 dien-3 20-dion

14 17-Ethano-19-norpregna-4 6-dien-3,20-dion,

14 17-Ethano-19-norpregna-4,15-dien-3 20-dion

14 17-Ethano-19-norpregna-4 6 15-trien-3 20-dion

14 17-Ethano-19-norpregna-4 9 15-trien-3,20-dion

21-Methyl-14,17-ethano-19-norpregn-4-en-3 20-dion

21-Methyl-14,17-ethano-19-norpregna-4,9-dien-3 20-dion

21-Methyl-14 17-ethano-19-norpregna-4 6-dien-3,20-dion

21-Methyl-14,17-ethano-19-norpregna-4,15-dien-3,20-dion

21-Methyl-14,17-ethano-19-norpregna-4 9 15-trien-3 20-dion

14,17-Etheno-19-norpregn-4-en-3 20-dion

14 17-Etheno-19-norpregna-4 6-dien-3 20-dion,

14,17-Etheno-19-norpregna-4 9-dien-3 20-dion

21-Methyl-14 17-etheno-19-norpregn 4-en-3 20-dion

21-Methyl-14 17-etheno-19-norpregna-4 6-dien-3,20-dion

21-Methyl-14,17-etheno-19-norpregna-4 9-dien-3 20-dion,

21-Methyl-14,17-etheno-19-norpregna-4 9 11-trien-3,20-dion

21-Hydroxy-14 17-etheno-19-norpregn-4-en-3 20-dion

21-Hydroxy-14,17-etheno-19-norpregna-4 9-dien-3 20-dion

17^1-Methyl-14 17-etheno-19-norpregn-4-en-3,20-dion

17^1-Methyl-14,17-etheno-19-norpregna-4 6-dien-3 20-dion

17^2-Methyl-14 17-etheno-19-norpregn-4-en-3,20-dion

17^2-Methyl-14,17-etheno-19-norpregna-4,9-dien 3 20-dion

15ß,16α-Dimethyl-14 17-etheno-19-norpregn-4-en-3,20-dion

6-Methyl-14,17-ethano-19-norpregna-4 6-dien-3 20-dion

6-Chlor -14,17-ethano-19-norpregna-4 6-dien-3 20-dion,

6α-Methyl-14 17-ethano-19-norpregn-4-en-3 20 dion

6 21-Dimethyl-14 17-ethano-19-norpregna-4 6-dien-3,20-dion

15ß,16α-Dimethyl-14,17-ethano-19-norpregn 4-en-3 20-dion

6-Chlor-21-methyl-14 17-ethano-19-norpregna-4 6-dien 3,20-dion,

16α-Methyl-14 17-ethano 19-norpregn-4-en-3 20-dion,

16α-Methyl-14 17-ethano-19-norpregna-4,6-dien-3,20-dion,

16α-Methyl-14 17-ethano-19-norpregna-4,9-dien-3 20-dion

16α,21-Dimethyl-14,17-ethano-19-norpregna-4 9-dien-3 20-dion

21-Hydroxy-16α-methyl-14 17-ethano-19-norpregn-4-en-3 20-dion

16α-Ethyl-14 17-ethano-19-norpregn-4-en-3,20-dion

16α-Ethenyl-14,17-ethano-19-norpregn-4-en 3,20-dion,

16-Methyl-14 17-ethano-19-norpregna-4 15-dien-3,20-dion

(17^1R)-17^1-Methyl-14,17-ethano-19-norpregn-4-en 3,20-dion

(17^1S)-17^1-Methyl-14,17-ethano-19-norpregn-4-en-3 20-dion

(17^1R)-17^1-Methyl-14,17-ethano-19-norpregna-4 9-dien-3 20-dion

(17^1S)-17^1-Methyl-14,17-ethano-19-norpregna-4,9-dien-3 20-dion

(17^2R)-17^2-Methyl-14,17-ethano-19-norpregn-4-en-3 20-dion

(17^2R)-17^2-Methyl-14 17-ethano-19-norpregna-4 6-dien-3 20-dion

(17^2R)-17^2-Methyl-14,17-ethano-19-norpregna-4,9-dien-3,20-dion

(17^2R)-17^2,21-Dimethyl-14 17-ethano-19-norpregna-4,6-dien-3 20-dion

(17^2R)-17^2,21-Dimethyl-14,17-ethano-19-norpregna-4,9-dien-3 20-dion

(17^2R)-17^2,21-Dimethyl-14 17-ethano-19-norpregna-4 9 11-trien-3,20-dion

16-Methylen-14,17-ethano-19-norpregn-4-en-3 20-dion

16-Methylen-14,17-ethano-19-norpregna-4 6-dien-3 20-dion

16-Methylen-14 17-ethano-19-norpregna-4 9-dien-3,20-dion

21-Hydroxy-14 17-ethano-19-norpregn-4-en-3 20-dion

21-Hydroxy-14 17-ethano-19-norpregna-4 6-dien-3 20-dion

21-Hydroxy-14,17-ethano-19-norpregna-4 9-dien-3 20-dion,

21-Hydroxy-14,17-ethano-19-norpregna-4 9,15-trien-3 20-dion

(21*R*)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregn-4-en 3 20-dion

(21*S*)-21-Hydroxy-21-methyl 14 17-ethano-19-norpregn-4-en-3,20-dion,

(21*R*)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4,9-dien-3,20-dion,

(21*S*)-21-Hydroxy-21 methyl-14 17-ethano-19-norpregna-4 9-dien-3 20-dion
(21*R*)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4,6-dien- 3 20-dion,
(21*S*)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4 6-dien- 3 20-dion,
(21*R*)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4 9 15-trien-3 20-dion
(21*S*)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4 9 15-trien-3 20-dion
14 17-Ethano-18a-homo-19-norpregn-4-en-3 20-dion
14 17-Ethano-18a-homo-19-norpregna-4 6-dien-3 20-dion
14 17-Ethano-18a-homo-19-norpregna-4 9-dien-3 20-dion
14 17-Ethano-18a-homo-19-norpregna-4 15-dien-3,20-dion
21-Methyl-14 17-ethano-18a-homo-19-norpregn-4-en-3 20 dion
21-Methyl-14 17-ethano-18a-homo-19-norpregna-4 6-dien-3 20-dion
21-Methyl-14 17-ethano-18a-homo-19-norpregna-4 9-dien-3,20-dion
(21*R*)-21-Hydroxy-21-methyl-14 17-ethano-18a-homo-19-norpregn-4-en-3 20-dion
(21*S*)-21-Hydroxy-21-methyl-14 17-ethano-18a-homo-19-norpregn-4-en-3 20-dion
(21*R*)-21-Hydroxy-21-methyl-14,17-ethano-18a-homo-19-norpregna-4,9-en-3 20-dion
(21*S*)-21-Hydroxy-21-methyl-14,17 ethano-18a-homo-19-norpregna-4,9-en-3 20-dion
(21*R*)-21-Hydroxy-21-methyl-14,17-ethano-18a-homo-19-norpregna-4 6-en-3 20-dion
(21*S*)-21-Hydroxy-21-methyl-14 17-ethano-18a-homo-19-norpregna-4 6-en-3 20-dion

Wirksamkeit der Kombination

Nach oraler Gabe bildet sich am gastrointestinalen Resorptions - Ort aus dem Komplex aus Gestagen und Zuckerderivat ein Gleichgewicht zwischen dem nicht - dissoziierten Komplex und den Einzelkomponenten Dabei wird durch Verdrängung des Gestagens aus dem komplexierenden Zuckerderivat der freie Wirkstoff schnell freigesetzt und gelangt zur Resorption Das Zuckerderivat hingegen wird nicht resorbiert und unverändert über den Darm ausgeschieden Die pharmakologische Wirkung des Gestagens ist in WO096/20209 beschrieben

Im Gestagenrezeptor - Bindungstest auf gestagene Wirkung unter Verwendung von Cytosol aus Kaninchenuterushomogenat und von ^{3}H-Progesteron als Bezugssubstanz zeigen das Gestagen eine sehr starke Affinität zum Gestagenrezeptor Im Schwangerschaftserhaltungstest an der Ratte zeigen die Gestagene der allgemeinen Formel (I) eine sehr hohe gestagene Wirksamkeit.

Zusätzlich zur sehr hohen gestagene Wirksamkeit im Schwangerschaftserhaltungstest zeigen die Gestagene der allgemeinen Formel I im Gegensatz zur bereits bekannten Verbindung 14,17-Ethano-19-norpregn-4 en 3,20-dion aber größtenteils auch nach oraler Gabe eine gute gestagene Wirkung

Aufgrund ihrer hohen gestagenen Wirksamkeit können die Gestagene der allgemeinen Formel (I) beispielsweise allein oder in Kombination mit Estrogenen in Präparaten zur Kontrazeption verwendet werden Aber auch alle anderen heutzutage für Gestagene bekannten Verwendungsmöglichkeiten stehen dem neuen Komplex offen

Die Dosierung der erfindungsgemäßen Komplexen in Kontrazeptionspräparaten soll vorzugsweise 0,01 bis 2 mg berechnet als freies Gestagen pro Tag betragen Geeignete Dosierungen können routinemäßig bestimmt werden zum Beispiel durch Bestimmung der Bioäquivalenz gegenüber einem bekannten Gestagen für eine bestimmte Verwendung, beispielsweise eine Menge die bioäquivalent zu 0,030 bis 0 150 mg Levonorgestrel für die Kontrazeption ist Diese Eichung gilt auch für die weiteren Angaben der Dosierungen zu den Gestagenen

Die gestagenen und estrogenen Wirkstoffkomponenten werden in Kontrazeptionspräparaten vorzugsweise zusammen oral appliziert Die tägliche Dosis wird vorzugsweise einmalig verabfolgt Neben der oralen ist z.B auch eine transdermale Verabreichung möglich

Als Estrogene kommen vorzugsweise synthetische Estrogene wie Ethinylestradiol 14α,17α-Ethano-1,3 5(10)-estratrien-3 17β-diol (WO 88/01275) oder 14α 17α-Ethano-1,3 5(10)-estratrien-3 16α 17β-triol (WO 91/08219) in Betracht
Das Estrogen wird in einer Menge verabfolgt, die der von 0 01 bis 0 05 mg Ethinylestradiol entspricht

Die neuen Kombination aus mindestens einem Gestagen der Formel I und aus einem ß – Cyclodextrin oder γ - Cyclodextrin, oder Derivaten dieser Cyclodextrine können auch in Präparaten zur Behandlung gynäkologischer Störungen und zur Substitutionstherapie eingesetzt werden Wegen ihres günstigen Wirkungsprofils sind die erfindungsgemäßen Kombinationen besonders gut geeignet zur Behandlung prämenstrueller Beschwerden wie Kopfschmerzen depressive Verstimmung Wasserretention und Mastodynie Die Tagesdosis bei der Behandlung prämenstrueller Beschwerden liegt bei etwa 1 bis 20 mg berechnet als freies Gestagen

Schließlich können die neuen Kombinationen auch als gestagene Komponente in den neuerdings bekannt gewordenen Zusammensetzungen fur die weibliche Fertilitätskontrolle die sich durch die zusätzliche Verwendung eines kompetitiven Progesteronantagonisten auszeichnen zum Einsatz kommen (H B Croxatto und A M Salvatierra in Female Contraception and Male Fertility Regulation ed by Runnebaum Rabe & Kiesel - Vol 2 Advances in Gynecological and Obstetric Research Series, Parthenon Publishing Group - 1991, Seite 245)

Die Dosierung liegt im bereits angegebenen Bereich die Formulierung kann wie bei konventionellen OC-Präparaten erfolgen Die Applikation des zusätzlichen kompetitiven Progesteronantagonisten kann dabei auch sequentiell vorgenommen werden

Die Formulierung der pharmazeutischen Präparate auf Basis der neuen Kombinationen erfolgt in an sich bekannter Weise indem man den Wirkstoff, gegebenenfalls in Kombination mit einem Estrogen mit den in der Galenik gebräuchlichen Trägersubstanzen Verdünnungsmitteln gegebenenfalls Geschmackskorrigentien usw verarbeitet und in die gewünschte Applikationsform überführt

Für die bevorzugte orale Applikation kommen insbesondere Tabletten Dragees Kapseln Pillen Suspensionen oder Lösungen in Frage

Für die transdermaleApplikation sind Insbesondere Matrix- oder Membranpflaster geeignet

Die Kombinationen mit Verbindungen der allgemeinen Formel (I) können auch kontinuierlich durch ein intrauterines Freisetzungssystem (IUD) appliziert werden, die Freisetzungsrate der aktiven Verbindung(en) wird dabei so gewählt, daß die täglich freigesetzte Dosis innerhalb der bereits angegebenen Dosierungsbereiche liegt

Die Herstellung der Gestagene ist in der WO 96/20209 (Publikationsdatum 4 Juli 1996) ausführlich beschrieben

Bevorzugt ist eine Kombination mit dem Gestagen (21S)-21-Hydroxy-21-methyl 14,17-ethano-19-norpregna-4,9,15-triene-3 20-dion

Cyclodextrine

ß – Cyclodextrin γ - Cyclodextrin und Derivate dieser Cyclodextrine die durch Verätherung oder Veresterung freier alkoholischer Funktionen der Cyclodextrine

88

erhalten werden sind beschrieben in J Pharm Sci 74 (1985) S 987-990 oder Int J Pharm 29 (1986) S 73-82

Mehr bevorzugt ist eine Kombination aus einem Gestagen und einem Cyclodextrin wobei das Cyclodextrin ein ß-Cyclodextrin ist

Am meisten bevorzugt ist die Kombination aus dem Gestagen (21S)-21-Hydroxy-21 methyl-14,17-ethano-19-norpregna-4 9 15-triene-3,20-dion und dem ß-Cyclodextrin

Vorteile

Werden Gestagene, insbesondere (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4,9,15-triene-3,20-dion mit Hilfsstoffen wie Lactose Maisstärke Mannitol mikrokristalline Cellulose Polyvidon Hydroxypropylmethylcellulose Dicalciumphosphat und Maltodextrin vermengt, so ist ein beschleunigter Abbau festzustellen Hierbei handelt es sich um eine Acyloinumlagerung Dabei entsteht eine Mischung aus zwei Paaren von Diastereomeren mit jeweils getauschten Positionen der Ketogruppe und der Hydroxylgruppe am C_{20} und C_{21} Atom Von den vier möglichen Strukturen entspricht lediglich eine der zuvor genannten Substanz (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4 9 15-triene-3,20-dion

So verringert sich bei einer Lagerung bei 25 °C (60% rel Feuchte) über 3 Monate der Gehalt an nicht komplexiertem (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4,9,15-triene-3 20-dion auf unter 90% des Startwertes, wenn die Substanz (i) entweder mit den Hilfsstoffen Lactose, Maisstärke modifizierte Maisstärke, Polyvidon 25 000 und Magnesiumstearat (ii) oder mit den Hilfsstoffen mit Mannitol, Hydroxypropylmethylcellulose und Magnesiumstearat tablettiert wird Auch die Formulierungen mit den Hilfsstoffen (iii) direkttablettierbares Mannitol oder (iv) mikroknstalline Cellulose und Magnesiumstearat oder (v) Glyceryltribehenat zeigen einen vergleichbaren Abbau der Substanz (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4 9 15-triene-3 20-dion

Durch die erfindungsgemäße Kombination (Komplexierung des Gestagens mit β-Cyclodextrin) lassen sich Tabletten erhalten, die trotz Lagerung bei den kritischen Temperaturen einen Wirkstoffgehalt aufweisen welcher nach 6-monatiger Lagerung bei 40°C 75% relativer Feuchte im offenen Standglas noch über 90% des Startwertes bleibt

Weitere Ausführungsformen zu Cyclodextrinen

Vorteilhaft ist eine erfindungsgemäße Kombination bei der das Cyclodextrin und das Gestagen

beim ß – Cyclodextrin in einem Komplex 1 n (Gestagen Cyclodextrin n ≥ 1) vorliegt bevorzugt ist ein Verhältnis von 1 2 (Gestagen Cyclodextrin), und beim γ - Cyclodextrin ebenfalls in einem Komplex 1 n (n ≥ 1) (Gestagen Cyclodextrin) vorliegt bevorzugt ist ein Verhältnis von 1 2 (Gestagen Cyclodextrin)

Neben der Stabilitätserhöhung läßt sich die Stöchiometrie der Komplexbildung ermitteln Dabei ist offensichtlich, daß die Komplexbildung bei den Komplexen (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4 9 15-triene-3 20-dion und γ - Cyclodextrin im Verhältnis 1 1 bis 1 2 (Gestagen Cyclodextrin) stattfindet Vorteilhaft ist ein Komplexierungsverhaltnis von 1 2 (Gestagen Cyclodextrin)

Bei dem Komplex aus (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4 9,15-triene-3 20-dion und ß – Cyclodextrin liegt ein Verhältnis von 1 2 (Gestagen Cyclodextrin) vor

Derartige Komplexe weisen ein zum Teil niedrigeres Löslichkeitsprodukt als das Sterold allein auf Somit können die Komplexe durch eine Fällungsreaktion (z B Copräzipitation) dargestellt werden

Weitere Ausführungsformen als Arzneimittel

Bevorzugt ist die erfindungsgemäße Kombination als Arzneimittel Die Wirkung der Substanzen ist zuvor beschrieben (vgl WO96/20209)

Mehr bevorzugt ist ein Arzneimittel oder ein pharmazeutisches Präparat, enthaltend einen erfindungsgemäße Kombination einschließlich pharmazeutischer Trägerstoffe und Hilfsstoffe

Noch mehr bevorzugt ist ein Arzneimittel oder pharmazeutisches Präparat enthaltend eine erfindungsgemäße Kombination zur peroralen oralen parenteralen transdermalen pulmonalen nasalen rektalen vaginalen oder intrauterinen Anwendung

Die Erfindung betrifft weiterhin die Verwendung von erfindungsgemäßen Kombinationen zusammen mit pharmakologischen Hilfs- und Trägerstoffen die physiologisch verträglich sind zur Herstellung eines Medikaments zur Behandlung von klimakterischen Beschwerden Solche Hilfs- und Trägerstoffe sind in Remington's Pharmaceutical Science 15th ed Mack Publishing Company Easton Pennsylvania (1980) beschrieben

Die erfindungsgemäßen Kombinationen zeigen die Wirkung in den zuvor genannten Test bei Konzentrationen von 0 1 bis 1000 ng/ml des Gestagens

Für die therapeutische Wirkung ist die geeignete Dosis unterschiedlich und hängt beispielsweise von der verwendeten Kombinationen mit Gestagenen der allgemeinen Formel I dem Wirt, der Art der Verabreichung und der Art und der Schwere der zu behandelnden Zustände ab Im allgemeinen sind jedoch bei Tieren zufriedenstellende Resultate zu erwarten bei täglichen Dosen an Gestagen von 1 bis 3000 µg/kg Tierkörpergewicht Bei größeren Säugetieren, beispielsweise Menschen, beträgt eine empfohlene tägliche Dosis an Gestagen 0 1 bis 200 mg Bevorzugt sind Werte von 0 3 bis 60mg pro Tag mehr bevorzugt 1 bis 20 mg pro Tag und am meisten bevorzugt 2 bis 10 mg pro Tag

Die Erfindung liefert weiterhin

(i) die Verwendung eines der erfindungsgemäßen Kombination zur Herstellung eines Medikaments zur Behandlung von klimakterische Beschwerden,

(ii) ein Verfahren zur Behandlung von klimakterische Beschwerden welches Verfahren eine Verabreichung einer Kombinationsmenge gemäß der Erfindung umfaßt, wobei die Menge die Krankheit unterdrückt und wobei die Kombinationsmenge einem Patienten gegeben wird, der ein solches Medikament benötigt

(iii) eine pharmazeutische Zusammensetzung zur Behandlung von klimakterische Beschwerden, welche Behandlung eine der erfindungsgemäßen Kombinationen und wenigstens einen pharmazeutischen Hilfs- und/oder Trägerstoff umfaßt

Die Erfindung liefert weiterhin

(i) die Verwendung eines der erfindungsgemäßen Kombination zur Herstellung eines Medikaments zur Behandlung prämenstrueller Beschwerden wie Kopfschmerzen depressive Verstimmung Wasserretention und Mastodynie

(ii) ein Verfahren zur Behandlung prämenstrueller Beschwerden wie Kopfschmerzen depressive Verstimmung Wasserretention und Mastodynie welches Verfahren eine Verabreichung einer Kombinationsmenge gemäß der Erfindung umfaßt wobei die Menge die Krankheit unterdrückt und wobei die Kombinationsmenge einem Patienten gegeben wird der ein solches Medikament benötigt,

(iii) eine pharmazeutische Zusammensetzung zur Behandlung prämenstrueller Beschwerden wie Kopfschmerzen depressive Verstimmung, Wasserretention und Mastodynie, welche Behandlung eine der erfindungsgemäßen Kombinationen und wenigstens einen pharmazeutischen Hilfs- und/oder Trägerstoff umfaßt

Die Tagesdosis bei der Behandlung pramenstrueller Beschwerden liegt bei etwa 1 bis 20 mg, berechnet als freies Gestagen

Weitere Ausführungsformen als orales Kontrazeptivum

Die Erfindung umfaßt eine erfindungsgemäße Kombination für die Fertilitätskontrolle

Aufgrund ihrer hohen gestagenen Wirksamkeit können die neuen Kombinationen mit Gestagenen der allgemeinen Formel (I) beispielsweise allein oder in Kombination mit Estrogenen in Präparaten zur Kontrazeption verwendet werden Aber auch alle anderen heutzutage fur Gestagene bekannten Verwendungsmöglichkeiten stehen den neuen Verbindungen offen

Die Dosierung der erfindungsgemäßen Kombination in Kontrazeptionspräparaten soll vorzugsweise 0,01 bis 2 mg pro Tag berechnet als freies Gestagen betragen

Die gestagenen und estrogenen Wirkstoffkomponenten werden in Kontrazeptionspräparaten vorzugsweise zusammen oral appliziert Die tägliche Dosis wird vorzugsweise einmalig verabfolgt

Als Estrogene kommen vorzugsweise synthetische Estrogene wie Ethinylestradiol 14α,17α-Ethano-1 3 5(10)-estratrien-3 17β-diol (WO 88/01275) oder 14α,17α-Ethano-1 3 5(10)-estratrien-3 16α 17β-triol (WO 91/08219) in Betracht

Das Estrogen wird in einer Menge verabfolgt, die der von 0 01 bis 0 05 mg Ethinylestradiol entspricht

Schließlich können die neuen Kombinationen auch als gestagene Komponente in den neuerdings bekannt gewordenen Zusammensetzungen für die weibliche Fertilitätskontrolle die sich durch die zusätzliche Verwendung eines kompetitiven Progesteronantagonisten auszeichnen, zum Einsatz kommen (H B Croxatto und A M Salvatierra in Female Contraception and Male Fertility Regulation ed by Runnebaum Rabe & Kiesel - Vol 2 Advances in Gynecological and Obstetric Research Series Parthenon Publishing Group - 1991 Seite 245)
Die Dosierung liegt im bereits angegebenen Bereich, die Formulierung kann wie bei konventionellen OC-Präparaten erfolgen Die Applikation des zusätzlichen kompetitiven Progesteronantagonisten kann dabei auch sequentiell vorgenommen werden

Weitere Ausführungsformen als Stabilisierungsverfahren

Vorteilhaft ist ein Verfahren zur Stabilisierung eines Gestagens nach der Formel I unter Verwendung von einem ß – Cyclodextrin oder γ - Cyclodextrin oder Derivaten dieser Cyclodextrine die durch Verätherung oder Veresterung freier alkoholischer Funktionen der Cyclodextrine erhalten werden Der bevorzugte Komplex aus Gestagen und Cyclodextrin ist der Komplex aus (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4,9,15-triene-3 20-dion und ß – Cyclodextrin

Bevorzugt ist ein Verfahren zum Komplexieren von einem Gestagen und von einem ß – Cyclodextrin oder γ - Cyclodextrin unter Verreiben als Trockenmischung Röntgenspektren des Pulvers welches als Trockenmischung hergestellt wurde zeigen daß die Komplexierung partiell bereits vorliegt jedoch noch nicht vollständig vollzogen worden ist. Diese Komplexierung bereits als Trockenmischung ist überraschend

Mehr bevorzugt ist die Darstellung der Komplexe durch Fällungsreaktion, z B Copräzipitation, indem zu einer wässrigen Cyclodextrinlösung eine ethanolische Lösung des Gestagens zugetropft wird Die durch Fällung hergestellten Komplexe aus Gestagenen und Cyclodextrin können vor der Formulierung zum Arzneimittel durch

geeignete Vermahlungstechniken z.B die der Luftstrahlvermahlung auf die gewünschte Partikelgrößenverteilung gebracht werden

Bevorzugt zur Herstellung der Formulierung ist eine Verkapselung oder Granulierung und anschließende Tablettierung

Mehr bevorzugt ist ein Verfahren der Direkttablettierung des Komplexes aus einem Gestagen mit ß – Cyclodextrin oder γ - Cyclodextrin unter Zugabe von pharmazeutisch verträglichen Hilfsstoffen Dabei wird auf Granulierungsschritte verzichtet Ein Granulierungsschritt beinhaltet die Gefahr daß der Cyclodextrin - Komplex zerstört wurde, indem das Steroid aus dem Cyclodextrin - Wirt durch Hilfsstoffmoleküle als Gast verdrängt würde

Es wurde daher eine Direkttablettierung unter Zugabe der Hilfsstoffe mikrokristalline Cellulose Lactose Croscarmellose-Na hochdisperses Siliciumdioxid und Magnesiumstearat durchgeführt

Beispiel

Die Komplexe aus (21S)-21 Hydroxy-21-methyl 14 17 ethano-19-norpregna-4,9,15-triene-3 20-dion und aus β - und γ - Cyclodextrin wurden in folgender Weise hergestellt

19 mmol des Cyclodextrins wurden in 610 ml 45°C warmem Wasser gelöst und innerhalb von 30 min 7,6 mmol ZK 187226 gelöst in 10 ml Ethanol zugetropft Mit weiteren 5 ml Ethanol wurde nachgespült auf Raumtemperatur abkühlen lassen 24h bei RT gerührt 2h im Eisbad (2 °C) gerührt und der Niederschlag über eine G2-Fritte abgesaugt Der erhaltene Komplex wurde anschließend noch 2 mal mit je 50 ml Eiswasser und einmal mit eiskaltem Aceton gewaschen Nach Trocknung im Exsikator über Phosphorpentoxid wurde der Komplex durch Karl-Fischer-Wasserbestimmung HPLC DSC und Röntgenpulverdiffraktometrie charakterisiert

Die Tatsache daß selbst nach der vergleichend durchgeführten bloßen Verreibung eine deutliche Veränderung sowohl im Rötgenpulverspektrum als auch in der DSC beobachtet wird, deutet darauf hin daß eine partielle aber nicht vollständige Komplexierung bereits bei der Verreibung von (21S)-21-Hydroxy-21-methyl-14,17 ethano-19-norpregna-4 9 15-triene-3 20-dion mit β - oder γ - Cyclodextrin stattfindet

Aus den hergestellten Cyclodextrinkomplexen von (21S)-21-Hydroxy-21-methyl 14 17-ethano-19-norpregna-4 9 15-triene-3 20-dion wurden nun nach Vermahlung der Komplexe Tabletten hergestellt Für die Tablettierung ist von Bedeutung, daß sie als Direkttablettierung durchgeführt wird ohne einen Granulierschritt Ein solcher Granulierprozess würde nämlich die Gefahr beinhalten, daß die Cyclodextrinkomplexe zerstört werden, indem (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4 9 15-triene-3,20-dion aus dem Cyclodextrin Wirt durch Hilfsstoffmoleküle als Gast verdrängt wurde

Es wurde daher eine Direkttablettierung unter Zugabe der Hilfsstoffe mikrokristalline Cellulose, Lactose Croscarmellose-Na hochdisperses Siliciumdioxid und Magnesiumstearat durchgeführt

Die hergestellten Tabletten sowie eine aus nicht komplexiertem Wirkstoff hergestellte Formulierung und die Komplexe aus (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4 9 15-triene-3 20-dion und β- und γ-Cyclodextrin wurden zur Stabilitätsprüfung eingelagert und der Gehalt an (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4,9,15-triene 3 20-dion (bei den Tabletten bezogen auf den

Sollgehalt von 0,1mg Wirkstoff pro Tablette bei den Komplexen als Massenprozent) nach 1,5 und 3-monatiger Lagerung bestimmt Die Ergebnisse sind in den Tabellen 1 bis 5 dargestellt

Die aus den β - Cyclodextrin- und γ - Cyclodextrin - Clathraten zeigen im Vergleich zu den mit unkomplexiertem Wirkstoff hergestellten Tabletten eine deutlich verbesserte Stabilität Das β - Cyclodextrin - Clathrat zeigt die beste Stabilisierung ist in guter Qualität herstellbar und auch ökonomisch gegenüber γ - Cyclodextrin zu bevorzugen Aufgrund der Ergebnisse der 3 Monats-Auslagerung ergibt sich für die mit dem Komplex aus (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4 9 15-triene-3 20-dion und β-Cyclodextrin hergestellten Tabletten eine für eine Marktformulierung ausreichende Stabilität

Tabelle 1 ß - Cyclodextrin - Clathrat Tabletten

Monate	-18°C	+25°C	+25°C 60% r F	+40°C	+40°C 75% r F	+60°C	+60°C 75% r F
0	97 0% (1 0%)			-			-
1 5	97 4% (0 8%)	97 0% (0 6%)	96 7% (0 7%)	95 5% (1 8%)	93 5% (0 9%)	92 9% (0 7%)	89 7% (0 8%)
3	97 0% (0 8%)	97 1% (1 0%)	96 6% (0 7%)	95 2% (0 5%)	91 8% (1 0%)	92 6% (1 2%)	89 0% (1 7%)

Tabelle 2 γ-CD-Clathrat Tabletten

Monate	-18°C	+25°C	+25°C 60% r F	+40°C	+40°C 75% r F	+60°C	+60°C 75% r F
0	93 0% (8 3%)	-	-		-		
1 5	97 9% (2 6%)	99 4% (2 5%)	98 8% (2 7%)	98 5% (3 6%)	95 1% (7 3%)	90 0% (4 7%)	85 1% (5 1%)
3	99 8% (4 2%)	96 5% (3 9%)	99 9% (5 7%)	97 9% (3 4%)	88 7% (3 0%)	77 1% (4 7%)	79 1% (1 6%)

Tabelle 3 (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4,9,15-triene-3,20-dion Tabletten

Monate	-18°C	+25°C	+25°C 60% r F	+40°C	+40°C 75% r F	+60°C	+60°C 75% r F
0	100 1% (0 8%)		-	-	-	-	
1 5	nicht untersucht	90 6% (0 5%)	80 3% (0 3%)	26 6% (0 8%)	27 9% (1 1%)	0 3% (1 7%)	0 1% (14 3%)
3	101 2% (0 5%)	80 1% (0 6%)	63 9% (1 0%)	8 5% (5 2%)	14 1% (4 1%)	0 3% (88 0%)	0 1% (65 6%)

97

Tabelle 4 (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4 9 15-triene-3 20-dion - β-Cyclodextrin-Komplex Gehalt in %

Monate	-18°C	+25°C	+25°C 60% r F	+40°C	+40°C 75% r F	+60°C	+60°C 75% r F
0	12 5% (0 3%)			-		-	-
1 5	12 5% (0 7%)	nicht untersucht	12 5% (0 4%)	nicht untersucht	12 4% (0 9%)	nicht untersucht	12 3% (0 8%)
3	12 5% (0 5%)	nicht untersucht	12 5% (0 3%)	nicht untersucht	12 6% (0 3%)	nicht untersucht	12 3% (0 5%)

Tabelle 5 (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4 9 15-triene-3,20-dion - γ-Cyclodextrin-Komplex Gehalt in %

Monate	-18°C	+25°C	+25°C 60% r F	+40°C	+40°C 75% r F	+60°C	+60°C 75% r F
0	13 6% (2 8%)	-	-	-		-	
1 5	13 8% (1 2%)	nicht untersucht	13 7% (0 8%)	nicht untersucht	13 3% (0 5%)	nicht untersucht	12 0% (1 3%)
3	13 9% (2 5%)	nicht untersucht	13 5% (1 3%)	nicht untersucht	13 0% (0 5%)	nicht untersucht	10 0% (1 1%)

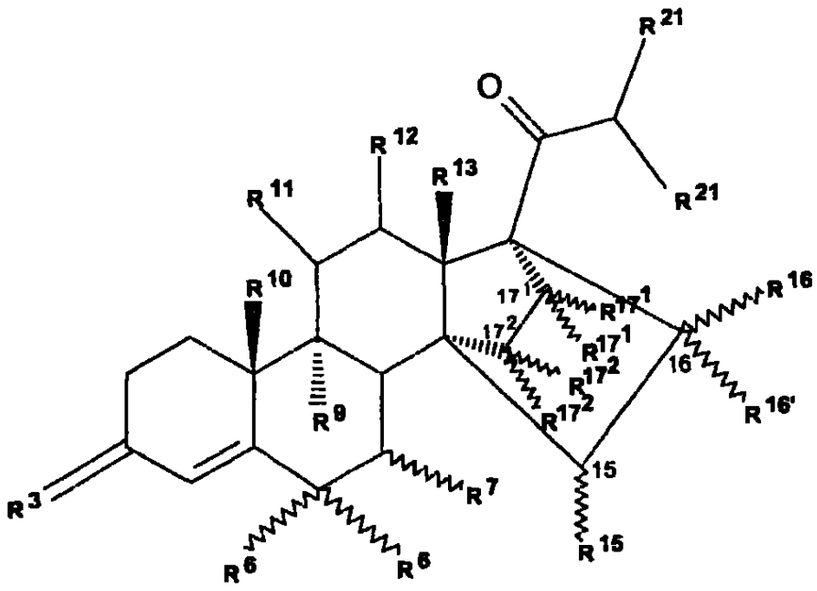
r F = relative Luftfeuchte eingestellt in der Klimakammer

98

Patentansprüche

1 Kombination aus mindestens einem Gestagen und einem ß – Cyclodextrin oder γ - Cyclodextrin oder Derivaten dieser Cyclodextrine, die durch Verätherung oder Veresterung freier alkoholischer Funktionen der Cyclodextrine erhalten werden wobei das Gestagen ein 14 17-C_2 - überbrücktes Steroid ist

2 Kombination nach Anspruch 1 wobei die Gestagene zur Gruppe der Formel I zählen



(I)

worin

R^3 für ein Sauerstoffatom die Hydroxyiminogruppe oder zwei Wasserstoffatome

R^6 für ein Wasserstoff- Fluor- Chlor- oder Bromatom oder für einen α- oder β ständigen C_1-C_4-Alkylrest, wobei dann $R^{6'}$ und R^7 Wasserstoffatome darstellen, oder aber

$R^{6'}$ für ein Wasserstoff- Fluor- Chlor oder Bromatom oder für einen C_1-C_4-Alkylrest wobei dann R^6 und R^7 eine gemeinsame zusätzliche Bindung darstellen

R^7 für einen α- oder β-ständigen C_1-C_4-Alkylrest wobei dann R^6 und R^6 Wasserstoffatome darstellen oder aber

R^6 und R^7 gemeinsam für eine α- oder β ständige Methylengruppe und R^6 für ein Wasserstoffatom oder

R^6 und $R^{6'}$ gemeinsam für eine Ethylen- oder Methylengruppe und R^7 für ein Wasserstoffatom

R^9 und R^{10} jeweils für ein Wasserstoffatom oder eine gemeinsame Bindung

R^{11} und R^{12} jeweils für ein Wasserstoffatom oder eine gemeinsame Bindung

R^{13} für eine Methyl- oder Ethylgruppe

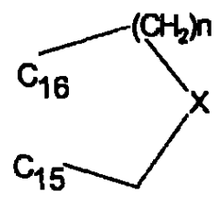
R^{15} für ein Wasserstoffatom oder einen C_1-C_3-Alkylrest

R^{16} und $R^{16'}$ unabhängig voneinander für ein Wasserstoffatom einen C_1-C_3-Alkylrest

oder einen C_2-C_4-Alkenylrest oder gemeinsam für eine C_1-C_3-Alkylidengruppe

R^{15} und R^{16} für eine gemeinsame Bindung sowie R^{16} für ein Wasserstoffatom oder einen C_1-C_3-Alkylrest oder

R^{15} und R^{16} gemeinsam für einen Ring der Teilformel



worin n = 1 und 2 und X eine Methylengruppe oder ein Sauerstoffatom bedeuten sowie

R^{16} für ein Wasserstoffatom,

R^{171} für ein Wasserstoffatom oder einen C_1-C_3-Alkylrest

R^{172} für ein Wasserstoffatom einen C_1-C_3-Alkylrest oder einen C_2-C_4-Alkenylrest

$R^{171'}$ und $R^{172'}$ jeweils für ein Wasserstoffatom oder für eine gemeinsame Bindung

R^{21} für ein Wasserstoffatom oder einen C_1-C_3-Alkylrest,

100

$R^{21'}$ für ein Wasserstoffatom einen C_1-C_3-Alkylrest oder eine Hydroxygruppe stehen

3 Kombination nach Anspruch 2 wobei das Gestagen ein (21S)-21-Hydroxy-21-methyl-14 17-ethano-19-norpregna-4 9 15-triene-3 20-dion ist

4 Kombination nach einem der vorhergen Ansprüche, wobei das Cyclodextrin ein ß-Cyclodextrin ist

5 Kombination nach einem der vorherigen Ansprüche wobei das Cyclodextrin und das Gestagen

beim ß – Cyclodextrin in einem Komplex 1 n (Gestagen Cyclodextrin $n \geq 1$) vorliegt und

beim γ - Cyclodextrin in einem Komplex 1 n ($n \geq 1$) (Gestagen Cyclodextrin) vorliegt

6 Kombination nach einem der vorhergen Ansprüche als Arzneimittel

7 Kombination nach Anspruch 6 als stabile orale Formulierung

8 Kombination nach Anspruch 6 oder 7 zur Herstellung eines Arzneimittels zur Behandlung von klimakterischen Beschwerden

9 Kombination nach einem der vorherigen Ansprüche 1 bis 5 fur die Fertilitätskontrolle

10 Arzneimittel oder pharmazeutisches Präparat enthaltend eine Kombination nach einem der vorhergen Ansprüche mit pharmazeutisch verträglichen Hilfsstoffen und Trägerstoffen

11 Arzneimittel oder pharmazeutisches Präparat enthaltend eine Kombination nach einem der vorherigen Ansprüche zur peroralen oralen parenteralen transdermalen pulmonalen nasalen, rektalen vaginalen oder intrauterinen Anwendung

12 Verwendung einer Kombination nach einem der vorherigen Anspruche 1 bis 9 zur Herstellung eines Medikaments zur Behandlung pramenstrueller Beschwerden wie Kopfschmerzen depressive Verstimmung Wasserretention und Mastodynie

13 Verfahren zur Fertilitätskontrolle unter Verabreichung einer Kombination nach einem der Ansprüche 1 bis 9

14 Verfahren zur Stabilisierung eines Gestagens nach der Formel I gemäß Anspruch 2 unter Verwendung von einem ß – Cyclodextrin oder γ - Cyclodextrin oder Derivaten dieser Cyclodextrine die durch Verätherung oder Veresterung freier alkoholischer Funktionen der Cyclodextrine erhalten werden

15 Verfahren zum Komplexieren von einem Gestagen nach einem der Ansprüche 1 und 2 und von einem ß – Cyclodextrin oder γ - Cyclodextrin unter Verreiben als Trockenmischung oder durch Fällungsreaktion vorzugsweise Copräzipitation

16 Verfahren der Direkttablettierung von einem Gestagenkomplex nach einem der Ansprüche 1 und 2 mit einem ß – Cyclodextrin oder γ - Cyclodextrin unter Zugabe von pharmazeutisch verträglichen Hilfsstoffen

ANEXO 5

350

US005798338A

United States Patent [19]

Backensfeld et al

[11] Patent Number 5,798,338

[45] Date of Patent* Aug. 25, 1998

[54] **SOLID DOSAGE FORMS THAT CONTAIN CLATHRATES OF 17α-ETHINYL ESTRADIOL**

[75] Inventors: **Thomas Backensfeld**, Johannes Tack both of Berlin, Germany

[73] Assignee: **Schering Aktiengesellschaft**, Berlin Germany

[21] Appl. No. 765,823

[22] PCT Filed. Jul. 10, 1995

[86] PCT No. PCT/EP95/02656

§ 371 Date Apr 2, 1997

§ 102(e) Date Apr 2, 1997

[87] PCT Pub. No. WO96/02277

PCT Pub. Date Feb. 1, 1996

[30] Foreign Application Priority Data

Jul. 20 1994 [DE] Germany 44 26 709 6

[51] Int. Cl.[6] A61K 31/705 A61K 31/565

[52] U.S. Cl 514/26 514/58 514/182

[58] Field of Search 514/58, 182 26

[56] References Cited

U.S. PATENT DOCUMENTS

4,877,774 10/1989 Pitha et al 514/26

OTHER PUBLICATIONS

Pitha et al Int J Pharm. 29(1) 73–82 (1986)

Primary Examiner—Phyllis Spivack

Attorney, Agent, or Firm—Millen, White Zelano, & Branigan P.C

[57] **ABSTRACT**

A method and pharmaceutical compositions are disclosed for reducing oxidative degradation of 17 α-ethinylestradiol comprising combining the estradiol with an effective amount of cyclodextrin, thus forming a cyclodextrin clathrate of the steroid.

14 Claims, No Drawings

104

SOLID DOSAGE FORMS THAT CONTAIN CLATHRATES OF 17α-ETHINYL ESTRADIOL

The invention relates to solid dosage forms that contain steroidal sex hormones

As is generally known natural and especially synthetically derived sex hormones are generally highly effective active ingredients of pharmaceutical agents Consequently in most cases solid dosage forms contain these active ingredients at very low dosages these are usually 0.01 μg to 500 μg and especially 0.1 μg to 200 μg per single-dosed dosage form. This means that both the preparation and the storage and use of these dosage forms are often problematical in nature.

In the preparation of such low-dosed dosage forms, strong fluctuations of the active ingredient concentrations in the dosage units occur almost unavoidably (inadequate content uniformity), which manifest themselves more strongly the smaller the amount of the active ingredient.

In the storage of such low-dosed preparations, moreover a reduction in the active ingredient concentration is often additionally observed as a result of in most cases, oxidative degradation reactions of the active ingredient.

In addition, at such low dosage the bioavailability of the active ingredient is subject to a pronounced first-pass effect and exhibits great inter and intra-individual fluctuations.

It has now been found that the drawbacks that are observed especially in the preparation and storage of dosage forms which contain low-dosed steroidal sex hormones can be avoided, at least to a large extent, if dosage forms are prepared that contain powdery cyclodextrin clathrates of these active ingredients

Steroidal sex hormones that are suitable for the production of dosage forms according to the invention are estrogenically gestagenically androgen anabolically antiestrogenically antigestagenically and antiandrogenically active compounds as well as mixtures of these substances.

For example estrone estradiol estriol 17α-ethinylestradiol, mestranol, 14α,17α-ethanoestra-1,3,5(10)-triene-3 17β-diol (WO88/01275), 14α,17α ethanoestra-1,3,5(10)-triene-3 16α,17β-triol (WO and their esters such as estradiol-dipropionate, estradiol-dihexanoate and estradiol-didecanoate (EP-A 163 596) can be mentioned as examples of suitable estrogens.

Suitable gestagens are for example norethisterone, levonorgestrel gestodene desorgestrel and 3-ketodesorgestrel.

Suitable androgen-anabolically active compounds are, i.a. testosterone, mesterolone methenolone, and esters of these substances such as testosterone propionate testosterone enanthate, testosterone nicotinate, and testosterone phenylacetate.

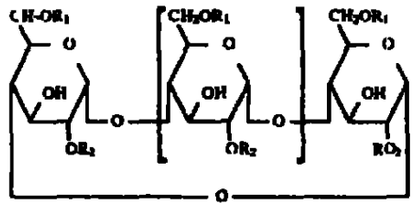
Suitable antiestrogens are, i.a. 1-methyl-androsta-1,4-diene-3 17-dione (atamestane) and 7α-[9-[(4,4,5,5,5-pentafluoropentyl)-sulfinyl]-nonyl]estra-1,3,5(10)-triene-3 17β-diol (ICI 182780).

As suitable antigestagens 11β-[4 (dimethylamino) phenyl]-17β-hydroxy-17α-(3-hydroxypropyl)-13α-estra-4,9-dien-3-one (onapristone) and 11β-[4-dimethylamidophenyl]-17β-hydroxy-17α-(1-propynyl)-estra-4,9-dien-3-one (mifepristone) can be mentioned.

Antiandrogenically active compounds that are suitable for the production of dosage forms according to the invention are for example 17α-acetoxy-6-chloro-pregna-4,6-diene-3,20-dione (chloromadinone acetate) 17α-acetoxy-6-chloro-1β,2β-dihydro-3H-cyclopropa[1,2] pregna-1,4,6-triene-3,20-dione (cyproterone acetate) (topterone) and 17β-hydroxy-1α-methyl-17α-propyl-androstan-3-one (propylmesterolone)

It was already mentioned that the dosage forms according to the invention contain powdery cyclodextrin clathrates of these active ingredients

Cyclodextrins that are suitable for the production of these clathrates are for example those of general formula



In which

R_1 means a hydrogen atom a methyl group a 2-hydroxyethyl group, or a 2-hydroxypropyl group

R_2 means a hydrogen atom or if R_1 represents a methyl group, also a methyl group and

n means a number from 4 to 7

Such cyclodextrins are preferably α-cyclodextrin γ-cyclodextrin dimethyl-β-cyclodextrin 2-hydroxyethyl β-cyclodextrin 2-hydroxypropyl-β-cyclodextrin and especially β-cyclodextrin (Drug Dev and Ind. Pharm. 17 1991 1503–1549 J Incl. Phenom. 1 1983 135–150 and WO 93/13138). For the production of clathrates the steroid hormones can be very intimately mixed with the cyclodextrin, optionally with the addition of other pharmaceutical adjuvants (for example by stirring, kneading) or the solvent can be removed from a solution of the components in water and/or a suitable solvent (such as for example, a C1–C4 alcohol such as methanol, ethanol or isopropanol or a C_3–C_4 ketone such as acetone or methyl ethyl ketone) by for example, vacuum distillation, freeze-drying or spray drying. By contrast it is also possible however to feed the steroid hormone that is dissolved in a suitable solvent (such as for example, one of the above-mentioned alcohols or ketone) into an aqueous cyclodextrin solution, and to filter off and dry the precipitated clathrate

Just like the active ingredients themselves, the clathrates can then also optionally be processed into the desired dosage forms such as tablets powder granulates etc after the addition of the commonly used additives such as for example lactose, starch, polyvinylpyrrolidone magnesium stearate and preservatives

It is obvious to one skilled in the art that several common preliminary tests are required to determine what cyclodextrin is optimally suited for inclusion of the desired steroidal steroid hormone. In the case of very small steroid molecules the use of α-cyclodextrin may be optimum, while in the case of inclusion of quite large steroid molecules, it may be necessary to use γ- or even δ-cyclodextrin as a host molecule Normally the ratio of cyclodextrin to steroid hormone is selected such that 1:1 mol-mol complexes are formed which does not rule out the possibility however that in individual cases it may be more advantageous to select the molar ratio such that for example, 2:1 3:1 3:2 or 1:2 complexes are formed

The embodiments below are used for a more detailed explanation of the invention

EXAMPLE 1

20.96 g of 17α-ethinylestradiol is dissolved in 20 ml of ethanol 28.38 g of β-cyclodextrin (relative to anhydrous

β-cyclodextrin) is dissolved in 900 ml of water while being stirred at 45° C. The ethanolic ethinylestradiol solution is added in drops to aqueous cyclodextrin solution within 40 minutes while being stirred so that a slightly cloudy solution develops. Within 2 hours the solution is cooled to 25° C. It is stirred for another 20 hours to 25° C. The precipitated solid is suctioned off and washed twice with 50 ml of water each. The crystallizate is suspended twice with 40 ml of acetone each and suctioned off. Then it is rewashed with 50 ml of water. The wet crystallizate is dried in a vacuum with phosphorous pentoxide.

The content of 17α-ethinylestradiol in the inclusion bond is determined by means of high pressure liquid chromatography and is 10.2%.

EXAMPLE 2

2.37 g of β-cyclodextrin is dissolved in 200 ml of water. 118.6 mg of 17α-ethinylestradiol is weighed into the aqueous cyclodextrin solution. The suspension is stirred for 48 hours. The solid is suctioned off and washed twice with 25 ml of water each. The crystallizate is suspended twice with 20 ml of acetone each and suctioned off. Then it is rewashed with 20 ml of water. The wet crystallizate is dried in a vacuum with phosphorous pentoxide.

The content of ethinylestradiol in the inclusion bond is determined by means of high-pressure liquid chromatography and is 10.4%.

EXAMPLE 3

A β-cyclodextrin inclusion complex (produced according to Example 1) is ground and triturated in portions with lactose. Corn starch and modified starch are mixed in. The powder is processed into a granulate in a fluidized-bed granulator with an aqueous polyvinylpyrrolidone 25000 solution. After magnesium stearate is mixed in, the press dust that is obtained is pressed into tablets with a weight of 55 mg and a diameter of 5 mm.

Composition of a Tablet:	
Ethinylestradiol/β-cyclodextrin inclusion compound in 10 µg of 17α-ethinylestradiol	0.098 mg
lactose	35.102 mg
corn starch	9.900 mg
modified starch	6.600 mg
polyvinylpyrrolidone 25000	2.750 mg
magnesium stearate	0.550 mg
	55.000 mg

EXAMPLE 4

A β-cyclodextrin inclusion complex (produced according to Example 2) is ground. 9.615 g of the complex (corresponding to 1 g of ethinylestradiol) is homogeneously added to a powder mixture that consists of 2360.385 g of lactose, 1300 g of microcrystalline cellulose, and 310 mg of corn starch. After 20 g of magnesium stearate is added, the powder press dust that is obtained is pressed with a tablet press into tablets with a 6 mm diameter and a tablet weight of 80 mg. They come with an active ingredient content of 20 µg of ethinylestradiol per tablet.

We claim

1. A pharmaceutical composition comprising an effective amount of 17α-ethinylestradiol and an amount of a β-cyclodextrin which is effective in reducing the oxidative degradation of the 17α-ethinylestradiol, wherein the composition is a clathrate.

2. A composition of claim 1 wherein the composition comprises about 10% w/w of 17α-ethinylestradiol to β-cyclodextrin.

3. A composition of claim 1 wherein the amount of 17α-ethinylestradiol is 0.01 µg–200 µg.

4. A composition of claim 1 wherein the amount of 17α-ethinylestradiol is 0.1 µg–200 µg.

5. A composition of claim 1 wherein the amount of 17α-ethinylestradiol is 10 µg–20 µg.

6. A composition of claim 1 wherein the 17α-ethinylestradiol is an inclusion in the β-cyclodextrin.

7. A method of reducing oxidative degradation of 17α-ethinylestradiol comprising combining an amount of 17α-ethinylestradiol and an amount of β-cyclodextrin which is effective in reducing the oxidative degradation of said estradiol.

8. The method of claim 7 wherein the 17α-ethinylestradiol and the β-cyclodextrin are in a 1:1 mole:mole ratio.

9. The method of claim 7 wherein the amount of 17α-ethinylestradiol is 0.01 µg–200 µg.

10. The method of claim 7 wherein the amount of 17α-ethinylestradiol is 0.1 µg–200 µg.

11. A method of making a pharmaceutical composition comprising an effective amount of 17α-ethinylestradiol and an amount of a β-cyclodextrin which is effective in reducing the oxidative degradation of the 17α-ethinylestradiol wherein the composition is in a solid dosage form comprising combining an amount of 17α-ethinylestradiol and an amount of β-cyclodextrin which is effective in reducing the oxidative degradation of said estradiol.

12. The method of claim 11 further comprising dissolving the 17α-ethinylestradiol in a suitable solvent, dissolving the β-cyclodextrin in an aqueous solution containing said solutions of 17α-ethinylestradiol and β-cyclodextrin, and isolating the resulting precipitated clathrate.

13. The method of claim 11 further comprising dissolving the β-cyclodextrin in an aqueous solution, adding solid 17α-ethinylestradiol to said aqueous solution, and isolating the resulting clathrate.

14. A method of achieving an estrogenic effect comprising, administering a pharmaceutical composition comprising an effective amount of 17α-ethinylestradiol and an amount of β-cyclodextrin which is effective in reducing the oxidative degradation of the 17α-ethinylestradiol wherein the composition is in a solid dosage form.

* * * * *

353

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D C ,

Doctor
Gustavo Hollmann Restrepo
Apoderado

Oficio N° 12168

ASUNTO	Radicación PCT N°	03-59764
	Trámite	011
	Evento	379
	Actuacion	440
	Folios	009

Con fundamento en lo previsto por el articulo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor Luis Fernando Rincón Cuellar, en su calidad de apoderado de Gynopharm S.A , reune los requisitos formales exigidos por la ley al momento de su presentación

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días habiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001

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

18 FEB 2005

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

202021

VF
FOB 18 2005
RETIRE COPIAS TRASLADO
JORGE VILLAMIL