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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-077244- -00005-0000

Fecha: 2009-03-04 16:30:13 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 10

Re: Expediente No. 04.077.244

Solicitud de patente de invención titulada: "FORMA DE DOSIFICACIÓN ORAL QUE PROPORCIONA LIBERACIÓN CONTROLADA".

Solicitante: GLAXO GROUP LIMITED

Nuestra Ref: P2004/000126

RESPUESTA AL OFICIO No. 15553, NOTIFICADO POR FIJACIÓN EN LISTA No. 394,
DE FECHA 05 DE DICIEMBRE DE 2008.
(EXAMEN DE FONDO)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 45 de la Decisión 486:

1. En primer lugar, y con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado**, que reemplaza en su totalidad al Capítulo Reivindicatorio presentado al momento de radicar la presente solicitud. Para tal efecto, **adjunto un recibo de pago** que cubre la tasa de modificación correspondiente.

El Capítulo Reivindicatorio Modificado contiene los siguientes cambios:

Reivindicaciones Originales	Descripción
1	Se limita específicamente a modalidades que contienen el Compuesto (A).
2	Se integra en la nueva Reivindicación 1.
11 a 14	Eliminadas

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Valga anotar que las modificaciones efectuadas al Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial.

2. a- El Examinador argumenta que la Reivindicación 14 no es patentable debido a que ésta reclama métodos de tratamiento.

b- Considero superada la anterior objeción ya, que la Reivindicación 14 fue eliminada del Capítulo Reivindicatorio Modificado.

3. a- El Examinador argumenta que los documentos US6068859 (D1), WO90/01925 (D2) y US5393765 (D3), afectan la novedad y el nivel inventivo de la presente invención.

El Examinador sostiene que D1 revela formas de liberación controlada que contienen azitromicina, correspondientes a formas de liberación sostenida y retardada. Las formas de liberación sostenida de D1 se refieren a núcleos de matriz polimérica (acetato de celulosa), que liberan el principio activo a la superficie de la tableta o lo exponen al medio ambiente por erosión. Formas de liberación retardadas comprenden una primera capa de polímeros dependientes del pH (soluble a un $\text{pH} > 5,0$) y un núcleo (opcionalmente, un núcleo con múltiples cubiertas) que contiene azitromicina, un desintegrante, un lubricante y uno o más vehículos farmacéuticos. El Examinador anota que D1 también revela núcleos de liberación osmótica que comprenden un recubrimiento polimérico.

D2 revela formas de liberación controlada que contienen un recubrimiento polimérico impermeable, que tienen una abertura para liberar el principio activo desde el núcleo, en el que dicho núcleo comprende uno o más agentes de liberación, como osmógenos, surfactantes y polímeros insolubles. Además, el núcleo puede estar recubierto por una primera capa erosionable o soluble, tal como etilcelulosa.

El Examinador también anota que la Reivindicación 1 de la presente invención es excesivamente amplia y general, y por lo tanto, está anticipada de manera general por la materia revelada en D1 y D2. Además, D1 y D2 también divulgan métodos para la producción de formas de liberación controlada que afectan el procedimiento de Reivindicación 13.

El Examinador además sostiene que D2, al igual que D1, revela formas de liberación controlada que contienen polímeros con un recubrimiento impermeable y con una abertura para liberar el principio activo desde el núcleo, donde el revestimiento, en general, se compone de derivados de celulosa. El Examinador anota que cualquier persona medianamente versada en la materia sabe,

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por ejemplo, que la HPMC es acido-resistente y sólo se disuelve a un $\text{pH} > 5.0$, el Eudragit se disuelve a un pH entre 6.7 y 5.5 y el shellac o PVAP se erosiona o se disuelve a un $\text{pH} > 5.0$.

En cuanto a la D3, el Examinador argumenta que esta referencia revela composiciones farmacéuticas de liberación controlada erosionables por orden cero, que comprenden un núcleo que contiene un principio activo y excipientes seleccionados, tales como lactosa y HPMC, y derivados de los mismos.

El Examinador concluye que D1 a D3 proporcionan sugerencias que conducen al desarrollo de la presente invención. Además, D1 y D2 demuestran que las formas farmacéuticas de la presente invención son ampliamente conocidas, y por lo tanto, evidentes para cualquier persona medianamente versada en la materia. Por ejemplo, el uso de polímeros para la protección de los ingredientes activos es habitual en el ámbito farmacéutico. Por último, el Examinador señala que el problema de proporcionar formas farmacéuticas dependientes del pH se había resuelto previamente en el estado de la técnica.

En conclusión, el Examinador concluye que la presente invención no es inventiva en relación con D1 a D3 y no proporciona efectos sorprendentes e inesperados.

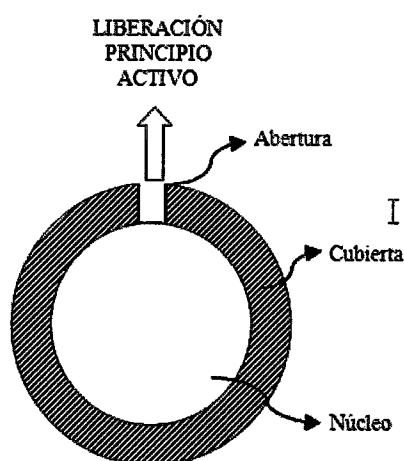
b- i) En primer lugar, me permito señalar que la Reivindicación 14 original, que reclamaba procedimientos para la preparación de las composiciones de la presente invención, ha sido eliminada del Capítulo Reivindicatorio Modificado.

ii) Ahora bien, vale la pena resaltar que la presente invención intenta resolver un problema persistente en la técnica, relacionado con recubrimientos impermeables del estado del arte (particularmente reveladas en D2) que no son adecuados para la liberación controlada de principios activos correspondientes a bases débiles o sales o solvatos farmacéuticamente aceptables de las mismas (estos ingredientes activos muestran una marcada solubilidad dependiente de pH).

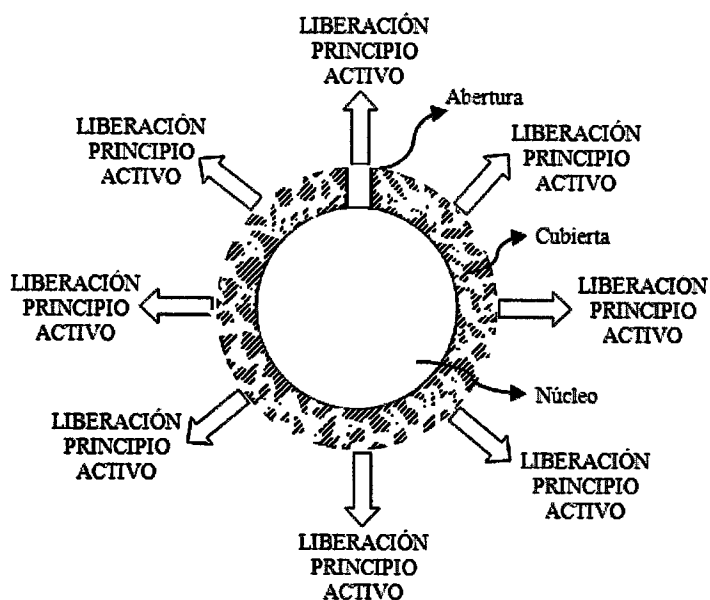
Así las cosas, la presente invención proporciona una forma de dosificación oral que comprende un núcleo que libera el principio activo (al desintegrarse parcial o completamente, disolverse o volverse poroso) que contiene una base débil farmacéuticamente aceptable (5-[4-[2-(N-metil-N-(2-piridil)amino)etoxy]bencil]tiazolidin-2,4-diona -Compuesto A-), donde el núcleo posee un recubrimiento con una o más aberturas que conducen al núcleo, caracterizado porque el recubrimiento es erosionable bajo determinadas condiciones de pH (se desintegra parcial o completamente, o se disuelve, o se vuelve poroso). Aunque las bases débiles farmacéuticamente activas son más solubles en el estómago que en el intestino, el núcleo del invento está diseñado

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para que se erosione y libere el ingrediente activo sustancialmente en el mismo grado en cualquiera de los dos ambientes ácido o básico, pero preferiblemente en el intestino. Así, la presente invención está caracterizada porque las composiciones reivindicadas liberan el principio activo desde el núcleo, tanto mediante la abertura en la cubierta (a $\text{pH} < 4.5$), como mediante la erosión de la cubierta (a $\text{pH} > 4.5$), tal como se ilustra a continuación:



$\text{pH} < 4.5$



$\text{pH} > 4.5$

En la presente invención, las aberturas en la cubierta mantienen su integridad y su perfil de liberación a pH ácido; de otra parte, la cubierta tiene un umbral de resistencia al pH (la cubierta no se erosiona, excepto en el intestino -pH básico-). Por lo tanto, la cubierta que se erosiona solamente a niveles de $\text{pH} > 4.5$, limita la cantidad de principio activo liberado en condiciones ácidas, pues la liberación de principio activo en dichas condiciones está restringida a la difusión del principio activo a través de la abertura de la cubierta. A niveles de pH mayores a 4.5, la cubierta se erosiona y expone mayores extensiones del núcleo, permitiendo una mayor difusión del principio activo hacia el exterior.

Por lo tanto, la presente invención se dirige a corregir el problema de *dose dumping* (liberación prematura) en el estómago de compuestos básicos que son más solubles a pH ácido, gracias a la liberación limitada en dicho ambiente por una abertura en la cubierta. A su vez, el tránsito de la tableta a través del sistema digestivo conduce hacia un pH intestinal más alto, allí, la cubierta se disuelve para exponer el núcleo y estimular la mayor liberación del principio activo básico. Es decir, la presente invención logra compensar la disminución de la solubilidad en pH básico del principio activo con un aumento en el área superficial del núcleo expuesto. El resultado es un perfil de liberación del principio activo más balanceado en ambos ambientes ácido y básico, tal

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como se ilustra en la Figura del Capítulo Descriptivo, que enseña el control del perfil disolución en función del pH.

En particular, la presente invención está dirigida a la formulación de bases débiles (más solubles en el rango de pH de 1 a 3, en comparación con su solubilidad en el rango de pH de 4.5 a 8), que incluyen específicamente el Compuesto A como base libre o en forma de una de sus sales. Esta base débil, farmacéuticamente activa, puede ser incorporada dentro de una tableta convencional de administración oral, o una matriz de liberación controlada, que luego es recubierta con un material de erosionabilidad dependiente del pH, por ejemplo un recubrimiento soluble a $\text{pH} > 4.5$, tal como un copolímero de polimetacrilato. En resumen, el material de recubrimiento se selecciona teniendo en cuenta que sea insoluble en ambientes ácidos ($\text{pH} 1.5\text{--}2.0$) y que sea soluble o erosionable en ambientes alcalinos ($\text{pH} 5.5$ o $\text{pH} 7$), donde la forma farmacéutica final además incluye al menos una abertura en la cubierta que permite la difusión controlada del principio activo a pH ácido.

iii) En relación con el estado del arte citado por el Examinador, es importante llamar la atención sobre lo siguiente:

- D1 revela tabletas antihiperlipémicas de liberación controlada, que comprenden: un núcleo que contienen un principio activo, un recubrimiento de membrana semipermeable y un conducto de paso en la membrana. La membrana semipermeable es permeable al paso del agua y de fluidos biológicos y es impermeable al paso del principio activo;
- D2 se relaciona con una forma farmacéutica que tiene un recubrimiento impermeable, con un orificio que conduce al núcleo el cual contiene un principio activo, lo cual permite su liberación. El orificio tiene un diámetro que normalmente corresponde del 10 al 60% de la tableta aproximadamente, preferiblemente 30% de diámetro;
- D3 revela una composición farmacéutica erosionable que contiene un ingrediente activo con una solubilidad no mayor de 80mg/mL, un derivado de HPMC y modificadores de la erosión, tales como lactosa, derivados de polioxoalquilenos de propilenglicol. Esta composición se erosiona con un volumen constante de erosión por un periodo deseado de tiempo, dependiente del espesor de la cubierta.

En resumen, es claro que D1 solamente describe tabletas de liberación controlada que comprenden una membrana semipermeable, la cual es permeable al paso de agua y fluidos biológicos y es impermeable al paso del principio activo, y D2 comprende un recubrimiento

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impermeable con un orificio que conduce al núcleo de la tableta. En lo referente a D3, esta referencia no enseña, ni sugiere, el uso de un núcleo recubierto si no solamente un núcleo erosionable convencional, por lo tanto, D3 no se relaciona con la presente invención.

Ahora bien, una persona medianamente versada en la materia siguiendo las enseñanzas de D1 y/o D2, no estaría motivada a desarrollar una tableta como las reivindicadas en la presente solicitud, caracterizada porque la cubierta, que contiene al menos una abertura, es erosionable bajo predeterminadas condiciones de pH, es decir, insoluble en ambientes ácidos (pH 1.5 – 2.0) y soluble o erosionable en ambientes más alcalinos (pH 5.5 o pH 7.0). Contrario a lo descrito por la presente invención, D1 enseña a la persona versada en la materia el control osmótico (no por difusión como en el invento reclamado) de la liberación del agente activo.

Así mismo, los recubrimientos impermeables sugeridos por D2 no son adecuados para la liberación controlada de agentes activos, para los cuales su solubilidad depende del pH del ambiente, en este caso, bases débiles. Además, aunque D2 enseña el uso de aberturas en la capa de recubrimiento, esta referencia sugiere que la liberación del principio activo ocurre en función del tiempo de exposición de la tableta a los fluidos gástricos (liberación dependiente del tiempo – espesor de la cubierta); nada en D2 se refiere a la liberación del principio activo en función del pH, como ocurre en la presente invención.

En resumen, el estado de la técnica citado por el examinador no afecta la novedad o la altura inventiva de la presente invención, ya que ninguno de los documentos D1 a D3 revela específicamente, o siquiera sugiere, la liberación de bases débiles activas a través de una abertura en una capa de recubrimiento y posteriormente por erosión de un recubrimiento bajo condiciones predeterminadas de pH.

iv) En este punto, llamo respetuosamente la atención del Examinador a los resultados de disolución ilustrados en el Capítulo Descriptivo, mostrando que el uso de una cubierta erosionable provee una liberación sustancialmente completa (superior al 90%) del ingrediente activo después de aproximadamente 8-12 horas. Sorprendentemente, la tasa de liberación es sustancialmente uniforme a valores de pH de 1.5 y 6.8. Esta uniformidad sería imposibles de alcanzar para un principio activo cuya solubilidad es altamente dependiente del pH, usando una simple capa entérica impermeable como la revelada en D2 o el control osmótico mediante una cubierta semipermeable, como la usada en D1.

Es inadecuado que el Examinador considere a priori que los resultados sorprendentes logrados con la presente invención son obvios, solamente porque el estado de la técnica revela en general formulaciones de liberación controlada, las que valga subrayar, no están relacionadas con las

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composiciones específicas aquí reivindicadas. Dicho análisis corresponde a una evaluación de tipo “hindsight”, en el que el Examinador, contrario a abstraerse al momento en que la solicitud fue presentada, como lo requiere la práctica de patentes, utiliza la misma solicitud en estudio para que el arte previo se ajuste en retrospectiva a la invención desarrollada. Por el contrario, es tarea del Examinador enseñar cómo el arte previo por sí mismo conduce de manera inequívoca e inevitable al desarrollo planteado que proporcione los resultados alcanzados, sin necesidad de acudir a información adicional o experimentación alguna.

El hecho de implementar herramientas conocidas en el estado de la técnica no desvirtúa automáticamente el nivel inventivo de una invención. Es decir, la existencia de cubiertas entéricas, aun que contengan aberturas en su superficie, que controlen la liberación del principio activo, por ejemplo, mediante el fenómeno de ósmosis o el tiempo de resistencia de una capa de recubrimiento, no sugiere el concepto inventivo desarrollado en la presente invención. El Examinador parece desatender la jurisprudencia establecida por el Tribunal de Justicia Andino, que con relación al nivel inventivo en el área de los inventos químicos y biotecnológicos ha manifestado que frecuentemente “...**aplicando procedimientos conocidos** pueden obtenerse resultados inesperados para una persona normalmente versada en la materia...”, pero que “...por ello, el juicio del nivel inventivo no puede ser elaborado con criterios generales, sino que dependerá de las especiales circunstancias de cada caso.”¹

En ese sentido, me permito subrayar que la evaluación de nivel inventivo en el análisis de patentes debe realizarse sobre la base de qué hubiera sido obvio para una persona versada en el arte. Una vez más, en el presente caso, tal como se explica en el Capítulo Descriptivo, las composiciones reivindicadas presentan ventajas en la liberación del compuesto 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxy]bencil]tiazolidin-2,4-diona. Lo anterior constituye a todas luces un aporte significativo al estado de la técnica, dado que el producto reivindicado presenta propiedades que le permiten alcanzar determinadas concentraciones del medicamento en el organismo, que se traducen en un efecto terapéutico mejorado.

4. Finalmente, deseo anotar que el concepto inventivo comprendido en la presente solicitud se han concedido patentes en China, Eurasia, México, Nueva Zelanda, Perú, Pakistán, Rusia, Taiwán y Ucrania.

Si bien es cierto que las concesiones de patentes en oficinas de otros países no son vinculantes en el sentido que obliguen a la Superintendencia a tomar una decisión en el mismo sentido, considero que dichas concesiones sugieren el cumplimiento de los requisitos de patentabilidad de la materia reivindicada, ya que los criterios de evaluación y estudio aplicados para concluir la aceptación de dichas patentes resultan equivalentes a los que la Superintendencia debe emplear.

¹ Proceso 105-IP-2000, página 7, líneas 45 a 50.

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CAPÍTULO REIVINDICATORIO MODIFICADO
(EXAMEN DE FONDO)

1. Una forma de dosificación oral que comprende:
 - (i) Un núcleo que comprende 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidin-2,4-diona ó una sal ó solvato farmacéuticamente aceptable del mismo; y
 - (ii) un recubrimiento en torno a dicho núcleo, que comprende una ó más aberturas que se extienden a través de dicho recubrimiento pero que no penetran en dicho núcleo y que comunican el medio exterior con dicho núcleo;
caracterizada porque la liberación de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidin-2,4-diona ó de una sal ó solvato farmacéuticamente aceptable del mismo a partir de la forma de dosificación ocurre a través de dicha(s) abertura(s) por la erosión de dicho núcleo y a través de la erosión de dicho recubrimiento en un pH > 4,5.
2. Una forma de dosificación oral según la Reivindicación 1, en la cual el material de recubrimiento se selecciona entre polímeros de polimetacrilato, ftalato de polivinilacetato coprocesado, acetato-trimelitato de celulosa, acetato-ftalato de celulosa, shelac, polímeros de ftalato de hidroxipropilmetilcelulosa y sus copolímeros, y mezclas de ellos.
3. Una forma de dosificación oral según cualquier Reivindicación precedente, en la que el recubrimiento tiene un espesor en el intervalo de 0,05 a 0,5 mm.
4. Una forma de dosificación oral según cualquier Reivindicación precedente, en la que los tamaños de la(s) aberturas(s) están en el intervalo de 0,5 mm a 8 mm.
5. Una forma de dosificación oral según cualquier Reivindicación precedente, en la que el recubrimiento comprende dos aberturas.
6. Una forma de dosificación oral según cualquier Reivindicación precedente, en la que el núcleo está en una forma que consta de varias capas.
7. Una forma de dosificación oral según cualquier Reivindicación precedente en la que la(s) aberturas(s) en el recubrimiento representan 10 a 70% de la superficie total de las caras de la forma de dosificación.
8. Una forma de dosificación oral según cualquier Reivindicación precedente, en la cual el núcleo es predominantemente hidroxipropilmetilcelulosa y lactosa.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Act. 444 RESPUESTAREQUE Folios: 10

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105276194	26/02/2009	2,389,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LENAS COMERCIALES	111,000.00
		TOTAL :	\$ 111,000.00

SON: CIENTO ONCE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/20		A1	(11) International Publication Number: WO 98/33489 (43) International Publication Date: 6 August 1998 (06.08.98)
(21) International Application Number: PCT/US98/01710 (22) International Filing Date: 29 January 1998 (29.01.98) (30) Priority Data: 08/791,999 31 January 1997 (31.01.97) US Not furnished 12 December 1997 (12.12.97) US (71) Applicant: ANDRX PHARMACEUTICALS, INC. [US/US]; Suite 201, 4001 S.W. 47th Avenue, Fort Lauderdale, FL 33314 (US). (72) Inventors: CHEN, Chih-Ming; 10680 S.W. 40th Manor, Davie, FL 33328 (US). CHOU, Joseph, C., H.; 5755 N.W. 54th Place, Coral Springs, FL 33067 (US). (74) Agent: COSTIGAN, James, V.; Hedman, Gibson & Costigan, P.C., 1185 Avenue of the Americas, New York, NY 10036 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, 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, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: ONCE DAILY PHARMACEUTICAL TABLET HAVING A UNITARY CORE			
(57) Abstract A controlled release tablet is disclosed which comprises: (a) a homogeneous compressed core which comprises: (i) a medicament which is very slightly soluble to practically insoluble in water at 25 °C; (ii) a water soluble osmotic compound; (iii) one or more osmotic polymers; and (b) a membrane coating which completely covers said core tablet which comprises a mixture of a: (i) a water insoluble pharmaceutically acceptable polymer; and (ii) a pH dependent polymer such as an enteric coating polymer, the weight ratio of the pH dependent polymer to the water insoluble pharmaceutically acceptable polymer being 0.1:1 to 0.75:1. A controlled release tablet which comprises: (a) a medicament; (a) a homogenous compressed core which comprises: (i) a medicament; (ii) a water soluble osmotic compound; (iii) one or more osmotic polymers; and (b) a membrane coating which completely covers said core tablet which comprises a mixture of: (i) a water insoluble pharmaceutically acceptable polymer; and (ii) an enteric polymer.			

FIG. 2 is a cross-section of a tablet of the invention which shows the extrusion of a portion or portions of the core through a portion of the edge of the tablet which is observed within one hour after a tablet is placed in an aqueous fluid.

DETAILED DESCRIPTION OF THE INVENTION

Various medicaments may be administered using the osmotic tablet of the present invention. These medicaments include medicaments which are very slightly soluble to practically insoluble in water at 25°C. The term very slightly soluble is used to include those medicaments which are soluble at a level of one part of solute to 1,000 parts of water and the term practically insoluble is used to include those substances which are soluble at a level of 1 part of solute to more than 10,000 parts of water.

Examples of categories of these medicaments include anti-hypertensives, calcium channel blockers, analgesics, anti-neoplastic agents, anti-microbials, anti-malarials, non-steroidal anti-inflammatory agents, diuretics, anti-arrythmia agents, hypoglycemic agents and the like. Specific examples of medicaments include nifedipine, nisoldipine, nicardipine, nilvadipine, felodipine, bendroflumethazide, acetazolamide, methazolamide, chlorpropamide, methotrexate, allopurinol, erythromycin, hydrocortisone, triamcinolone, prednisone, prednisolone, norgestrel, norethindone, progesterone, norgesterone, ibuprofen, atenolol, timolol, cimetidine, clonidine, diclofenac, glipizide, lovastatin, fluvastatin, simvastatin, pravastatin, fexofenadine, and the like. Useful water soluble medicaments include various therapeutic agents such as decongestants, antihistamines, analgesics, sedatives, anti-inflammatory, anti-depressants, antihypertensives and the like at therapeutic dosage levels.

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relatively thin membrane at edges 14 and 16 is shown by the cross-section. The relatively thin membrane at edges 14 and 16 is typical of the membrane thicknesses obtained when a controlled release coating is applied to any
5 tablet core. The extruding portions of the core 18 which is observed after the tablet is placed in an aqueous fluid appear to resemble an irregularly shaped elastic mass of a portion of the core tablet.

The controlled release tablet of the invention
10 has been used to administer the calcium channel blocker nifedipine.

The preferred water soluble osmotic agents include water soluble organic and inorganic compounds such as sucrose, lactose, dextrose, sodium chloride,
15 sorbic acid, potassium chloride, polyethylene glycol (weight av. molecular weight 380-420), propylene glycol and mixtures thereof. These materials are utilized at a level of 20-60% and preferably from 35-50% based on the weight of the core of the tablet.

The core composition will contain one or more osmotic polymers. If two osmotic polymers are used, one osmotic polymer may be a pharmaceutically acceptable, water soluble polyvinyl pyrrolidone having a weight
20 average molecular weight of 25,000 to 200,000. Other pharmaceutically acceptable water soluble polymers
25 include hydroxy propyl cellulose, hydroxyethylcellulose and the like.

The pharmaceutically acceptable, water soluble osmotic polymer may be employed in an effective amount
30 that will exert an osmotic effect on the release of the calcium channel blocking agent. These amounts will generally be from about 15 to 40%, preferably from about 20 to 30% based on the weight of the compressed tablet core.

The composition of the core also preferably
35 includes as a second osmotic polymer, a pharmaceutically acceptable, water swellable osmotic polymer such as

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polyethylene oxide having a weight average molecular weight of 100,000 to 6,000,000. Other water swellable osmotic polymers include hydroxypropyl methylcellulose, poly(hydroxy alkyl methacrylate) having a molecular weight of from 30,000 to 5,000,000; poly(vinyl)alcohol, having a low acetal residue, which is cross-linked with glyoxal, formaldehyde or glutaraldehyde and having a degree of polymerization of from 200 to 30,000; a mixture of methyl cellulose, cross-linked agar and carboxymethyl cellulose; a water insoluble, water swellable copolymer produced by forming a dispersion of a finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, butylene or isobutylene cross-linked with from 0.001 to 0.5 moles of saturated cross-linking agent of saturated cross-linking agent per mole of maleic anhydride in the copolymer; Carbopol[®] acidic carboxy polymers having a molecular weight of 450,000 to 4,000,000; Cyanamer[®] polyacrylamides; cross-linked water swellable indenemaleic anhydride polymers; Goodrite[®] polyacrylic acid having a molecular weight of 80,000 to 200,000; starch graft copolymers; Aqua-Keeps[®] acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polyglucan and the like. Other polymers which form hydrogels are described in U.S. 3,865,108; U.S. 4,002,173 and U.S. 4,207,893 all of which are incorporated by reference. The pharmaceutically acceptable, water swellable polymers may be employed in an effective amount that will control the swelling of the tablet core. These amounts will generally be from about 5 to 15%, preferably from about 7 to 12% based on the weight of the compressed tablet core.

The membrane coating which completely covers said core comprises a water insoluble pharmaceutically acceptable polymer in combination with an enteric polymer. Suitable water insoluble polymers include cellulose esters, cellulose ethers and cellulose ester ethers. These materials include cellulose acylate,

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cellulose ethyl ether, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkyls, mono-, di- and tricellulose aroyls and the like.

- 5 Cellulose acetate is the preferred polymer. Other water insoluble polymers are disclosed in U.S. 4,765,989 which is incorporated by reference. If desired the above polymer may be combined with from 10 to 40%, and preferably 20-30% of a pH sensitive polymer which
- 10 functions as an enteric polymer in that it does not begin to disperse until pH conditions in excess of the stomach region are encountered. Stated differently, a weight ratio of 0.1:1 to 0.75:1 or preferably 0.11:1 to 0.66:1 or more preferably 0.25:1 to 0.42:1 of enteric polymer to
- 15 water insoluble polymer may be used. Generally, the pH sensitive material or enteric polymers do not degrade and begin to release the active drug until a pH above 3.0 is reached and preferably above 5.5. Materials such as Eudragit L (poly(methacrylic acid methylmethacrylate);
- 20 1:1 ratio; MW No. Av. 135,000 - USP Type A) or Eudragit S (poly(methacrylic acid, methylmethacrylate); 1:2 ratio; MW No. Av. 135,000 - USP Type B). hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate and the like may be used as
- 25 the pH sensitive or enteric polymer to modify the permeability of the membrane coating around the core.

Generally, the membrane coating around the core will comprise from about 1 to 4% and preferably about 2% based on the total weight of the core tablet.

- 30 The water insoluble polymer-enteric polymer mixture may contain an optional plasticizer or a water soluble channeling agent as the modifier. The water soluble channeling agent is a material that dissolves in water to form a porous polymer shell that allows water to
- 35 be imbibed into the core. This material is used in a sufficient amount to control the lag time for the formation of the initial openings of the coated tablet.

³Myvaplex 600

10 III Color Coating

water qs (evaporated during processing)

(d) The yellow color suspension is applied to the tablets prepared in Step (c) in a perforated coating pan. The coating level is 4% by weight.

IV Sustained Release Coating

(e) A sustained release coating is applied to the tablet prepared in Step (d) by coating the tablets in a fluidized-bed coater. The coating level is 2% for this membrane.

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acetone qs (evaporated during processing)

⁵acetyl content 39.8%)

(e) A sustained release coating is applied to the tablet prepared in Step (d) by coating the tablets in a fluidized-bed coater. The coating level is 2% for this membrane.

A cross-section of a dissolving tablet of Example 1 is shown in Fig. 2. The core 10 is surrounded with membrane 12.

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If desired, the membrane coated tablet may be overcoated with an enteric coating such as the following:

hydroxy propyl methyl cellulose phthalate	70%
(releases at pH 5.5)	
pore forming agent	0-30% or 5-25%
talc, U.S.P.	(no pore former) 23%
acetyltributyl citrate (no pore former)	7%
acetone (evaporated during processing)	

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The overcoat is coated onto the membrane coated tablets to add 2 to 5wt% and preferably about 4.3%

The term "%" as used herein refers to weight percent.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

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We claim:

1. A controlled release tablet which comprises:
 - (a) a homogeneous compressed core which comprises:
 - 5 (i) a medicament which is very slightly soluble to practically insoluble in water at 25°C.;
 - (ii) a water soluble osmotic compound
 - (iii) one or more osmotic polymers; and
 - (b) a membrane coating which completely covers said core
- 10 tablet which comprises a mixture of a:
 - (i) a water insoluble pharmaceutically acceptable polymer; and
 - (ii) a pH dependent polymer such as an enteric coating polymer, the weight ratio of the pH dependent
 - 15 polymer to the water insoluble pharmaceutically acceptable polymer being 0.1:1 to 0.75:1.
2. A controlled release pharmaceutical tablet as defined in claim 1 wherein the medicament is a calcium channel blocker
- 20 compound.
3. A controlled release pharmaceutical tablet as defined in claim 2 wherein the medicament is nifedipine.
- 25 4. A controlled release pharmaceutical tablet as defined in claim 1 which includes two osmotic polymers.
5. A controlled release pharmaceutical tablet as defined in claim 1 wherein one of the osmotic polymers is a water
- 30 swellable osmotic polymer.
6. A controlled release pharmaceutical tablet as defined in claim 5 wherein the water swellable polymer is selected from the group consisting of poly(ethylene oxide),
- 35 hydroxypropylmethylcellulose and mixtures thereof.
7. A controlled release pharmaceutical tablet as defined in



US005543155A

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195**United States Patent** [19]

Fekete et al.

[11] **Patent Number:** 5,543,155[45] **Date of Patent:** Aug. 6, 1996

[54] **DIFFUSION-OSMOTIC CONTROLLED
DRUG-RELEASE PHARMACEUTICAL
COMPOSITION AND PROCESS FOR
PREPARING SAME**

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[21] **Appl. No.:** 341,209

[22] **Filed:** Dec. 5, 1994

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.⁶** A61K 9/24; A61K 9/32

[52] **U.S. Cl.** 424/473; 424/468; 424/472;
424/482; 514/772.3; 514/781; 514/960

[58] **Field of Search** 424/468, 472,
424/473, 482

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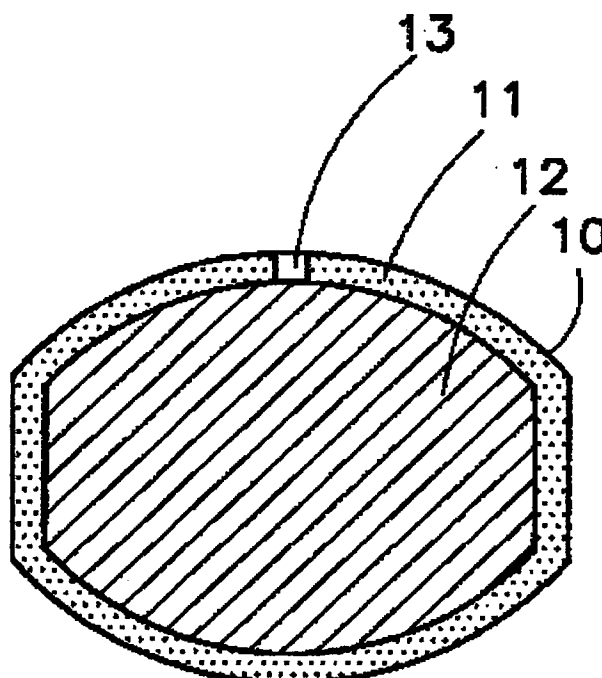
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[57] **ABSTRACT**

The invention relates to a novel diffusion-osmotic controlled drug-release pharmaceutical composition containing a one-layer tablet core including a polymeric film-coat, a therapeutically active agent and a hydrophilic polymer; if desired, a two-layer tablet core including active agent and hydrophilic polymer in the first layer thereof and a hydrophilic polymer in the second layer thereof; at least one bore on the part of film-coat in contact with the core or core layer containing the active agent; and, if desired, containing one or more bore(s) in the part thereof in contact with the second layer containing the hydrophilic polymer, which comprises an ammonium methacrylate copolymer as coating material and hydroxypropyl-methylcellulose as hydrophilic polymer. The composition according to the invention is useful for preparing controlled drug-release tablets containing as active agents e.g. β -adrenergic inhibitors (e.g. propranolol) calcium-antagonists (e.g. nifedipine), angiotensin convertase enzyme (ACE) inhibitors (e.g. captopril); prazosin; or nitroglycerol, all used in heart and circulation diseases; vasodilatory active agents (e.g. pentoxifylline), nonsteroidal antiinflammatory agents (e.g. naproxene), analgetic drugs (e.g. morphine) and drugs acting on the central nervous system (e.g. amitriptyline, buspiron). The invention furthermore relates to a process for the preparation of the above compositions.

51 Claims, 6 Drawing Sheets



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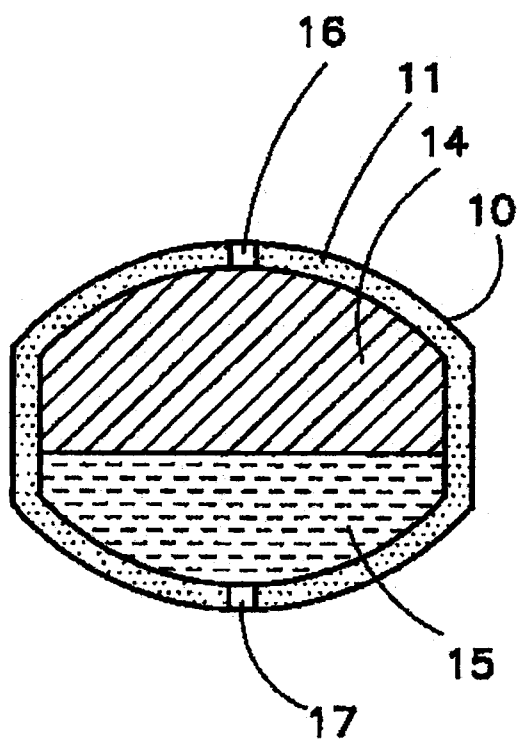


FIG. 5

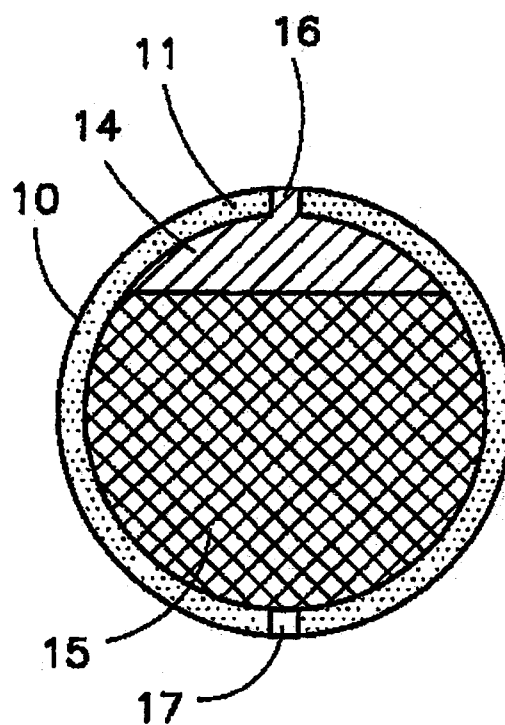


FIG. 6

DIFFUSION-OSMOTIC CONTROLLED DRUG-RELEASE PHARMACEUTICAL COMPOSITION AND PROCESS FOR PREPARING SAME

The invention relates to novel diffusion-osmotic controlled drug-release pharmaceutical compositions. More particularly, the subject of the invention is an one-layer or two-layer tablet superficially coated with ammonium methacrylate copolymer film and containing polymer(s) dissolving in aqueous media, from which the active agent is released partly by molecular diffusion through the ammonium methacrylate copolymer wall, partly by pressing out through the hole(s) bored on the coat together with the aqueous dispersion or solution of the polymer(s). The invention furthermore relates to a process for the preparation of the above compositions.

Compositions known in the art are osmotic drug-release systems which became known in the pharmaceutical technology in the past decades. Osmotic compositions prepared according to the first patent specifications (U.S. Pat. Nos. 3,845,770 and 3,916,899) consisted of the active agent and a semipermeable coat surrounding it. Being permeable to water, the coat makes possible the penetration of water from the environment into the interior of the composition; however, the coat is impermeable to the active agent and therefore it impedes the molecules of the active agent to get out through the coat into the environment. Thus, the getting-out of the active agent of the composition is provided by one or more hole(s) formed on the coat. During the release of the active agent the composition takes up water from the environment through the coat, then the solution or suspension of the active agent is pressed out into the environment through the opening(s) being present on the coat under effect of the osmotic pressure developing in the system. The rate of water uptake and consequently the rate of active agent release is determined by the permeability to water of the wall; or the potential difference between the osmotic pressure, more precisely the difference between the chemical potential of the solution formed within the composition and that of the environment (the decrease of osmotic pressure through the coat or the extent of difference of chemical potentials), respectively.

However, a composition of this type is useful only for water-soluble active agents or for substances slightly soluble in water when those are employed in a mixture with water-soluble, so-called osmotic additives (auxiliaries). An additional drawback of these compositions lies in that, after cessation of the saturation concentration, the osmotic pressure within the composition decreases and therefore the zero-order, i.e. time-constant rate of active agent release, a great advantage of the composition, is changed.

For eliminating the above drawbacks, a composition has been prepared according to the U.S. Pat. No. 4,111,202, which contains two layers instead of one layer and having osmotic properties within the semipermeable coat. One layer contains the active agent, eventually in a mixture together with an osmotic additive; whereas the other layer, separated from the first layer by an elastic membrane, comprises only osmotic additive. A hole is bored only on the outer semipermeable coat comprising both layers, from the side of the layer containing the active agent. During the release of the active agent, water diffuses into both layers through the semipermeable coat; under effect of development of the osmotic pressure, the pressing-out of solution (or suspension) formed in the layer containing the active agent begins through the opening formed in the wall. This layer is

widened towards the elastic membrane under effect of the osmotic pressure of additive dissolving within the layer which contains only osmotic additive and is separated from the first layer by the elastic membrane. While widening, this layer pushes the solution or suspension of the active agent forwards and completely presses it out of the chamber part provided with the opening.

Although these compositions have completely met the desired purpose, i.e. the assuring of the release of water-insoluble active agents at a steady rate, they proved to be unsuitable for practical use. Namely, the development of an elastic membrane separating the layer of osmotic additive from the layer of active agent and the sticking, respectively of the layer containing the osmotic additive together with the layer comprising the active agent, required complicated technical solutions making the preparation of these compositions highly expensive.

According to U.S. Pat. No. 4,327,725, the technical difficulties discussed above can be eliminated by using high molecular crosslinked substances, so-called hydrophilic polymers swelling by water uptake, instead of low molecular osmotic substances in the osmotic layer containing no active agent. Namely, in this case the polymeric substance swells with a sharp interface under effect of water uptake and, while pushing forwards the aqueous solution or suspension of the layer containing the active agent, presses it out through the opening being present on the coat. Thus, the elastic membrane between the layers containing active agent and that containing no active agent can be omitted by this solution and the two-layer tablet can be prepared on industrial scale by using layer-tabletting equipments known and employed for several decades in tabletting technology. Subsequently, the two-layer tablets are provided with a semipermeable coat, usually by employing solutions of cellulose esters in methylene chloride/methanol in a manner known from earlier patent specifications and then a hole of proper size is bored on the coat, in the layer containing the active agent.

In practice, however, this solution also proved to be unsuitable since in the cases of semipermeable coats used the hydrogels employed were unable to resorb sufficient amount of liquid at an appropriate rate through the coat to swell to such an extent which is required for the complete pressing-out of the aqueous solution or suspension of the active agent being in the other layer through the opening formed on the coat. In order to solve the above problem an osmotic composition was developed wherein the layer containing no active agent comprises also a low molecular osmotic substance in addition to the swelling polymer. Thus, the osmotic pressure of this layer is enhanced and the flowing-in of water is accelerated. This osmotic pharmaceutical composition is disclosed in German patent No. 3,417,113 and U.S. Pat. No. 4,612,008.

The composition according to the above patents is a film-coated two-layer tablet, one layer of which contains active agent, low molecular osmotic substance, high molecular osmotic substance and hydrophilic polymer; and the other layer of which incorporates osmotic hydrophilic polymer and low molecular osmotic substance. For assuring the release of the active agent, a hole is bored on the coat from the side of the layer comprising the active agent.

Although the above composition can successfully be used for the preparation of osmotic, prolonged-action compositions, it is burdened by several unpreferable properties, the elimination of which could mean a substantial progress in the preparation of prolonged-action dosage forms.

Such an unadvantageous property of these pharmaceutical compositions lies therein that, beside the hydrophilic polymer, low molecular osmotic substances should also be used in the "placebo" layer for increasing the rate of penetration of water through the semipermeable coat. Conclusively, this leads to an increase in the mass of this layer, and as a final outcome and to an increase in the tablet mass and to an expansion of the physical dimension of the tablet which may be inconvenient on ingestion of the tablet.

Another common drawback of all osmotic compositions known in the art appears in that the semipermeable coat is prepared from a solution of the coating material in an organic solvent, namely methylene chloride/methanol. The reason for this lies in that the inventors enumerate many polymers which could be useful to develop the semipermeable coat, however, various cellulose esters are only used in practice for dissolving which the use of chlorinated solvents is indispensable according to the knowledge in the art.

Thus, for the preparation of osmotic compositions known in the art, chlorinated solvents are employed which are dangerous to an increased degree both to health and to the environment. Although the harmful effects of these can be eliminated by maintaining the appropriate technical measures (laminar-flow work-places, recovery of the solvents), this is accompanied by a considerable increase in the production costs.

An additional drawback of two-layer osmotic compositions is that the layer containing the active agent should be bored out. If the so-called "placebo" layer is bored through, the active agent is of course not released; whereas on boring both layers of the tablet the placebo layer is also pressed out in an aqueous medium; therefore, the tablet essentially behaves as a "simple" osmotic system which cannot provide the complete pressing-out of the layer containing the active agent. For this reason, such a technical solution of the preparation of two-layer tablets known in the art has also to be used which distinguishes the two parts (halves) of tablet before the boring and insures that the coat covering the tablet part incorporating the active agent is only bored through. Thus, an important progress in manufacturing of the composition would be by developing a composition wherein, by boring out both tablet parts, the layer containing the active agent is only pressed out from the tablet because of the peculiar property of the "osmotic" pressing-out layer. The boring-out on both tablet parts is easy to carry out by suitably directing the way of light in boring systems using a laser ray.

Thus, a person skilled in the art of preparing sustained drug-release compositions would consider it to be a very important progress to abandon the osmotic additives from beside the osmotic polymer in osmotic drug-release systems or to eliminate the use of organic solvents e.g. chlorinated solvents during formation of the coats; as well as to provide that, by boring out both parts of the two-layer tablet, the pressing-out proceeds only from the layer containing the active agent.

According to the present invention there is provided a diffusion-osmotic controlled drug-release pharmaceutical composition containing a one-layer tablet core including a polymeric film-coat, a therapeutically active agent and a hydrophilic polymer, if desired, a two-layer tablet core including active agent and hydrophilic polymer in the first layer thereof and a hydrophilic polymer in the second layer thereof, at least one bore on the part of film-coat in contact with the core or core layer containing the active agent, and, if desired, containing one or more bore(s) in the part thereof in contact with the second layer containing the hydrophilic

polymer, which comprises an ammonium methacrylate copolymer as coating material and hydroxypropyl-methylcellulose as hydrophilic polymer.

The present invention is based on the recognition that the combination of the diffusion effect with the osmotic effect provides excellent results.

During our work aimed to eliminate the above problems it has surprisingly been found that all of the three tasks can be solved by preparing a simultaneously diffusive and osmotic drug-release composition instead of an only osmotic drug-release composition. Thus, ammonium methacrylate copolymers, till now used as coating materials of diffusion-controlled pharmaceutical compositions according to the known art, are employed for coating the tablets whereas hydroxypropyl-methylcellulose is employed as hydrophilic swelling material. In this way the release of active agent from the composition by diffusion is insured on the one hand; and on the other hand, hole(s) is (are) bored on the coat and it is provided thereby that in the interior of the composition the solution or suspension of the active agent is released from the composition also by pressing-out through the hole(s) under the pressure developing due to the swelling of hydroxypropyl methylcellulose.

Ammonium methacrylate copolymers used in the coating of the new-type diffusion-osmotic drug release compositions are employed since the middle of the Fifties in the pharmaceutical industry. For the preparation of prolonged-action compositions such copolymers are chiefly employed which are completely insoluble in water but all permeable to various extent and provide thereby the diffusion of molecules of the active agent.

Such copolymers are listed hereinafter.

Ammonium methacrylate copolymer RL (Eudragit RL) (Ammonio Methacrylate Copolymer, Type A—USP/NF) (Aminoalkyl Methacrylate Copolymer RL—JSP I) (Ethyl acrylate)-(methyl methacrylate)-(trimethylammonio)-ethylmethacrylate](1:2:0.2) copolymer, molecular weight 150,000.

Commercially available products (Röhm Pharma, Weierstadt):

Eudragit RS 100: solid polymer

Eudragit RL 12.5: 12.5% solution in solvent

Eudragit RL 30 D: 30% aqueous dispersion

Ammonium methacrylate copolymer RS (Eudragit RS) (Ammonio Methacrylate Copolymer, Type B—USP/NF) (Aminoalkyl Methacrylate Copolymer RS—JSP I) (Ethyl acrylate)-(methyl methacrylate)-[(trimethylammonio)ethyl methacrylate (1:2:0.1) copolymer, molecular weight 150,000.

Commercially available products:

Eudragit RS 100: solid copolymer

Eudragit RS 12.5: 12.5% solution in solvent

Eudragit RS 30 D: 30% aqueous dispersion

Films prepared from ammonium methacrylate RL/RS copolymers are insoluble in water and digestive juices but swell and are permeable to the dissolved substances. This means that, when used according to the known art, the release of the active agent proceeds by diffusion through these films. The sign RL means the property that the film is easily permeable; whereas the sign RS indicates a difficultly permeable film. Between pH 2 and pH 8 the quaternary ammonium groups of the copolymers are fully dissociated; thus, the permeability of the films is independent of the pH-value and can be controlled by varying the mixing ratio of the two polymers. The manufacturer indicates the field of utilization of Eudragit RL/RS copolymers as follows:

cosity in 2% aqueous solution and successively until an additional 28 mg of coat weight was achieved by using a coating dispersion of the following ingredients. ("AM copolymer" means ammonium methacrylate copolymer.)

Ingredients of the coating dispersion	Parts by weight
AM copolymer RL 30%	105
AM copolymer RS 30%	105
Triethyl citrate	12
Dimethylpolysiloxane emulsion of 35%	6.7
Water filled up to	350

One hole of 0.3 mm in diameter each was bored on the side containing the active ingredient of one part of the tablets; and two holes were bored on both sides of another part of the tablets. The drug-release of the tablets was determined as described in Example 3. The following dissolution data were obtained:

Hours	Amount %
3	1.7
5	12.4
8	20.7
24	94.9

We claim:

1. A diffusion-osmotic controlled drug-release pharmaceutical composition comprising a tablet core containing a therapeutically active agent and a hydrophilic polymer, wherein said tablet core is coated with a polymeric film-coat, and said film-coat contains at least one bore in said film-coat in contact with said tablet core, said film-coat comprising an ammonium methacrylate copolymer and said hydrophilic polymer comprising hydroxypropyl methylcellulose, said film-coat being present in an amount of 3 to 25 mg/cm² in relation to the surface of said tablet core.

2. The composition according to claim 1, wherein said hydroxypropyl methylcellulose is present in an amount of 5 to 30% by weight in relation to the weight of said tablet core.

3. The composition according to claim 1, said tablet core further comprising 0 to 90% by weight of filling material, 0 to 5% by weight of binding material, and 0 to 5% by weight of lubricant in relation to the weight of said tablet core.

4. The composition according to claim 3, wherein said filling material is cellulose, microcrystalline cellulose, starch, lactose, mannitol, or secondary calcium phosphate.

5. The composition according to claim 3, wherein said binding material is hydroxypropyl-cellulose, methylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, ethylcellulose, gelatine, water-soluble starch, polyvinylalcohol, polyoxyethyleneglycol, or polyvinylbutyral.

6. The composition according to claim 3, wherein said lubricant is magnesium stearate, talc, stearic acid, hydrogenated castor oil, or colloidal silicon dioxide.

7. The composition according to claim 1, wherein said ammonium methacrylate copolymer has a relative molecular weight of 100,000 to 200,000 and contains 1 molar part of ethyl acrylate, 2 molar parts of methyl methacrylate and 0.1 to 0.2 molar part of (trimethylammonio)-ethyl methacrylate.

8. The composition according to claim 1, wherein said ammonium methacrylate copolymer comprises a 1:10 to 10:1 ratio of an ammonium methacrylate copolymer with a relative molecular weight of 150,000 containing 1 molar part of ethyl acrylate, 2 molar parts of methyl methacrylate and 0.1 molar part of (trimethylammonio)-ethyl methacrylate to an ammonium methacrylate copolymer with a relative

molecular weight of 150,000 containing 2 molar parts of methyl methacrylate, 1 molar part of ethyl methacrylate and 0.2 molar part of (trimethylammonio)-ethyl methacrylate.

9. The composition according to claim 1, wherein said hydroxypropyl methylcellulose contains 20 to 30% by weight of methoxy groups and 5 to 12% by weight of hydroxypropyl groups and has a viscosity of 3 to 100,000 cP in a 2% aqueous solution.

10. A diffusion-osmotic controlled drug-release pharmaceutical composition comprising a tablet core containing a therapeutically active agent, 5 to 30% by weight of hydroxypropyl methylcellulose, 0 to 90% by weight of filling material, at most 5% by weight of binding material and at most 5% by weight of lubricant in relation to the total weight of said tablet core; wherein said tablet core is coated with a polymeric film-coat of an ammonium methacrylate copolymer, and said film-coat contains at least one bore in said film-coat in contact with said tablet core, said film-coat being present in amount of 3 to 25 mg/cm² in relation to the surface of said tablet core, and said film-coat contains one or more bores of 0.1 to 1.0 mm² in cross-section.

11. A diffusion-osmotic controlled drug-release pharmaceutical composition comprising a two-layer tablet core, wherein the first layer of said two-layer tablet core contains a therapeutically active agent and a hydrophilic polymer, and the second layer of said two-layer tablet core contains a hydrophilic polymer, said two-layer tablet core being covered with a polymeric film-coat, the part of said film-coat in contact with said first layer contains at least one bore and the part of said film-coat in contact with said second layer optionally contains at least one bore, said film-coat comprising an ammonium methacrylate copolymer and said hydrophilic polymer comprising hydroxypropyl methylcellulose, said film-coat being present in an amount of 3 to 25 mg/cm² in relation to the surface of said two-layer tablet core.

12. The composition according to claim 11, wherein said hydroxypropyl methylcellulose in said first layer is present in an amount of 5 to 30% by weight in relation to the weight of said first layer.

13. The composition according to claim 11, wherein said hydroxypropyl methylcellulose in said second layer is present in an amount of 30 to 100% by weight in relation to the weight of said second layer.

14. The composition according to claim 11, wherein said first layer further comprises 0 to 90% by weight of filling material, 0 to 5% by weight of binding material, and 0 to 5% by weight of lubricant in relation to the weight of said first layer.

15. The composition according to claim 11, said second layer further comprising 0 to 70% by weight of filling material, 0 to 5% by weight of binding material, and 0 to 5% by weight of lubricant in relation to the weight of said second layer.

16. The composition according to claim 14, wherein said filling material is cellulose, microcrystalline cellulose, starch, lactose, mannitol, or secondary calcium phosphate.

17. The composition according to claim 14, wherein said binding material is hydroxypropyl-cellulose, methylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, ethylcellulose, gelatine, water-soluble starch, polyvinylalcohol, polyoxyethyleneglycol, or polyvinylbutyral.

18. The composition according to claim 14, wherein said lubricant is magnesium stearate, talc, stearic acid, hydrogenated castor oil, or colloidal silicon dioxide.

19. The composition according to claim 15, wherein said filling material is cellulose, microcrystalline cellulose, starch, lactose, mannitol, or secondary calcium phosphate.

United States Patent [19]

Zaffaroni et al.

[11] 4,096,238

[45] Jun. 20, 1978

[54] METHOD FOR ADMINISTERING DRUG TO THE GASTROINTESTINAL TRACT

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[73] Assignee: Alza Corporation, Palo Alto, Calif.

[21] Appl. No.: 775,774

[22] Filed: Mar. 9, 1977

Related U.S. Application Data

[60] Division of Ser. No. 536,006, Dec. 23, 1974, Pat. No. 4,036,227, which is a continuation-in-part of Ser. No. 354,344, Apr. 25, 1973, abandoned.

[51] Int. Cl.² A61K 9/22

[52] U.S. Cl. 424/15; 128/260

[58] Field of Search 128/260; 424/14-22

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Attorney, Agent, or Firm—Paul L. Sabatine; Thomas E. Ciotti; Edward L. Mandell

[57] ABSTRACT

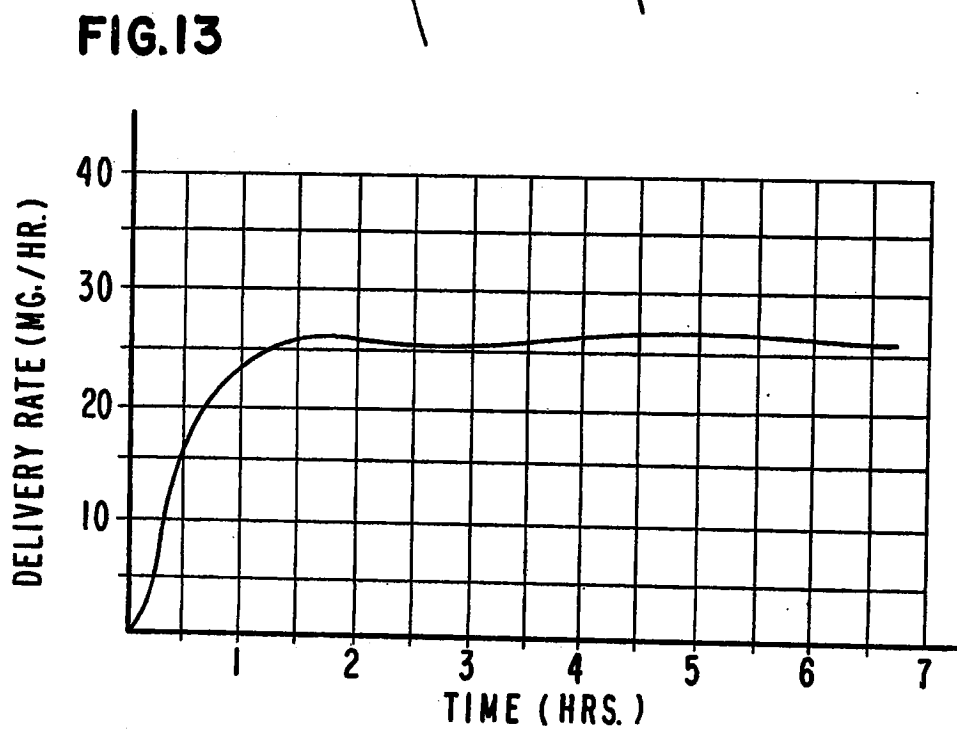
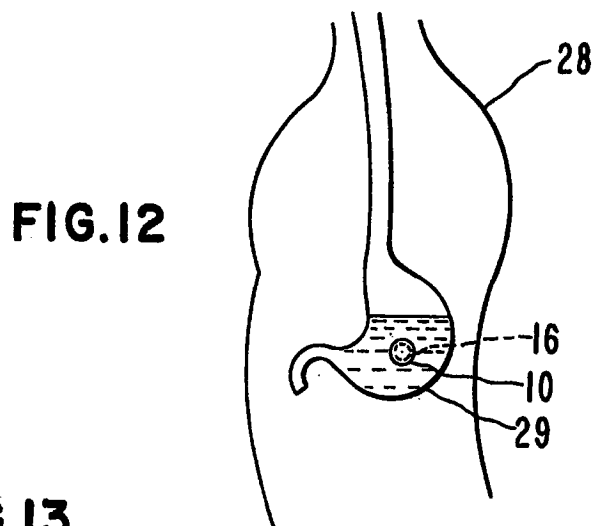
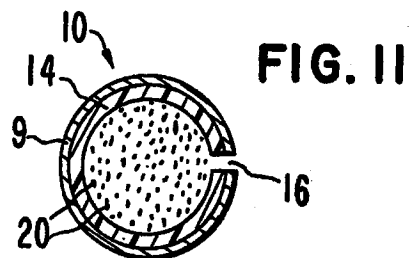
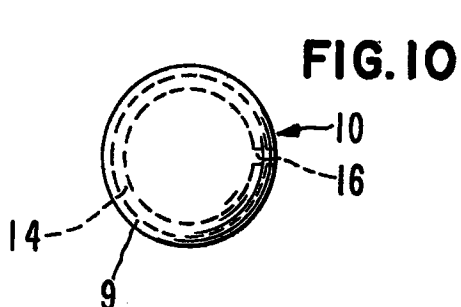
An osmotic device for releasing a useful agent at differ-

ent release rate patterns from the device in a selected environment is disclosed. The device is comprised of a wall surrounding and forming a compartment as a means for containing a useful agent and having a passageway for releasing the agent. The wall is comprised in at least a part of a material permeable to an external fluid and impermeable to the agent. A layer of a pattern rate controlling material that erodes in a selected environment for changing the release rate pattern of the device is carried on the semipermeable wall distant from the compartment. The agent is soluble in the fluid and exhibits an osmotic pressure gradient across the semipermeable wall against the fluid or the agent has limited solubility and is admixed with an osmotically effective solute soluble in the fluid that exhibits an osmotic pressure gradient across the semipermeable wall against the fluid. In operation, agent is released from the device at different release rate patterns by the pattern rate controlling material eroding at a controlled rate to increase the amount of fluid available to the semipermeable wall for imbibition, which fluid is imbibed through the wall into the compartment producing a solution of the soluble agent or a solution of the osmotically effective solute containing the agent which is released through the passageway to the exterior of the device at a rate controlled by the permeability of the semipermeable wall and the osmotic pressure gradient across the wall of the device.

1 Claim, 18 Drawing Figures

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the length of the diffusional path change, the amount of medication released becomes unpredictable and, as such, this device cannot be relied upon for use in the management of health and disease.

Other prior art attempts to provide a controlled dosage release is described in U.S. Pat. No. 3,247,066. In this patent a device is described comprised of a polymeric wall that fully surrounds a drug colloid mixture. Drug is released from the device under the influence of water entering the mixture to cause an increased internal swelling pressure of the colloid that builds up sufficiently to exceed the strength of the polymer wall. The build-up is followed by a rupture of the wall that immediately releases drug in an undetermined amount. This action, plus any subsequent drug release, is by seemingly uncontrolled dissolution which features tend to inherently limit the acceptability of this device for the controlled and prolonged administration of drug. Similarly, in U.S. Pat. No. 3,538,214 there is disclosed a tablet comprised of a drug matrix coated with a microporous film permeable to fluid and drug as another prior art means for the controlled release of drug. The device of this patent releases drug by letting water pass through the pores to dissolve drug which is released through the pores. The rate of drug release is again influenced by environmental factors such as pH dependency and this coupled with both an unspecified number of pores of variable sizes arising through manufacture and material limitations limits the use of this device in the useful arts and sciences.

In copending patent application U.S. Ser. No. 259,469, filed on June 5, 1973, now U.S. Pat. No. 3,845,770 and U.S. patent application Ser. No. 440,281, filed on Feb. 7, 1974, which applications are assigned to the same assignee of this patentable invention, there are disclosed novel and useful dispenser devices that represent both a pioneer contribution and improvement to the dispensing art. While the devices of that invention give outstanding, operable and useful results and release their agent at an osmotically controlled rate, it has now been found that a unique means for letting the device release their agent only in certain environments or for changing the release rate pattern of the agent can be manufactured into the device. It will be appreciated by those versed in the art to which the invention pertains that this means not only increases the usefulness of the device but enhances its range of operation as a useful article of manufacture.

OBJECTS OF THE INVENTION

Accordingly, it is an immediate object of this invention to provide a novel dispensing device for the dispensing of a useful agent to produce a beneficial effect, which device overcomes the aforesaid disadvantages associated with the prior art devices.

Another object of the invention is to provide a new and useful delivery device for the administration of an active agent wherein the device is nonrupturable and maintains its physical and chemical integrity throughout its agent-release history.

Yet another object of the invention is to provide a new and useful delivery device for the controlled and uniform release of an active agent wherein the agent is released from the device in a selected environment at a rate controlled by the device.

Still another object of the invention is to provide an osmotic agent delivery device for the prolonged essen-

tially zero order release of agent wherein agent is released independently of pH.

Yet still a further object of the invention is to provide a novel and useful osmotic drug delivery device that releases active agent essentially free of any stirring rate dependency at a constant and controlled rate over a prolonged time.

Yet still a further object of the invention is to provide a novel and useful drug delivery device wherein the drug is essentially released by osmotic action and the device is adapted for animal, including humans, animal orifices and passageways, or for implantation into animal, including human, bodies.

Still a further object of the invention is to provide an osmotic delivery device for osmotically dispensing an active agent into fields, rivers, streams and the like.

Still another object of the invention is to provide a novel dispensing device for dispensing a composition of matter at a controlled rate for a prolonged period of time.

Yet still another object of this invention is to provide a device that is simple in construction, designed with a minimum number of parts, easy to use, and in operation exhibits all the practical and useful benefits obtained by the controlled, continuous, long-term administration of various compositions of matter, that is, active agents to animals, avians, humans and into other environments.

Yet another object of the invention is to provide a device containing agent surrounded with a coated semipermeable membrane except for a passageway through which drug is released. In use, the exterior coat erodes to expose the semipermeable membrane for the osmotically controlled release of agent for a prolonged period of time from the device.

A further object of this invention is to provide a device containing agent surrounded with a coated semipermeable membrane except for a passageway through which drug is released. In use, the exterior coat erodes to increase the amount of fluid available to the wall for imbibition which is imbibed into the compartment for osmotically controlled release of agent.

Another object of this invention is to provide an improved dispensing device which will permit high concentration of an active agent to be contained therein, and which high concentration of the agent will not exhibit the tendency to be leached from the device nor have its potency decreased by chemical breakdowns.

Yet still a further object of the invention is to provide a novel product dispensing device that contains a useful agent which agent can also be used as an osmotically effective solute to exhibit an osmotic pressure gradient against an external fluid.

Yet a further object of the invention is to provide an agent dispensing device that contains an agent in a form suitable for storage thereby giving the device an improved shelf life.

Yet another immediate object of this invention is to provide a dispensing device for the administration of locally acting or systemically acting drugs to produce a physiologic or pharmacologic effect and which device can release the drug in preselected biological environment, at different release patterns and at a rate that does not vary with time.

Still yet another object of the invention is to provide a device bearing an exterior layer on a semipermeable membrane and containing drugs in various physico-

chemical forms that can be sterilized when needed by operable conventional techniques.

Yet another object is to provide a device for dispensing an agent which device can have a variety of release rates ranging from low to very high by using polymeric wall forming materials in combination with a semipermeable membrane and wherein the polymeric wall material controllably erodes to correspondingly expose or increase the amount of fluid available to the semipermeable membrane for subsequent release of agent from the device.

Yet still another object of the invention is to provide a novel and useful erodible or biodegradable device that erodes or degrades after the device has released the active agent, or at the end of the drug release rate pre-programmed history.

Yet still a further object of the invention is to provide an osmotic device having a means for letting the device release in certain environments of use, or for letting the device incrementally change the amount of agent to be subsequently released at a continuous and controlled rate over a prolonged period of time.

Other objects, features, and advantages of the invention will be apparent to those skilled in the art from the detailed description of this specification, taken in conjunction with the drawings and the accompanying claims.

SUMMARY OF THE INVENTION

The invention concerns a device comprised of a wall surrounding a compartment as a means for containing a useful agent, such as a composition of matter, a drug, a beneficial product or the like, and having a passageway communicating with the compartment and the exterior of the device for releasing the agent, or the like, from the compartment. The wall of the device is comprised in at least a part of a material that is semipermeable to external fluid common to the environment of use and essentially impermeable to the useful agent or the like. A layer or coat of an erodible material that erodes in certain environments is carried exteriorly on the semipermeable wall. Agent is released from the device by the coat eroding to let the external fluid permeate through the wall into the compartment to dissolve the agent or to dissolve an osmotically effective compound admixed with agent having limited solubility in the fluid in the compartment, producing thereby an essentially saturated solution of the agent or an essentially saturated solution of the osmotic compound containing the latter agent, which solution in either instance is released from the device by a constant influx of fluid from the environment and wherein the influx is generated by the continuous internal dissolution of the agent or the osmotically effective compound in the fluid diffusing at a controlled rate through the wall under the osmotic pressure gradient across the wall into the compartment. The device can in operation dispense agent at a zero order rate of release for a prolonged period of time by maintaining the rate of internal dissolution of the agent, or the osmotic compound in the fluid constant. In the device the latter is accomplished when the dissolution rate is larger than the rate of release of the agent or the osmotic compound in the fluid in the device. This fluid enters the device as the outside coating erodes, and fluid leaves the device at a rate controlled by the permeability of the semipermeable wall and the osmotic pressure gradient across the semipermeable wall of the device.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, which are not drawn to scale, but rather are set forth to illustrate various embodiments of the invention, there appears as follows:

FIG. 1 is an illustration of a delivery device of the invention with a portion of the wall removed to illustrate the general structure of the device comprised of an exterior coat on a semipermeable wall.

FIG. 2 is a perspective, top view of an ocular dispensing device of the invention illustrating as one embodiment of the invention a device manufactured, in this embodiment, as an ocular drug delivery device.

FIG. 3 is an enlarged cross-sectional view of the ocular drug delivery device of FIG. 2 through 3—3 depicting an exterior coat on a wall distant from a like structure with their interior peripheral surfaces in intimate contact with the surfaces of a wall positioned between the two walls.

FIG. 4 is an exploded view illustrating three walls with at least one distant wall carrying a coating prior to their union wherein they act in concert to form a novel ocular drug delivery device.

FIG. 5 is a partly diagrammatic, front view of a human eye illustrating an ocular drug delivery device of this invention in an operative position after its insertion into the eye.

FIG. 6 is a view partly in vertical section and partly diagrammatic of an eyeball and the upper and lower eyelids associated therewith showing the novel ocular product dispensing device of this invention in product administration operative position.

FIG. 7 is a frontal, fragmentary view of a uterine cavity showing an agent releasing intrauterine device manufactured in accordance with the invention and positioned in a uterine cavity.

FIG. 8 is still another embodiment of the invention illustrating a side, fragmentary view of an anal osmotic drug delivery device for releasing a drug in a body cavity.

FIG. 9 is similar to FIG. 8 except the exterior coat carried on the wall increased in thickness from the passageway to the bottom of the device.

FIG. 10 illustrates an oral osmotic drug delivery tablet for osmotically administering a physiologically or pharmacologically-effective amount in the gastrointestinal tract of animals including veterinary animals and humans.

FIG. 11 is a cross-sectional of the device of FIG. 9 with the top portioned section to lay open the interior structure of the osmotic oral dosage form of FIG. 9.

FIG. 12 is a view diagrammatically illustrating an osmotic drug delivery device manufactured according to the invention in an environment of use, such as the stomach.

FIG. 13 is a graph showing a controlled and constant rate of release for the device over a prolonged period of time.

FIG. 14 illustrates a device releasing active agent independent of the pH of the exterior of the device.

FIG. 15 illustrates in vivo results obtained by using the device.

FIG. 16 illustrated an oral drug delivery device manufactured to release drug in a selected biological environment, the intestine.

FIG. 17 illustrates a drug delivery device of the invention illustrating a device having different drug re-

sage of fluid through a permeable coat 9 for regulating the amount of fluid available to wall 14 for imbibition.

The embodiment of the invention as set forth in FIG. 9 makes possible many programs of therapy that require different quantities of medication administered at varying times. For example, in antibiotic therapy, an initially large dose of drug can be administered followed by smaller doses. Also, in desensitizing against allergens, the therapeutic regime indicates doses of the allergen to progressively increase over the time of treatment is now possible with the devices of this invention. Thus, as the coating gradually erodes or dissolves at a predetermined rate in the body fluids, it lets fluid contact the semipermeable wall to obtain preselected release patterns with the devices made according to the mode and manner of the invention.

In FIG. 10 the present invention is seen in another operative embodiment comprised of a controlled release device 10 for releasing medication at a zero order rate to a preselected environment. Device 10 is suitably adapted for the oral administration of a medication to humans, primates, laboratory animals, farm animals, household animals, avians and sport animals. Device 10 is comprised of a wall 14 formed either fully or in at least a part of a semipermeable film forming membrane that surrounds medication. A layer 9 of constant or varying thickness that erodes or undergoes dissolution in the gastrointestinal tract is coated onto the exterior of wall 14. Layer 9 can be an enteric coat which is not disintegrated in the stomach but readily undergoes dissolution in the upper intestinal tract, or it can be a material that gradually and continually erodes or undergoes dissolution as the device travels through the gastrointestinal tract. A passageway 16 releases medication to the exterior of the device. Device 10 has at least one passageway and it can have additional passageways to release the same amount of drug or more drug at various osmotic pumping rates to the host or the environment. In FIG. 11, device 10 of FIG. 10 is seen in open section illustrating semipermeable, non-digestible, nontoxic, biologically inert wall 14 surrounding drug 20 and passageway 16. A time release profile layer 9, is carried on wall 14. The amount of drug 20 in the osmotic device will, of course, vary with the host and the length of time it is to remain in the host before it is discharged from the body.

The amount of agent present in the just described osmotic device, and similar devices, is initially in excess of the amount that can be dissolved in the fluid present in the interior of the device. Under this physical state, that is, when the agent is in excess, the device will osmotically operate to give essentially zero order rate of release. The rate of agent release pattern can also be varied by selecting different amounts of agent that can be confined in the agent compartment, that is, smaller or larger amounts than is soluble in the fluid in the compartment may be housed therein. Thus, the device can contain from 0.05 mg to 25 grams or higher with individual devices containing for example 1 mg, 5 mg, 10 mg, 100 mg 250 mg, 500 mg, 1.5 g, 3 g, 5 g, and the like. In FIG. 12 device 10 is seen comprised in operation in an outline of a human 28 in stomach 29 osmotically administering drug 20 to the drug receptor.

In FIG. 13 there is presented a graph illustrating an essentially zero order rate of release for an osmotic device made according to the invention. This release pattern is obtained by coat 9 instantly eroding to expose semipermeable wall 14 to let fluid permeate there-

through to release agent from device 10. This coat protects the device during storage and the like. In FIG. 14 there is seen a graph depicting an osmotic device releasing drug at a constant rate independent of the pH of the exterior fluid. The device releases agent at this release rate profile after dissolution of coat 9 to expose the semipermeable wall. The two fluids mentioned on the graph are gastric fluid and intestinal fluid. The gastric fluid had a pH of about 1 to 2 and the intestinal fluid had a pH of about 7 to 8. FIG. 15 shows an osmotic device delivering potassium chloride throughout the gastrointestinal tract of dogs. The rate of release for the device during the first 2 hours was ascertained by assaying devices recovered from the stomach; while, the rate delivered at longer terms was determined by evaluating devices recovered from the intestines. FIG. 16 illustrates the results obtained with a device coated with an enteric coat that prevents agent release in the stomach but erodes to give a zero order rate of release in the intestine. FIG. 17 illustrates the release rate profile for a device coated with a material that has a changing release rate profile. This graph illustrates one release rate profile in the stomach with subsequent erosion to give a second release rate profile in the intestine. FIG. 18 illustrates the release rate profile obtained as a coat 9 gradually and continually erodes to expose more wall to give the corresponding increased release rate profile.

While the above FIGS. 1 through 18 inclusive are illustrative of various operative, osmotic agent delivery devices that can be made according to the invention, it is to be understood that these delivery devices of the invention can take a wide variety of shapes, sizes and forms for administering, for example, the useful agent, drug, product or the like at controlled rates at different release rate profiles to different areas, for example, of the body or to different drug receptor sites or to animal body passages or for administering other active agents to other environments. For example, the invention includes oral drug delivery devices such as tablets, pills and capsules, vaginal delivery devices, osmotic implants, osmotic buccal devices, pessaries, prosthesis, artificial glands, cervical rings, intrauterine drug delivery devices of cylindrical, bullet, elliptical, circular, bulbous, loops, bows, or any other geometrical shape that readily lends itself to intrauterine placement such as Birnberg's Bow in U.S. Pat. No. 3,319,625, Comet in U.S. Pat. No. 3,256,878, Majzlin Spring in U.S. Pat. No. 3,397,691, Inhiband in U.S. Pat. No. 3,323,520, Bakunin in U.S. Pat. No. 3,405,711, Shamrock in U.S. Pat. No. 3,077,879, the ring with tail, Ota ring and the like. The devices also include osmotic ocular drug delivery devices of any convenient geometric shape for comfortable retention in the cul-de-sac of the eye such as ellipsoid, bean-shaped, banana-shaped, circular-shaped, rectangular-shaped, trapezoidal, doughnut-shaped and the like. In cross-section, it can be doubly convex, concavo-convex, rectangular and the like, as the osmotic ocular device in operation will tend to conform to the configuration of the eye. The general dimensions of the osmotic ocular device can vary with the size of the device and conforming to the amount of agent in the device's agent compartment, the rate at which the agent is to be administered to the eye and by the size of the eye. Satisfactory devices for insertion in the cul-de-sac of the eye generally have a length of 4 to 20 millimeters, a width of 1 to 15 millimeters, and a thickness of 0.1 to 4 millimeters, a reservoir with a diameter of 1.2 to 14.9 millimeters, and contain from 1 microgram to 100 milligrams of

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drug or more, and the like. The ocular drug delivery device can be made of a material that is biologically inert, non-allergenic and essentially insoluble in tear fluids, or it can be made from a bioerodible, non-allergenic material that erodes after it has fulfilled its drug release therapy. The oral osmotic tablets made according to the invention can also be of various conventional sizes such as 3/16 in, 7/32 in, 11/32 in, 7/16 in, 1/2 in, 3/4 in, 1 in, 1 1/4 in, 1 1/2 in, 2 1/2 in and the like smaller or larger dimensions. The oral tablet can also have an elongated shape with a size corresponding to conventional capsule dimensions such as triple zero, double zero, zero, 1 through 8 and the like. Additionally, the novel and useful dispensing device can be used for release of a wide variety of active agents and the term agents as used in this specification and the accompanying claims includes any compound, mixture of compounds, composition of matter or mixture thereof, product, drug, which, when dispersed, produces a predetermined beneficial and useful result. The active agents include pesticides, herbicides, germicides, biocides, algicides, rodenticides, fungicides, insecticides, anti-oxidants, plant growth promoters, plant growth inhibitors, preservatives, surfactants, disinfectants, sterilization agents, catalysts, chemical reactants, medicants, fermentation agents, cosmetics, foods, nutrients, food supplements, plant food, drugs, vitamins, plant minerals, six sterilants, plant hormones, fertility inhibitors, fertility promoters, air purifiers, micro-organism attenuators, and other like agents that benefit man, animals, avians, fish and the environment. Also, all of the dispensing devices are of appropriate known shapes and sizes for implantation, insertion or positioning in the desired body cavities, passageways or in the desired environment, such as streams, aquariums, fields, reservoirs, laboratory facilities, manufacturing facilities, transport means and the like.

DETAILED DESCRIPTION OF THE DISCLOSURE

In accordance with the practice of the present invention, it has now been found that the novel delivery device of the invention provides many important advantages over previously-known dissolution operated, diffusional operated, sustained and prolonged delivery devices, of both the non-erodible or bioerodible type and the like. One advantage of the novel device is the ease of construction of the drug delivery device by standard manufacturing techniques into devices of various shapes, sizes and forms for delivering products to a recipient or environment. A more important advantage of the claimed delivery device is that it can be manufactured comprised of a minimum number of parts, that is, a wall and a composition of matter. Another important advantage resides in the ability to manufacture the devices of the invention by standard, conventional methods of manufacture. Another important advantage is the present and future ability of the device to contribute to the art different release rate profiles, with zero order rate of release, or other order rate of release within the various release rate profiles. Other advantages will become apparent to those versed in the art from the specification, the drawings and the accompanying claims.

The wall 14, forming the osmotic device of the invention is made from a material that is semi-permeable, can form films, and does not adversely effect the drug, animal body, or the host. For example, it is a material that is permeable to an external fluid such as water and the

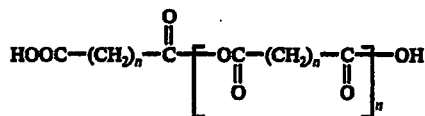
like while essentially impermeable to a selected product, drugs, agents or to other compounds in the device. The selectively-permeable material or membrane forming the wall is insoluble in body fluids and non-erodible or it can be bioerodible after a predetermined period with bioerosion corresponding to the end of the active drug release period or release of agent to the environment of use. In each instance it is semi-permeable to external solvent but not to solute and is suitable for construction of the osmotic powered device. Typical materials for forming the wall include membranes known to the art as osmosis and reverse osmosis membranes such as commercially-available unplasticized cellulose acetate, plasticized cellulose triacetate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, cellulose acetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methyl sulfonate, cellulose acetate butyl sulfonate, cellulose ethers, cellulose acetate propionate, poly(vinyl methyl) ether copolymers, cellulose acetate diethylaminoacetate, cellulose acetate octate, cellulose acetate laurate, methyl cellulose, cellulose acetate p-toluene sulfonate, triacetate of locust gum bean, cellulose acetate with acetylated hydroxyethyl cellulose, hydroxylated thylenevinylacetate, cellulose acetate butyrate having a viscosity of from about 10 seconds to about 50 seconds, cellulose acetate butyrate containing about 17 percent of combined butyryl and about 29.5 percent acetyl, permselective, aromatic nitrogen-containing polymeric membranes that exhibit water permeability and essentially no solute passage, osmosis membranes made from polymeric epoxides, osmosis membranes made from copolymers of an alkylene oxide and alkyl glycidyl ether, semi-permeable polyglycolic or polylactic acid and derivatives thereof, the selectively-permeable membranes of ionically associated polyelectrolytes, the selectively-permeable polymers formed by the coprecipitation of polycation and a polyanion as described in U.S. Pat. Nos. 3,276,586; 3,541,005; 3,541,006; 3,546,142; and 3,173,876; and the like. Generally, membranes having a fluid permeability of 0.01 to 10 cc/cm² × hour or day/or higher at atmospheric pressure against a saturated product solution or saturated solute solution at the temperature of use while simultaneously possessing a high degree of impermeability to the product or solute are useful for manufacturing the devices of the invention. Also, among the suitable semi-permeable membranes operable for the purpose of the invention are film forming membranes that possess a water sorption greater than one percent and less than 40 percent by weight at ambient temperatures with a presently preferred semi-permeable membranes having a water sorption of greater than 5 and less than 30 percent by weight at ambient temperatures. Of course, other semi-permeable membranes operable for the purposes of the invention can also be used within the spirit of the invention.

The coating 9, carried on the semi-permeable wall 14 can comprise suitable materials for the purpose of this invention. One class of suitable materials are the enteric coatings that give a predetermined release rate profile by resisting the action of stomach fluid to prevent water permeating through the wall, while disintegrating in the intestine to let fluid enter the device. Acceptable enteric

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coatings are non-toxic, the components of the coating and their degradation product should be physiologically inactive, the coating should not dissolve or disintegrate in the stomach during the time the device remains in the stomach, and, the enteric coating should disintegrate to expose the semi-permeable wall once the device enters the intestine. The enteric coating suitable for the present invention include those materials digestible by the enzymes in the intestinal tract and materials containing an ionizable polyacid, frequently a long-chain polymer with ionizable carboxyl groups, and the like. Typical materials for forming enteric coating include keratin, keratin over sandaractolu, β -naphthyl benzoate and acetotannin, balsam of peru, balsam of tolu, stearic acid and shellac, gum resin and salol-shellac formalized gelatin, cellulose ester and a non-volatile organic substance such as fat, wax or bile, cellulose ether and fat, wax or bile, fatty acids, myristic acid-hydrogenated castor oil, stearic acid-mutton tallow or sodium taurocholate, stearic acid-castor oil over shellac-silica gel, shellac, ammoniated shellac, shellac n-butyl stearate, amstic with cetyl alcohol, cellulose acetate phthalate with resinous carrier, polyvinyl acid phthalate, methylcellulose acid phthalate, acid phthalates of glucose, fructose or mannitol, zein, alkyl resin unsaturated fatty acids shellac, hippuric acid with and without cetyl alcohol, styrene maleic acid copolymer and combinations containing dibutyl phthalate and talc, ternary copolymers of styrene, methacrylic acid with butyl half-ester of maleic acid, and the like. Typical enteric coatings are discussed in *Remington's Pharmaceutical Sciences*, Thirteenth Ed., pages 604 to 605, 1965 Mack Publishing Co., Eaton, Penna.; and in *Biopharmaceutics and Relevant Pharmacokinetics*, First Ed., pages 158 to 165, 1971 Drug Intelligence Publications, Hamilton, Ill.

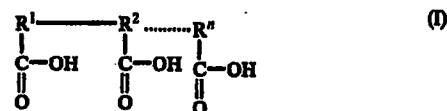
The coating 9 carried on wall 14 can also be made of a material that gradually erodes at a predetermined rate in body fluids to expose wall 14 to fluid or it erodes and becomes thin to let fluid diffuse through to wall 14. By adjusting the thickness of the coating and desired release profile can be programmed. Exemplary materials include those materials which slowly dissolve in body fluids, and coating materials that hydrolyze in body fluids for example, the polymeric essentially linear, dibasic acid anhydride of the formula



are also suitable for use as coatings herein. Typical coatings include polyanhydride polymers of sebacic and azelaic acid, polyhydroxyacetic acids as described in U.S. Pat. Nos. 2,668,162 and 2,676,945, and polysulfite polymers. Other polymers useful for coatings include polymers cleaved by enzymes present in body fluids such as chitin which is enzymatically cleaved by lysozyme, and the like.

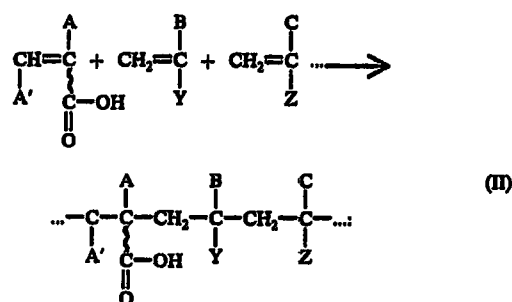
Coating 9 can also be a release rate profile material comprised of a hydrophobic poly(carboxylic acid) having an average of one ionizable hydrogen for each 8 to 22 carbon atoms. These polyacid coatings erode in response to the essentially constant pH environment at a controlled rate by a process of carboxylic hydrogen ionization. This erosion extends over a prolonged period of time and exposes the semi-permeable wall over a corresponding prolonged period of time. Exemplary

poly(carboxylic acids) materials useful as coatings are the hydrophobic polyacids which are represented by the general formula:

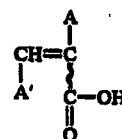


wherein the R's are organic radicals independently selected to provide, on average, from 8 to 22 total carbon atoms for each carboxylic hydrogen. Variations of this ratio within this range can vary the erosion rates prepared from these polymeric acids. Organic radicals represented by $\text{R}^1, \text{R}^2, \dots, \text{R}^n$ may be selected from hydrocarbon radicals and heteroatom containing organic radicals. Suitable hetero atoms for employment in $\text{R}^1, \text{R}^2, \dots, \text{R}^n$ include oxygen, nitrogen, sulfur, and phosphorus as well as other hetero atoms. The value of n and hence the average molecular weight of the polymer is not critical and may vary over a wide range. Suitable molecular weights, for example, range from about 10,000 to about 800,000. Materials within this range erode to products which may be easily and innocuously passed from the environment of use. Preferred molecular weights are from about 15,000 to about 500,000.

Suitable polymeric coatings of the polyacid type are prepared from monomers that contain polymerizable olefinic carbon-carbon double bonds, wherein at least a portion of these monomers will have bonded thereto one or more carboxyl radicals, or suitable precursors thereof and optionally other hetero atom radicals. The polymer is synthesized by the addition of these monomers, one to another, across the polymerizable double bonds. This general method for forming polyacids is well known and does not comprise a part of the present invention. This preparative method may be generally represented by the reaction:



wherein A represents hydrogen or a hydrocarbon and



represents a carboxyl group, or carboxyl group precursor containing monomer also containing a polymerizable olefinic double bond. Such monomers include, for example, acrylic acid, substituted acrylic acid, maleic acid, maleic anhydride, crotonic acid and the like. Wherein

mers are available commercially. Others can be prepared by bulk, solution, emulsion or suspension polymerization using free radical initiators at 40°-100° C, all methods well known in the art. The partial esterification may be conveniently carried out by contacting the acid-containing polymers with a controlled quantity of the esterifying alcohol at elevated temperature, optionally in the presence of an acidic esterification catalyst. Alcohols suitable for partially esterifying the above-noted polyacids include the hydrocarbon alcohols, preferably the alkanols of from about one to about 16 carbon atoms; for example, methanol, ethanol, isopropanol, n-butanol, cyclohexanol, octanol, the decanols, and n-dodecanol. Combinations of alcohols may also be employed. In general formula I the ether groups may be incorporated by copolymerizing an unsaturated carboxylic acid with an unsaturated ether, for example, acrylic acid, maleic acid, crotonic acid and the like with the vinyl ethers of from about 3 to about 10 carbon atoms such as methyl vinyl ether, ethyl vinyl ether, butyl vinyl ether, hexyl vinyl ether and the like, for example by the method described in U.S. Pat. No. 2,927,911. Because of the small number of carbon atoms in many of these unsaturated ethers and acids it may be desirable, to achieve the required carbon/acidic hydrogen ratio, to terpolymerize these materials with a non-carboxylic hydrogen-containing material, most suitably an unsaturated terpolymerizable unsaturated hydrocarbon of from 2 to 8 carbon atoms such as ethylene, butadiene, or styrene.

The coatings embraced by the R's of general formula I, as oxyhydrocarbons may also contain alcohol linkages. Additionally, nitrogen sulfur and phosphorous atoms may also be incorporated in R groups employed in the polymer coatings. Nitrogen may be present as cyano, amide, or imide groups. Sulfur atoms can be present as mercaptan or disulfide linkage while phosphorous atoms may be present as phosphate linkages.

One group of coating materials used to coat the osmotic dispensing device of the invention comprise hydrophobic polymers of an acid selected from acrylic acid, lower alkyl acrylic acids of from 4 to 6 carbon atoms per monomeric unit, and maleic acid; either alone or copolymerized with up to about 2 moles, per mole of acid of a copolymerizable olefinically unsaturated group such as ethylene or lower such as 1 to 4 carbon, alkyl vinyl ethers wherein from about 20 to 90% of the acid groups have been esterified with an alkanol of from 1 to about 10 carbon atoms and wherein the ratio of total carbon atoms to acidic carboxylic hydrogens is in the range of from about 9:1 to about 20:1. Also, suitable coatings include the hydrophobic partially esterified copolymers of acrylic acid, methacrylic acid or maleic acid with from 0.2 to 1.5 moles, per mole of acid of ethylene or lower (1-4 carbon) alkyl vinyl ether having from about 35 to about 70% of their total carboxylic groups esterified with lower alkanol of from about 3 to about 10 carbon atoms, said copolymers having a carbon to acidic carboxylic hydrogen ratio of from about 10:1 to about 15:1. Coat 9 further includes hydrophobic copolymers of maleic acid with about 1 mole, per mole of maleic acid, of ethylene or methyl vinyl ether, said copolymer having about half of its total carboxyl groups esterified with a lower monalkanol of from 4 to 8 carbon atoms, wherein the carbon to acidic carboxylic hydrogen ratio has a value of from about 10:1 to about 14:1, and the like. Other time delay materials include fatty acids having 10 to 22 carbons, fatty alcohols hav-

ing from 14 to 30 carbons, the esters of mono-, di-, or triglyceryl esters formed from fatty acids having 10 to 22 carbon atoms, silicone and substituted silicone derivatives and the like.

Representative of agent that can be released from the device and can function as a solute are without limitation those agents soluble in fluids inside the compartment. The fluid is originally present in the environment of use in various forms, for example, such as an aqueous type fluid such as tear fluid, tissue juices, extra-cellular fluid, intra-cellular fluid, water, organic solvents, mixed solvent systems and the like. The expression "agent" as previously noted and as used in this disclosure is meant to include the terms product, useful active agent, beneficial agent, drug, composition of matter, and the like, and these terms are deemed as functionally equivalent for the present invention. These agents, in one embodiment, are both useful to environment or host and preferably osmotically effective as solutes since they can generate a solvent concentration gradient between the exterior medium and the medium inside the device. In the specification and the accompanying claims, useful active agent embraces the term "drug" and broadly includes physiologically or pharmacologically active substance for producing a localized or systemic effect or effects in mammals including humans and primates, avians, valuable domestic household, sport or farm animals such as sheep, goats, cattle, horses, etc., or for administering to laboratory animals such as mice, rats, guinea pigs and the like. That is, the novel osmotic drug delivery device can be used for administering drugs that are physiologically or pharmacologically active at a point in near relation to the osmotic drug delivery device, or, for administering a systemically active substance which will produce a physiological or pharmacological response at a site remote from the point of application of the osmotic drug delivery device. The active agents that may be administered include inorganic and organic compounds without limitation, those materials that transport across a vessel, for example, drugs acting on the central nervous system such as hypnotics and sedatives, mixtures thereof such as pentobarbital sodium, phenobarbital, secobarbital, thiopental, etc., heterocyclic hypnotics such as dioxopiperidines, and glutarimides, hypnotics and sedatives such as amides and ureas exemplified by diethylisovaleramide and α -bromo-isovaleryl urea and the like, and hypnotic and sedative urethanes, disulfanes and the like, psychic energizers such as isocarboxazid, nialamide, phenelzine, imipramine, tranlycypromine, pargylene and the like, tranquilizers such as chlorpromazine, promazine, fluphenazine reserpine, deserpidine, meprobamate, benzodiazepines such as chlordiazepoxide and the like, anticonvulsants such as primidone, diphenylhydantoin, ethitoin, pheneturide, ethosuximide and the like, muscle relaxants and anti-parkinson agents such as mephenesin, methocarbamol, trihexylphenidyl, biperiden, levodopa, also known as L-dopa and L- β -3-4-dihydroxyphenylalanine, and the like, analgesics such as morphine, codeine, meperidine, nalorphine and the like, antipyretics and anti-inflammatory agents such as aspirin, salicylamide, sodium salicylamide and the like, local anesthetics such as procaine, lidocaine, naepaine, piperocaine, tetracaine, dibucane and the like, antispasmodics and antiulcer agents such as atropine, scopolamine, methscopolamine, oxyphenonium, papaverine, prostaglandins such as PGE₁, PGE₂, PGF_{1 α} , PGF_{2 α} , PGA and the like, anti-microbials such as penicillin,

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example, *Diffusion in Polymers*, by Crank, J. and Park, G. S., Chapter 8, pages 259 to 313, 1968, published by Academic Press, N.Y.

The flux of an external fluid, for example, the rate of water vapor transmission through various wall forming materials is determined by using the procedures of *Diffusion in Polymers*, pages 1 to 39 and then expressing the results as WVTR or water vapor transmission rate through a film in grams/100 in²/24 hr/one mil thick film. Known WVTR values can also be found in *Plastic Film Technology*, Park, W. W. R., 1969, published by Van Nostrand-Reinhold Inc., and in *Diffusion in Polymers*, pages 274 to 276. Typical values are set forth in Table 1 immediately below wherein film is the material and WVTR is as defined.

TABLE 1

Film	WVTR
Polyvinyl alcohol	100
Polyurethane	30-150
Methylcellulose	70
Cellulose acetate	40-75
Ethylcellulose	75
Cellulose acetate butyrate	50
Polyvinylchloride, cast	10-20
Polyvinylchloride, extruded	6-15
Polycarbonate	8
Polyvinylfluoride	1-3
Polyesters	2
Cellophane, polyethylene coated	> 1.2
Polyvinylidene fluoride	1.0
Polyethylene	0.5-1.2
Ethylene propylene copolymer	0.8
Polypropylene	0.7
Polyvinyl chloride, rigid	0.7

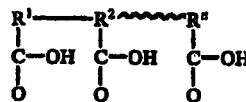
The coating materials used herein may be coated onto the semi-permeable wall according to their respective properties. For example, the poly(carboxylic acids) coatings employed in the devices of this invention are generally soluble in organic solvents and this feature lends itself to be used as a means for coating same. Accordingly, the polyacids coatings may be conveniently applied by standard film casting techniques. An organic solvented solution of the polyacid is prepared and cast or drawn to a film. The solvent is then evaporated to yield a continuous film of the polyacid.

A wide range of organic solvents may be used for the casting of the coating. With poly(carboxylic acid) materials having total carbon to carboxylic hydrogen ratios at the lower end of the range specified for this invention, such as ratios in the range of from about 8:1 to about 11:1, it is generally preferred to use relatively polar organic solvents, that is, organic solvents having dielectric constants, as listed in the 51st Edition of the Chemical Rubber Company "Handbook of Chemistry and Physics" at pages E-62 through E-64, of greater than about 15, for example; lower alkanols such as methanol, ethanol, the propanols, 1 and 2-butanol; lower alkanones such as acetone, diethyl ketone, ethyl methyl ketone and cyclohexanone and halogenated and nitrogenated solvents such as 2-chloroethanol, and nitrobenzene. With polycarboxylic acids having higher ratio of total carbon atoms to ionizable hydrogens, such as from about 14:1 to 22:1 it is generally preferred to use less polar organic solvents, such as those having dielectric constants of less than about 15, especially less than about 10, for example; ethers such as diethyl ether, isopropyl ether and the like; hydrocarbons such as cyclohexane, benzene and toluene, and other low dielectric materials such as ethyl acetate. With the intermediate ratio poly(carboxylic acids) either group of solvents may be used with the alkanols and alkanones generally

being favored. The casting and drying of the poly(carboxylic acids) are carried out at moderate conditions such as at ambient temperature and pressure. Solvent removal may be facilitated by the use of vacuum or slightly elevated temperatures.

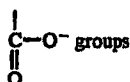
It is often desired to incorporate plasticizers in the coatings, for example in the poly(carboxylic acid) coatings, to improve or vary their physical properties. Exemplary plasticizers suitable for use for the present purpose are the pharmaceutically acceptable plasticizers conventionally used, such as acetyl tri-n-butyl citrate, epoxidized soy bean oil, glycerol monoacetate, polyethylene glycol, propylene glycol dilaurate, decanol, dodecanol, 2-ethyl hexanol-2,2-butoxyethoxyethanol and the like. The proportion of optional plasticizer used will vary within broad limits depending upon the characteristics of the poly(carboxylic acid) involved. In general, from about 0.01 parts to about 1.0 parts by weight of plasticizer for each part by weight of the poly(carboxylic acid) can be used. When plasticizers are included in the poly(carboxylic acid) coatings, they are most suitably added prior to coating the final formed structure, such as by dissolving or dispersing them in the solution from which the form is cast.

The release rate profile for the coating is governed by the coating and the environment in which the device is placed for release of agent. Thus, controlled rates of erosion of a coating of a poly(acid) type can occur in environments having a pH throughout the period of use of the device in the range of about 6.0 to about 9.0. In actual application, the osmotic drug delivery devices find use in many environments. For example, these include, in addition to the gastrointestinal tract which presents both acidic and base pH environments, the ocular cavity with a pH of about 7.4, the rectum with a pH of about 7.5, the pH of the uterus at 7.3, or vagina at about 7.3, and the pH of blood which is normally constant at about 7.2. When a device in accord with this invention carrying drug is applied to any of these body areas, or similar body areas, coat 9 erodes at a controlled and constant rate over a prolonged period of time to exposure or let fluid migrate to wall 14. Additionally, the products of this erosion of the coat 9 are innocuously passed from the body. Coatings made of poly(carboxylic acid) have proven especially advantageous for erosion-controlled release rate profile materials. Without intent to limit the scope of this invention by theoretical considerations, it is believed that the uniform and controllable rates or erosion observed with the coatings hydrophobic poly(carboxylic acids) having an average of 8 to 22 carbons for each ionizable acidic-carboxylic hydrogen are the result of equilibria inherent in the erosion of these poly(carboxylic acids). As shown in general formula I, the poly(carboxylic acids) of this invention may be represented as:



The carboxyl groups are weak acids which, in their unionized form, are hydrophobic. When placed in an aqueous fluid a portion of the carboxyl groups ionized to yield hydrophilic

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and hydronium ions (H_3O^+). As more of the carboxyl groups in an initially hydrophobic polymer chain ionize, the chain assumes an increasingly hydrophilic character and eventually erodes in the fluid. This erosion by ionization occurs on the outer surfaces of the polycarboxylic acid bodies, while continually migrating with the newly formed surface. Even if minor amounts of fluid do penetrate the coating, insignificant ionization can occur there since the inner carboxyl groups, being surrounded by an essentially organic medium exhibit a far higher pKa than do the carboxyl groups on the surface which are in a more aqueous medium.

The bioerosion by surface ionization for the poly(carboxylic acid) coatings is sensitive to pH. As hydronium ions are generated, they tend to cluster about the coating from which they were generated to inherently somewhat lower the pH in the specific area of the body, which inherently governs further ionization. Some of the clustered hydronium ions gradually disperse or are consumed by the fluid and are replenished by further ionization while exposing more surface. The overall erosion rate which results with the poly(carboxylic acids), as used herein, is therefore suited for use as erodible release rate profile coatings to expose surface over prolonged periods of from about 1 to 2 hours to about 120 days, or longer.

The rate of erosion of coatings used in the invention can be determined experimentally in vitro by testing them under simulated environmental conditions. For example, the rate of erosion of a coating in a moving aqueous stream can be determined by placing a coating on a substrate in such a stream and repeatedly weighing it to determine its weight loss. Similarly, the rate of erosion of a coating in tear fluids, as would occur with an ocular drug delivery device, may be measured by placing a small weighed sample of the material in a 0.026 M HCO_3^- solution of pH about 7.4, which is simulated tear fluids, at body temperature (37°C), agitating for a timed interval, and periodically measuring the amount of coating eroded into the solution. Other procedures will become apparent to those versed in the art from a reading of this disclosure and its accompanying examples.

The novel devices of the invention are fabricated by standard techniques. For example, in one embodiment the agent, or the agent and a binder and/or a solute is mixed or formulated into a solid, semi-solid, or like form by conventional methods, such as ball milling, calendaring, stirring, shrinking, roll milling and the like and then charged into the compartment of the device. The wall material forming the device and having the agent contained therein can be formed into a given shaped device, in one embodiment, by molding or casting the one wall, pressing a middle wall thereto, charging the compartment, and then sealing a third wall to form the device. A passageway leading through one wall is fabricated by drilling, punching, casting around a fiber that is removed therefrom, casting around a wire of known diameter that is then removed, cutting, or depositing a tube in one wall during assembly of the device. The device can also be formed of a continuous wall by pouring, casting or the like a wall forming material around a removable mold of any desired shape. The devices

when formed of more than one wall can be joined by various joining techniques, such as high frequency electronic sealing that provides clean edges and firmly sealed devices. By using, for example, high frequency sealing, the wall forming materials flow melt at the point of contact to suitably join the walls into a composite article of manufacture. The ability to design and shape the wall into an osmotic device of highly reproducible shapes of controllable composition, readily results in the fabrication of osmotic delivery devices with controlled characteristics and thus overcome a significant disadvantage of previously-described devices. Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia*, Vol. 46, pages 62 to 70, 1969, and these are well-known to those skilled in the art and can be used to fabricate the osmotic delivery devices of the invention.

The devices can be coated with a release rate profile coating by standard means. One suitable method includes the steps of dispersing a coating material in a volatile solvent. To this liquid coating composition may be added dyes and complexing agents. The resulting mixture is applied to the device in a coating pan, by dipping, spraying or the like. The coating composition is distributed over the surface of the device and additional portions of the coating are added as the solvent from the previous portion evaporates. Each of these steps results in a dry film formed on the semi-permeable wall. The procedure is repeated until a coating of the desired thickness is obtained for the device.

The novel and oral osmotic drug delivery devices of the invention can be of any preselected shape and in a presently-preferred embodiment it is of standard tablet configuration. Generally, the tablet is discoid in shape, although it may be oval, oblong, round, cylindrical, triangular and the like. The upper and lower surfaces may be flat, round, concave, convex or the like. The oral osmotic tablet may be manufactured by standard manufacturing methods such as the wet granulation method, drum granulation, compression, slugging and the like. The oral tablet may be coated with a semi-permeable osmotic membrane of varying thickness by pan coating, spray-pan coating, laminating coating techniques, dip coating, Wurster air-suspension coating, and the like. The semi-permeable membrane is then coated with a release rate profile coating in like technique or according to the procedure previously described. The oral device may be glazed, polished, colored and the like to esthetically enhance the oral device. These procedures and similar manufacturing techniques are known to the art in *Remington's Pharmaceutical Science*, Fourteenth Edition, pages 1649 to 1968, 1970, published by Mack Publishing Company, Easton, Penna., and in *The Theory and Practice of Industrial Pharmacy*, by Lachman et al., pages 197 to 225, 1970, published by Lea & Febiger, Philadelphia, Penna.

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, drawings, and the accompanying claims.

EXAMPLE 1

An osmotic ocular drug delivery device for the continued release of pilocarpine nitrate at a release rate of

$$\left(\frac{V}{t}\right)_1 = k_1 \pi \frac{A}{h_1}$$

where the permeability is k_1 , ρ is the drug density in g/cc, S is the solubility of the drug in the fluid in the device, π is the osmotic pressure of the drug, A is the membrane area of the device, and h_1 is the semi-permeable membrane thickness. The ratio of the fluid permeability of the erodible coating k_2 to the erodible coating thickness h_2 is as follows: $k_1/h_1 \cong k_2/h_2$ which makes the erodible coating essentially impermeable to the fluid of the environment so that essentially no pumping of agent occurs until the outside coating is eroded. An osmotic drug delivery device completely coated with such an enteric coating will have a delayed action with the onset of drug delivery completely delayed until the external enteric coating is eroded past the stomach. The delivery release rate profile for a fully enteric coated osmotic device containing 500 mg of potassium chloride is seen in FIG. 16. The device is made with cellulose acetate E-320 semi-permeable membrane and the sole delivery passageway had a diameter of 8.3 mils. *The Theory and Practice of Industrial Pharmacy*, by Lachman, L., et al., pages 209 to 220, 1970, published by Lea and Febiger, Philadelphia, Penna.; and *Biopharmaceutics and Relevant Pharmacokinetics*, by Wagner, J. G., First Edition, Chapter 23, pages 158 to 165, 1971, published by Drug Intelligence Publications, Hamilton, Ill.

EXAMPLE 10

An osmotic drug delivery device coated on one side with a drug release rate profile enteric coating that resists gastric juice, pH about 2, and capable of disintegrating in intestinal juice, pH about 7, is manufactured according to the procedure set forth in the previous examples. This device, during its residence time in the stomach will have a release rate of $R_s = FR$ where R is the release rate of an uncoated device M/t and F is the fraction of the total membrane area which is uncoated. For example a 50% enteric coated device where F is equal to 0.5, formed of several coats of shellac-n-butyl stearate-coated from an absolute alcohol acetone one to one ratio is dried to a smooth surface and it will have the release rate profile as seen in FIG. 17, wherein the initial rate R_s is equal to 0.5 times R . On disintegration of the coating in the alkaline pH, there is a second release rate profile for the device. The device had a semi-permeable membrane coated of cellulose acetate, that compartment contained 500 mg of potassium chloride and the passageway had an orifice of 8.3 mils. The device had a zero order rate of release within each drum release rate profile.

EXAMPLE 11

An osmotic drug delivery device shaped like a cylinder and coated with a release rate profile coating that has a constant erosion rate at preselected pH is prepared according to the specification and is illustrated in FIG. 9. The coating on the semi-permeable wall is increased from the passageway to the distant end of the device. The release rate profile materials continually erode at a rate in the range from 10 micron per hour to 1000 micron per hour while simultaneously exposing semi-permeable membrane surface. A specific device of cylindrical shape in which the coat is applied under an angle θ , that is the angle between the outside of the semi-permeable wall and the outside coated plane, with

the length of the cylinder l_c and a final thickness of d will have an initial drug delivery rate

$$\left(\frac{M}{t}\right)_0 = k\pi \frac{S}{1 + \frac{S}{\rho}} \cdot \frac{A_0}{h}$$

All the symbols have their previously described meaning and A_0 is the initial exposed surface area of the device. The increase in rate is given by

$$\frac{d\left(\frac{M}{t}\right)}{dt} = k\pi \frac{S}{\left(1 + \frac{S}{\rho}\right)} \cdot \frac{1}{h} \frac{dA}{dt}$$

in which

$$\frac{dA}{dt} = \pi r^2 \frac{d\theta}{dt}$$

wherein r is the radius of the cylindrical device,

$$\frac{d\theta}{dt} = \frac{dx}{\sin \theta dt}$$

and dx/dt is the erosion rate of the coating as set forth above. The increase in rate per unit time is given by

$$\frac{d\left(\frac{M}{t}\right)}{dt} = \frac{1}{l_c} \left(\frac{M}{t}\right)_{\text{cylinder}} \frac{1}{\sin \theta} \frac{dx}{dt}$$

where $(M/t)_{\text{cylinder}}$ is the rate from the device contributed by the totally uncoated cylindrical area of the device which for a linear increase in rate is also given by

$$\frac{d\left(\frac{M}{t}\right)}{dt} = \left(\frac{M}{t}\right)_0 \frac{t}{t_i}$$

where t_i is the total time necessary for erosion of all the coating material. A device with an initial rate $(M/t) = 5$ mg/hr and a total rate from the total uncoated cylinder as previously described of $(M/t) = 20$ mg/hr, with the device having a lifetime of $t_i = 10$ hr and the erosion rate of the coating $dx/dt = 100 \mu$ /hour, and a final coating thickness where d is equal to 1000 μ will give an increasing result of release as seen in FIG. 18.

The novel, osmotic product delivery device of this invention employs a unique means which facilitates the attainment of precisely-conducted product release rates in the environment of use. While there has been described and pointed out the fundamental novel features of the invention as applied to the presently preferred embodiments, those skilled in the art will appreciate that various modifications, changes and omissions in the osmotic product delivery devices illustrated and described can be made without departing from the spirit of the invention.

We claim:

1. A method for orally administering an active agent at a controlled rate to the gastrointestinal tract of a warm blooded animal comprising,

A. admitting into the gastrointestinal tract a device comprising;

(1) a shaped wall formed of a semipermeable material that is permeable to the passage of gastroin-

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- testinal fluid and substantially impermeable to active agent, said wall surrounding and forming;
- (2) a compartment containing the active agent that is soluble in fluid that enters the compartment and which agent exhibits an osmotic pressure gradient across the wall against the gastrointestinal fluid;
- (3) a layer formed of an erodible enteric material on the exterior surface of the semi-permeable wall;
- (4) a passageway in the wall for releasing said agent from said device, said passageway having a maximum cross-sectional area A_p of

$$\frac{L}{F} \times \frac{Q_p}{t} \times \frac{1}{DS}$$

wherein L is the length of passageway, Q_p/t is the mass of agent released per unit time, D is the diffusion coefficient of agent in the released solution, S is the solubility of agent in the fluid and F has a value of approximately 2 to 1000, said passageway having a minimum area, A , defined by

$$\left[\frac{L_p}{t} \times 8 \times \frac{\pi \eta}{\Delta P} \right]^4$$

wherein L is the length of the passageway, t is the volume of agent released per unit time, π is 3.14, η is the viscosity of the solution being released, and ΔP is the hydrostatic pressure differences between the inside and the outside of the compartment and having a value of up to about 20 atmospheres;

B. bioeroding the enteric layer in the gastro-intestinal fluids in the environment of use at a controlled rate to regulate the amount of fluid available to the wall for imbibition, with fluid imbibed through the wall into the compartment in a tendency towards osmotic equilibrium at a rate determined by the permeability of the wall and the osmotic pressure gradient across the wall thereby continuously dissolving said active agent and, thereby

C. dispensing said active agent from the device to the gastro-intestinal tract through the passageway at a controlled rate over a prolonged period of time.

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(21) International Application Number: PCT/US98/12563 (22) International Filing Date: 17 June 1998 (17.06.98) (30) Priority Data: 08/878,406 18 June 1997 (18.06.97) US (71) Applicant: THE GENERAL HOSPITAL CORPORATION [US/US]; 55 Fruit Street, Boston, MA 02114 (US). (72) Inventors: SEED, Brian; Apartment 5J, Nine Hawthorne Place, Boston, MA 02114 (US). JIANG, Chengyu; Apartment #15G, 10 Emerson Place, Boston, MA 02114 (US). (74) Agent: ELBING, Karen, L.; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, 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, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: USE OF PPARγ AGONISTS FOR INHIBITION OF INFLAMMATORY CYTOKINE PRODUCTION (57) Abstract Disclosed herein are methods for reducing or preventing cytokine production associated with an inflammatory response, involving administering to a mammal a therapeutically effective amount of a thiazolidinedione PPARγ agonist.		

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272:3406-3410 (1997)).

Summary of the Invention

In a first aspect, the invention features a method for reducing or preventing inflammatory cytokine production associated with rheumatoid arthritis in a mammal, involving administering to the mammal a
5 thiazolidinedione PPAR γ agonist in an amount which is sufficient to produce a 50% inhibition of cytokine production in a mammalian monocyte culture.

In a second aspect, the invention features a method for reducing or preventing inflammatory cytokine production associated with inflammatory
10 bowel disease in a mammal, involving administering to the mammal a therapeutically-effective amount of a thiazolidinedione PPAR γ agonist.

In a third aspect, the invention features a method for reducing or preventing inflammatory cytokine production associated with an immunodeficiency syndrome in a mammal, involving administering to the
15 mammal a therapeutically-effective amount of a thiazolidinedione PPAR γ agonist.

In a fourth aspect, the invention features a method for reducing or preventing inflammatory cytokine production associated with multiple sclerosis in a mammal, involving administering to the mammal a therapeutically-
20 effective amount of a thiazolidinedione PPAR γ agonist.

In a fifth aspect, the invention features a method for reducing or preventing inflammatory cytokine production associated with cachexia (for example, resulting from a neoplasia or chronic infectious disease) in a mammal, involving administering to the mammal a therapeutically-effective
25 amount of a thiazolidinedione PPAR γ agonist.

In related aspects, the invention also features methods for preparing

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form of liquid solutions or suspensions (as, for example, for intravenous administration); for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

5 Methods well known in the art for making formulations are described, for example, in "Remington's Pharmaceutical Sciences," Mack Publishing Company, Easton, PA. Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated
10 naphthalenes.

 If desired, slow release or extended release delivery systems may be utilized. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral
15 delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of
20 nasal drops, or as a gel.

 The PPAR γ agonists of the invention are administered at a dosage appropriate to the effect to be achieved and are typically administered in unit dosage form. As noted above, the preferred route of administration for most indications is oral. For treatment of rheumatoid arthritis, intra-articular
25 administration is also appropriate.

 An effective quantity of a PPAR γ agonist is employed to treat the diseases or conditions described herein. The exact dosage of a compound is

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	Folios	033

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/GB03/00594
Fecha de Presentación Internacional 12-02-2003

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

1. Documentos estudiados:

1.1. Descripción: (Folios: 27 a 43) como se radicó inicialmente.

1.2. Reivindicaciones: 1 a 14 (Folios: 44 a 46) como se radicó inicialmente. Modificadas: 1 a 8 (folio: 135).

1.3. Rta. del solicitante: Folios: 127 a 134.

1.4. Prioridad: 12/02/2002 y 12/02/2002, GB 0203296.9 y GB 0203297.7.

2. Análisis de la Prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. Objeto de la invención:

La presente solicitud se titula: "Forma de dosificación oral que proporciona liberación

controlada".

El objeto de la presente solicitud se refiere a una forma de dosificación oral que proporciona liberación controlada de un agente farmacéutico activo en diferentes medios corporales, a un procedimiento para preparar dicha forma de dosificación y al uso de dicha forma de dosificación en medicina.

De acuerdo con la descripción de la presente solicitud, el uso de un recubrimiento para controlar la velocidad de liberación de un agente activo ha sido centro de atención y se han desarrollado muchos dispositivos diferentes para tal fin.

Se ha encontrado que para la administración de una base débil farmacéuticamente activa o una base o solvato de la misma farmacéuticamente aceptable, en que es deseable que la liberación del compuesto activo tenga lugar en más de un medio de pH, es beneficioso que el recubrimiento sea erosionable o soluble de una manera dependiente del pH.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 8 (folio: 135): Una forma de dosificación oral que comprende:

- (i) Un núcleo que comprende 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidin-2,4-diona o una sal o solvato farmacéuticamente aceptable del mismo; y
- (ii) Un recubrimiento en torno a dicho núcleo, que comprende una o más aberturas que se extienden a través de dicho recubrimiento pero que no penetran en dicho núcleo y que comunican el medio exterior con dicho núcleo;

Caracterizada porque la liberación de 5-[4-[2-(N-metil-N-(2-piridil) amino) etoxi] bencil] tiazolidin-2,4-diona o una sal o solvato farmacéuticamente aceptable del mismo a partir de la forma de dosificación ocurre a través de dicha(s) abertura(s) por la erosión de dicho núcleo y a través de la erosión de dicho recubrimiento en un pH>4.5.

El problema planteado en esta solicitud es formas de liberación controlada para liberación de fármacos en más de un medio de pH.

La solución propuesta por la presente solicitud consiste en una forma de dosificación oral caracterizada porque la liberación de una base débil farmacéuticamente aceptable ocurre sustancialmente a través de una(s) abertura(s) por erosión de un núcleo erosionable donde está el fármaco y a través de la erosión del recubrimiento erosionable, que está en torno a dicho núcleo, en condiciones predeterminadas de pH.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/426.

4. Determinación del Estado de la Técnica:

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

Fecha de presentación de la solicitud prioritaria 12-02-2002.

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

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

Nº	Documento	Título	Fecha de Publicación
D1	WO 98/33489	Once daily pharmaceutical tablet having a unitary core	6 de agosto de 1998
D2	US 5543155	Diffusion-osmotic controlled drug-release pharmaceutical composition and process for preparing same	6 de agosto de 1996
D3	US 4096238	Method for administering drug to the gastrointestinal tract	20 de enero de 1978
D4	WO 98/57631	Use of PPARγ agonists for inhibition of inflammatory cytokine production	23 de diciembre de 1998

5. Análisis de patentabilidad (artículo 14 D486)

5.1. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica lo siguiente:

Una forma de dosificación oral que comprende:

- (iii) Un núcleo que comprende 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidin-2,4-diona o una sal o solvato farmacéuticamente aceptable del mismo; y
- (iv) Un recubrimiento en torno a dicho núcleo, que comprende una o más aberturas que se extienden a través de dicho recubrimiento pero que no penetran en dicho núcleo y que comunican el medio exterior con dicho núcleo;

Caracterizada porque la liberación de 5-[4-[2-(N-metil-N-(2-piridil) amino) etoxi] bencil] tiazolidin-2,4-diona o una sal o solvato farmacéuticamente aceptable del mismo a partir de la forma de dosificación ocurre a través de dicha(s) abertura(s) por la erosión de dicho núcleo y a través de la erosión de dicho recubrimiento en un pH>4.5.

El documento WO 98/33489 (folios: 137 a 144) se relaciona con una tableta de liberación controlada que comprende un núcleo en donde se encuentra el fármaco y dicho núcleo contiene un componente osmótico soluble, el núcleo va recubierto por una membrana que está compuesta por un polímero insoluble en el agua, un polímero pH dependiente tal como un polímero de cubierta entérica. Entre los fármacos que pueden estar en esta forma de presentación se encuentran los que tienen actividad hipoglicémica; el polímero osmótico que puede estar en el núcleo es hidroxipropilmetilcelulosa y el polímero soluble que puede estar en la capa de recubrimiento puede ser Eudragit o derivado de polimetacrilato o ftalato de hidroxipropilmetilcelulosa. Los polímeros entéricos o que son sensibles al pH liberan el fármaco a pH entre 3.0 y 5.5. La tableta descrita en este documento menciona que la mezcla del polímero insoluble en agua y polímero entérico puede contener además un agente acanalante soluble en agua como modificador y este material es el responsable de la formación de “aberturas” u “orificios” iniciales en la cubierta de la tableta para la liberación de fármaco.

La anterioridad US 5543155 (folios: 145 a 149) se relaciona con una composición farmacéutica de liberación controlada de difusión osmótica, que tiene un núcleo en el cual está el fármaco y el polímero hidrofílico hidroxipropilmetilcelulosa y puede contener un agente de relleno como la lactosa. El núcleo está recubierto por una película de material polimérico que puede ser un derivado de poli metacrilato. Dicho polímero es soluble en agua y puede presentar abertura(s) para el paso de fármaco.

El documento US 4096238 (folios: 150 a 161) se relaciona con métodos para administrar fármacos al tracto gastrointestinal y entre ellos están los sistemas osmóticos orales los cuales cuentan con una cubierta de material polimérico y pueden tener una o más aberturas para el paso de fármaco al medio. Este documento menciona los pH de los diferentes medios en los cuales se puede liberar el fármaco, y sus valores oscilan entre 6.0 y 9.0 (son pH superiores a 4.5, como lo dice el capítulo reivindicatorio de la presente solicitud).

El documento WO 98/57631 (folios: 162 a 164) se relaciona con el uso de tiazolidindionas como agonistas PPAR γ para reducir la producción de citoquinas asociadas con la respuesta inflamatoria. Este documento indica que se pueden hacer distintos tipos de formulaciones para la administración de estas tiazolidindionas, entre las cuales se encuentran los sistemas de liberación controlada que emplean copolímeros de polioxietileno-polioxipropileno. Como bien sabe la persona medianamente versada en la materia, la rosiglitazona es un tipo de tiazolidindiona y que entre los copolímeros de polioxietileno se encuentra el Eudragit.

Como se puede apreciar, estos documentos le sugieren a una persona medianamente versada en la materia que fármacos derivados de tiazolidindionas como por ejemplo la rosiglitazona también conocida como: 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidin-2,4-diona, se pueden incorporar en una forma farmacéutica oral para liberación controlada, que tengan un recubrimiento entérico de tal manera que no se libere en el estómago sino a nivel de intestino, obviamente al pH adecuado para este medio que es superior a pH 4.5 y entre los recubrimientos más empleados están los derivados de metacrilato tipo Eudragit o polímeros de ftalato de celulosa, que son los que se mencionan en la reivindicación 2 de la presente solicitud. También es obvio que se empleen sistemas de liberación controlada como son los osmóticos que emplean aberturas en la cubierta para la liberación del fármaco y que estas cubiertas sean solubles o "erosionables" para que se facilite también la liberación del principio activo.

El problema técnico planteado en esta solicitud: formas de liberación controlada para liberación de fármacos en más de un medio de pH, se había resuelto previamente mediante formas de liberación controlada ya conocidos(as). Por esta razón se considera que la forma de dosificación oral reivindicada en la presente solicitud es evidente para una persona medianamente versada en la materia.

Las reivindicaciones 1 a 8 de esta solicitud no mencionan una característica que conceda un efecto inesperado o especial a la forma de dosificación oral, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia.

Además, puesto que D1-D2-D4, D1-D3-D4 divulgaban previamente formas de liberación controlada (folios: 137 a 164), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto de esta solicitud forma de dosificación oral de rosiglitazona; de manera que para una persona medianamente versada en la materia sería obvio combinar estos documentos. Por lo cual puede no haber Nivel Inventivo.

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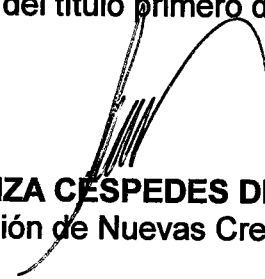
6. Conclusión:

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

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	WO 98/33489	1 a 8	Nivel Inventivo
D2	US 5543155	1 a 8	Nivel Inventivo
D3	US 4096238	1 a 8	Nivel Inventivo
D4	WO 98/57631	1 a 8	Nivel Inventivo

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.


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

El anterior requerimiento fue notificado por fijación en lista, de fecha 27 MAR 2009

CONCEPTO TÉCNICO No. 949	EXAMINADOR TÉCNICO Código No. 202005
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