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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-007005- -00011-0000

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Act. 444 RESPUESTAREQUE Folios: 11

Re: Expediente No. 05-007.005

**Solicitud de patente titulada: "FORMULACIÓN DE LAMOTRIGINA DE
LIBERACIÓN PROLONGADA Y USO DE LA MISMA PARA SU
PREPARACIÓN"**

Solicitante: GLAXO GROUP LIMITED.

Ntra. Ref.: P2005/000009

RESPUESTA AL OFICIO No. 3557, NOTIFICADO POR FIJACIÓN EN LISTA No. 90
DE FECHA 12 DE MARZO DE 2010
(PRIMER 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, en los siguientes términos:

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 Modificado presentado mediante mi memorial del 20 de abril de 2007 en respuesta a la oposición interpuesta por PROCAPS S.A.

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Así entonces, el Capítulo Reivindicatorio Modificado contiene los siguientes cambios:

- se incluyen en la Reivindicación 1 los componentes específicos de la formulación reclamada, así como la proporción en que se encuentran;
- en la Reivindicación 2 se indica el tipo de polímero de HPMC;
- se eliminan las Reivindicaciones 3 y 4;
- en la nueva Reivindicación 3 (antigua Reivindicación 5), se especifica el copolímero de metacrilato;
- las nuevas Reivindicaciones 4 a 6 corresponden a modalidades preferidas de la invención;

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 1 no describe la composición de la invención mediante de sus componentes, sino mediante una caracterización funcional. El Examinador también anota que la Reivindicación 3 pretende definir la composición por sus componentes, pero falla en especificar los ingredientes que atribuyen el efecto técnico a la invención (liberación controlada).

b- Con el ánimo de superar la anterior objeción el contenido de las Reivindicaciones 2 a 5 ha sido incluido en la nueva Reivindicación 1, de tal forma que ahora se especifican en ésta las cantidades de los ingredientes, así como la naturaleza de los polímeros de recubrimiento de liberación retardada, lo que diferencia la presente invención del arte previo.

La caracterización de la invención en la nueva Reivindicación 1 permite entonces identificar la combinación de ingredientes esenciales en la formulación, que son responsables del efecto técnico logrado. Adicionalmente, los componentes no esenciales de la invención, como diluentes, adyuvantes de compresión y lubricantes, han sido definidos de manera genérica, en tanto que su reemplazo por sustitutos similares no altera el efecto técnico declarado y pueden ser seleccionados entre auxiliares de formulación ampliamente conocidos en el arte.

Particularmente, la nueva Reivindicación 1 ahora reclama:

“Una formulación para liberación sostenida que comprende:

(i) un núcleo que comprende:

351 3
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- a) 2.5% a 80% en peso de lamotrigina, o un derivado farmacéuticamente aceptable del mismo;
- b) 17.5% a 70% en peso de un polímero de liberación retardada que corresponde a hidroxipropilmetilcelulosa;
- c) 0 a 60 % en peso de un diluyente;
- d) 0 a 20 % en peso de un auxiliar de compresión;
- e) 0.1% a 2.5% en peso de un lubricante y

(ii) una cubierta externa que comprende de 0.05 mm a 0.30 mm de un copolímero del ácido metacrílico que cubre el núcleo,

donde el grosor de dicha cubierta exterior ha sido adaptada de tal forma que la misma es sustancialmente impermeable a la entrada de los fluidos del ambiente y sustancialmente impermeable la salida de lamotrigina o de un derivado farmacéuticamente aceptable del mismo; y

donde dicha cubierta externa incluye uno o más orificios que se extienden desde el exterior de la cubierta, sustancialmente completamente a través de dicha cubierta pero sin penetrar el núcleo, permitiendo la liberación de la lamotrigina o de un derivado farmacéuticamente aceptable del mismo, desde el núcleo hacia los fluidos del ambiente, dicho orificio u orificios presentan un área o área combinada del 10-60% del área externa de dicha formulación donde la liberación de lamotrigina o un derivado farmacéuticamente aceptable de ésta, ocurre sustancialmente a través de dicho orificio y donde el recubrimiento externo se disuelve cuando el pH ambiental es mayor a 5.”

Adicionalmente, las Reivindicaciones 2 a 6 reclaman modalidades preferidas específicas de la presente invención.

3. a- El Examinador establece que la Reivindicación 6 reclama resultados a alcanzar con las formulaciones de la invención (área bajo la curva), es decir, el problema a solucionar como tal, más no la invención que proporciona dichos resultados o que soluciona el problema mencionado.

b- En relación con la antigua Reivindicación 6 (nueva Reivindicación 7), llamo respetuosamente la atención del Examinador al hecho que el Manual Andino de Patentes (MAP) establece que una vez la materia de la invención se encuentra perfectamente definida mediante sus características técnicas estructurales en las reivindicaciones (componentes y proporciones), las reivindicaciones dependientes pueden complementar la caracterización estructural con la indicación de características funcionales.¹ Es más, vale la pena recordar que el MAP establece que las Reivindicaciones dependientes especifican características particulares y por definición incluyen todas las características listadas en la reivindicación independiente.² De acuerdo con lo

¹ Manual Andino de Patentes. OMPI, EPO, Secretaría de la Comunidad Andina, 2004. Sección 4.6.6.

² Manual Andino de Patentes. OMPI, EPO, Secretaría de la Comunidad Andina, 2004. Sección 4.5.2.

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anterior, la Reivindicación 7, al ser dependiente de la Reivindicación 1, comprende las características técnicas listadas en ésta y simplemente definen y complementan la caracterización técnica (estructural) indicando los parámetros farmacocinéticos alcanzados con la formulación.

4. a- El Examinador establece que las patentes WO97/14415 (D1), WO98/47491(D2) y US2001/0008889 (D3), afectan el nivel inventivo de la presente invención.

El Examinador argumenta que D1 revela composiciones farmacéuticas de liberación controlada (liberación sostenida) que comprenden un núcleo matriz que incluyen antagonistas de NMDA (p.ej. lamotrigina). Las composiciones en D1 corresponden a tabletas multicapa que contienen excipientes usuales, tales como ingredientes solubles (sacarosa, lactosa, fructosa, manitol, PEG, HPMC, HPC, laurilsulfato de sodio, cremofor, tween, span, pluronics), componentes insolubles (celulosa microcristalina, fosfato de calcio, talco, aerosil) y materiales de cubierta (PEG, HPMC, ceras, ácidos grasos y dispersiones que incluyen polímeros).

A su vez, D2 revela composiciones de liberación controlada que comprenden polímeros inteligentes, donde el ingrediente activo presenta un ángulo de mojado cuyo coseno se encuentra entre +0.9848 y -0.9848. Adicionalmente, la composición comprende un primer componente inteligente de tipo polimérico (etil celulosa) y un segundo componente inteligente (una mezcla entre hidroxietilcelulosa y HPMC) donde el segundo componente presenta propiedades de humectación opuestas. Adicionalmente, las composiciones de D2 incluyen dióxido de silicona, un surfactante (lauril sulfato de sodio) y un agente facilitador de la compresión.

D3 revela composiciones que comprenden agentes anticonvulsivantes (lamotrigina) en la forma de tabletas para administración oral que comprenden diluentes sólidos, tales como carbonato de calcio, fosfato de calcio o caolín.

El Examinador argumenta que la única diferencia entre la presente invención y D1 es el uso de un aditivo de compresión; en cuanto a D2 la única diferencia es el uso de agentes lubricantes, y en referencia a D3, la diferencia es el empleo de cubiertas que contienen polímeros, adyuvantes de compresión y lubricantes.

Finalmente, el Examinador anota que la necesidad de proporcionar formulaciones de liberación controlada de lamotrigina fue resuelta previamente en el arte; D1 y D3 ya habían divulgado formulaciones de lamotrigina de liberación controlada y sostenida.

353 353

b- i) Apparently, the Examiner has not clearly understood in what consists the form of dosification of the present invention, nor its differences with the formulations of the prior art. The present invention consists in a core with base in a modified release matrix, surrounded by an enteric coating that presents two relatively wide openings.

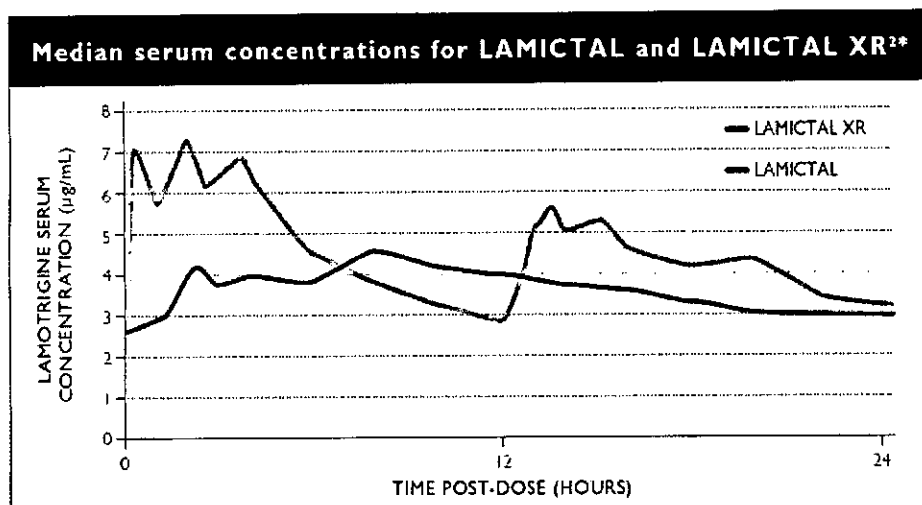
The tablets of lamotrigine existing in the market provide an immediate release of the active ingredients once the tablet reaches the stomach. The peak in the concentration of plasma occurs between 1.4 to 4.8 hours after its administration. The disadvantage of this is that the concentration in plasma (pharmacokinetic profile -PK, by its English siglas-) reached with the conventional tablets is cyclic, with peaks that occur after the administration followed by valleys that are presented just before the next administration of the drug.

In particular, in the treatment of epilepsy it is thought that the valleys can lead to attacks intratreatment and that the peaks of concentration in plasma can result in adverse events (EA) in some patients. Alternatively, the increase in the concentration in plasma in the initial stages before reaching the maximum peak can also affect the profile of EA.

As such things, the present invention, corresponds to a formulation of lamotrigine of sustained release that presents two phases in the release of the drug, in which the velocity of release in the first phase in the stomach is slower than the release in the second phase (once the pH is superior to 5, that is, in the small intestine).

When comparing the pharmacokinetics of the formulation of sustained release of the present invention (Lamictal XR™), which is administered once a day, with the formulation of immediate release (Lamictal™), which is administered twice a day, it is clear that the average levels of concentration in plasma for the valleys and peaks of the sustained release formulation, are found within the levels reached for the immediate release formulation. Additionally, the sustained release formulation presents lower fluctuations in plasma, as is shown in the following graph:

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Con base en los anteriores datos, la FDA aprobó la formulación de liberación sostenida Lamictal XRTM para la administración una vez al día de lamotrigina. Esta formulación se ha comercializado por más de un año con una excelente reducción de los efectos adversos asociados a las formas de liberación inmediata.

Ahora bien, la reducción de los picos y valles (fluctuaciones) en las concentraciones en plasma de lamotrigina, administrada como Lamictal XRTM, es alcanzada mediante un control cuidadoso de qué tan rápido y en dónde se libera la lamotrigina a partir de la formulación de liberación sostenida.

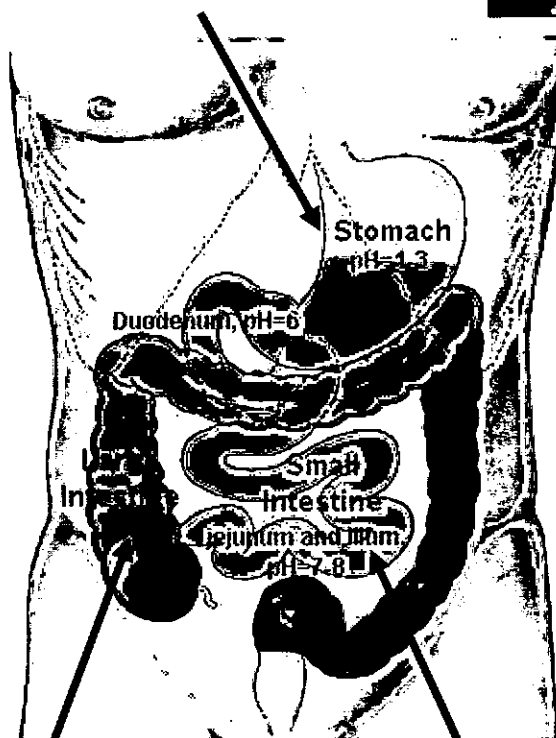
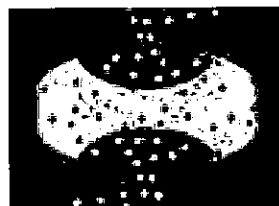
Los orificios en la cubierta entérica de Lamictal XRTM controlan qué tanta porción del núcleo está expuesta en el estómago (disminuyendo la velocidad de liberación). A su vez, los polímeros de liberación retardada presentes al interior del núcleo disminuyen la velocidad de liberación de lamotrigina. La primera fase de la liberación de lamotrigina es por lo tanto lenta. Una vez la tableta alcanza el pH elevado del intestino delgado, la cubierta entérica se disuelve, exponiendo completamente la superficie del núcleo, permitiendo tanto su erosión como la difusión de lamotrigina, lo que incrementa la velocidad de liberación. Por lo tanto, la segunda fase de liberación es más rápida que la primera. *

Las dos fases de liberación de lamotrigina desde la formulación de la presente invención se ilustran en los siguientes diagramas:

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1. Tableta en el estómago

La liberación controlada de lamotrigina a través de los orificios de la cubierta entérica, que limita la porción del núcleo que es expuesta a las condiciones ácidas del estómago.

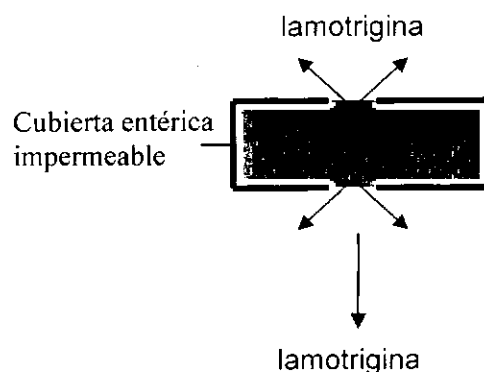


2. Tableta en intestino delgado

La cubierta entérica se disuelve, exponiendo totalmente el núcleo, permitiendo la erosión y difusión de lamotrigina en el intestino delgado.

3. Tableta en intestino grueso

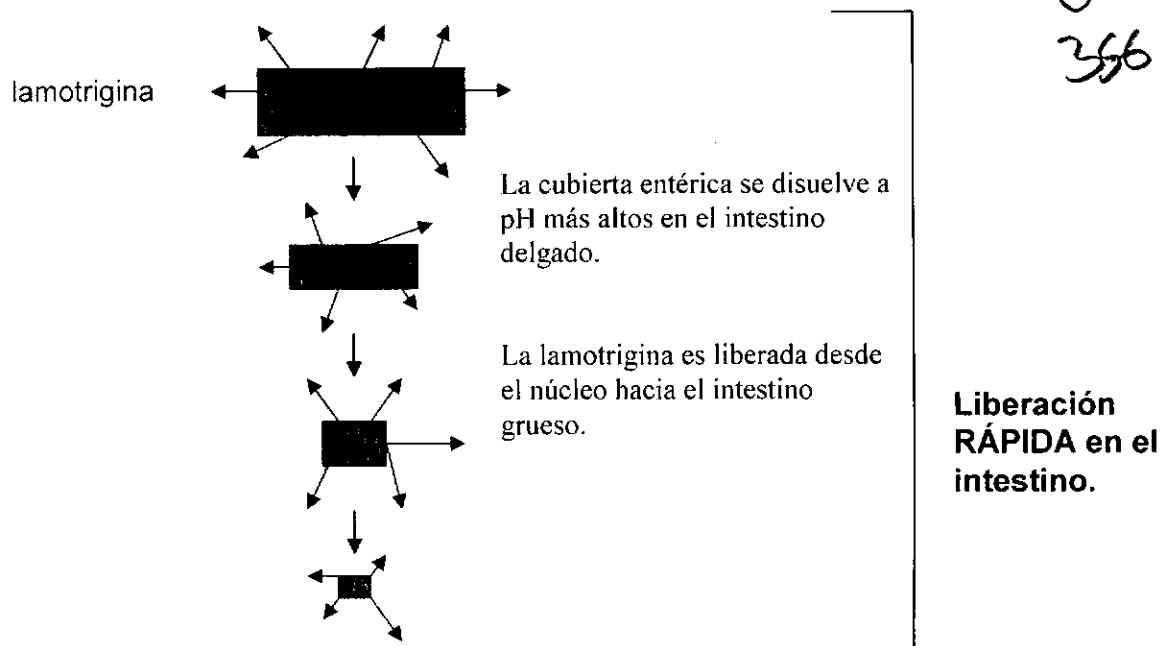
La absorción de lamotrigina como un remanente de la tableta en el intestino



La lamotrigina es liberada a través de los orificios de la cubierta entérica, mientras la tableta se encuentra en el estómago.

Liberación LENTA en el estómago

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Al retardar la liberación en el estómago usando la formulación de la invención, también se supera la solubilidad dependiente de pH de la lamotrigina en el tracto gastrointestinal (es casi 20-30 veces más soluble en el pH ácido del estómago que en el intestino grueso). Esto, produce una menor velocidad de absorción hacia el torrente sanguíneo que la forma de liberación inmediata creando el efecto de control mejorado de ataques y la reducción de los efectos adversos en pacientes con epilepsia.

ii) En relación con el arte previo citado, D1 revela composiciones farmacéuticas que incluyen antagonistas del receptor NMDA en una forma de liberación inmediata, en asociación con otro antagonista del receptor NMDA, en una forma de liberación controlada (liberación sostenida). Las dos formas se encuentran usualmente asociadas en una tableta multicapas, donde ambas capas presentan ingrediente activo.

En cuanto a D2, dicha referencia se dirige a composiciones que contienen polímeros inteligentes, tales como etilcelulosa (EC), hidroxietilcelulosa (HEC) e hidroxipropilmetilcelulosa (HPMC); HEC y HPMC en una proporción de 1:100 a 100:1.

D3 revela composiciones que comprenden agentes anticonvulsivantes en combinación con antagonistas NMDA.

El Examinador reconocerá que ninguna de las referencias citadas proporciona enseñanzas que conduzcan a desarrollar el concepto de administrar lamotrigina en un sistema de liberación dual o de dos fases.

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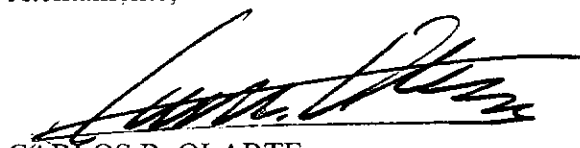
De hecho, ninguna de las referencias D1 a D3 independientemente o en combinación, sugiere específicamente:

- emplear una cubierta entérica que se disuelva a pHs superiores a 5, y que además contenga orificios suficientemente grandes para exponer al ambiente la matriz del núcleo que contiene el fármaco, pero no totalmente;
- que al emplear la configuración estructural reivindicada, se obtendría un sistema de liberación de dos fases que combina dos mecanismos de liberación (a través de los orificios y al momento de disolver la cubierta);
- que el sistema de liberación de dos fases permitiría: (i) evitar los eventos adversos generados por los picos de concentración en plasma, seguidos a la administración del medicamento, y (ii) evitar los ataques intratratamiento durante los valles previos a la siguiente administración, que son típicos de las formulaciones de liberación inmediata empleadas antes de la presente invención;
- que se podría obtener una reducción de la fluctuación de los niveles plasmáticos del fármaco;
- adoptar una aproximación contraria a la intuición para producir una formulación con una cubierta con orificios y además una matriz en el núcleo que permita una liberación lenta del fármaco desde el núcleo a través de los orificios de la cubierta hacia al ambiente, y una posterior disolución de la cubierta a pH superiores a 5, en donde ocurre una liberación rápida.

En conclusión, ninguno de los documentos citados por el Examinador sugiere las características estructurales y funcionales de la presente invención, y por lo tanto, no afectan su nivel inventivo.

5. Por todo lo anterior, considero que las objeciones presentadas por el Examinador en su examen de fondo No. 930 han sido resueltas y por consiguiente solicito respetuosamente que el Despacho tenga por cumplidos los requisitos de patentabilidad, en tanto no se desvirtuó ninguno de ellos, y se proceda con la concesión de la patente.

Atentamente,



CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Anexos:

- Capítulo Reivindicatorio Modificado

358

358

CAPÍTULO REIVINDICATORIO MODIFICADO
(Primer Examen de Fondo)

1. Una formulación para liberación sostenida que comprende:
 - (i) un núcleo que comprende:
 - a) 2.5% a 80% en peso de lamotrigina, o un derivado farmacéuticamente aceptable del mismo;
 - b) 17.5% a 70% en peso de un polímero de liberación retardada que corresponde a hidroxipropilmetilcelulosa;
 - c) 0 a 60 % en peso de un diluyente;
 - d) 0 a 20 % en peso de un auxiliar de compresión;
 - e) 0.1% a 2.5% en peso de un lubricante y
 - (ii) una cubierta externa que comprende de 0.05 mm a 0.30 mm de un copolímero del ácido metacrílico que cubre el núcleo, donde el grosor de dicha cubierta exterior ha sido adaptada de tal forma que la misma es sustancialmente impermeable a la entrada de los fluidos del ambiente y sustancialmente impermeable la salida de lamotrigina o de un derivado farmacéuticamente aceptable del mismo; y donde dicha cubierta externa incluye uno o más orificios que se extienden desde el exterior de la cubierta, sustancialmente completamente a través de dicha cubierta pero sin penetrar el núcleo, permitiendo la liberación de la lamotrigina o de un derivado farmacéuticamente aceptable del mismo, desde el núcleo hacia los fluidos del ambiente, dicho orificio u orificios presentan un área o área combinada del 10-60% del área externa de dicha formulación donde la liberación de lamotrigina o un derivado farmacéuticamente aceptable de ésta, ocurre sustancialmente a través de dicho orificio y donde el recubrimiento externo se disuelve cuando el pH ambiental es mayor a 5.
2. Una formulación de liberación sostenida de acuerdo con la Reivindicación 1, donde el polímero de hidroxipropilmetilcelulosa es una mezcla de metocel E4M y KL100LV.
3. Una formulación de liberación sostenida de acuerdo con las Reivindicaciones 1 y 2, donde el copolímero de ácido metacrílico es eudragit L30 D55.

389

4. Una formulación de liberación sostenida de acuerdo con cualquiera de las Reivindicaciones 1 a 3, donde el diluyente es lactosa.

389

5. Una formulación de liberación sostenida de acuerdo con cualquiera de las Reivindicaciones 1 a 4, donde el auxiliar de compresión es seleccionado del grupo que consiste en: polividon K30, estearato de magnesio y dióxido de silicona.

6. Una formulación de liberación sostenida de acuerdo con cualquiera de las Reivindicaciones 1 a 5, donde el lubricante es estearato de magnesio.

7. Una formulación de liberación sostenida como se reivindica en la Reivindicación 1, que luego de la administración a un humano produce valores de Área Bajo la Curva por fuera del rango de 80 a 125% y un C_{max} aproximadamente 30% menor que el de una tableta de liberación inmediata que contiene la misma cantidad de lamotrigina o un derivado farmacéuticamente aceptable de la misma.

United States Patent [19]
Zentner et al.

[11] **Patent Number:** 4,968,507
[45] **Date of Patent:** * Nov. 6, 1990

[54] **CONTROLLED POROSITY OSMOTIC PUMP**

[75] **Inventors:** Gaylen M. Zentner; Gerald S. Rork,
both of Lawrence, Kans.; Kenneth J.
Himmelstein, Irvine, Calif.

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

[*] **Notice:** The portion of the term of this patent
subsequent to Jul. 25, 2006 has been
disclaimed.

[21] **Appl. No.:** 73,781

[22] **Filed:** Jul. 15, 1987

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 850,576, Apr. 11,
1986, abandoned, which is a continuation of Ser. No.
689,540, Jan. 7, 1985, abandoned, which is a continua-
tion-in-part of Ser. No. 622,808, Jun. 20, 1984, aban-
doned.

[51] **Int. Cl.:** A61K 9/64

[52] **U.S. Cl.:** 424/465; 604/890.1;
604/892.1; 424/473

[58] **Field of Search:** 424/465, 473;
604/890.1, 892.1

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,538,214 11/1970 Polli et al. 424/473

3,845,770 11/1974 Theeuwes et al. 424/469
3,916,899 11/1975 Theeuwes et al. 424/469
4,160,452 7/1979 Theeuwes 424/469
4,200,098 4/1980 Ayer et al. 424/424
4,256,108 3/1981 Theeuwes 424/469
4,285,987 8/1981 Ayer et al. 427/3
4,557,925 12/1985 Lindahl et al. 424/469
4,687,660 8/1987 Baker et al. 424/465
4,851,228 7/1989 Zentner et al. 424/456

Primary Examiner—Ronald W. Griffin

Attorney, Agent, or Firm—Kevin J. McGough; Joseph
F. DiPrima; Michael C. Sudol, Jr.

[57] **ABSTRACT**

The instant invention is directed to an osmotic pump
comprising:

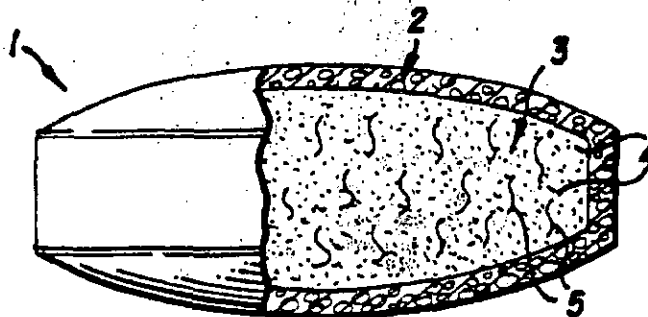
(A) at least one active agent surrounded by

(B) a rate controlling water insoluble wall, having a
fluid permeability of 6.96×10^{-18} to 6.96×10^{-14} cm³
sec/g and a reflection coefficient of less than 1, pre-
pared from:

(i) a polymer permeable to water but impermeable to
solute and

(ii) 0.1 to 60% by weight, based on the total weight of
(i) and (ii), of at least one pH insensitive pore form-
ing additive dispersed throughout said wall.

17 Claims, 19 Drawing Sheets



CONTROLLED POROSITY OSMOTIC PUMP

BACKGROUND OF THE INVENTION

This invention concerns an osmotically activated system for dispensing pharmacologically active agent(s). The system comprises an inner core compartment of osmotically active composition surrounded by an enclosing wall material. The core comprises pharmacologically active agent(s) soluble in an external fluid, or a mixture of agent(s) having a limited solubility in the external fluid with osmotically effective solute(s) that is/are soluble in the fluid, which exhibit an osmotic pressure gradient across the wall against the external fluid. The wall constitutes a layer of controlled porosity that is substantially permeable to both the external fluid and the core composition. Agent is released from the system by fluid imbibition through the wall into the inner core compartment at a rate controlled by the wall composition and dimensions, producing a solution containing agent that is released through the wall at a controlled rate in response to fluid volume flux, dV/dt , resulting from the osmotic pressure gradient, and diffusive flux, $(dM/dt)_D$, driven by the chemical potential gradient of the agent across the wall. The total rate of agent release, $(dM/dt)_T$, is given by Equation 1 where C is the concentration

$$\left(\frac{dM}{dt} \right)_T = \left(\frac{dV}{dt} \right)_C + \left(\frac{dM}{dt} \right)_D \quad \text{Eq. 1}$$

of the active agent in the dissolved core composition and remains constant when excess solid core mass is present. For the special case where the core mass is pure active agent, the dissolved concentration is equal to the active agent solubility, S , in the fluid. In the present invention the volume flux contribution, $(dV/dt)_C$, to the total rate is greater than the diffusive contribution, $(dM/dt)_D$, and forms the basis for the osmotic pump action of the device.

The object of this invention is to provide an osmotically actuated system for controlled delivery of pharmacologically active agents to biological receptor sites over a prolonged period of time.

The controlled porosity wall of the present invention is substantially permeable to both solute and external fluid. The wall is composed of materials that maintain their physical and chemical integrity during the controlled dispensing of agent in mixture with materials that can be leached into the external fluid. The wall has programmable fluid transmission and agent release rates which provide for controlled release of agent which is free from environmental influences including pH and degree of external fluid agitation.

The wall may be composed of either insoluble, non-erodible materials mixed with leachable additives, or bioerodible materials containing leachable additives. Bioerodible materials would be selected to bioerode after a predetermined period with bioerosion occurring subsequent to the period of agent release.

Another object of the invention is to provide an osmotic system that is readily manufactureable to deliver a pre-determined dose of agent at a programmed rate from compositions of matter in the varied geometries and sizes of tablets, pellets, multi-particulates, and such related dosage forms as familiar to those skilled in the art for oral, buccal, vaginal, rectal, nasal, ocular, aural,

parenteral and related routes of administration. Another object of the invention is to provide an osmotic system that delivers agent on an equivalent mass per unit surface area basis.

The use of pore formers in substantially water impermeable polymers, such as polyvinyl chloride, is disclosed in J. Pharm. Sci. 72, 772-775 and U.S. Pat. No. 4,244,941. These devices are not osmotic pumps. The devices release the core contents by simple diffusion through the pores in the coating.

U.S. Pat. No. 3,957,523 discloses a device which has pH sensitive pore formers in the wall.

U.S. Pat. Nos. 4,256,108; 4,160,452; 4,200,098 and 4,285,987 disclose devices with pore formers in only one of at least two wall layers. These devices contain a drilled hole for the release of the core contents.

A BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an embodiment of the osmotic pump.

FIG. 2 is the release profile (statistical average of several pumps) of the pumps produced in Examples 1 through 3.

FIGS. 3, 4, 6, 7 and 9 through 16 are the release profiles of the pumps produced in Examples 4 through 15, respectively.

FIG. 5 is a plot of $1/(\text{wall thickness})$ versus mean release rate of the pumps produced in Example 5.

FIG. 8 is a plot of release rate versus the net osmotic pressure difference for the pumps produced in Example 7.

FIG. 17 is a scanning electron micrograph of a leached wall sample from the device described in Example 16, illustrating porosity and pore sizes.

DESCRIPTION OF THE INVENTION

The instant invention is directed to an osmotic pump, comprising:

(A) at least one active agent surrounded by
(B) a rate controlling water insoluble wall, having a fluid permeability of 6.96×10^{-18} to 6.96×10^{-14} cm³ sec/g and a reflection coefficient of less than 1, prepared from:

(i) a polymer permeable to water but impermeable to solute and
(ii) 0.1 to 60% by weight, based on the total weight of (i) and (ii), of at least one pH insensitive pore forming additive dispersed throughout said wall.

The phrase "permeable to water but impermeable to solutes" means the water permeates through the polymer preferably to solute, under a pressure differential.

Referring to FIG. 1, the osmotic pump device (1) is typically in the form of a single coated tablet or shaped for rectal or vaginal applications, and coated pellets, and multi-particulates having the essential features and elements of FIG. 1, yet of a size such that several such devices may be loaded into a soluble gelatin capsule for oral administrations or suspended in a suitable vehicle for injection or spraying.

The water insoluble, permeable wall (2) of controlled porosity may be applied to osmotically active core composition masses (3) by spray coating procedures. The wall is comprised of (a) polymeric material that is insoluble in the fluids of the environment of intended use (usually water); (b) other added excipients that will dissolve in the environmental fluids and leach out of the wall. Referring to FIG. 17, the leached wall is a sponge-like structure composed of numerous open and closed

364
361

nate, ferrous sulfate, ferrous fumarate and sodium lactate; and drugs that act on α -adrenergic receptors such as clonidine hydrochloride.

Additional preferred drugs include quinoline and naphthyridine carboxylic acids and related compounds, such as 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid; 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid; 5-ethyl-5,8-dihydro-8-oxo-1,3-dioxolo-[4,5-g]quinoline-7-carboxylic acid; 8-ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-d]pyrimidine-6-carboxylic acid; 9-fluoro-6,7-dihydro-5-methyl-1-oxo-1H,5H-benzo[*ij*]quinoxolizine-2-carboxylic acid; 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic acid; 1-ethyl-1,4-dihydro-4-oxo-[1,3]dioxolo[4,5-g]cinnoline-3-carboxylic acid; 9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid; 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-1,8-naphthyridine-3-carboxylic acid; 1-ethyl-6-fluoro-1,4-dihydro-7-(1-piperazinyl)-4-oxo-1,8-naphthyridine-3-carboxylic acid; 1-cyclopropane-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid; 1-methylamino-6-fluoro-1,4-dihydro-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinolinecarboxylic acid; 1-(4-fluoro-1-phenyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid; 1-(4-fluoro-1-phenyl)-6-fluoro-1,4-dihydro-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinolinecarboxylic acid; 1-(4-fluoro-1-phenyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid; and 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(3-ethylaminomethyl-1-pyrrolidinyl)-8-fluoro-3-quinolinecarboxylic acid.

Additional preferred drugs include drugs which affect the respiratory tract such as budesonide, enprofylline, tranilast, albuterol, theophylline, aminophylline, brompheniramine, chlorpheniramine, promethazine, diphenhydramine, azatadine, cyproheptadine, terbutaline, metaproterenol, and isoproterenol; drugs which are antidepressants such as amiflamine, alaproclate, doxepin, trazodone, maprotiline, zimelidine, fluvoxamine; antipsychotic drugs such as haloperidol, thioridazine, trifluoperazine, MK-0212, and remoxipride; sedative hypnotic and anti-anxiety drugs such as triazolam, temazepam, chlorazepate, alprazolam, diazepam, flurazepam, lorazepam, oxazepam, hydroxyzine, prazepam, meprobamate, butalbital, and chlorzoxazone; antiparkinson drugs such as benzotropine and L-647,339; hormonal and steroidal drugs such as conjugated estrogens, diethylstilbesterol, hydroxy progesterone, medroxy progesterone, norethindrone, betamethasone, methylprednisolone, prednisone, thyroid hormone, levothyroxine and MK-0621; antihypertensive and cardiovascular drugs such as isosorbide dinitrate, digoxin, nadolol, disopyramide, nifedipine, quinidine, lidocaine, diltiazem, verapamil, prazosin, captopril, enalapril, lisinopril, metyrosine, felodipine, tocainide, mexiletine, mecamlamine, and metyrosine; diuretic drugs such as spironolactone, chlorthalidone, metolazone, triamterene, methyclothiazide, and indacrinone; anti-inflammatory drugs such as ibuprofen, phenylbutazone, tolmetin, piroxicam, melclofenamate, auranofin, flurbiprofen and penicillamine; analgesic drugs such as acetaminophen, oxycodone, hydrocodone, and propoxyphene; anti-infective drugs such as cefoxitin, cefazolin, cefotaxime, cephalixin, nicarbazine, amprolium, ampicillin, amoxicillin, cefaclor, erythromycin, nitrofurantoin, minocycline,

doxycycline, cefadroxil, miconazole clotrimazole, phenazopyridine, clorsulon, fludalanine, pentizidone, cilsatin, phosphonomycin, imipenem, arprinocid, and foscarnet; gastrointestinal drugs such as bethanechol, clidinium, dicyclomine, meclizine, prochlorperizine, trimethobenzamide, loperamide, ranitidine, diphenoxylate, famotidine, metoclopramide and omeprazole; anti-coagulant drugs such as warfarin, phenindione, and anisindione; and other drugs such as trientine, cambendazole, ronidazole, rafoxinide, dactinomycin, asparaginase, nalorphine, rifamycin, carbamazepine, metaraminol bitartrate, allopurinol, probenecid, diethylpropion, dihydrogenated ergot alkaloids, nystatin, pentazocine, phenylpropanolamine, phenylephrine, pseudoephedrine, trimethoprim and mevinolin.

The above list of drugs is not meant to be exhaustive. Many other drugs will certainly work in the osmotic pump of the instant invention.

Examples of beneficial drugs are disclosed in *Remington's Pharmaceutical Sciences*, 16th Ed., 1980, published by Mack Publishing Co., Easton, Penna.; and in *The Pharmacological Basis of Therapeutics*, by Goodman and Gilman, 6th Ed., 1980, Published by The MacMillan Company, London.

The drug can be in various forms, such as uncharged molecules, molecular complexes, pharmacologically acceptable salts such as hydrochlorides, hydrobromides, sulfate, laurylate, palmitate, phosphate, nitrite, borate, acetate, maleate, tartrate, oleate, and salicylate.

For acid drugs, salts of metals, amines or organic cations, for example quaternary ammonium can be used. Derivatives of drugs such as esters, ethers and amides which have solubility characteristics suitable for use herein can be used alone or mixed with other drugs. Also, a drug that is water insoluble can be used in a form that is a water soluble derivative thereof to effectively serve as a solute, and on its release from the device, is converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original form, or to a biologically active form. The agent can be in the reservoir as a solution, dispersion, paste, cream, particle, granule, emulsion, suspension or powder. Also, the agent can be mixed with a binder, dispersant, emulsifier or wetting agent and dyes.

The amount of active agent or active agent admixed with other osmotically active solutes present in the device is initially in excess of the amount that can be dissolved in the fluid that enters the reservoir. Under this physical state when the agent is in excess, the device will osmotically operate to give a substantially constant rate of release. The rate of agent release pattern can also be varied by having different amounts of agent in the reservoir to form solutions containing different concentrations of agent for delivery from the device. Generally, the device can house from 0.05 ng to 5 grams or more, with individual devices containing, for example, 25 ng, 1 mg, 5 mg, 250 mg, 500 mg, 1.5 g and the like.

Mixtures of drug agent(s) with other osmotically effective compounds may be used to attract fluid into the device producing a solution of compound which is delivered from the device concomitantly transporting drug agent to the exterior of the device. Examples include magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, calcium bicarbonate, sodium sulfate, calcium sulfate, potassium acid phosphate, calcium lactate, d-

362
362

mannitol, urea, inositol, sorbitol, magnesium succinate, tartaric acid, carbohydrates such as raffinose, sucrose, glucose, α -D-lactose monohydrate, and mixtures thereof. The compound is initially present in excess and it can be in any physical form such as particle, crystal, pellet, tablet, strip, film or granule. The osmotic pressure of saturated solutions of various osmotically effective compounds and for mixtures of compounds at 37° C., in water, is listed in Table 2. In the table, the osmotic pressure π , is in atmospheres, atm. The osmotic pressure is measured in a commercially available osmometer that measures the vapor pressure difference between pure water and the solution to be analyzed, and according to standard thermodynamic principles, the vapor pressure ratio is converted into osmotic pressure difference. In Table 2, osmotic pressures of from 20 atm to 500 atm are set forth; of course, the invention includes the use of lower osmotic pressures from greater than zero, and higher osmotic pressures than those set forth by way of example in Table 2. For example, in the gastrointestinal tract, the osmotic pressure gradient across the wall in the compartment will be from greater than 0 up to 500 atm per membrane thickness. That is, the osmotic pressure in the compartment will be typically in excess of 8 atm up to 500 atm.

TABLE 2

COMPOUND OR MIXTURE	OSMOTIC PRESSURE (atm)
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose-Fructose	430
Mannitol-Fructose	415
Sodium Chloride	356
Fructose	335
Lactose-Sucrose	250
Potassium Chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Mannitol-Sucrose	170
Sucrose	150
Mannitol-Lactose	130
Dextrose	82
Potassium Sulfate	39
Mannitol	38
Sodium Phosphate Tribasic. 12H ₂ O	36
Sodium Phosphate Dibasic. 7H ₂ O	31
Sodium Phosphate Dibasic. 12H ₂ O	31
Sodium Phosphate Dibasic Anhydrous	29
Sodium Phosphate Monobasic. H ₂ O	28

The resulting device will have a water permeability driven by a saturated solution of the active agent, or mixtures of active agents with other osmotically active solutes, at the temperature of use, of 0.01 ml per cm² of surface area per day to 10 ml per cm² of surface area per hour.

EXAMPLE 1

A plurality of osmotic systems for the osmotically controlled release of the beneficial drug potassium chloride were made as follows: First, 650 mg aliquots of commercially-available reagent grade potassium chloride (active agent) were compressed to a hardness of 15Kg by standard compression techniques in a Stokes tableting machine fitted with a $\frac{1}{8}$ inch extra deep concave punch. A total of 700 g of such tablets were prepared as osmotic core composition masses of the invention. Next, 36 g of Eastman cellulose acetate 398-10 (polymer) were added to methylene chloride (solvent), with subsequent addition of methanol (solvent) with high speed mechanical stirring to complete the dissolu-

tion of the polymer. To this was added 7.9 g of polyethylene glycol 400 (plasticizer, liquid pore forming additive and flux regulator). To this solution was added in dropwise fashion with stirring a second solution of water and methanol (solvent) containing 18 g of dissolved sorbitol (solid pore forming additive), to constitute the solution utilized to form the controlled porosity wall of the invention. The final solution contained approximately 2%, by weight, polymer in a solvent system of methylene chloride, methanol, and water in the approximate weight ratio of 15:10:1. The fluid permeability of the wall was 2.28×10^{-15} cm³ sec/g and its reflection coefficient was measured at 8.66×10^{-4} . Next, 700 g of the potassium chloride osmotic core tablets was charged into a commercial Uni-Glatt fluidized bed machine wherein the wall forming solution was applied to the cores until a thickness of 0.016 cm was attained. The finished osmotic systems were dried in an oven at 50° C. to facilitate removal of residual solvents.

Finally, the potassium chloride release from these osmotic systems into distilled water was monitored conductimetrically at 37° C. in a commercial Applied Analytical standard dissolution apparatus Providing 100 rpm stirring. The release profile is depicted in FIG. 2 labelled as MMP-50 (modified microporous, sorbitol 50% of polymer wt) and was found to be continuous at a mean rate of 139 mg per hour for a prolonged period of approximately 4 hours. Since the solute is passing through the wall, it has a reflection coefficient substantially less than 1 and was determined to be less than 0.1. The amount of potassium chloride released with zero-order kinetics was consistent with the theoretically anticipated amount which was calculated with Equation 1 to be 82.7% of the initial KCl loaded into the core mass

$$100 \times \frac{M_2}{M_1} = \left(1 - \frac{S}{\rho} \right) \times 100 \quad (\text{Eq. 1})$$

where M_2 is the amount released in zero-order fashion, M_1 is the initial KCl load, S is the KCl solubility (343 g/ml), and ρ is the density of solid KCl (2 g/cm³).

EXAMPLE 2

A plurality of osmotic systems were manufactured according to the procedure of Example 1, wherein the conditions were as described except that the sorbitol content of the wall forming solution was 9 g. Potassium chloride release from these systems was monitored according to the procedure of Example 1. The release profile is depicted in FIG. 2 labelled as MMP-25 and was found to be continuous for a prolonged period at a mean rate of 120 mg per hour for approximately 5 hours. The fluid permeability of the wall was 1.69×10^{-15} cm³ sec/g and the reflection coefficient of the wall was less than 0.1.

EXAMPLE 3

A plurality of osmotic systems were manufactured according to the procedure of Example 1, wherein the conditions were as described except that the sorbitol content of the wall forming solution was 3.6 g. Potassium chloride release from these systems was monitored according to the procedure of Example 1. The release profile is depicted in FIG. 2 labelled as MMP-10 and

363
363

flux of water, dV/dt , from the first chamber into the second was measured by following the rise of fluid in the capillary with a cathetometer accurate to 0.01 cm. The diffusive flux of potassium chloride from the second chamber into the first chamber was measured conductimetrically under the same conditions as the water flux measurements except that the capillary was eliminated. Fluid levels in both chambers were kept equal throughout the diffusion experiments to eliminate hydrostatic pressure effects.

The membranes examined were identical in composition to walls applied to core tablets in Examples 1, 2 and 3 and were prepared by spraying onto a flat glass substrate. The measured volume flux of water, dV/dt , of Equation 1, for each membrane was multiplied by the potassium chloride solubility, $S=0.343$ g/cm³, and normalized to a wall thickness of 0.016 cm and area of 2.67 cm² to correspond to the wall dimensions of the devices in Examples 1, 2 and 3. This was the calculated osmotic pump contribution to the total release.

The diffusive contribution, $(dM/dt)_D$, was measured directly and normalized to a wall thickness of 0.016 cm and area of 2.67 cm². The sum of the normalized osmotic pump and diffusive contributions was the calculated total release rate anticipated for devices similar to those of Examples 1, 2 and 3. These values were compared to the actual observed Performance of the devices in FIG. 16. The calculated rates agreed with the actual rates, with osmotic pumping the dominant contribution in all cases. The fractional contribution of osmotic pumping increased as the weight percentage of pore former in the films increased, while the diffusional contribution reached a constant value.

In all cases the walls were highly permeable to both water and salt. The agreement between the calculated rates and the actual rates indicated that the walls had a low level of selectivity between water and salt flux. The reflection coefficient, σ , is an established indicator of membrane selectivity and has been defined in *Biochimica et Biophysica Acta*, Vol. 27, page 236, such that $\sigma=0$ for a totally non-selective membrane and $\sigma=1$ for a totally selective membrane that is permeable to solvent (water) only. The low selectivity observed clearly indicated that σ was less than one. The data of FIG. 16 were consistent with σ values in the range 0 to 0.8. In fact, the σ values for MMP-50 was determined to be 8.66×10^{-4} and the σ values from MMP-25 and MMP-10 estimated at less than 0.1.

EXAMPLE 16

Sections of the walls from devices described in Example 2 were equilibrated in deionized water for 8 hours to leach out the water soluble pore forming additives. These samples were critical point dried with carbon dioxide by standard methods and viewed with a scanning electron microscope. A typical micrograph is presented in FIG. 17. The walls were sponge-like in appearance with a distribution of pores that were less than 100 microns in diameter.

What is claimed is:

1. An osmotic pump, for the controlled release of a pharmaceutically active agent to an environment of use, said pump consisting essentially of:

- (A) a core comprises at least one pharmacologically active agent soluble in an external fluid, or a mixture of an agent having a limited solubility in the external fluid with an osmotically effective solute that is soluble in the fluid, which exhibit an osmotic pressure gradient across the wall against the external fluid surrounded by

(B) a rate controlling water insoluble wall, having a fluid permeability of 6.96×10^{-18} to 6.96×10^{-14} cm³ sec/g and a reflection coefficient of less than 0.5, prepared from:

- (i) a polymer permeable to water but impermeable to solute and
(ii) 0.1 to 60% by weight, based on the total weight of (i) and (ii), of at least one pH insensitive pore forming additive dispersed throughout said wall.

2. The osmotic pump of claim 1, wherein said pore forming additive comprises:

- (a) 0.1 to 50%, by weight, solid additive, based on the total weight of (i) and (ii), and/or
(b) 0.1 to 40%, by weight, liquid additive, based on the total weight of (i) and (ii), not to exceed a total weight % of pore forming additive of 60%.

3. The osmotic pump of claim 1, wherein said reflection coefficient is less than 0.1.

4. The osmotic pump of claim 1, further comprising:
(C) 0 to 50 parts per 100 parts of (i) and (ii) of plasticizer and flux regulating additives and
(D) 0 to 40 parts per 100 parts of (i) and (ii), of surfactant additive.

5. The osmotic pump of claim 1, wherein said water insoluble wall is 1 to 1,000 microns thick and wherein 5 to 95% of the resulting wall pores are between 10 angstroms and 100 microns in diameter.

6. The osmotic pump of claim 5 wherein said wall is 20 to 500 microns thick and said wall pores are between 10 angstroms and 25 microns in diameter.

7. The osmotic pump of claim 1, wherein at least 0.05 ng of active agent are used.

8. The osmotic pump of claim 7, wherein at least 1 microgram of active agent is used.

9. The osmotic pump of claim 1, wherein said polymer is selected from the group consisting of cellulose esters, acylated polysaccharides, polyurethane, polymers of acrylic and methacrylic acid and esters thereof, poly(ortho esters), polyacetals and mixtures thereof.

10. The osmotic pump of claim 9, wherein said polymer is selected from the group consisting of cellulose esters and acylated polysaccharides.

11. The osmotic pump of claim 9 wherein said polymer is selected from the group consisting of polyurethanes and polymers of acrylic and methacrylic acid and esters thereof.

12. The osmotic pump of claim 9, wherein said polymer is selected from the group consisting of poly(ortho esters) and polyacetals.

13. The osmotic pump of claim 1, wherein said pore forming additive is selected from the group consisting of water, alkali metal salts, alkaline earth metal salts, saccharides, aliphatic polyols, aromatic polyols and mixtures thereof.

14. The osmotic pump of claim 1, wherein 0.1 to 50%, by weight, of said pore forming additive is used.

15. The osmotic pump of claim 1, wherein said pH insensitive pore forming additive is selected from the group consisting of polyethylene glycol, sorbitol, glucose and mixtures thereof.

16. The osmotic pump of claim 1, wherein said active agent is selected from the group consisting of potassium chloride, sodium indomethacin trihydrate and cyclobenzaprine HCl.

17. The osmotic pump of claim 1, wherein said active agent is selected from the group consisting of quinoline carboxylic acids, naphthyridine carboxylic acids, pyrimidine carboxylic acids, and cinnoline carboxylic acids.

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364
369

United States Patent [19]
Morella et al.



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[54] SUSTAINED RELEASE PHARMACEUTICAL COMPOSITION

[75] Inventors: Angelo M. Morella, Campbelltown;
Mark C. Fisher, Birkenhead, both of
Australia

[73] Assignee: F. H. Faulding & Co. Limited,
Salisbury South, Australia

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424/495; 424/497

[58] Field of Search 424/497; 461, 462, 490,
424/617, 682, 468, 493-495

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Primary Examiner—Thurman K. Page

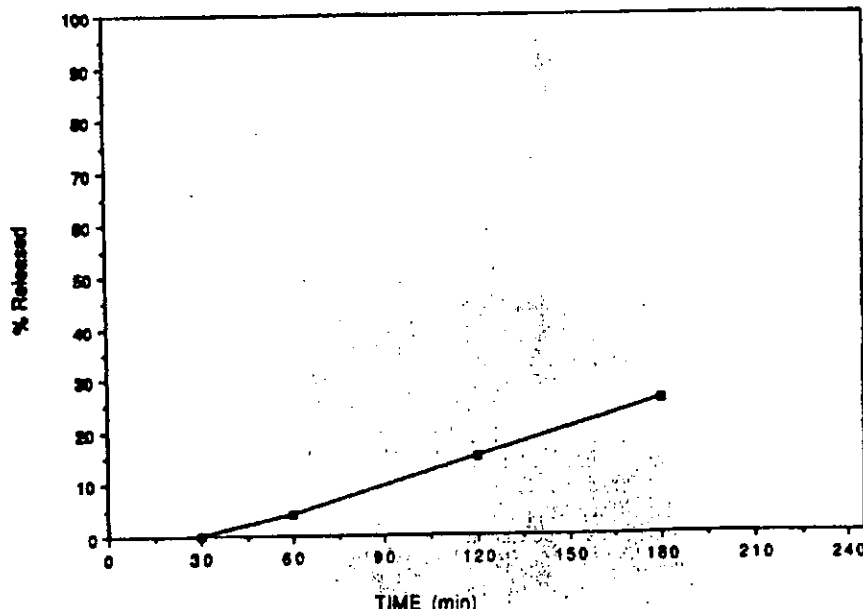
Assistant Examiner—G. S. Kishore

Attorney, Agent, or Firm—Darby & Darby

[57] ABSTRACT

The present invention relates to a pharmaceutical pellet composition having a core element including at least one highly soluble active ingredient and a core coating which is partially soluble at a highly acidic pH. The pharmaceutical composition provides a slow release of active ingredient at a highly acidic pH and provides a constant, relatively faster rate of release at a more alkaline pH such as that of the intestine. Oral administration of the pharmaceutical pellet composition of the present invention to a patient is effective to deliver to the blood levels of active ingredient within the therapeutic range and to maintain such levels over an extended period of time.

26 Claims, 6 Drawing Sheets



spraying nozzle is located above the contents of the bed and facing downwards. The spray nozzle may reside in the mid-section of the fluidised bed and be oriented such as to spray tangentially to the rotating core elements.

The sustained release pharmaceutical pellet composition may be administered under a similar dosage regimen to that used in the prior art. The multi-pellet encapsulated form may for example be administered every eight to twenty-four hours in sustained release form.

In a further preferred aspect of the present invention the pharmaceutical pellet composition incorporating morphine compound may provide effective pain relief with twice or three times or four times daily administration. Versatility of dosing may be achieved with 10 mg, 20 mg, 50 mg, 100 mg, 200 mg, 500 mg or any other dose strength of capsules required.

The pharmaceutical pellet composition may be in multi-pellet encapsulated, sprinkle sachet or tableted forms.

In accordance with a further aspect of the present invention, there is provided a method of treating pain associated conditions in patients requiring such treatment which method includes administering to a patient an effective amount of a sustained release pharmaceutical pellet composition including

a core element including at least one morphine compound of high solubility; and

a core coating for the core element which is partially soluble at a highly acidic pH and wherein the morphine compound is available for absorption at a relatively constant rate in the intestine over an extended period of time.

The method of treatment according to this aspect of the present invention is particularly applicable to the treatment of acute and chronic pain, particularly pain associated with terminal disease such as cancer and chronic backpain, as well as post-operative pain.

Preferably the pharmaceutical sustained release composition is provided in a unit dosage form and administration occurs at intervals of approximately 8 to 24 hours.

The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however, that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention specified above.

EXAMPLE 1

1. Formulation 1

Core Composition

Morphine Sulphate pentahydrate	194 g
Core seeds	170 g
Polyvinyl pyrrolidone	37 g
Ethanol*	185 g

Hybrid Core Coating Composition

Polyethylene Glycol	12 g
Ethylcellulose	25 g
Diethyl phthalate	2 g
Methacrylic acid:acrylic acid ethyl ester 1:1 copolymer	5 g
Talc	22 g
Ethanol*	667 g

2. Formulation 2

Core Composition

Morphine Sulphate pentahydrate	194 g
Core Seeds	170 g
Polyvinyl pyrrolidone	37 g
Ethanol*	185 g

-continued

Hybrid Core Coating Composition

Polyethylene Glycol	25 g
Ethylcellulose	41 g
Diethyl phthalate	3 g
Methacrylic acid:acrylic acid ethyl ester 1:1 copolymer	4 g
Talc	37 g
Ethanol*	1106 g

3. Formulation 3

Core Composition

Morphine Sulphate Pentahydrate	264 g
Core Seeds	722 g
Hydroxypropylmethylcellulose	14 g
Ethanol*	881 g
Water*	105 g

Hybrid Core Coating Composition

Polyethylene Glycol	47 g
Ethylcellulose	90 g
Diethyl phthalate	19 g
Methacrylic acid:acrylic acid ethyl ester 1:1 copolymer	20 g
Talc	88 g
Ethanol*	2509 g

4. Formulation 4

Core Composition

Morphine Sulphate pentahydrate	217.0 g
Core seeds	771.6 g
Hydroxypropyl methylcellulose	11.4 g
Water*	86.1 g
Ethanol*	723.9 g

Hybrid Core Coating

Polyethylene glycol	35.3 g
Ethylcellulose	100.6 g
Diethylphthalate	19.4 g
Methacrylic acid:acrylic acid ethyl ester 1:1 copolymer	21.2 g
Talc	88.25 g
Ethanol*	2508.0 g

5. Formulation 5

Core Composition

Morphine Sulphate pentahydrate	80.7 g
Core seeds	1000.0 g
Hydroxypropylmethylcellulose	8.9 g
Water*	67.6 g
Ethanol*	568.5 g

Hybrid Core Coating

Polyethylene glycol	14.6 g
Ethylcellulose	138.2 g
Diethylphthalate	21.1 g
Methacrylic acid:acrylic acid ethyl ester 1:1 copolymer	18.1 g
Talc	96.0 g
Ethanol*	2922.0 g

6. Formulation 6

Core Composition

Morphine Sulphate pentahydrate	80.7 g
Core seeds	1000.0 g
Hydroxypropylmethylcellulose	8.9 g
Water*	67.6 g
Ethanol*	568.5 g

Hybrid Core Coating

Polyethylene glycol	28.8 g
Ethylcellulose	115.2 g
Diethylphthalate	21.1 g
Methacrylic acid:acrylic acid ethyl ester 1:1 copolymer	26.9 g
Talc	96.0 g
Ethanol*	2922.0 g

7. Formulation 7

Core Composition

Morphine Sulphate pentahydrate	264 g
Core seeds	722 g
Hydroxypropylmethylcellulose	14 g
Water*	881 g
Ethanol*	105 g

Hybrid Core Coating

Polyethylene glycol	27.6 g
Ethylcellulose	77.2 g

TABLE 11

PARAMETER	SOLUTION	FORMULATION 3	
	MEAN (n = 8)	MEAN (n = 9)	OBSERVED DIFFERENCE
AUC (0-18 h) (ng · h/mL)	374.21	361.03	-13.18
SD	155.52	131.94	
CV %	42	37	
C _{max} (ng/mL)	157.72	34.24	-123.48
SD	59.76	12.25	
CV %	38	36	
T _{max} (h)	0.63	7.67	7.04
SD	0.23	2.06	
CV %	37	27	
Bioavailability (F %)	100.00	102.06	2.06
SD	00.00	18.47	
CV %	0	18	
t _{1/2} (h)	3.48	5.77	2.29
SD	2.20	3.70	
CV %	63	64	
T _{0.75} C _{max} (h)	NA	6.25	NA
SD		1.28	
CV %		20	

NA = not applicable

Finally, it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

What is claimed is:

1. A pH-dependent sustained release pharmaceutical pellet composition for administration to a patient at a predetermined dosage and interval which comprises: a core element containing a therapeutically effective amount of at least one active ingredient having an aqueous solubility of at least 1 in 30 and a coating on said core element which comprises the following components:

- at least 35% by weight of a matrix polymer which is insoluble at a pH of from 1 to 7.5 and contributes to the control of the rate of release of the active ingredient in the stomach and intestines;
- from 1 to 30% of an enteric polymer which is substantially insoluble at a pH of from 1 to 4, sufficient to delay the release of the active ingredient in the stomach, but which is soluble at a pH of from 6 to 7.5 so as not to substantially delay release in the intestines;
- from 1 to 60% of a compound soluble at a pH of from 1 to 4, sufficient to enable initiation of release of the active ingredient in the stomach;

said percentages being by weight based on the total weight of components (a), (b), and (c); the ratio of the components (a), (b), and (c) in said coating being effective to allow the initiation of the release of the active ingredient in the stomach at a slow rate and to control the release in the intestines at a rate faster than that in the stomach such that a dose of the pellet composition delivers to the patient a therapeutically effective amount of said active ingredient over the course of said predetermined interval.

2. The sustained release pharmaceutical pellet composition of claim 1 wherein the coating contains:

as component (a), ethyl cellulose, a quaternary ammonium acrylic or methacrylic polymer, an acrylic

or a methacrylic ester copolymer or a mixture thereof;

as component (b), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, methacrylic acid:acrylic acid ester copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and mixtures thereof; and

as component (c), polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol having a molecular weight of from 1700 to 20,000, polyvinyl alcohol and monomers therefor and mixtures thereof.

3. The sustained release pharmaceutical pellet composition of claim 35 wherein the active ingredient of high solubility is selected from the group consisting of antihistamines, antibiotics, antituberculosis agents, cholinergic agents, antimuscarinics, sympathomimetics, sympatholytic agents, autonomic drugs, iron preparations, haemostatics, cardiac drugs, antihypertensive agents, vasodilators, non-steroidal antiinflammatory agents, opiate agonists, anticonvulsants, tranquilizers, stimulants, barbiturates, sedatives, expectorants, antiemetics, gastrointestinal drugs, heavy metal antagonists, antithyroid agents, genitourinary smooth muscle relaxants and vitamins.

4. The sustained release pharmaceutical pellet composition of claim 3 wherein the active ingredient is an opiate agonist selected from the group consisting of the salts of codeine, dextromoramide, hydrocodone, hydromorphone, pethidine, methadone, morphine and propoxyphene.

5. The sustained release pharmaceutical pellet composition of claim 1 wherein the active ingredient has a first dissolution profile measured at a pH of from 1 to 4, and a second dissolution profile measured at a pH of about 7.5 and wherein said first and second dissolution profile are each at least equal to the minimum dissolution required to provide substantially the same bioavailability as with an immediate release oral dosage form.

6. The sustained release pharmaceutical pellet composition of claim 5 wherein the composition, in use, minimizes fluctuations in the plasma concentration of the active ingredient in said patient.

7. The sustained release pharmaceutical pellet composition of claim 2 wherein the coating comprises:

- 35 to 75% by weight of component (a);
- 2-20% by weight of component (b); and
- 15-50% by weight of component (c).

8. The sustained release pharmaceutical pellet composition of claim 2 wherein the coating also includes up to 50% of plasticizer selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triethyl acetin, tributyl citrate, polyethylene glycol having a molecular weight of from 200 to less than 1700 or glycerol and up to 75% of a filler selected from silicon dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrillin potassium, powdered cellulose and microcrystalline cellulose and mixtures thereof, said percentages being based on the total weight of the coating.

9. The sustained release pharmaceutical pellet composition of claim 8 wherein the coating contains:

component (a)	35 to 70%
component (b)	4 to 20%
component (c)	15 to 35%

-continued

plasticizer

4 to 30%.

10. A pH-dependent sustained release pharmaceutical pellet composition for administration to a patient at a predetermined dosage and interval which comprises: a core element containing a therapeutically effective amount of an acid addition salt of morphine and a coating on said core element which comprises the following components:

- (a) at least 35% by weight of a matrix polymer which is insoluble at a pH of from 1 to 7.5 and contributes to the control of the rate of release of the active ingredient in the stomach and intestines;
 - (b) from 1 to 30% of an enteric polymer which is substantially insoluble at a pH of from 1 to 4, sufficient to delay the release of the active ingredient in the stomach, but which is soluble at a pH of from 6 to 7.5 so as not to substantially delay release in the intestines;
 - (c) from 1 to 60% of a compound soluble at a pH of from 1 to 4, sufficient to enable initiation of release of the active ingredient in the stomach;
- said percentages being by weight based on the total weight of components (a), (b), and (c); the ratio of the components (a), (b), and (c) in said coating being effective to allow the initiation of the release of the active ingredient in the stomach at a slow rate and to control the release in the intestines at a rate faster than that in the stomach such that a dose of the pellet composition delivers to the patient a therapeutically effective amount of said active ingredient over the course of said predetermined interval.

11. The sustained release pharmaceutical pellet composition of claim 10 wherein said acid addition salt of morphine is morphine sulphate.

12. The sustained release pharmaceutical pellet composition of claim 10 wherein the rate of release in the intestine is 1.2 to 3 times greater than the rate of release in the stomach.

13. The sustained release pharmaceutical pellet composition of claim 10 wherein the composition, in use, minimizes fluctuations in the morphine compound concentration in the plasma of said patient.

14. The sustained release pharmaceutical pellet composition of claim 13 wherein, in use, the time during which the concentration of the morphine compound is greater than or equivalent to 75% of maximum morphine compound concentration in the plasma is at least 3 hours.

15. The sustained release pharmaceutical pellet composition of claim 10 wherein the coating contains:

- as component (a), ethyl cellulose, a quaternary ammonium acrylic or methacrylic polymer, an acrylic or a methacrylic ester copolymer or a mixture thereof;
- as component (b), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, methacrylic acid ester copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and mixtures thereof; and
- as component (c), polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol having a molecular weight of from 1700 to 20,000, polyvinyl alcohol and monomers therefor and mixtures thereof.

16. The sustained release pharmaceutical pellet composition of claim 15 wherein the coating comprises:

- 35 to 75% by weight of component (a);
- 2-20% by weight of component (b); and
- 15-40% by weight of component (c).

17. The sustained release pharmaceutical pellet composition of claim 49 wherein the coating comprises:

[high molecular weight] polyethylene glycol having a molecular weight of from 1700 to 20,000	15 to 40%
ethylcellulose	45 to 65%
methacrylic acid:acrylic acid ethylester 1:1 copolymer	4 to 20%

18. A method for treating a pain associated with a condition in a patient which comprises administering to said patient at a predetermined dosage and interval a pH-dependent sustained release pharmaceutical pellet composition which comprises: a core element containing a therapeutically effective amount of an active compound having an aqueous solubility of at least 1 in 30 and a coating on said core element which comprises the following components:

- (a) at least 35% by weight of a matrix polymer which is insoluble at a pH of from 1 to 7.5 and contributes to the control of the rate of release of the active ingredient in the stomach and intestines;
 - (b) from 1 to 30% of an enteric polymer which is substantially insoluble at a pH of from 1 to 4, sufficient to delay the release of the active ingredient in the stomach, but which is soluble at a pH of from 6 to 7.5 so as not to substantially delay release in the intestines;
 - (c) from 1 to 60% of a compound soluble at a pH of from 1 to 4, sufficient to enable initiation of release of the active ingredient in the stomach;
- said percentage being by weight based on the total weight of components (a), (b), and (c); the ratio of the components (a), (b), and (c) in said coating being effective to allow the initiation of the release of the active ingredient in the stomach at a slow rate and to control the release in the intestines at a rate faster than that in the stomach such that a dose of the pellet composition delivers to the patient a therapeutically effective amount of said active ingredient over the course of said predetermined interval.

19. The method of claim 18 wherein the pain associated conditions relate to the treatment of acute and chronic pain.

20. The method of claim 19 wherein the sustained release pharmaceutical pellet composition is provided in a unit dosage form and the predetermined interval is approximately 8 to 24 hours.

21. The method of claim 18 wherein the active ingredient is an acid addition salt of morphine.

22. The method of claim 21 wherein the acid addition salt is morphine sulphate.

23. The method of claim 21 wherein the acid addition salt is morphine hydrochloride.

24. A pH-dependent sustained release pharmaceutical pellet composition for administration to a patient at a predetermined dosage and interval which comprises: a core element containing a therapeutically effective amount of at least one active ingredient having an aqueous solubility of a least 1 in 30 and a coating on said core element which comprises the following components:

- (a) at least 35% by weight of a matrix polymer which is insoluble at a pH of from 1 to 7.5 and is composed of ethyl cellulose, a quaternary ammonium acrylic or methacrylic polymer, an acrylic or a methacrylic ester copolymer or a mixture thereof which contributes to the control of the release of the active ingredient in the stomach and intestines;
- (b) from 1 to 30% of an enteric polymer which is substantially insoluble at a pH of from 1 to 4, sufficient to delay the release of the active ingredient in the stomach, but which is soluble at a pH of from 6 to 7.5 so as not to substantially delay release in the intestines;
- (c) from 1 to 60% of a compound soluble at a pH of from 1 to 4, sufficient to enable initiation of release of the active ingredient in the stomach;

said percentages being by weight based on the total weight of components (a), (b), and (c); the ratio of the components (a), (b), and (c) in said coating being effective to allow the initiation of the release of the active ingredient in the stomach at a slow rate and to control the release in the intestines at a rate faster than that in the stomach such that a dose of the pellet composition delivers to the patient a therapeutically effective amount of said active ingredient over the course of said predetermined interval.

25. A pH-dependent sustained release pharmaceutical pellet composition for administration to a patient at a predetermined dosage and interval which comprises: a core element containing a therapeutically effective amount of an acid addition salt of morphine and a coating on said core element which comprises the following components:

- (a) at least 35% by weight of a matrix polymer which is insoluble at a pH of from 1 to 7.5 and is composed of ethyl cellulose, a quaternary ammonium acrylic or methacrylic polymer, an acrylic or a methacrylic ester copolymer or a mixture thereof which contributes to the control of the release of the active ingredient in the stomach and intestines;
- (b) from 1 to 30% of an enteric polymer which is substantially insoluble at a pH of from 1 to 4, sufficient to delay the release of the active ingredient in the stomach, but which is soluble at a pH of from 6 to 7.5 so as not to substantially delay release in the intestines;

- (c) from 1 to 60% of a compound soluble at a pH of from 1 to 4, sufficient to enable initiation of release of the active ingredient in the stomach;
- said percentages being by weight based on the total weight of components (a), (b), and (c); the ratio of the components (a), (b), and (c) in said coating being effective to allow the initiation of the release of the active ingredient in the stomach at a slow rate and to control the release in the intestines at a rate faster than that in the stomach such that a dose of the pellet composition delivers to the patient a therapeutically effective amount of said active ingredient over the course of said predetermined interval.

26. A method for treating a pain associated with a condition in a patient which comprises administering to said patient at a predetermined dosage and interval a pH-dependent sustained release pharmaceutical pellet composition which comprises: a core element containing a therapeutically effective amount of an active compound having an aqueous solubility of at least 1 in 30 and a coating on said core element which comprises the following components:

- (a) at least 35% by weight of a matrix polymer which is insoluble at a pH of from 1 to 7.5 and is composed of ethyl cellulose, a quaternary ammonium acrylic or methacrylic polymer, an acrylic or a methacrylic ester copolymer or a mixture thereof which contributes to the control of the release of the active ingredient in the stomach and intestines;
 - (b) from 1 to 30% of an enteric polymer which is substantially insoluble at a pH of from 1 to 4, sufficient to delay the release of the active ingredient in the stomach, but which is soluble at a pH of from 6 to 7.5 so as not to substantially delay release in the intestines;
 - (c) from 1 to 60% of a compound soluble at a pH of from 1 to 4, sufficient to enable initiation of release of the active ingredient in the stomach;
- said percentage being by weight based on the total weight of components (a), (b), and (c); the ratio of the components (a), (b), and (c) in said coating being effective to allow the initiation of the release of the active ingredient in the stomach at a slow rate and to control the release in the intestines at a rate faster than that in the stomach such that a dose of the pellet composition delivers to the patient a therapeutically effective amount of said active ingredient over the course of said predetermined interval.

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Current Status of Drug Delivery Technologies and Future Directions

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370

Rajan K. Verma and Sanjay Garg *

Evolution of an existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety, and efficacy. These days, drug delivery companies are engaged in the development of multiple platform technologies to get competitive advantage, extend patent life, and increase market share of their products.

The number of products based on new drug delivery systems has significantly increased in the past few years, and this growth is expected to continue in the near future. Recent advances in the field of genomics have accelerated research of biopharmaceuticals, and today a large number of companies are busy developing protein- and peptide-based drugs. These biopharmaceuticals present challenges to drug delivery scientists because of their unique nature and difficulty in delivery through conventional routes. Therefore, future research will focus on the delivery of these complex molecules through different routes, including oral, nasal, pulmonary, vaginal, rectal, etc. This review is an update on some of the existing drug delivery technologies for oral controlled-release, delivery of large molecules, liposomes, taste masking, fast-dispersing dosage forms, and technology for insoluble drugs. Nasal, pulmonary, vaginal, and rectal routes also are briefly reviewed.

In the 21st century, the pharmaceutical industry is caught between the downward pressure on prices and the increasing cost of successful drug discovery and development. The average cost and time for the development of a new chemical entity are much higher (approximately \$500 million and 10-12 years) than those required to develop a novel drug delivery system (NDDS) (\$20-50 million and 3-4 years). In the form of an NDDS, an existing drug molecule can get a new life, thereby increasing its market value and competitiveness and extending patent life. Limited formularies, patent expiry with subsequent entry of generic competition, and vertical integration have the entire pharmaceutical industry (approximately

350 drug delivery companies and 1000 medical device companies) focused on designing and developing new and better methods of drug delivery. There has been a significant increase in approvals of NDDSs in the past couple of years, and this is expected to continue at an impressive rate in the near future. The sale of drug delivery products is valued at more than \$22 billion worldwide, and this growth is expected to continue into the present century. It is estimated that the drug delivery market will be at \$120 billion by 2007.

At present, there are so many existing drug delivery technologies that a total compilation is not within the scope of this article. Yet an attempt is being made to compile some of the most successfully marketed drug delivery technologies. Most of the information is derived from the Internet sites of the major drug delivery companies.

Current status of drug delivery technologies

Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety, and improved patient compliance. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the development of new drug delivery systems. Today, drug delivery companies are engaged in the development of multiple platform technologies for controlled release, delivery of large molecules, liposomes, taste-masking, oral fast-dispersing dosage forms, technology for insoluble drugs, and delivery of drugs through intranasal, pulmonary, transdermal, vaginal, colon, and transmucosal routes.

Rajan K. Verma is a PhD scholar and Sanjay Garg* is assistant professor in the department of pharmaceuticals at the National Institute of Pharmaceutical Education and Research (NIPER), sector 67, SAS Nagar, Punjab 160 062, India, tel. 91 11 214682, fax 91 11 214692, e-mail gargsanjay@yahoo.com.

*To whom all correspondence should be addressed.

Oral controlled release

Oral ingestion is the traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of the drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which, in most situations, often results in constantly changing, unpredictable, and often sub- or supra-therapeutic plasma concentrations leading to marked side effects. An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled-release (CR) delivery systems provide a uniform concentration/amount of the drug at the absorption site and thus, after absorption, allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. CR products are formulations that release active drug compounds into the body gradually and predictably over a 12- to 24-hour period and that can be taken once or twice a day. Typically, these products provide numerous benefits compared with immediate-release drugs, including greater effectiveness in the treatment of chronic conditions, reduced side effects, greater convenience, and higher levels of patient compliance due to a simplified dosing schedule. Because of the above advantages, such systems form the major segment of the drug delivery market.

A number of techniques are used to achieve controlled release of drugs via the oral cavity. Some of these techniques are reviewed briefly as follows.

Osmotic systems utilize osmotic pressure as the driving force for the delivery of drugs. In its simplest design, it consists of an osmotic core (a drug with or without an osmagent), which is coated with a semipermeable membrane, and a delivery orifice is created with a mechanical or laser drill. When the dosage form comes in contact with water, water is imbibed because of the resultant osmotic pressure of the core and the drug is released from the orifice at a controlled rate. This system, known as elementary osmotic pump (EOP), was first developed by Felix

Theeuwes of Alza Corporation (USA). A number of modifications of this system are available today, like the push-pull osmotic pump, which is a bilayer tablet and is suitable for the delivery of highly or poorly water-soluble drugs. The upper layer consists of a drug along with osmotic agents. The lower layer consists of polymeric osmotic agents. The tablet is coated with a semi-permeable membrane, and a delivery orifice is created similar to that of an EOP. Figure 1 shows the schematic diagram of these two types of systems. Alza Corporation is a leader in the field of oral osmotic systems, and some of the commercially marketed products based on this technology are listed in Table 1.

MacroCap (Biovail Corporation International, Canada) utilizes a controlled-release pellet system, which is based on the coating of pellets containing pharmaceutical compounds with specialized polymers and plasticizers to control the rate and location of drug release in the gastrointestinal (GI) tract. The MacroCap system uses the features of pH-activated or pH-independent diffusion, osmotic diffusion, or a combination of these mechanisms. The pH-activated diffusion system uses specifically designed coating polymers to control the delivery of drugs depending on the pH environment of the GI tract. Under the osmotic diffusion system, the rate of release of the drug from the pellets is controlled by a combination of principles involved in osmosis and diffusion.

Micropump Oral Controlled Delivery System (Flamel Technologies, France) is suitable for drugs that require an extended absorption time in the small intestine. Each Micropump dosage form is composed of thousands of microparticles ranging in size between 200 and 400 μm and having a bioadhesive surface. Each

microparticle contains a drug crystal or granule enclosed in a polymer coating that acts as a shell through which the drug can be released under the effect of osmotic pressure. Modulating the thickness and composition of the polymer coating can control the rate and duration of drug delivery.

MODAS or **Multiporous Oral Drug Absorption System** (Elan Corporation, Ireland) is surrounded by a non-disintegrating, timed-release coating, which after coming in contact with gastrointestinal fluid is transformed into a semipermeable membrane through which the drug diffuses in a rate-limiting manner. The tablet consists of a core of active drug plus excipients. This is then coated with a solution of insoluble polymers and soluble excipients. After ingestion, the fluid of the gastrointestinal tract dissolves the soluble excipients in the outer coating leaving just the insoluble polymer, thereby forming a network of tiny, narrow channels connecting fluid from the GI tract to the inner drug core of water-soluble drug. This fluid passes through these channels into the core, dissolves the drug, and a resultant solution of drug diffuses out in a controlled manner to the outside. The addition of excipients, such as buffers can help produce a microenvironment within the

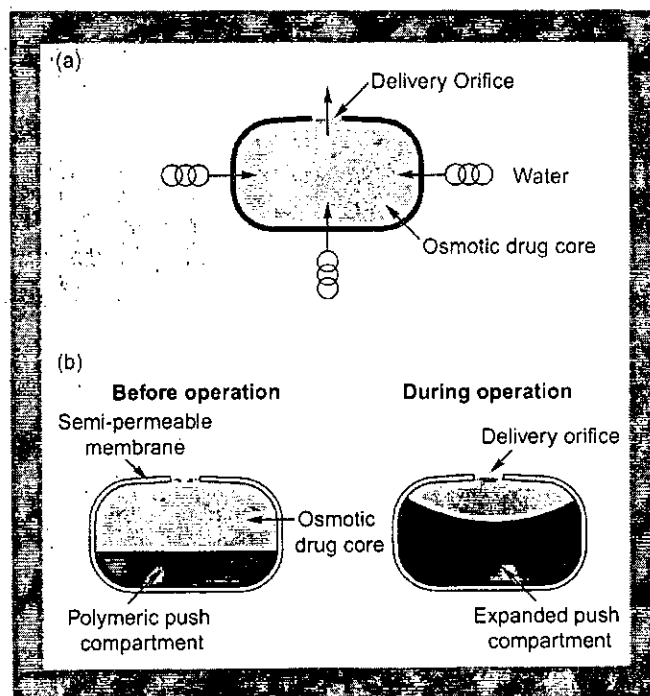


Figure 1: Schematic diagram of an elementary osmotic pump (a) and a push-pull osmotic pump (b).

tablet that facilitates more predictable release rates and absorption. Examples of MODAS products developed by Elan include Bron-12 (a 12-hour multicomponent over-the-counter [OTC] cough and cold product) and once-daily potassium chloride.

SCOT or Single Composition Osmotic Tablet System (Andrx Pharmaceuticals, USA) is also based on osmotic principles and utilizes various osmotic modulating agents as well as polymer coatings to provide a zero-order release of a drug. Portab System (Andrx Pharmaceuticals) utilizes an osmotic core, typically containing a water-soluble drug. The core includes a water-soluble component and a continuous polymer coating. The purpose of the soluble agent is to expand the core and thereby create microporous channels through which the drug is released.

Zer-Os tablet technology (ADD Drug Delivery Technologies AG, Switzerland) is an osmotic system developed specifically for the delivery of lipophilic compounds. The tablet consists mainly of a core of poorly water soluble drug along with gel-

forming agents and standard excipients. The gel-forming agent, after coming in contact with water, forms a gel of an appropriate viscosity, and a suspension of a poorly water-soluble agent is formed and is pushed out of the orifice at a controlled rate. Tegretol XR, a successful product on the US market, is based on this technology as well.

In addition to osmotic principles, numerous other approaches also exist for the delivery of drugs in a controlled manner, some of which are briefly reviewed in the following sections.

Ceform microsphere technology (Fuisz Technology Ltd., USA) allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. These microspheres are almost perfectly spherical, having a diameter that is typically 150 to 180 μm , and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres can be formulated for enhanced absorption (Ceform EA) or taste

isolation (Ceform TI) and may be coated for controlled release (Ceform CR), provided with an enteric coating (Ceform EC), or combined into a fast/slow release combination (Ceform EA/CR).

CONSURF or Constant Surface Area Drug Delivery Shuttle (Biovail Corporation International) releases drug by the concurrent swelling and dissolution of a matrix tablet. A constant surface area is presented during the drug's transit through the GI tract.

Contramid (Labopharm Inc., Canada) utilizes excipients (mainly starch) for the controlled delivery of drugs. The chemical cross-linking of a starch consisting mainly of amylose leads to Contramid. During the cross-linking, bridges are formed between the polysaccharides. Varying the quantity of cross-linking reagent used in the manufacturing process can control the degree of the cross-linking. Once the Contramid dosage form is in the stomach, gastric fluids turn Contramid's surface to gel and the resulting semipermeable membrane stabilizes rapidly. This membrane, which does not begin to

17 Most commercially marketed oral osmotic systems			
Product name	Chemical	Developer/Marketer	Indication
Acutrim	Phenylpropanolamine	Alza/Heritage	Appetite suppressant
Alpress LP	Prazosin	Alza/Pfizer (France)	Hypertension
Calan SR	Verapamil	Alza/GD Searle & Co.	Hypertension
Cardura XL	Doxazosin mesylate	Alza/Pfizer (Germany)	Hypertension
Concerta	Methylphenidate	Alza	Attention Deficit Hyperactivity Disorder
Covera HS	Verapamil	Alza/G.D. searle	Hypertension
Ditropan	Oxybutynin Chloride	Alza/UCB Pharma	Overactive bladder
DynaCirc CR	Isradipine	Alza/Novartis	Hypertension
Efidac/24	Pseudoephedrine	Alza/Novartis	Cold medication
Efidac 24	Chlorpheniramine	Alza/Novartis	Anti-allergic
Chlorpheniramine			
Efidac 24	Pseudoephedrine and Brompheniramine	Alza/Novartis	Anti-allergic and cold treatment
Glucotrol XL	Glipizide	Alza/Pfizer	Anti-diabetic
Minipress XL	Prazosin	Alza/Pfizer	Hypertension
Procardia XL	Nifedipine	Alza/Pfizer	Hypertension/angina
Sudafed 24 hour	Pseudoephedrine	Alza/Warner Lambert	Nasal decongestant
Teczem	Enalapril and Diltiazem	Merck/Aventis	Hypertension
Tiamate	Diltiazem	Merck/Aventis	Hypertension
Volmax	Albuterol	Alza/Muro Pharmaceuticals	Bronchospasm

372 373

break down until it reaches the colon, ensures that there is a regular release of the active ingredients contained in the dosage form.

Dimatrix or Diffusion Controlled Matrix System (Biovail Corporation International) consists of either beads made by extrusion-spheronization or by powder/solution layering on nonpareil beads or in the form of a tablet matrix. The mechanism of release is by diffusion of dissolved drug molecules. **Multipart** or Multiparticle Drug Dispersing Shuttle (Biovail Corporation International) consists of a tablet that carries controlled-release beads or pellets through the GI tract while maintaining their integrity and release properties. Release and distribution of the beads is triggered by superdisintegration of the tablet.

DPHS or Delayed Pulsatile Hydrogel System (Andrx Pharmaceuticals) is designed for use with hydrogel matrix products that are characterized by an initial zero-order release of drug followed by rapid release. This release profile is achieved by the blending of selected hydrogel polymers to achieve a delayed pulse.

DUREDAS or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer-tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the Duredas technology is the production of controlled-release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each is controlled to maximize therapeutic effect of the combina-

tion. Again both immediate-release and controlled-release combinations of the two drugs are feasible.

Gastric retention system (DepoMed Inc., USA) consists of a drug containing polymeric units that, if taken with a meal, remain in the stomach for an extended period of time to provide continuous, controlled delivery of an incorporated drug.

Geomatrix (Skye Pharma Plc., USA) is a platform of oral controlled-release technology that controls the amount, timing, and location of the release of drug compounds into the body. Geomatrix system is a multilayer tablet with a matrix core containing the active ingredient and one or more modulating layers (barriers) applied to the core during the tableting process. The function of these barriers is to delay the interaction of the core with the dissolution medium. Eight Geomatrix technologies are designed to meet a wide range of therapeutic objectives: Zero-order release provides a constant rate of drug release over a defined period of time; binary release is used to provide the controlled release of two different drugs in a single tablet; quick-slow release provides a quick burst of drug release followed by a constant rate of release over a defined period of time; slow-quick release provides an initial constant rate of release followed by a quick burst of drug release at a predetermined time; positioned release delivers the drug to a predetermined position in the digestive system before it begins to release the active drug compounds; accelerated release provides a constantly accelerating rate of drug release; delayed release provides a predetermined time lag before it begins releasing drug molecules; multiple pulse provides an initial quick burst of drug release followed by a predetermined period of no release. Some of the drugs that are marketed based on this technology are diltiazem hydrochloride, nifedipine, and diclofenac sodium.

GMHS or Granulated Modulating Hydrogel System (Andrx Pharmaceuticals) incorporates hydrogel and binding polymers with the drug, which is formed into granules and then pressed into tablet form.

IPDAS or Intestinal Protective Drug Absorption System (Elan Corporation) is a multiparticulate tablet technology, that has been developed to enhance the gastrointestinal tolerability of potentially

irritant or ulcerogenic drugs. Unlike other tablet formulations, IPDAS is composed of numerous high-density controlled-release beads. Each bead is manufactured by a two-step process that involves the initial production of a micromatrix of drug embedded in polymer and the subsequent coating of this micromatrix with time-release coatings that are transformed into a rate-limiting semipermeable membrane in vivo. After ingestion, the tablet rapidly disintegrates and beads are dispersed into the stomach and subsequently pass into the duodenum and along the GI tract in a controlled and gradual manner, independent of the feeding state. Drug release from each bead occurs by a diffusion process through the micromatrix and subsequently through the pores in the rate-controlling semipermeable membrane. The intestinal protection of IPDAS is by virtue of the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the GI tract. The controlled-release characteristics of the individual bead avoids the high concentrations of drug being released locally and absorbed systemically. An immediate-release granulate also can be included in the tablet and may be required for a fast onset of action. IPDAS products are approved worldwide, and Elan's Napreelan product (once-daily naproxen sodium) is sold in the US market.

Multipor technology (Ethical Holdings Plc., UK) consists of a tablet core of an active drug, which is surrounded by a water-insoluble polymer membrane. The membrane consists of minute water-soluble particles that, after coming in contact with water, dissolve and form pores from which the drug is released. This technology also can be applied to pellets, granules, or minitabets. One or more drug substances also can be incorporated into the membrane, which can provide an immediate-release layer.

Pharmazome or Microparticulate Drug Delivery Technology (Elan Corporation) consists of combinations of polymers and drugs in the size range of 5 to 125 μm . Each microparticle is a micromatrix of drug embedded uniformly throughout an insoluble polymer and is produced by either a spray drying or emulsion technique. By varying the amount and nature of the polymer used to form the micro-

373
374

particle, this technology allows controlled- and/or delayed-release of drug from the formulation. In addition, this technology also can be used for taste masking because it acts as a means of physically preventing a drug from going into solution in the mouth and coming into direct contact with taste receptors. For the purpose of palatability, 125 μm is set as the upper limit for Pharmazomes because these particles have a gritty feeling that may be unacceptable to consumers. Pharmazomes can be subsequently incorporated into a variety of delivery systems like chewable tablets, effervescent tablets, oral ready-made aqueous and non-aqueous suspensions, reconstitutable powders, and unit-dose sachet or sprinkle systems. Products using Pharmazome technology are currently approved in Japan, Europe, and Central and South America and include twice-daily theophylline.

PPDS or Pelletized Pulsatile Delivery System (Andrx Pharmaceuticals) is designed for use with products that require a pulsed release of the drug. This technology uses pellets that are coated with specific polymers and agents to control the release rate of the microencapsulated drug. By varying the proportion and composition of the polymer mixtures, formulations can practically control the release rate of the drug. **Peltab System** (Andrx Pharmaceuticals) utilizes polymer-coated drug pellets or drug crystals that are manufactured into tablets. In order to provide controlled release, a water-insoluble polymer is used to coat discrete drug pellets or crystals that then can resist the action of fluids in the GI tract. This technology incorporates a strong polymer coating enabling the coated pellets to be compressed into tablets without significant breakage.

PRODAS or Programmable Oral Drug Absorption System (Elan Corporation) is a multiparticulate drug delivery technology that is based on the encapsulation of controlled-release minitabets in the size range of 1.5 to 4 mm in diameter. This technology represents a combination of multiparticulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form. Minitabets with different release rates can be combined and incorporated into a single dosage

form to provide the desired release rates. These combinations may include immediate-release, delayed-release, and/or controlled-release minitabets. In addition to controlled absorption over a specified period, PRODAS technology also enables targeted delivery of drug to specified sites of absorption throughout the GI tract. Combination products also are possible by using minitabets formulated with different active ingredients.

Reduced irritation system (DepoMed, Inc.) is designed to significantly reduce local gastrointestinal irritation from the effects of certain drugs. This system consists of an outer gelatin capsule that is designed to rapidly disintegrate upon ingestion to deliver multiple small spherical pellets. The spherical pellets are composed of an inert matrix of polymeric material in which the active ingredient is homogeneously dispersed in its solid state.

RingCap (Alkermes Inc., USA) combines matrix tablets and existing capsule banding processes to create controlled-release solid oral dosage forms. The RingCap system utilizes bands of insoluble polymer on a matrix tablet. The manufacturing process involves compressing the drug into cylindrical matrix tablets that are subsequently film coated. Then, existing capsule-banding technology is used to apply two or more polymeric rings around the circumference of the matrix tablet. These bands lower the initial release of the drug by reducing the surface area exposed. As the matrix tablet erodes, new surface areas are created underneath and around the bands, thus increasing the rate of release. The release rate of the drug substance can be designed to remain nearly constant or even increase with time by adjusting the number and width of polymer bands.

SODAS or Spheroidal Oral Drug Absorption System (Elan Corporation) is a multiparticulate drug-delivery technology and consists of controlled-release beads that can be produced in the range from 1 to 2 mm in diameter. Each bead begins as an inert core onto which the drug is applied, followed by a number of layers of soluble and insoluble polymers combined with other excipients to produce the rate-controlling layer. Drug release from these beads occurs by a diffusion process. Within the GI tract, the soluble polymers dissolve, leaving pores

within the outer membrane. Fluid then enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the in vivo dissolution and absorption phases. The immediate environment of the drug within the seed core can be manipulated by use of excipients to ensure optimal stability and solubility. These controlled-release beads can be packaged into a capsule or compressed into a tablet to produce the final dosage form. Products utilizing SODAS technology are approved and marketed throughout Europe, the US, and Japan and include once-daily diltiazem and once-daily verapamil. Cardizem SR and CD are twice- and once-daily formulations, respectively, of diltiazem hydrochloride (based on SODAS technology) developed by Elan in partnership with Hoechst Marion Roussel. Verelan was the first verapamil controlled-release formulation (based on SODAS technology) in which the extent or rate of absorption was not affected by food intake. In addition, the capsule could be opened and the beads sprinkled on soft food for those patients unable to swallow traditional dosage forms.

SMHS or Solubility Modulating Hydrogel System (Andrx Pharmaceuticals) is designed for products utilizing a hydrogel-based dosage system that provides sustained release without the need to use special coatings or structures, both of which add to the cost of manufacturing. This technology avoids the initial burst effect commonly observed with other sustained-release hydrogel formulations. Diltia XT, marketed by Andrx Pharmaceuticals, is based on this technology and is used for the treatment of hypertension and angina.

SPDS or Stabilized Pellet Delivery System (Andrx Pharmaceuticals) is designed specifically for unstable drugs and incorporates a pellet core of drug and protective polymer outer layer(s).

SQZGel oral controlled-release system (Macromed, Inc., USA) is an oral delivery system based on patented pH-sensitive hydrogels comprised of combinations of FDA-approved generally recognized as safe (GRAS) polymers. In response to internal or external pH levels, and by design, this system evenly releases a drug over an

374
375

8- to 20-hour period based on the delivery needs of the therapy. SQZGel is manufactured by an inexpensive standard tablet dosage form technique.

TIMERx (Penwest Pharmaceuticals Co., USA) is a controlled-release drug delivery technology applicable to a broad range of orally administered drugs. This technology is based on an agglomerated hydrophilic matrix. The matrix consists of two pharmaceutically acceptable polysaccharides, locust bean gum and xanthan gum. Interactions between these components in an aqueous environment form a tight gel with a slowly eroding core from which the drug is released at a controlled rate for an extended period of time. Sifedipine XL (nifedipine) and Cystrin CR (oxybutynin) are based on this technology and are marketed in Europe.

KV Pharmaceuticals (USA) has developed technologies for controlled delivery of drugs that includes KV/24, which is a multiparticulate technology that can combine several different drug compounds, each requiring its own unique release profile, in a single tablet form that can be taken orally once every 24 hours. **Meter Release** is a twice-a-day dosing, polymer-based drug delivery system that offers different release characteristics than KV/24 and is used for products that require a drug release rate of 8 to 12 hours. **Symatrix** is a microparticulate formulation that employs smaller particles than KV/24 and **Meter Release**. **Symatrix** encapsulates therapeutic agents that improve a drug's absorption in the body when precise release profiles are less important. **Spheroid** combines equipment technology with formulation expertise. Each particle has its own matrix as the rate-controlling mechanism for the release of its contents. These particles can be filled into hard gelatin capsules or can be compressed into tablets. **Orasert** is designed as a solid oral dosage system that possesses bioadhesive and controlled-release properties. **Orasite** is a controlled-release muco-adhesive delivery system administered orally in solid or liquid form.

Triglas technology (Ethical Holdings Plc.) is mainly for water-insoluble drugs and is based upon formulating drug with appropriate additives to form a solid solution of drug that can be coated onto the carrier particles. These particles then can be made into tablets. **Rhotard** (Ethical

Holdings Plc.) is based on double-matrix technology that involves two granulation stages during the manufacturing process.

Large-molecule delivery

Research efforts in the field of genomics are expected to accelerate the discovery of new therapeutic biomolecules, placing an increased demand on the development of delivery systems for these drugs. This class of drugs is usually characterized by large size, fragile nature, short biological half-life, and limited ability to cross cell membranes. These properties, along with the methods of administration of biopharmaceuticals, can limit their clinical applications to certain disease states that warrant the expense and inconvenience of frequent injection. At present, a large number of companies are working in this area, as evidenced by the increasing number of available technologies for delivering these compounds.

BEODAS or Bioerodable Enhanced Oral Drug Absorption System (Elan Corporation) is an oral microparticulate drug delivery technology designed for the delivery of macromolecules and is based on the entrapment of active pharmaceutical entities in a range of submicron sizes within biodegradable polymer matrices. Further modifications to the BEODAS platform technology have the potential for targeted delivery and enhanced absorption of pharmaceutical entities that normally are not amenable to oral administration.

DepoFoam (DepoTech Corporation, USA) drug delivery system consists of microscopic spherical particles composed of hundreds to thousands of nonconcentric chambers (depots) encapsulating the drug to be delivered. The individual chambers are separated by a bilayer lipid membrane made up of synthetic duplicates of lipids found naturally in the body, resulting in a material that is both biodegradable and biocompatible. The **DepoFoam** system provides either local site or systemic delivery and can be administered by a number of routes, including intrathecal, subcutaneous, intramuscular, and intra-articular. Typically, a **DepoFoam** particle consists of less than 10% lipid and 90% aqueous drug solution, giving it a high loading factor. **DepoFoam** formulations maintain a drug in its therapeutic window for periods ranging from days to many

weeks, allowing lower initial drug levels and significantly fewer doses. **DepoFoam** technology is applicable across a variety of compounds, including small molecules, proteins, peptides, DNA, and vaccines. Some of the products like **DepoCyt** (cytarabine), **DepoMorphine** (morphine sulfate), and **DepoAmikacin** (amikacin) are based on this technology.

DUROS (Alza Corporation) is based on implant technology, which provides an alternative for the delivery of a wide range of therapeutic compounds, including peptides, proteins, and other bioactive macromolecules. These implants are miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body for up to one year. Following implantation, **DUROS** implants enable continuous, precise delivery of the therapeutic compound at rates as low as 1% of a drop of water per day. The cylinder is manufactured from titanium because of the material's tolerability to human tissue and its long use in medical devices such as implantable defibrillators and joint replacements. The cylinder protects therapeutic agents from degradation in the body and enables a drug to remain stable for extended periods of time. Recently, **Viadur** (leuprolide acetate implant), which is based upon this technology, has been approved for once-yearly palliative treatment of advanced prostate cancer.

LOCODAS or Localized Drug Absorption System (Elan Corporation) is a novel targeted oral drug delivery technology. This technology utilizes targeting ligands, that specifically bind to certain absorption sites located on the apical surface of the epithelium cells of the human GI tract. These ligands are attached to coated microparticles of protein and peptide drugs that serve to protect their contents from the hostile environment of the GI tract. These are subsequently packaged in enteric-coated capsules that deposit the particles at appropriate sites of absorption within the GI tract.

Macromol Systems (Cortecs International Ltd., UK) enable polypeptides and proteins to be administered by the oral route rather than by injection. **Oral Mucosal Vaccines** (Cortecs International Ltd.) can be administered by mouth and act by presenting the antigen to specialized cells within the intestine that pick up small par-

375
376

ticles via the Peyer's Patch and can process them into the immune system to stimulate a defensive response at mucosal sites.

Medipad (Elan Corporation) is a patient-friendly system that enables controlled parenteral delivery while minimizing discomfort. This system is designed for the delivery of a broad range of compounds, from small molecules to proteins and peptides. Medipad is a low-cost, disposable, single-use system that combines unique microinfusion technology with an integral subcutaneous probe. An adhesive backing fixes the system discreetly against the user's chest or abdomen where it continuously dispenses drug for up to 48 hours. It is the only technology that currently combines the simplicity of a patch with the delivery capabilities of an infusion pump. The Medipad technology can be tailored to a range of delivery volumes, delivery rates, and delivery profiles (bolus, extended bolus, continuous, or continuous plus bolus).

Oral vaccines: Elan Corporation and Endorex Corporation, a US biotechnology company, have formed a joint venture to develop a portfolio of technologies that will permit the oral administration of vaccines. The technology focuses on two different approaches for oral delivery of antigen through intestinal epithelial tissue. These are the production of micro- and nanoparticles of a defined size range containing antigens dispersed within a bioerodable polymer matrix and polymerized liposomal vesicles in which antigens are enclosed in a stable membrane. Both of these technologies protect antigens from the hostile environment of the GI tract and ensure that they are presented in an intact form to the mucosal surface for absorption.

ProLease and Medisorb (Alkermes Inc., USA) are two patented and proprietary processes for creating injectable sustained-release products lasting from days to months. ProLease is specifically designed

for complex and fragile bioactive molecules such as proteins, and Medisorb is designed for traditional small molecules and peptides. Both technologies are microsphere-based delivery systems composed of the desired bioactive molecule incorporated into a matrix of poly-(DL-lactide-coglycolide), a common biodegradable medical polymer. Microspheres are packaged in vials as a dry free-flowing powder. Before administration the microspheres are suspended in an aqueous vehicle and administered by subcutaneous or intramuscular injection. Release profiles can be adjusted by manipulation of formulation parameters and by control of the fabrication process.

Transdermal and topical delivery

Systemic delivery of drugs via transdermal routes has generated considerable interest during the last decade. Transdermal drug delivery systems (TDDS) deliver drugs through the skin into the systemic circulation at a predetermined rate,

Table II: Some of the commercially marketed transdermal systems			
Product name	Chemical	Developer/Marketer	Indication
Alora	Estradiol	TheraTech/Proctor and Gamble	Postmenopausal syndrome
Androderm	Testosterone	TheraTech, Inc./GlaxoSmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	Alza/Boehringer Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings, Plc/Wyeth-Ayerest	Postmenopausal syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenopausal syndrome
CombiPatch	Estradiol/ Norethindrone	Noven Pharmaceuticals, Inc. Aventis	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Duragesic	Fentanyl	Alza/Janssen Pharmaceutica	Moderate/severe pain
Estraderm	Estradiol	Alza/Novartis	Postmenopausal syndrome
Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare Ltd.	Postmenopausal syndrome
FemPatch	Estradiol	Parke-Davis	Postmenopausal syndrome
Habitraol	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Nicotrol	Nicotine	Cygnus Inc./McNeil Consumer Products, Ltd.	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Nuvelle TS	Estrogen/ Progesterone	Ethical Holdings, Plc./Schering	Hormone replacement therapy
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Testoderm TTS	Testosterone	Alza Corp.	Hypogonadism in males
Transderm-Scop	Scopolamine	Alza/Novartis	Motion sickness
Transderm Nitro	Nitroglycerin	Alza/Novartis	Angina pectoris
Vivelle	Estradiol	Noven Pharmaceuticals, Inc./ Novartis	Postmenopausal syndrome

377
376

Table II: Some of the commercially available liposomal/liquid-based products			
Trade Name	Chemical	Manufacturer	Indication
AmBisome	Amphotericin B	NeXstar Pharmaceuticals	Systemic fungal infections
Abelcet	Amphotericin B	The Liposome Company	Systemic fungal infections
Amphotec	Amphotericin B	Sequus Pharmaceuticals	Systemic fungal infections
Doxil	Doxorubicin	Sequus Pharmaceuticals	Kaposi's sarcoma
DaunoXome	Daunorubicin	NeXstar Pharmaceuticals	Kaposi's sarcoma

thereby avoiding metabolism in the GI tract and liver. Therefore, the amount of active ingredient required for transdermal delivery can be significantly less than that for oral systems. TDDSs provide constant blood levels for 1 to 7 days and increased patient compliance. Table II lists some of the commercially marketed transdermal patches.

Despite some of the advantages of transdermal systems, delivery of certain drugs can be difficult because of their poor permeability across the skin. Use of penetration enhancers and prodrugs can increase the transdermal permeability of drugs. Recently there has been a lot of interest in physical techniques like iontophoresis, electroporation, sonophoresis, and reverse iontophoresis as a means of increasing the permeability of drugs across the skin. Iontophoresis utilizes a small voltage (typically 10 V or less) and continuous constant current (typically 0.5 mA/cm²) to push a charged drug molecule into skin or other tissue. Electroporation utilizes a high-voltage (>100 V) pulse for a very short duration (μ s to ms) to create new aqueous pathways (pores) across lipid-containing barriers, forcing the drug molecule into systemic circulation. Sonophoresis is the application of ultrasound energy to enhance percutaneous drug absorption. Some of the successful technologies in this field are as follows

Dermaflex (Elan Corporation) is a passive transdermal patch employing a hydrogel matrix in which a pharmaceutical compound is incorporated. Dermaflex regulates the availability and the absorption of pharmaceutical compounds in a manner that may allow controlled and efficient delivery.

Dermasite (KV Pharmaceuticals) is a semisolid site-release configuration for topical applications to the skin.

E-trans (Alza Corporation) is a transdermal system that provides rate-controlled administration of drugs through the skin.

These systems resemble small adhesive bandages and can offer multiday or weekly dosing and improved patient compliance.

E-trans (Alza Corporation) is an electrotransport system that uses low-power electric current to control drug administration through intact skin. E-trans systems are being developed to provide continuous drug delivery as well as patient-controlled pulsatile delivery.

Microsponge systems (Advanced Polymer Systems Inc., USA) are based on microscopic polymer-based microspheres that can bind, suspend, or entrap a wide variety of substances and incorporate them into a formulated product, such as gel, cream, liquid, or powder. Microsponge systems are used primarily as reservoirs for releasing active ingredients in an extended period of time and as receptacles for absorbing undesirable substances, such as excess skin oil. EveryStep (odor-fighting foot powder), Exact acne treatment (a cream formulation of benzoyl peroxide), and Retino-A-Micro (tretinoin gel) are based on this technology.

Polytrap systems (Advanced Polymer Systems Inc.) are designed to absorb skin oils and eliminate shine, provide a smooth and silky feel to product formulations, entrap and deliver various ingredients in personal care products, and convert liquids into powders.

TheraDerm-LRS (Theratech, Inc., USA) is a liquid reservoir system. Numerous drug formulations can be incorporated into a TheraDerm-LRS patch because the system is not rate limiting to the administration of the drug and the drug reservoir is isolated physically from the adhesive within the system. **TheraDerm-MTX** (Theratech Inc.) is a matrix system based on an adhesive matrix patch design. The drug is incorporated into the adhesive, resulting in a light and flexible patch that conforms to the skin for maximum adhesion and comfort.

TheraPatch (LecTec Corporation, USA) is a self-adhering patch that delivers medications topically into the skin for local-

ized pain relief and therapeutic treatment.

Transdermal drug delivery systems (Cygnus Inc., USA) provide the controlled release of drugs directly into the bloodstream through intact skin. By delivering a steady flow of drugs into the bloodstream for an extended period of time, transdermal systems can avoid the peak- and effect of oral or injectable therapy and can enable more controlled effective treatment.

Liposomal delivery

Liposomes are microparticulate lipoidal vesicles and have been used as a carrier for the improved delivery of a variety of drugs such as chemotherapeutic agents, imaging agents, antigens, genetic materials, immunomodulators, etc. Liposomes are a family of vesicular structures based on lipid bilayers surrounding aqueous compartments. In the majority of cases, lipid complexes and liposomal pharmaceuticals provide less toxicity and better efficacy than the active ingredient.

Conventional liposomes are typically composed of only phospholipids (neutral and/or negatively charged) and/or cholesterol. These are characterized by a relatively short blood circulation time. To overcome this problem, long-circulating liposomes (also called stealth or sterically stabilized liposomes) have been developed. These stealth liposomes carry a polymer coating to obtain prolonged circulation times. Targeted liposomes (immunoliposomes) may be either conventionally or sterically stabilized and have specific antibodies or antibody fragments on their surface to enhance target site binding. Cationic liposomes are still under development for improving the delivery of genetic material. A number of products based on liposomes have already been approved for marketing (see Table III), and more are awaiting approval. Companies such as ADD Drug Delivery Technologies AG (Switzerland), DepoTech Corporation (USA), Nexstar Pharmaceuticals (USA), Novavax Inc. (USA), The Liposome Com-

378
377

pany Inc. (USA), and Sequus Pharmaceuticals Inc. (USA) are actively involved in the development of liposomal-based drug delivery systems.

Novasome lipid vesicles (Novavax, Inc., USA) are proprietary organized lipid structures in which drugs or other materials may be encapsulated for delivery into the body topically or orally. Novasome lipid vesicles are made using Novavax's patented manufacturing process from a variety of readily available chemicals called amphiphiles, which include fatty alcohols and acids.

Micellar nanoparticles (Novavax, Inc.) are submicron-sized, water-miscible lipid structures that have different structural characteristics and are generally smaller than Novasome lipid vesicles. Micellar nanoparticles are derived from amphiphile molecules.

Proliposomes (ADD Drug Delivery Technologies AG) overcome the stability, entrapment, and production problems associated with conventional liposomal formulations. This approach avoids many difficulties encountered with the manufacturing of liposomes by forming liposomes at the point of delivery, presenting opportunities for novel delivery systems designed for dermal, mucocutaneous, pulmonary, oral, and parenteral use.

Stealth liposomes (Sequus Pharmaceuticals Inc., USA) are stable in plasma and avoid rapid removal from the bloodstream. This is achieved by attaching polyethylene glycol to the surface of the liposomes to form long-circulating liposomes. Stealth liposomes are large enough that typically they do not leak out of the bloodstream and into tissues through normal, healthy blood vessels. As a consequence, they continue to circulate intact until they reach tissues where new blood vessels form, such as tumors, sites of inflammation, and sites of injury.

Taste masking

Oral pharmaceuticals often impart an unpleasant taste, primarily bitterness. The desire for improved palatability in these products has prompted the development of numerous methods for taste masking, such as complexation of the drug with resins or cyclodextrins, use of microcapsules, particle coating, etc. Many of these contributions have been successfully com-

mercialized in oral pharmaceutical preparations that are available over the counter or by prescription.

Chewable tablets (Elan Corporation) consist of a mild effervescent drug complex dispersed throughout a gum base. The drug is released from the dosage form as a result of physical disruption from chewing as well as chemical disruption from the interaction between the fluids in the oral cavity with the effervescent material. The taste of the compound is manipulated by a drug-coating technique that provides a physical barrier between the drug particles and the taste receptors of the mouth. These coating techniques are robust enough to withstand the mechanical onslaught caused by chewing so that taste masking is not compromised while patients take their medication.

KV Pharmaceuticals has developed a number of taste-masked technologies, including Flavortech, a liquid formulation technology designed to reduce the bad taste of therapeutic products. Micromask is a taste-masking technology that incorporates a dry-powder, microparticulate approach to reduce objectionable taste by sequestering the unpleasant drug agent in a specialized matrix. **Liquette** is a taste-masking technology that incorporates unpleasant tasting drugs into a hydrophilic and lipophilic polymer matrix to suppress the taste. **Oraquick** is a technology in which the bitter taste of a drug candidate is first enhanced by neutralizing its negative taste characteristics and then developed into a quick-dissolving tablet formulation.

Tastemasking (Ascent Pediatrics Inc., USA) technology is used to mask the objectionable or unpleasant taste of various common ingredients used in pediatric pharmaceuticals.

Oral fast-dispersing dosage forms

A solid dosage form that dissolves or disintegrates rapidly in the oral cavity, resulting in a solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. These are also known as fast-dissolving, rapid-dissolve, rapid-melt, mouth-dissolving, and quick-disintegrating tablets. Some of the advantages of oral fast-dispersing dosage forms include administration to patients who have diffi-

culty in swallowing, more rapid drug absorption, patient convenience, and compliance. These dosage forms are particularly helpful for pediatric and geriatric patients who have difficulty in swallowing (dysphagia) and also for traveling patients, for whom water may not be easily or readily accessible. The technologies, some of which have been successfully marketed, mainly utilize conventional tableting processes with slight modification, freeze-drying methods, and floss-formation techniques for manufacturing.

EFVDAS or Effervescent Drug Absorption System (Elan Corporation) is a drug delivery technology that has been used in the development of a number of both OTC and prescription medications. This is particularly advantageous for conditions such as colds and flu, for which Elan has modified its EFVDAS technology to develop hot drink sachet products that combine medicines and vitamins for OTC use. The granular contents of the sachets can be added to boiling water to produce pleasant-flavored solutions. In these cases the effervescence of the granulate mixture is modified to accommodate the use of heated water. Examples of products that Elan has developed include effervescent ibuprofen, paracetamol (acetaminophen), cimetidine, naproxen, and a paracetamol and codeine combination product.

Fast Melt (Elan Corporation) is a highly porous, microfine matrix tablet. Once placed on the tongue, this matrix rapidly absorbs liquid and disintegrates. The drug, in a stabilized, size-reduced form to ensure optimal solubility, dissolves rapidly. The combination of a mild effervescent base and drug processing ensures that the dosage form goes into solution in approximately 15 to 30 seconds. The drug is released rapidly within the oral cavity, where it dissolves to form a drug solution that is then swallowed. This is particularly advantageous in cases like migraine where a fast onset of clinical effect is required. A portion of the drug solution may be absorbed locally in the oral cavity and therefore may avoid first-pass metabolism in the liver that limits the bioavailability of many drugs. The fast-melt system rapidly disintegrates in the oral cavity; hence, patients do not have to swallow large cumbersome dosage forms, which discourages many from taking their medication. Thus,

370
378

the fast-melt dosage form combines the benefits of liquid formulations with those of a solid oral dosage form.

Flashdose (Fuisz Technologies, USA) utilizes shearform technology to form a matrix known as floss. The floss is a fibrous material similar to cotton candy fibers and is commonly made from saccharides such as sucrose, dextrose, etc. The candy floss can then be milled and blended with active ingredients and other processing aids and subsequently compressed into fast-dissolving tablets.

Flashtab (Prographarm, France) is a combination of taste-masked multiparticulate active drug substances with specific excipients compressed into tablets. This orodispersible tablet is placed in the mouth, where it disperses rapidly before the patient swallows. Some of the drugs that are marketed using this technology are acetaminophen (pediatric and adult), ketoprofen, and ibuprofen.

Multiflash (Prographarm) is a multi-unit tablet composed of coated microgranules and fast-disintegrating excipients. This multiparticulate tablet quickly disintegrates in the esophagus after being swallowed with a minimum amount of water. This tablet avoids mucosal adhesion, and coated pellets can match various dissolution rates.

Orasolv (Cima Labs Inc., USA) is obtained by direct compression and utilizes effervescent materials (for faster disintegration) and taste-masking agents. The technique involves the formation of microcapsules by a novel technique involving the dispersion of active ingredient into a suitable polymer along with other excipients such as mannitol and magnesium oxide. The active agents and mannitol are added to the polymeric dispersion (ethyl cellulose, acrylates, etc.) under stirring, followed by the addition of magnesium oxide. Magnesium oxide and mannitol are added to promote the release of the active agent. The mixture is dried for one hour at 50 °C, delumped, and dried for another hour at the same temperature. The material is then screened (8-mesh) and dried for one hour at 60 °C. The formed microcapsules, effervescent mixtures, and other standard excipients are mixed and compressed to form tablets. The tablets have a hardness of about 1–2

kp and an in vivo disintegration time of <1 min.

Wowtab tablets (Yamanouchi Pharma Technologies, USA) are usually made by conventional tableting methods and have fast disintegration (1–40 s). The formulation usually consists of a mixture of fast-disintegrating but poorly compressible saccharides (e.g., mannitol, lactose, glucose, etc.) and a slowly disintegrating saccharide that shows good hardness upon compression (e.g., maltose, sorbitol, etc.). The mixture is compressed after undergoing a humidification and drying process resulting in tablets that show adequate hardness and rapid disintegration.

Zydis (R.P. Scherer, UK) uses freeze-drying technology in the manufacture of fast-disintegrating dosage forms. These formulations are combinations of water-soluble matrix material along with the drug and some functional excipients that are formed in the blister pockets and freeze-dried to remove the water by sublimation. The resulting structures are very porous in nature and rapidly disintegrate or dissolve upon contact with water. Some of the drugs that are being marketed in the form of Zydis products are oxazepam, lorazepam, piroxicam, loperamide, famotidine, loratidine, enalapril, phenylpropanolamine/brompheniramine, and selegiline.

LYOC (Farmalyoc, France) and **Quicksolv** (Janssen Pharmaceutica, USA) also utilize freeze-drying technology to produce oral fast-dispersing tablets.

Technology for insoluble drugs

Drug solubility may be the rate-limiting step in absorption (e.g., in drugs belonging to Class 2 or drugs having good permeability but poor solubility) and therefore may affect the bioavailability of the drug. More than 40% of potential drug products suffer from poor water solubility. This frequently results in potentially important products not reaching the market or not achieving their full potential. A good deal of research has been done in this area, and currently a number of technologies are available to address the poor solubility of drugs.

INDAS or Insoluble Drug Absorption System (Elan Corporation) addresses the problem of poor solubility by manipulating the physicochemical characteristics of

a drug to create a high-energy adsorbate that demonstrates enhanced solubility. This high-energy adsorbate is subsequently combined with Elan's other controlled absorption technologies to deliver the required plasma profile. The drug in question, usually crystalline in nature, is converted into an amorphous form by a combination of energy, excipients, and unique processing procedures. Once the drug is converted to the desirable physical form, an adsorption process utilizing a novel polymer cross-linked technology prevents recrystallization and stabilizes the resulting high-energy complex. The combination of the change in the physical state of the drug coupled with the solubilizing characteristics of the excipients employed ensures that the solubility of the active ingredient is enhanced. Nifedipine, a once-daily nifedipine formulation, is based on this technology and is marketed in Europe and Southeast Asia.

Liquid-Oros technology (Alza Corporation) is designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a self-emulsifying formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pushes the drug formulation through an orifice in the capsule.

NanoCrystal technology (Elan Corporation) reduces a drug to extremely small particles (< 400 nm in diameter) using a specialized milling technique. A suspension of the insoluble drug in a stabilizing solution, consisting of GRAS stabilizers and other excipients, is used for the milling process to prevent aggregation of the resulting nanoparticles and also serves to increase the dissolution rate of the nanoparticles by acting as a surfactant within the GI tract. Additionally, NanoCrystal technology serves as a platform for targeting drugs to specific anatomical sites or to control delivery over time. Once the NanoCrystal form of the insoluble drug has been transformed into a more physically stable form, it can be incorporated into other drug delivery systems such as oral controlled-release or highly concentrated parenteral solutions. Recently, Elan obtained marketing approval from FDA for a tablet form of American Home Products Corporation's drug Rapamune, which represents the first approval for a

3800
379

drug presentation containing NanoCrystal technology. Rapamune is indicated for the prevention of organ rejection in kidney transplant patients, and the new tablet provides easier administration and storage than the currently marketed Rapamune oral solution.

SoftGel (R.P. Scherer) is a soft gelatin capsule formulation that contains a high concentration of a hydrophobic drug in solution (or fine particles of drug in suspension) in a hydrophilic or lipophilic liquid. This technology has been specifically developed to improve the solubility, stability, bioavailability, and rate of absorption of drug molecules. ACT-3 (ibuprofen) marketed in Australia by Whitehall Laboratories (Australia), and Fortovase (saquinavir) marketed by Roche Labs, Inc. (USA) are some of the products based on this technology.

ADD Drug Delivery Technologies AG utilizes solubilizing properties of patented blends of phospholipids to increase solubility and bioavailability of poorly water-soluble drugs.

Colon-specific delivery

Although the small intestine is the primary site for drug absorption and is therefore a preferred area of the GI tract to target with various controlled-release technologies, considerable interest has been shown in the past few years in colon targeting of drugs. The main reasons for this interest are the reduced proteolytic activity in the colon, which may be advantageous in targeting certain drugs such as proteins and peptides that are enzymatically degraded in the stomach or small intestine, and the topical treatment of carcinomas and inflammatory bowel diseases. In the past few years many colon-specific dosage forms have been developed, including prodrugs, cross-linked hydrogels, matrices, and coated dosage forms. Coated dosage forms are preferred because of innovations in the coating technology and wide flexibility in the design. These coated dosage forms are mainly based upon one of the following:

- The pH-controlled release coatings that are insoluble at the lower pH of the stomach and dissolve in the lumen of the small intestine. To achieve release in the colon, the start of the drug release is controlled by increasing the thickness

of the coating, allowing a pH- and time-controlled polymer dissolution and drug release. These pH-sensitive enteric polymers dissolve in a pH between 6 and 7 and thus release the drug as soon as the pH of the intestine reaches 6 or 7. Some of these enteric polymers are cellulose acetate phthalate, HPMC phthalate, and Eudragit L and S.

- Time-controlled release coating in which the lag time depends upon coating thickness and drug release can be accomplished by changes in osmotic pressure or disruption of the coating by swelling of the core.

Oros-CT (Alza Corporation) is a system that can be used as a once- or twice-a-day colon-targeted dosage form and is based on the principles of osmotic pressure. Oros-CT can be a single osmotic unit or can be comprised of as many as five to six push-pull osmotic units filled in a hard gelatin capsule. Each bilayer tablet consists of an upper compartment (drug along with osmotic agents) and a lower compartment (polymeric osmotic agent), surrounded by a semipermeable membrane. An orifice is created in the membrane next to the drug layer. After coming into contact with the GI fluids, the gelatin capsule dissolves and the enteric coating prevents entry of water from the stomach. As the system enters into the small intestine, the enteric coating dissolves and water is imbibed into the core, thereby causing the push compartment to swell. At the same time, flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate that is precisely controlled by the rate of water transport across the semipermeable membrane.

Pulsincap (R.P. Scherer) consists of a water-insoluble capsule body and a water-soluble cap. The drug formulation is contained inside the capsule. The soluble cap dissolves in the intestine, thereby allowing the hydrogel plug to swell and expand. Ejection of the swollen plug occurs after a lag time that depends on the hydrogel plug, the length of the plug, and the fit ratio (plug diameter to body diameter).

Colon Specific Systems (Advanced Polymer Systems, Inc.) uses Microsponge systems to protect the active agent from the environment of the stomach and delivers the drug to the colon in a controlled fashion.

Intranasal delivery

Intranasal delivery of certain drugs offers significant advantages. The nasal cavity can be used for the delivery of several compounds and offers rapid absorption into the systemic circulation, providing rapid onset of desired therapeutic effect, lower required dosages, fewer side effects, and improved patient compliance. Moreover, this route may also permit the delivery of challenging molecules such as proteins and peptides.

In the past drops were instilled in the nose, but with the advent of insufflator technology, drops are seldom used now. Nasal dosage forms consist mainly of preparations containing dispersed or dissolved drugs placed in a container that is squeeze- or spray-activated. Alternatively, liquid solutions can be delivered using metered atomizing pumps or metered-dose pressurized nasal inhalers. Butorphanol (Stadol NS Nasal Spray, Bristol Myers Squibb Co., USA), calcitonin (Miacalcin Nasal Spray, Novartis), dihydroergotamine (Migranal Nasal Spray, Novartis, Inc.), sumatriptan (Imitrex Nasal Spray, Glaxo-SmithKline), and desmopressin (DDAVP Nasal Spray, Aventis Pharma, USA) are some of the drugs marketed in the form of a nasal spray. Cromolyn sodium (Nasal-crom Nasal Solution, Fisons Pharmaceuticals) is available in a solution form. Budesonide (Rhinocort Nasal Inhaler, Astra) and beclomethasone dipropionate (Rino Clenil, Chiesi Farmaceutici) are marketed in the form of metered-dose pressurized aerosols. Beclomethasone dipropionate is also available in the form of a metered-dose manual spray unit (Beconase AQ, Glaxo-SmithKline, and Vancenase AQ, Schering Plough Corporation).

Nasal powders are an alternative dosage form and may show improved stability. Administration of powders requires nasal insufflators that are either mechanically or respiration actuated. In mechanical devices, a rubber bulb is connected through the dose reservoir to a nasal adapter. Squeezing the rubber bulb provides a stream of air that is capable of emitting the loaded powder in the insufflator. Rinoflatore (Fisons, Italy), Miat Nasal Insufflator (Miat, Italy), and Puvlizer (Teijin, Japan) are some of the marketed insufflators for nasal administration of

381
380

powders. Respiration-actuated devices are a nose-adapted version of dry powder inhalers (DPIs). With both types of devices, the drug is loaded in a gelatin capsule that is pierced just before activation. The capsule is located between the air jet producer and the nose adapter, and the flowing airstream creates turbulence inside the capsule, which aerolizes and releases the powder from the capsule.

Nasal gels also can be used to provide an enhanced bioavailability compared with oral delivery. EnerB (Nature's Bounty, Inc.), a vitamin B-12 dietary supplement, is available in gel form.

Pulmonary delivery

Until now, pulmonary delivery has been used primarily for the treatment of respiratory disease. More recently, the lung's natural ability to transfer molecules into the bloodstream has been utilized for delivering drugs to the systemic circulation. This method is a noninvasive alternative to painful injections and can lead to the rapid onset of action and good bioavailability. Inhalation devices broadly fall into three categories: pressurized metered-dose inhalers (MDIs), nebulizers, and DPIs. MDIs contain the drug as a solution or a suspension of fine particles in a liquefied propellant held under high pressure. The drug is emitted through an orifice from a metering valve. Nebulizers, on the other hand, do not require propellants and can generate large quantities of small droplets capable of penetrating into the lung. Recently, a great deal of work has been done in the field of DPIs. In DPIs, the drug is stored in a dry state, thereby ensuring long-term stability and sterility.

Some of the single dose breath-driven DPIs that are currently marketed are Rotahaler (GlaxoSmithKline), Flowcaps (Hovione), and Cyclohaler (Pharmachemie). Diskhaler and Accuhaler (GlaxoSmithKline) are multidose factory-metered inhalers. In addition, several multidose patient/device-metered DPIs are available; Clickhaler (M L Labs), Easyhaler (Orion), Pulvinal (Chiesi), Turbohaler (AstraZeneca), and Ultrahaler (Aventis Pharma).

AERx system (Aradigm Corporation, USA) is based on aerosol-generation technology capable of producing low-velocity small particles suitable for efficient and

reproducible pulmonary delivery. The system aerosolizes liquid formulations that are prepackaged in unit-dose packets for inhalation. Each unit-dose packet consists of a small blister package that stores a liquid drug formulation and an aerosolization nozzle with a membrane incorporating an array of micro-machined holes. The AERx device creates a respirable aerosol by releasing a mechanical actuator that is activated automatically when the patient's inhalation is optimal for drug delivery. The actuator compresses the blister packet, thereby forcing open the sealed channel and extruding the liquid drug through the aerosolization nozzle. The aerosolized drug produced by this process is inhaled through the mouthpiece of the AERx device. The aerosolization of the liquid drug via the disposable nozzle takes about 1 s and produces a low-velocity, fine-particle aerosol necessary for optimized deposition within the lungs.

Spiros (Dura Pharmaceuticals Inc., USA) is designed to deliver a relatively consistent drug dose to the lungs over a wide range of inspiratory flow rates. The core technology contained in Spiros is an aerosol generator that uses electro-mechanical energy to disperse drug powder to form an aerosol for inhalation. The main components of the aerosol generator include the impeller, the motor, the breath-actuated switch, and the dosing chamber. When the switch is activated, the electric circuit is completed and the impeller rotates. The action of the impeller on the dry powder formulation supplies the energy to disperse the drug and provides a zero-velocity cloud of aerosolized drug for inhalation. The cloud of aerosolized drug is suspended in the dosing chamber and is delivered to the lungs only as the patient inhales.

Vaginal/rectal delivery

The vagina has been studied as a favorable site for the local and systemic delivery of drugs, and this route offers certain advantages such as the avoidance of the gut and hepatic first-pass metabolism, reduction in gastrointestinal and hepatic side effects, and local targeting of drugs to the reproductive organs. Vaginally administered agents and formulations are being developed mainly to provide dual prophylaxis for contraception and protection

against microbial infections, including AIDS and other sexually transmitted diseases. This route also has potential for uterine targeting by the so-called first uterine pass effect of active agents such as progesterone and danazol.

Hycore-V (Core Group Plc, Scotland) uses hydrogel polymer technology to absorb fluid and swells without losing its physical form. As the hydrogel swells, the drug is released in a controlled manner. Drug release can be controlled over a period of a few hours to several days by varying the shape and the physical and chemical properties of the polymer. Hycore-V is delivered through the vagina in the form of a pessary. Hycore-R (Core Group Plc) uses similar technology and delivers the drug through the rectum in the form of a suppository.

Vagisite (KV Pharmaceuticals) is a semi-solid system intended for drug administration within the vaginal vault. Biosert (KV Pharmaceuticals) is a bioadhesive controlled-release system that is a solid rectal or vaginal suppository at room temperature and, after insertion, becomes a bioadhesive long-acting cream.

Site-specific drug delivery

One of the goals of effective drug delivery is to control and optimize the localized release of drug at the target site and rapidly clear the nontargeted fraction. In the past few years, there has been considerable interest in the development of a delivery system that will release the drug locally in a highly selective fashion. Some of the benefits of this type of delivery system are the delivery of a calculated amount of drug at the site of action and limited access to other organs. The amount of drug reaching the systemic circulation theoretically will be less, thereby resulting in fewer side effects. At present, a number of technologies are available for site-specific delivery.

Atrigel (Atrix Laboratories, Inc., USA) comprises biodegradable polymer formulations that are administered as flowable compositions (solutions, gels, pastes, and putties) that solidify in situ upon contact with body fluids to form biodegradable implants. The Atrigel system is designed to provide extended localized or systemic drug delivery in a single application without the need for surgical implantation or removal.

382
381

Durasite (Insite Vision Inc., USA) is an eye drop formulation comprised of a cross-linked carboxyl-containing polymer that incorporates the drug to be delivered to the eye.

Matrix Delivery System (Matrix Pharmaceuticals, USA) is an aqueous-based protein system in which a chemotherapeutic drug is combined with a protein matrix and a vasoconstrictor to create an injectable gel. This gel enables targeted delivery of water-soluble drugs by direct injection into solid tumors and skin lesions. The Matrix delivery system localizes the release of the drug, maintaining high drug concentrations at the tumor or lesion site and increasing the duration of exposure of the targeted tissue to the therapeutic agent.

Microsphere Delivery System (Core Group Plc) uses biodegradable polymers and a method that facilitates the microencapsulation of water-insoluble and water-soluble compounds. Potential applications of this technology include the long-term controlled delivery of injectable compounds, the delivery of active agents to sites poorly accessible from systemic circulation, and site delivery of highly potent agents.

Oligosphere Injectable Microspheres (Macromed, Inc.) is a proprietary polymeric microsphere technology based on FDA-approved PLGA polymers. MacroMed's patented processing uses aqueous cosolvents providing a drug-friendly loading environment. MacroMed's process also creates a homogenous drug/polymer matrix. This enables a constant release profile with little or no initial burst. Oligosphere is injected parenterally and is designed for drug release profiles of greater than one month.

ReGel Injectable Controlled-Release System (Macromed, Inc.) is designed to deliver active agents systemically or locally for periods of one to six weeks. MacroMed formulates these systems with its proprietary thermosensitive and biodegradable class of hydrogels. These formulations are a liquid at or below room temperature and are injectable through a small 25-gauge needle. Upon injection as a liquid, the product quickly becomes a gel at body temperature, forming a depot that slowly degrades over a period of four to six weeks. The ReGel System is biodegradable and is made from GRAS components.

ReGel's solubilizing characteristics have been shown to increase syringability and consistency of dose.

Retinal delivery system (Insite Vision, Inc.) is a device that provides controlled nonsurgical delivery of ophthalmic drugs to the retina and other tissues in the posterior chamber of the eye.

Oral transmucosal delivery

Oral transmucosal systems address the need for a convenient noninvasive drug delivery vehicle that provides rapid onset of therapeutic action and allows the patient to control drug administration until the desired effect is achieved. The drug is released in the mouth, allowing rapid absorption through the oral mucosal tissues.

Bioadhesive Delivery System (Columbia Laboratories, Inc., USA) consists of a polymer, polycarboxophil, and an active ingredient. This system is based on the principle of bioadhesion, a process by which the polymer adheres to epithelial surfaces and to mucin, a naturally occurring secretion of the mucus membranes. The polymer remains attached to epithelial surfaces and the mucin and is discharged upon normal cell turnover or upon the detachment of the mucin from the mucus membranes, a physiological process that, depending on the area of the body, occurs every 12 to 72 h.

Oral transmucosal delivery (Theratech, Inc.) may enable the delivery of many large-molecule drugs, including peptides and polysaccharides that cannot readily be delivered orally or transdermally. TherTech's oral transmucosal delivery systems are solid dosage forms that will adhere to various surfaces in the oral cavity and deliver drugs within a period of time.

Future directions and conclusions

As discussed in this article, drugs can be delivered to a patient by many different delivery systems, including oral, transdermal, injection, implants, etc. Most of the drugs are amenable to these types of delivery systems. With the sequencing of the human genome, biotechnology companies are rapidly developing a large number of peptide- and protein-based drugs. It is expected that in the next 10 to 20 years, protein- and peptide-based drugs will constitute more than half of the new drugs introduced into the market, and more than

80% of these protein drugs will be antibodies. These biopharmaceuticals (proteins, peptides, carbohydrates, oligonucleotides, and nucleic acids in the form of DNA) present drug delivery challenges because these are often large molecules that degrade rapidly in the blood stream. Moreover, they have a limited ability to cross cell membranes and generally cannot be delivered orally. Such molecules will be much more difficult to deliver via conventional routes, and injections may be the only means of delivery (at least as of today).

The routes of administration will be dictated by the drug, disease state, and desired site of action. Some sites are easy to reach such as the nose, the mouth, and the vagina. Others sites are more challenging to access, such as the brain. Gene therapy is also likely to be one of the most exciting growth sectors as biotech companies become involved in drug delivery. Currently, no product in this category, which includes genetically engineered cells, has reached the market but several are in Phase III clinical trials. By 2005, some of these products will reach the market, and their value has been estimated to be close to \$5 billion.

In conclusion, the market for drug delivery systems has come a long way and will continue to grow at an impressive rate. Today's drug delivery technologies enable the incorporation of drug molecules into new delivery systems, thus providing numerous therapeutic and commercial advantages. A large number of companies are involved in the development of new drug delivery systems, which is evident by an increased number of products in the market and the number of patents granted in the recent past. Tomorrow's drugs definitely will be more challenging in terms of the development of delivery systems, and pharmaceutical scientists will have to be ready for a difficult task ahead.

Acknowledgments

R.K. Verma acknowledges CSIR, India, for awarding him financial assistance in the form of a Senior Research Fellowship.

Suggested reading

1. S. Engel, "Delivering Results," *R&D Directions*, 5 (2), 48-64 (1999).
2. S. Engel, "Smashing the Barriers," *R&D Directions*, 4 (4), 44-67 (1998).
3. S.V. Sastry, J.R. Nyshadham, and J.A. Fix, "Recent Technological Advances in Oral Drug

383
382

- Delivery — A Review," *Pharm. Sci. Technol. Today*, 3 (4), 138-145 (2000).
4. G. Storm and J.A. Cronmelyn, "Liposomes: Quo Vadis?," *Pharm. Sci. Technol. Today*, 1 (1), 19-31 (1998).
 5. C.S. Leopold, "Coated Dosage Forms for Colon-Specific Drug Delivery," *Pharm. Sci. Technol. Today*, 2 (5), 197-204 (1999).
 6. R.K. Verma, B. Mishra, and S. Garg, "Osmotically Controlled Oral Drug Delivery," *Drug Dev. Ind. Pharm.*, 26 (7), 695-708 (2000).
 7. R.K. Chang, et al., "Fast Dissolving Tablets," *Pharm. Technol.*, 24 (6), 52-5, (2000).
 8. I. Ashurst, et al., "Latest Advances in the Development of Dry Powder Inhalers," *Pharm. Sci. Technol. Today*, 3 (7), 246-256 (2000).
 9. *Encyclopedia of Controlled Drug Delivery*, Vols. 1 & 2, J.E. Mathiowitz, Ed. (John Wiley & Sons, Inc., New York, 1999). **PT**

383 **384**

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C., 26/07/2010

Abogado
Carlos R. Olarte
(Apoderado)

ASUNTO

Radicación **05 7005**
Trámite 002
Evento 001
Actuación 7430
Oficio
Folios 010

09519

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

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: 9 a 46
- 1.2. Reivindicaciones: Folios: 47 a 53
Folios: 335 a 336 Memorial de 30/04/2007
Folios: 358 y 359 Memorial de 10/06/2010
- 1.3. Datos PCT: Solicitud Internacional: PCT/EP03/008368
Capítulo II
Fecha Sol. Internacional: 28/07/2003
Publicación Internacional: WO04/012741
Fecha Pub. Internacional: 12/02/2004
Fecha Inicio Fase Nacional: 12/02/2005
Fecha Sol. Nacional: 28/01/2005
- 1.4. Oposiciones: Folios: 237 a 325 Memorial de 28/12/2006
- 1.5. Prioridad: GB0217493.6 de 29/07/2002
GB0217492.8 de 29/07/2002
GB0313801.3 de 13/06/2003
- 1.6. Respuesta del solicitante: Folios: 349 a 359 Memorial de 10/06/2010

2. Oposiciones

Mediante el memorial de fecha 28/12/2006, la sociedad PROCAPS S.A. a través de

su apoderada la Dra. Laura Catalina Silva Barrera, presentó un pliego de observaciones como fundamento de oposición a la patentabilidad de la materia técnica objeto de estudio, en el que hace mención al capítulo reivindicatorio presentado con motivo del primer examen de forma realizado sobre la solicitud – folios 47 a 52-. Y mediante memorial de fecha 01/06/2009 se sustituye el poder en la Dra. Eliana Isaura Moreno Bohorquez.

Al momento de la oposición la administración de búsqueda internacional –Oficina Europea de patentes- ya había publicado el informe de búsqueda para la solicitud PCT/EP03/08368 e indicaba los documentos que consideraba relevantes para efectos de la evaluación del requisito de novedad de la materia reivindicada. Estos mismos documentos son los que adjunta el señor opositor mediante memorial de fecha 28/12/2006, por lo que esta Superintendencia considera relevante el contenido de las publicaciones aportadas por el Señor opositor, documentos: WO97/14415 de los folios 255 a 293 y WO98/47491 de los folios 295 a 319 mediante el presente concepto técnico se permite señalar lo siguiente:

3. Objeto de la invención

Título de la solicitud

Formulación de lamotrigina de liberación prolongada y uso de la misma para su preparación

Reivindicaciones

Reivindicaciones 1 a 6: Se reivindica una formulación de liberación sostenida que comprende:

i) Un núcleo comprende:

- a) 2,5 a 80% en peso de lamotrigina o de un derivado
- b) 17,5 a 70% de un polímero que retarda la liberación
- c) 0 a 60% en peso de un diluyente
- d) 0 a 20% en peso de un auxiliar de compresión
- e) 0,1 a 2,5% en peso de lubricantes y un recubrimiento externo que comprende
- f) 0,05mm a 0,3mm de un polímero

ii) Una cubierta externa que comprende de 0,05mm a 0,30mm de un copolímero del ácido metacrílico que cubre el núcleo,

Donde el grosor de dicha cubierta exterior ha sido adaptada de tal forma que la misma es sustancialmente impermeable a la entrada de los fluidos del ambiente y sustancialmente impermeable a la salida de lamotrigina o de un derivado farmacéuticamente aceptable del mismo, y

Donde dicha cubierta externa incluye uno o más orificios que se extienden desde el exterior de la cubierta, sustancialmente completamente a través de dicha cubierta pero sin penetrar el núcleo, permitiendo la liberación de la lamotrigina o de un derivado farmacéuticamente aceptable del mismo, desde el núcleo hacia los fluidos del ambiente, dicho orificio u orificios presentan un área o área combinada del 10 – 60% del área externa de dicha formulación donde la liberación de lamotrigina o un derivado farmacéuticamente aceptable de ésta,

ocurre sustancialmente a través de dicho orificio y donde el recubrimiento externo se disuelve cuando el pH ambiental es mayor a 5.

Sustento Descriptivo

De acuerdo con la memoria descriptiva de la solicitud, las formulaciones de comprimido de lamotrigina que se comercializan actualmente proporcionan la liberación inmediata de los ingredientes activos una vez que el comprimido llega al estómago. La desventaja asociada a estas composiciones es que la concentración que se consigue en plasma es cíclica y durante el tratamiento de la epilepsia esto puede conducir a la generación de efectos secundarios.

Recientemente se ha descubierto la zona de absorción gastrointestinal de lamotrigina, tras efectuar estudios de absorción localizada, encontrando que el grado de absorción de lamotrigina es consistente en cualquier punto del tracto entre el estómago y el colon ascendente, por lo que la presente solicitud busca presentar un sistema de liberación prolongada de lamotrigina que permite la liberación del activo por un periodo comprendido entre 2 y 20 horas.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/38//³¹/425** de la **Clasificación Internacional de Patentes**.

4. De la solicitud de Patente

4.1 Reivindicaciones (artículo 30 D. 486)

Teniendo en cuenta el contenido y alcance de las modificaciones aportadas por el Señor solicitante mediante memorial de fecha 10/06/2010, esta Superintendencia se permite señalar lo siguiente:

- En la oportunidad jurídica anterior se mencionó que la definición de la composición farmacéutica en términos de las propiedades farmacocinéticas y en particular, de los valores de área bajo la curva para el caso del sistema de entrega de liberación prolongada de lamotrigina no resultaba admisible en la que medida que la definición por parámetros es exclusiva de aquellos productos que no se pueden definir de otra manera. Y dado que las composiciones farmacéuticas que presentan un área bajo la curva por fuera del rango de 80 a 125% y un C_{max} menor en un 30% con respecto a las tabletas convencionales de liberación inmediata se pueden definir por su composición cuali-cuantitativa, es decir, mediante la caracterización de cada uno de los elementos que componen la fórmula y la cuantificación de las proporciones dentro de la formulación es claro que no es posible recurrir a la incorporación de los parámetros farmacocinéticos para definirla.

Lo anterior, debido a que el señor solicitante insiste en incorporar dentro de la cláusula dependiente 7 estos parámetros obviando las recomendaciones señaladas en la oportunidad anterior y el hecho de que las propiedades de la formulación han sido mencionados dentro de la memoria descriptiva de la solicitud y constituyen precisamente parámetros relacionados con el efecto técnico que se logra mediante la combinación novedosa de los excipientes, con lo cual, el señor solicitante no solo se reivindica la composición cuali-cuantitativa objeto de su invención sino todas las alternativas presentes o futuras que lleguen a presentar la misma propiedad farmacocinética.

Por otra parte, es necesario reiterar que la formulación debe definirse por los elementos técnicos que la componen y no sólo en términos de la función que cumple cada uno dentro del sistema farmacéutico, como en el caso del componente c) que se describe por la función que cumple como auxiliar de compresión y del componente e) por su capacidad como lubricante.

- Con respecto al contenido de las cláusulas dependientes 2, 3 y 5 en las que se especifican las características técnicas de los elementos que componen la formulación en términos de sus denominaciones de fantasía, tal es el caso de Methocel E4M y KL100LV, Eudragit L30 D55 y polividon K30, es preciso recordar al Señor solicitante que la designación de los elementos químicos que componen la formulación debe efectuarse en términos de su denominación común, por lo que no resulta admisible la incorporación de los signos distintivos y marcas citadas.

Lo anterior, teniendo en cuenta las disposiciones normativas del artículo 30 D. 486 sobre definición precisa de la materia reivindicada.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 29/07/2002, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	WO97/14415	"Analgesic immediate and controlled release pharmaceutical composition"	24/04/1997
D2	WO98/47491	"Controlled release formulations using intelligent polymers"	29/10/1998
D3	US4968507	"Controlled porosity osmotic pump"	06/11/1990
D4	US5202128	"Sustained release pharmaceutical composition"	13/04/1993

Anterioridades D1 a D2 en los folios 255 a 325 y anterioridades D3 y D4 en los folios 360 a 369.

6. Análisis de patentabilidad (artículo 14 D. 486)

6.1 Nivel inventivo (artículo 18 D. 486)

El nivel inventivo del objeto reclamado se evaluó por comparación entre las características esenciales de la composición reivindicada y los elementos esenciales de las composiciones reveladas por el arte previo.

- Se reivindica:

Una formulación de liberación sostenida que comprende:

i) Un núcleo que comprende:

a) 2,5 a 80% en peso de lamotrigina o de un derivado

- b) 17,5 a 70% de un polímero de liberación retardada
- c) 0 a 60% en peso de un diluyente
- d) 0 a 20% en peso de un auxiliar de compresión
- e) 0,1 a 2,5% en peso de lubricante

ii) un recubrimiento externo que comprende 0,05mm a 0,3mm de un copolímero del ácido metacrílico que cubre el núcleo.

Donde el grosor de dicha cubierta exterior ha sido adaptada de tal forma que la misma es sustancialmente impermeable a la entrada de los fluidos del ambiente y sustancialmente impermeable a la salida de lamotrigina o de un derivado farmacéuticamente aceptable del mismo, y

Donde dicha cubierta externa incluye uno o más orificios que se extienden desde el exterior de la cubierta, sustancialmente completamente a través de dicha cubierta pero sin penetrar el núcleo, permitiendo la liberación de la lamotrigina o de un derivado farmacéuticamente aceptable del mismo, desde el núcleo hacia los fluidos del ambiente, dicho orificio u orificios presentan un área o área combinada del 10 - 60% del área externa de dicha formulación donde la liberación de lamotrigina o un derivado farmacéuticamente aceptable de ésta, ocurre sustancialmente a través de dicho orificio y donde el recubrimiento externo se disuelve cuando el pH ambiental es mayor a 5.

- El estado del arte previo a la invención presenta los siguientes documentos:

Anterioridad D1:

La publicación **D1** revela formulaciones farmacéuticas de liberación sostenida que comprenden núcleos o unidades matriciales en las que se encuentra un antagonista del receptor NMDA como lamotrigina (ver folio 284). Las formulaciones permiten la liberación sostenida y controlada del principio activo.

Los núcleos son tabletas o tabletas multicapas que contienen lamotrigina mezclada con componentes solubles como sacarosa, lactosa, fructosa, manitol y polímeros como polietilenglicol, HPMC, HPC, tensioactivos como laurilsulfato de sodio, cremophor, tweens, spans, pluronics, componentes insolubles como celulosa microcristalina, fosfato de calcio, talco, aerosil. Y el material de recubrimiento incluye polietilenglicol, HPMC, ceras, ácidos grasos, dispersiones de materiales como ceras y polímeros en aceites.

Anterioridad D2:

La publicación **D2** revela composiciones de liberación controlada que incluyen polímeros inteligentes. La composición se caracteriza porque el ingrediente activo presenta un ángulo de mojado cuyo Coseno se encuentra entre +0,9848 y -0,9848 y además presenta un primer componente inteligente de tipo polimérico y un segundo componente inteligente que presenta características opuestas de humectabilidad.

El primer componente inteligente es un polímero más hidrofóbico que el primer componente inteligente y es etilcelulosa y el segundo componente inteligente corresponde a una mezcla entre hidroxietilcelulosa e HPMC.

La composición comprende al menos un excipiente como dióxido de silicio, un agente de tensión superficial como laurilsulfato de sodio, lactosa anhidra como

agente que encauza la liberación del agente activo, además de un agente que facilita la compresión.

La composición cuali-cuantitativa de la fórmula revelada por el antecedente registra las siguientes características:

- a) 0,5 a 70% de sustancia activa
- b) no menos del 5% en etil-celulosa
- c) entre 1:100 y 100:1 de los polímeros hidroxietilcelulosa e hidroxipropilmetilcelulosa
- d) entre 0,25 y 5% en excipientes
- e) entre 0,5 y 15% en agentes de tensión superficial

Y adicionalmente puede comprender:

- f) 10 a 70% de un agente canalizador y
- g) 5 a 30% de un facilitador de la compresión

Y dentro de los principios activos que resultan de elección se encuentra la sustancia lamotrigina.

Anterioridad D3:

La publicación **D3** presenta un sistema de entrega farmacéutico tipo bomba osmótica que comprende al menos un compuesto activo con una cubierta o pared que controla la liberación del agente activo y que es insoluble en medio acuoso. La permeabilidad de la película oscila entre $6,96 \times 10^{-18}$ y $6,96 \times 10^{-14} \text{ cm}^3 \cdot \text{seg/g}$ y presenta un coeficiente de reflexión menor que 1.

La película se prepara a partir de los siguientes excipientes:

- i) un polímero permeable al agua pero impermeable al soluto, y
- ii) de 0,1 a 60% en peso de i) y ii), en el que al menos existe un aditivo formador de poros insensible al pH que se encuentra disperso alrededor de la película de recubrimiento.

El núcleo de la formulación contiene el agente activo que es soluble en los fluidos externos y se comporta como un fluido osmótico una vez que se encuentran en contacto con los mismos. Cuando el soluto se encuentra solubilizado en los fluidos que han penetrado la película por medio de los poros ejerce un gradiente de presión osmótica que le permite atravesar la película impermeable y alcanzar el fluido externo.

La película presenta un espesor de 20 a 500 micrones y permite la formación de poros que presentan un diámetro de 25 micrones y espacios entre ellos de 10 Å. Y el material polimérico del que está compuesta puede ser de polímeros de ácido acrílico y metacrílico o sus ésteres.

Anterioridad D4:

La publicación **D4** presenta una composición farmacéutica peletizada que se caracteriza porque los núcleos incluyen al menos un ingrediente activo soluble y una cubierta entérica que es parcialmente soluble en pH ácido.

La composición presenta las siguientes características y propiedades técnicas:

- a) Al menos el 35% de la matriz polimérica es insoluble en pHs entre 1 y 7,5 por lo que contribuye al control de la liberación del ingrediente activo,

b) de 1 a 30% del polímero entérico es insoluble en pHs que oscilan entre 1 y 4 pero soluble en pHs que se encuentran entre 6 y 7,5 con lo cual no se permite la liberación del agente activo a nivel estomacal pero si a nivel intestinal y de 1 a 60% y c) de 1 a 60% de un compuesto que es soluble en pH que oscila entre 1 y 4 con lo cual se facilita el inicio de la liberación del ingrediente activo a nivel estomacal.

La cubierta presenta la siguiente composición:

Como componentes de a) se encuentran: etilcelulosa, copolímeros de amonio acrílico o metacrílico, copolímeros de un éster de ácido acrílico o metacrílico o sus mezclas.

Como componentes de b) se encuentran: acetato ftalato de celulosa, HPMC ftalato, polivinil acetato ftalato, copolímeros de ésteres de ácido metacrílico: ácido acrílico, HPMC acetato succinato, goma shellac, entre otros.

Y como componentes de c) PVP, HPC, HPMC, polietilenglicol que tienen un peso molecular entre 1700 y 20000, polivinil alcohol y monómeros.

Ahora:
D4 D5

Tabla 1. Comparación técnica

Materia Reivindicada	Antecedente D1 (WO9714415)	Antecedente D2 (WO9847491)	Antecedente D3 (US4968507)	Antecedente D4 (US5202128)
Cláusula 1. Una formulación para liberación sostenida que comprende:	Formulación de liberación controlada y sostenida	Formulación de liberación controlada	Sistema de liberación controlado tipo bomba osmótica	Composición farmacéutica peletizada de liberación sostenida
i) Un núcleo que comprende: a) 2,5 a 80% en peso de lamotrigina o un derivado farmacéuticamente aceptable del mismo	Lamotrigina	Lamotrigina	Un núcleo que contiene un activo soluble	Un núcleo que contiene un activo soluble como sulfato de morfina
b) 17,5 a 70% en peso de un polímero de liberación retardada que corresponde a HPMC	Un polímero como HPMC	Polímeros HEC y HPMC	-	HPMC
c) 0 a 60% en peso de un diluyente	Un agente de relleno como dióxido de silicio, dióxido de titanio, talco, caolín, alúmina	Dióxido de silicio -lactosa anhidra	Manitol, d-lactosa, entre otros	Etilcelulosa
d) 0 a 20% en peso de un auxiliar de compresión	-	Celulosa microcristalina	-	-
e) 0,1 a 2,5% en peso de un lubricante y	Talco	-	Estearato de magnesio	-
ii) Una cubierta externa que comprende 0,05 a 0,3mm de un polímero que cubre el núcleo -Impermeable a la entrada de fluidos del ambiente y a la salida de lamotrigina -Incluye orificios que se extienden al exterior de la película en un porcentaje del 10 al 60% sin penetrar el núcleo y permiten liberar lamotrigina desde el núcleo hacia fluidos del ambiente -Recubrimiento se disuelve cuando el pH es mayor a 5.	Polímero de recubrimiento de ácido metacrílico	Recubrimiento con copolímeros de ácido metacrílico y metil-metacrilato, un agente plastificante, un pigmento, un agente aglutinante y un lubricante	Cubierta externa de un polímero de ácido metacrílico -Impermeable -Con orificios en su superficie del 5 al 95% de 10µm de diámetro y espacios interporo de 10Å.	Una cubierta entérica sensible al pH compuesta por a) un polímero de ácido metacrílico b) copolímero de ésteres de ácido acrílico: ácido metacrílico c) HPMC o un polivinilalcohol

Análisis de Diferencias Técnicas:

Con relación al contenido de las publicaciones del estado del arte esta Superintendencia logró identificar las siguientes diferencias técnicas:

Frente a las enseñanzas de **D1** las diferencias estriban en que las composiciones allí reveladas no incluye un auxiliar de compresión y no precisan las características asociadas a la película de recubrimiento.

Con respecto a **D2** las diferencias estriban en que la composición enseñada allí no incluye agentes lubricantes y no precisa las características de la película de recubrimiento.

Frente al contenido de **D3** las diferencias estriban en que el sistema osmótico allí divulgado no se aplica para la administración de lamotrigina.

Con respecto a **D4** las diferencias estriban en que el sistema divulgado allí no presenta dentro de los elementos del núcleo adyuvantes como auxiliares de compresión y lubricantes y el principio activo que se formula en el sistema no es lamotrigina.

Del problema técnico objetivo y del efecto inesperado:

De acuerdo con la memoria descriptiva de la solicitud la lamotrigina (3,5-diano-6-(2,3-diclorofenil)-1,2,4-triazina) es eficaz en el tratamiento de trastornos del sistema del sistema nervioso central, en particular, en el tratamiento de epilepsia, dolor, edema, esclerosis múltiple e indicaciones psiquiátricas como trastorno bipolar y sus formulaciones convencionales son de liberación inmediata a nivel del estómago, alcanzado concentración máxima en plasma a partir de las 1,4 y las 4,8 horas de la administración. La desventaja estriba que la concentración en plasma conseguida con los comprimidos convencionales es cíclica con valores máximos y más bajos producidos antes de la siguiente administración del fármaco.

De esta manera, era necesario diseñar una formulación de liberación prolongada que redujera los problemas asociados a la administración del fármaco por vía oral. Y en esencia el problema técnico objetivo reside en la necesidad de mantener una dosificación continua y conservar los niveles plasmáticos del principio activo dada la severidad de las patologías que trata el agente activo lamotrigina que tienen que ver con trastornos epilépticos.

Al respecto es preciso señalar que en virtud de las enseñanzas del estado del arte existía conocimiento de la necesidad de diseñar una fórmula de liberación modificada de lamotrigina, por lo que el estado del arte en dos documentos presenta sistemas de liberación controlada y sostenida de lamotrigina (ver documentos **D1** y **D2**).

La publicación **D3** por su parte revela sistemas osmóticos para la liberación controlada y sostenida de un agente activo, el que si bien no corresponde a lamotrigina, al combinar sus enseñanzas con cualquiera de las publicaciones **D1** o **D2** le permitiría una persona con conocimientos en la materia inferir razonablemente acerca de la posibilidad de diseñar sistemas de entrega farmacéuticos tipo bombas osmóticas, impermeables al medio y de liberación sostenida y controlada como el reivindicado.

Por su parte, la publicación **D4** presenta un sistema de liberación sostenida que presenta una cubierta entérica sensible al pH que permite dar inicio a la liberación desde el estómago y de manera controlada continuar liberando el principio activo hasta alcanzar el nivel intestinal. Como se indicó en apartes anteriores, esta publicación también presenta diferencias con respecto al estado del arte, sin embargo se ven superadas en la medida que se combinan sus enseñanzas con cualquiera de las publicaciones del estado del arte **D1** o **D2**.

En razón a esta circunstancia es claro que los elementos técnicos característicos de la composición reivindicada se derivan de manera evidente a partir de las enseñanzas que en conjunto revelan las publicaciones **[D3 y D1]** o **[D3 y D2]** o en su defecto **[D4 y D1]** o **[D4 y D2]**. Y dado que el objetivo principal de las publicaciones del estado del arte es modular la liberación de los agentes activos es claro que se anticipan a la solución que aporta el señor solicitante para el caso particular de lamotrigina, por lo que no se puede considerar que la materia objeto del presente análisis es producto de una actividad verdaderamente inventiva.

Se debe destacar que la bibliografía técnica relacionada con el tema sobre sistemas de liberación colon-específicos ha allanado el camino para el diseño de esta clase de formas de liberación mediante la identificación de algunos tópicos relevantes a tener en cuenta, tal es el caso del control en la liberación del activo por medio del manejo del pH y la aplicación de polímeros que se disuelven en pH 6 y 7, tal es el caso de acetato ftalato de celulosa, HPMC ftalato y copolímeros de ácido metacrílico¹, con lo que se comprueba que la solución que aporta la solicitud para el caso particular de lamotrigina ha sido estudiada con anticipación para solucionar problemas similares asociados a la administración de otros ingredientes activos.

Por las razones expuestas esta Superintendencia encuentra que la materia reivindicada carece de altura inventiva por lo que existe incumplimiento de las disposiciones normativas señaladas en el artículo 18 de la Decisión comunitaria 486.

7. Conclusión:

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO97/14415	1 a 6	Nivel Inventivo
D2	WO98/47491	1 a 6	Nivel Inventivo
D3	US4968507	1 a 6	Nivel Inventivo
D4	US5202128	1 a 6	Nivel Inventivo

8. Respuesta a los argumentos del señor solicitante:

Mediante memorial de fecha 10/06/2010 el señor solicitante clarifica el objeto de la invención y presenta una explicación detallada de la farmacocinética de la composición reivindicada y agrega lo siguiente:

- "(...) D1 revela composiciones farmacéuticas que incluyen antagonistas del receptor NMDA, en una forma de liberación inmediata, en asociación con otro antagonista del receptor NMDA, en una forma de liberación controlada (liberación sostenida). Las dos formas se encuentran

¹ Verma, Rajan K. Current status of drug delivery technologies and future directions. Pharmaceutical Technology, 25 (2), 1-14, February 2001.

392 393
usualmente asociadas en una tableta multicapas, donde ambas capas presentan ingrediente activo".

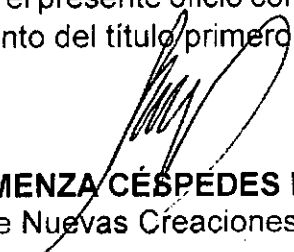
Al respecto es preciso señalar que la publicación contempla la posibilidad de obtener composiciones farmacéuticas multicapas, gránulos o pellets con recubrimiento o sin recubrimiento y bombas osmóticas, por lo que la afirmación del señor solicitante no contempla el contenido completo de los sistemas farmacéuticos que se pueden obtener con formulaciones como las que enseña el antecedente **D1** y se limita a señalar una de las opciones mencionadas en los ejemplos que acompañan el documento.

- "El examinador reconocerá que ninguna de las referencias citadas proporciona enseñanzas que conduzcan a desarrollar el concepto de administrar lamotrigina en un sistema de liberación dual o de dos fases".

En consideración a los argumentos del señor solicitante se han excluido las enseñanzas de las publicaciones D3 y D4 como arte previo cercano a la invención. Sin embargo, se debe destacar que cada una de las publicaciones del estado del arte **D1** y **D2** busca modular la liberación de los agentes activos mediante la combinación de métodos técnicos que permitan controlar el momento en que entra en contacto con los fluidos corporales el agente activo y así se demuestra en los ejemplos de **D1** sobre las formas pelletizadas de dextrometorfan (ver folios 273 y 274 de **D1**) y en **D2** sobre la composición de los núcleos que contienen verapamilo, nifedipino, entre otros activos y que presentan cubiertas fabricadas a partir de copolímeros de ácido metacrílico (ver folios 311 a 314 de **D2**).

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 notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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


ÁLIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha
30 JUL 2010

CONCEPTO TÉCNICO No. 2667

EXAMINADOR TÉCNICO
Código No. 202044