Señora Jefe
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y CO.
Bogotá, D.C.

Re.: Expediente No. 05 77.560
Fase nacional de Solicitud
de Patente PCT a nombre de
STRAKAN INTERNATIONAL LIMITED
Código 02 – 01 - 444

En relación con la solicitud contenida en el expediente de la referencia y, en particular, para dar respuesta al Concepto Técnico No. 1122, contenido en su último Oficio proferido dentro del mismo, dentro del término conferido, por medio del presente escrito me permito manifestarle:

1. Mi representada me ha dado precisas instrucciones de reemplazar el capítulo de reivindicaciones originalmente presentado.

   En consecuencia, acompaño al presente escrito las nuevas reivindicaciones 1 a 20.

   1.1 Conforme con la sugerencia del señor Examinador, se han suprimido las reivindicaciones relativas a un método de tratamiento.

2. La presente invención está dirigida a proporcionar un parche transdérmico de matriz para la administración de Granisetrón, y se limita al Granisetrón. La combinación de adhesivo que tiene grupos funcionales hidroxilo no ácidos y Granisetrón es notoriamente estable, y tiene unas propiedades de liberación del medicamento y flujo dérmico sorprendentemente buenas, como queda demostrado en los Ejemplos. Las propiedades de influjo y permeación son tan buenas, que no es necesario incorporar intensificadores de permeación. Esto resulta en extremo inusitado en los

parches dérmicos, y la reducción, o incluso eliminación, de los *intensificadores de permeación también significa que hay menos* probabilidad de irritación de la piel.

Intenso debate rodea la técnica de los parches para uso transdérmico. Son frecuentemente repetidas y bastante largas las listas de los tipos de componentes que se pueden usar para proporcionar un adhesivo sensible a la presión, y similarmente largas son las listas de posibles medicamentos de los que se *cree* se pueden beneficiar de la administración transdérmica. Muy pocas publicaciones en realidad consideran con algún grado de detalle al Granisetrón y nadie en el estado de la técnica ha identificado que la combinación particular de Granisetrón y un adhesivo que tiene grupos funcionales hidroxilo no ácidos alcance el efecto terapéutico deseado, o que sea capaz de mantener la estabilidad durante periodos de tiempo, que tengan ventajas tanto en el sentido comercial como en el regulatorio.

3. Con respecto a los documentos citados que, considera el señor *Examinador, afectan el requisito de nivel inventivo de la presente solicitud,* nos permitimos manifestarle:

   3.1 La presente invención se aplica de manera singular al Granisetrón. A este respecto, el documento más cercano citado es, de hecho, WO 98/53815, que proporciona ejemplos de Tropisetrón, pero también menciona ampliamente el Granisetrón a lo largo de la descripción.

   Sin embargo, lo más significativo de este documento es el Ejemplo 7 por cuanto éste es el único Ejemplo que emplea un adhesivo que tiene un grupo nucleofílico y también es el único Ejemplo que muestra que el contenido de Tropisetrón se reduce en un 10% en apenas cuatro semanas de almacenamiento a temperatura ambiente. Ésta es, claramente, una pérdida desastrosa, ya que cualquier producto comercial debe perder menos del 1% en un periodo de seis meses.

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3.2 La importancia del grupo nucleofílico es que éste es el grupo que la presente solicitud específicamente reivindica en la reivindicación 1. Lo que es particularmente sorprendente es que, lo que no funciona para el Tropisetrón, funciona supremamente bien para el Granisetrón. El documento citado WO 98/53815 ha asumido que el Tropisetrón y el Granisetrón son efectivamente iguales, pero los inventores de la presente solicitud encontraron exactamente lo contrario de manera que, por ejemplo, en la Tabla 5 del Ejemplo 2 de la presente solicitud se muestra que el Granisetrón permanece estable en éste tipo de adhesivo, incluso a temperaturas elevadas de 40°C por seis semanas.

3.3 Conforme con lo anterior, el señor Examinador podrá notar que, de hecho, el documento WO 98/53815 se aparta de las enseñanzas de usar adhesivos que contienen grupos nucleofílicos tanto para Tropisetrón como para Granisetrón. En efecto, el párrafo al final de la página 3 del documento WO 98/53815 dice:

"De preferencia, el monómero B está libre de grupos nucleofílicos, en particular, aquellos que son capaces de reaccionar con funciones estéricas en el copolímero. Aunque no es la intención quedar ligado a ninguna teoría, se cree que esos grupos nucleofílicos podrían reaccionar con funciones estéricas en el copolímero, lo cual conllevaría el establecimiento de enlaces cruzados de la capa de adhesivo y con ello la reducción de la estabilidad del almacenamiento del dispositivo de administración transdérmica. Es de suponer que dicha reacción sería catalizada por los medicamentos que son bases bastante fuertes. Por ejemplo, el tropisetrón tiene un pK de cerca de 9,5. De preferencia, el monómero B está desprovisto de grupos nucleofílicos seleccionados de entre el grupo compuesto por grupos amino hidroxi-tiol primarios, grupos amino secundarios y grupos ácidos".

3.4 La persona versada en la materia, por lo tanto, no tiene incentivo alguno para empezar con el documento WO 98/53815 como base para encontrar un adhesivo adecuado para el Granisetrón, por

cuanto este documento enseña específicamente en contra del uso de los grupos OH nucleofílicos.

La única conclusión a la que puede llegar la persona versada en la materia de una lectura apropiada del documento WO 98/53815 es que los acrilatos sólo se pueden usar para el Granisetrón si ellos *no contienen* grupos nucleofílicos.

El documento WO 98/53815 no puede ser usado en combinación con ningún otro documento para impugnar el Nivel Inventivo de la presente solicitud porque el adhesivo mismo, que es una característica esencial de ésta, en el documento WO 98/53815 se enseña explícitamente en contra.

3.5 El documento citado EP 1044684 se refiere a un parche reservorio. La presente invención, por el contrario, se relaciona específicamente con parches de matriz. Un parche reservorio consiste de un material que contiene el medicamento, el cual está separado del adhesivo. En contraste, los parches de matriz no tiene un reservorio, como tal, y el medicamento está presente en el adhesivo.

Estos son dos tipos muy diferentes de parche transdérmico, y los parches de reservorio han de evitarse en la medida de lo posible por cuanto son muy voluminosos, lo que hace que su uso sea muy molesto, y frecuentemente se despegan de la piel.

Los parches de matriz, por el contrario, no tienen el volumen del reservorio y son adhesivos en toda la extensión del parche.

El documento EP 1044684 se refiere enteramente a los parches de reservorio, particularmente para la administración de Ketoprofeno y Metoprolol. Aunque en el parágrafo [0024] se discuten una amplia gama de medicamentos alternativos, incluyendo los antieméticos, no se hace mención alguna del Granisetrón.

Existe un gran número de publicaciones que cubren los parches de reservorio, tal como el EP 1044684, pero los mismos son esencialmente irrelevantes por cuanto el ingrediente activo no esta cargado en el adhesivo, tal y como se encuentra en los parches de la presente invención.

3.6 El documento citado US 6,136,807 se refiere específicamente al Lerisetrón. Como se mencionó anteriormente, hay muy poca similitud entre los "isetrones". Es por ésta razón que la mayoría de los autores no se refieren simplemente a los "isetrones" ya que ellos tienen muy poco en común aparte de ser antagonistas de $5HT^3$.

En éste documento en particular, US 6,136,807, columna 1, líneas 27-30, se sugiere que la elección del medicamento necesita ser individualmente combinada con el adhesivo. Adicionalmente, éste documento se limita muy específicamente al Lerisetrón, ya que su estructura tiene poca o ninguna similitud con cualquier otro "isetrón" como claramente lo reconocen los autores, por lo que no es posible extender las enseñanzas de este documento al Granisetrón.

También es necesario tener en cuenta que ésta patente requiere la presencia de grandes cantidades de intensificador de la impregnación (20-30%) con el fin de lograr la administración transdérmica. Esto se encuentra en agudo contraste con la presente invención, la cual demuestra que se necesita poco o ningún intensificador de la impregnación.

3.7 El documento citado WO 98/37111 describe un adhesivo acrílico para la administración de estrógenos y progesterona. Los antieméticos están incluidos en una lista de posibles alternativas en la página 15, pero no se menciona el Granisetrón.

Por lo tanto, no se puede encontrar en éste nada que enseñe la combinación de Granisetrón con un acrilato. Adicionalmente, tampoco se puede encontrar nada que enseñe los acrilatos

específicos de la presente invención que necesariamente deben comprender un grupo OH no ácido.

4. Con fundamento en lo anteriormente expuesto, consideramos que no existe razón para combinar ninguno de los documentos citados y, aún si la hubiera, no se puede extraer nada que lleve a la presente invención.

   Ninguno de los documentos del estado de la técnica trata el problema de cómo administrar el Granisetrón a través de un parche de matriz estable, por lo que las reivindicaciones que se acompañan cumplen con el requisito de Nivel Inventivo.

Le solicito se sirva agregar este escrito y su anexo al expediente y otorgar el privilegio solicitado.

De Usted Atentamente,

GERMAN CASTILLO GRAU
T.P. No. 2.978 del C.S.J.

Reivindicaciones:

1. Un parche adhesivo apropiado para la administración transdérmica de granisetrón, en donde el adhesivo es un adhesivo acrílico que contiene moléculas no ácidas de hidroxilo, con una cantidad fisiológicamente efectiva de granisetrón cargada en el adhesivo.

2. Un parche conforme a la reivindicación 1, en donde las moléculas no ácidas de hidroxilo son proporcionadas por comonómeros apropiadamente seleccionados.

3. Un parche conforme a la reivindicación 2, en donde los comonómeros seleccionados se seleccionan de entre acrilatos y metacrilatos sustituidos.

4. Un parche conforme a la reivindicación 3, en donde el acrilato se selecciona de entre acrilatos de hidroximetilo, hidroxietilo e hidroxipropilo.

5. Un parche conforme a la reivindicación 3, en donde el metacrilato se selecciona de entre los metacrilatos de hidroximetilo e hidroxietilo.

6. Un parche conforme a cualquiera de las reivindicaciones precedentes, que es sensible a la presión.

7. Un parche conforme a cualquiera de las reivindicaciones precedentes, que contiene una cantidad importante de un monómero de acrilato primario.

8. Un parche conforme a la reivindicación 7, en donde el monómero de acrilato primario es ya sea acrilato de 2-etilexilo, o bien acrilato de butilo.

9. Un parche conforme a cualquiera de las reivindicaciones precedentes, adaptado para proporcionar una cantidad farmacológicamente efectiva de granisetrón después de cerca de 2 horas.

10. Un parche conforme a cualquiera de las reivindicaciones precedentes, que comprende hasta cerca de 10% en peso de granisetrón.

11. Un parche conforme a la reivindicación 10, que tiene menos de 8% p/p de granisetrón.

12. Un parche conforme a cualquiera de las reivindicaciones precedentes, que tiene un nivel de granisetrón superior a 4% p/p.

13. Un parche conforme a la reivindicación 10, que tiene un nivel de granisetrón de entre 6% y 7,7% p/p.

14. Un parche conforme a cualquiera de las reivindicaciones precedentes, en donde no se observa ninguna cristalización después de un mes de almacenamiento a temperatura y presión ambientales.

15. Un parche conforme a cualquiera de las reivindicaciones precedentes, en donde el adhesivo está cargado con entre 3 y 12% p/p de granisetrón.

16. Un parche conforme a la reivindicación 15, en donde el adhesivo está cargado con entre 4 y 10% p/p de granisetrón.

17. Un parche conforme a la reivindicación 15, en donde el adhesivo está cargado con entre 5 y 8% p/p de granisetrón.

18. Un parche conforme a cualquiera de las reivindicaciones precedentes, que no incorpora plastificadores o intensificadores de la impregnación.

19. Un parche conforme a cualquiera de las reivindicaciones precedentes, en donde, con una carga adhesiva de 6% p/p de granisetrón, el adhesivo tiene una superficie de entre 10 y 100 cm^2.

20. Un parche conforme a la reivindicación 19, en donde el adhesivo tiene una superficie de entre 15 y 50 cm^2.

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(71) Applicant: **TEIJIN LIMITED**
1-1 Uchisaiwai-cho 2-chome
Chiyoda-ku Tokyo 100(JP)

(72) Inventor: **HIDAKA, Osafumi**
39-48, Nobe Akigawa-shi
Tokyo 197(JP)
Inventor: **MURAKAMI, Satoshi 4-41-2,**
Nishisunacho
Tachikawa-shi
Tokyo 190(JP)

(74) Representative: **Votier, Sidney David et al**
CARPMAELS & RANSFORD 43, Bloomsbury Square
London WC1A 2RA(GB)

(54) **PLASTER.**

(57) A plaster consisting of a film layer of a film wherein the thickness thereof is 0.5 - 4.9 μm, the strengths in *two directions intersecting substantially perpendicularly are* 8 - 85 g/mm, respectively, the elongations in two directions intersecting substantially perpendicularly are 30 - 150 %, respectively, and, an elongation ratio of one direction to the other is 1.5 - 5.0 (provided that, when the elongations in the two directions are not equal, a smaller elongation is used as a denominator) and an adhesive layer (a) formed of an adhesive agent containing a percutaneous absorptive pharmaceutical, laminated on one of the surfaces of the film layer and having a thickness of 2 - 60 μm. The possibility of skin poisoning is decreased and a pharmaceutical of a clinically effective amount can be percutaneously absorbed. Further, it is preferable to provide a layer such as a planar support member. For example, a plaster consisting of the film layer (3) and the adhesive layer (4), wherein a planar support member (1) and a peelable film (5) are further laminated through an adhesive layer (b) (2), is excellent to handle.

EP 0 484 543 A1

Field of the Art:

The present invention relates to pharmaceutical plasters which can be used in treatment for a variety of diseases.

Background of the Art:

As the administration routes of medicines, ointments or the like have been frequently used as a local administration in addition to conventional ones such as oral, injection or rectal administrations. Further in recent years, the technical development has made steady progress in transdermal application of systemically acting drugs and several kinds of drugs have come to be clinically used in practice.

Since the transdermal administration of drugs enables them to avoid the first-pass effect which they would suffer in liver, if they were orally given, drug concentration in blood is far more stable than in the case of oral or injection administration, and many advantages also can be obtained, for example, longer effective time, easier removal of the drug by detaching the preparation in case of serious side-effects, and the like.

These merits have received strong attention and changes of conventional oral route preparations to transdermal ones have been investigated on a variety of drugs.

As clinical application of the transdermal preparations has made advance, however, the difficulties and problems in the transdermal route have become clear.

Several of them are as follows:

(1) One of the most serious problems of the transdermal preparations is outbreak of local irritation and skin rash or contact dermatitis. According to a statistics, the incidence of rash is 20 to 50 % by transdermal preparations of a typical occlusive type tape.

In many cases, however, the patients must use such preparations for their merits, even when the application of such preparations results in rash development.

Further, many of the drugs used clinically today are generally resistant to transdermal absorption and, even in the drugs which are transdermally absorbable, the absorption of the clinically effective amount needs enlarged application areas and combination of additives such as an absorption-promoting agent.

The enlarged application areas and the use of absorption-promoting agent and the like frequently bring about increased areas and aggravation of skin rash.

Thus, a transdermally applicable preparation which enables the absorption of a clinically effective dose of the drug with skin rash eruption inhibited is desired.

(2) In addition, while a transdermal preparation is applied for a long time, the preparation is stained or becomes peelable with time, especially bathing accelerates the removability.

It is troublesome, however, to apply a new plaster, every time the old one peels off. Moreover, the dose control becomes difficult, satisfactory efficacy cannot be attained and problems remain in appearance and hygiene.

Thus, a transdermal preparation which is resistant to staining and peeling are desired even after prolonged application.

(3) By the way, a transdermal preparation is of a sustained release type and particularly effective for chronic diseases or diseases requiring long-term treatment. And the patients with such diseases are elder people of high age in many cases. Generally, however, elder people are not good at handling which requires complicated operation.

Thus, a transdermal preparation is desired to be easy to handle for the patients, in addition to pharmaceutic satisfactions such as high absorption and the like.

Conventionally, as a plaster aiming at absorption of a clinically effective amount of a drug with skin rash inhibited, for example, the plasters according to the present inventors are known, which bear a knitted fabric of microporous hollow fibers as a constituent (WO 87/00046, W087/04343 and W090/09784).

Such plasters have been satisfactory for skin rash reduction and absorption of a clinically effective amount of a drug, but other more excellent plasters which cause no skin rash and resist peeling, even when applied for a more prolonged time, thus revealing sufficient efficacy with no problem of appearance, have been still desired.

In other words, an object of the present invention is to provide a pharmaceutical plaster which can enable the absorption of a clinically effective amount of a drug causing extremely reduced skin rash and no breakage and no peeling from the skin because of its satisfactory stretchability enough to follow skin contraction and expansion.

Another object of the present invention is to provide a pharmaceutical plaster which has excellent handleability in addition to the good absorption of a clinically effective amount of a drug, extremely reduced skin rash, no breakage and no peeling because of good stretchability to follow skin contraction and expansion.

Further, another object of the present invention is to provide a pharmaceutical plaster which can expect to develop sufficient clinical efficacy with a reduced content of a drug, when an expensive bulk such as buprenorphine or buprenorphine hydrochloride or a drug which is desired to reduce the remaining after application according to the legislation on psychopharmaceuticals handling is employed.

Disclosure of the Invention:

The present inventors have made intensified studies on the measures for the plasters which can utilize the advantages of conventional transdermal preparations with skin rash decreased, enable the absorption of a clinically effective amount of drugs of as many kinds as possible even if they are resistant to transdermal absorption and have excellent handleability, and attained the present invention.

In other words, the present invention is a plaster comprising

(1) a film layer which is composed of a film having a thickness of 0.5 to 4.9 μm, a strength of 8 to 85 g/mm, elongations of 30 to 150 % in the two directions intersecting substantially at right angle, respectively, and the elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator, when the ratios of the elongations in the two directions are different), and

(2) an adhesive layer (a) which is laminated all over the above-stated film layer in 2 to 60 μm thickness and contains transdermally absorbable drugs.

Moreover, the present invention is a plaster comprising

(1) a film layer which is composed of a film having a thickness of 0.5 to 4.9 μm, a strength of 8 to 85 g/mm and elongations of 30 to 150 % in the two directions intersecting substantially at right angle, respectively, and the elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator, when the ratios of the elongations in the two directions are different),

(2) an adhesive layer (a) which is laminated on one surface of said film layer in 2 to 60 μ thickness and contains transdermally absorbable drugs, and

(3) a backing sheet which is laminated through an adhesive layer (b), with a higher adhesive force than 3 g/12 mm, partially or wholly on the other-side surface of said film layer whose one-side surface has said adhesive layer (a) laminated.

Moreover, the present invention is a plaster comprising

(1) a film layer (a) which is composed of a film having a thickness of 0.5 to 4.9 μm, a strength of 8 to 85 g/mm and elongations of 30 to 150 % in the two directions intersecting substantially at right angle, respectively, and the elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator, when the ratios of the elongations in the two directions are different),

(2) an adhesive layer (a) which is laminated on one surface of the above-stated film layer in 2 to 60 μ thickness and contains transdermally absorbable drugs,

(3) a backing sheet which is laminated through an adhesive layer (b1), with a higher adhesive force than 3 g/12 mm (a1), partially or wholly on the other-side surface of said film layer (a) whose one-side surface has said adhesive layer (a) laminated, and

(4) a film layer (b) a film having 0.5 to 4.9 μm thickness, 8 to 85 g/mm strength, 30 to 150 % elongations in the two directions intersecting substantially at right angle and 1.0 to 5.0 elongation rate (wherein the smaller elongation is used as the denominator, when the ratios of the elongations in the two directions are different), and is laminated through an adhesive layer (b2) with an adhesive force higher than 3 g/12 mm (b1), partially or wholly on the other-side surface of said backing sheet whose one-side surface is adhered to the adhesive layer (b1).

Brief Description of Figures:

Fig. 1 depicts the cross section of the plaster which has been prepared in Example 1 of the present invention. In the figure, 1 means the backing sheet (hollow fiber sample); 2, the adhesive layer (b); 3, the film layer (polyethylene terephthalate film); 4, the adhesive layer (a) (the progesterone-containing layer); and 5, a release liner (it can be peeled off, when the plaster is applied).

Fig. 2 depicts the cross section of the plaster which has been prepared in Example 4 of the present invention. In the figure, 1 is the film layer (polyethylene terephthalate film); 2, the adhesive layer (a) (progesterone-containing layer); and 3, a release liner.

Fig. 3 depicts the cross section of the plaster which has been produced in Example 22 of the invention. In the figure, 1 means the film layer (b) (polyethylene terephthalate film); 2, the adhesive layer (b2); 3, the backing sheet (hollow fiber sample); 4, the adhesive layer (b1); 5, the film layer (a); 6, the adhesive layer (a) (estradiol-containing layer) and 7, the release liner.

Best Embodiment of the Present Invention:

The plasters according to the present invention have a film layer which is composed of a film of 0.5 to 4.9 μm thickness, 8 to 85 g/mm strengths and 30 to 150 % elongations in the two directions intersecting substantially at right angle, respectively, and 1.0 to 5.0 elongation ratio (wherein smaller elongation is used as the denominator, when the elongation ratio is different in the two directions). In order to reduce skin rash, it is important, first of all, to reduce the physical stimulation caused by the plaster preparations. Thus, the film thickness is decreased to less than 4.9 μ, preferably less than 4.0 μ, because skin stimulation is weakened, as the film becomes thin. Particularly, less than 3.5 μm is preferred, since this tendency becomes pronounced. In the meantime, plasters are used by applying them to human skins and required to follow the expansion and contraction of the skins in body actions to some extent. The films may be often broken, when they are extremely thin, while the skin stimulation becomes severe, when they hardly follow the skin stretching. It was found that the physical stimulation scarcely changed, even when the thickness was reduced to less than 0.5 μm, in addition, the production of the plaster became troublesome.

The purposes of using the film layer as a substrate are to increase the seal tightness at the plaster application sites and promote the transdermal absorption, to cover the adhesion surface with the film and prevent the adhesive from sticking to clothes or other skin areas, and the like. As the film becomes thin, the seal tightness lowers, less than 5 μm reveals a tendency to decrease the tightness and less than 1 μm, particularly less than 0.5 μ becomes difficult to ensure the satisfactory seal tightness as a plaster.

As for the film strength, higher than 85 g/mm, respectively, in the two directions intersecting substantially at right angle cannot reduce the physical stimulation sufficiently, however the film thickness is thin, while less than 8 g/mm is apt to cause breakage of the plasters on or during the application and they cannot be used with high reliability.

As for the film elongation, over 150%, respectively, in the two directions intersecting substantially at right angle give the handleability damage, while less than 30% increases the physical stimulation and raises the frequency in film breakage on application.

Further, according to the investigation results by the present inventors, a film having the elongation ratio of 1.0 to 5.0 in said two directions (wherein the smaller elongation is used as the denominator, when the elongations are different in the two directions), preferably of 1.0 to 3.0, is preferably used to improve the application feeling. The films of over 5.0 ratio, namely of extremely low elongation in one direction, cannot follow the expansion and contraction of the skin satisfactorily to cause several problems or troubles, for example, making the application feeling unpleasant because of skin stretched, making the film easier peelable and damageable, thus being concluded to be unsuitable.

Accordingly, the film of the invention has 0.5 to 4.9 μm thickness, 8 to 85 g/mm strengths, respectively, in the two directions intersecting substantially at right angle, 30 to 150 % elongations, respectively, in the two substantially rectangular directions, and 1.0 to 5.0 elongation ratio in said two directions (wherein the smaller elongation is used as the denominator, when the ratios of the elongations in the two directions are different). Particularly, the film is preferred, which has less than 3.5 μm, more preferably 0.5 to 2.0 μm thickness, 8 to 85 g/mm strength, 45 to 150 % elongations and 1.0 to 3.0 elongation ratio.

The strength in the present invention shows a value which is obtained by measuring the maximum load at break of a film according to the measurement of tensile strength of plasters in Japanese Pharmacopoeia and turning the result into the load per unit length (g/mm) and the elongation means the elongation at break (%). The two directions intersecting substantially at right angle means so-called lengthwise direction and widthwise direction.

backing sheet has the role to improve the handleability. When the plaster of the invention comprises the film layer (a) and the film layer (b), the former film plays a role of backing the adhesive layer (a), as preventing the skin from erupting rash, while the latter improves the handleability.

The plaster according to the present invention has the adhesive layer (a) which is composed of an adhesive containing transdermally absorbable drugs and is spread on one surface of the above-stated film layer in 2 to 60 µm thickness.

Generally, the adhesive layer plays a role of retaining a needed amount of the principal ingredient, namely transdermally absorbable drugs, and stabilizing the application of the plaster to the skin, but a various kinds of solvents remaining in the adhesive layer after the layer formation become one of the major causes of rash eruption. Accordingly, if the adhesive layer can play these roles satisfactorily, its layer thickness is preferably as thin as possible because of easy removal of the remaining solvents and economic reasons.

In the present invention, because the above-stated specific films are used as the film layer, the thickness of the adhesive layer more than 2 µm can extremely reduce the peeling of the plaster during the application, and less than 60 µm, preferably less than 30 µm, can reduce skin rash caused by the remaining solvents because the remaining solvents themselves can be reduced to less than 100 ppm, more preferably less than 50 ppm as required, and stabilize the application with a needed amount of the drug retained.

As the adhesive including the drugs used in the present invention, a usual adhesive is used and can be selected from, for example, a rubber viscous composition such as silicone rubber, polyisoprene rubber, styrene-butadiene copolymer rubber, acryl rubber or natural rubber; a vinyl viscous composition such as a polyvinyl alcohol (PVA) or an ethylene-vinyl acetate copolymer; a viscous composition mainly containing, for example, a silicone adhesive, a polyurethane elastomer, polyester elastomer or polybutadiene elastomer; acrylic resin and the like. Particularly an acrylic resin is preferably used and, from the view points of more reduced skin irritation, proper tackiness and adhesion, high cohesion and high solvent resistance, an acrylic resin which is prepared by copolymerization of (1) at least 80 to 98 mole % of an alkyl (meth)acrylate in which the alkyl is of 4 or more carbon atoms and (2) 2 to 20 mole % of acrylic acid and/or methacrylic acid. The examples of alkyl (meth)acrylate whose alkyl group is of 4 or more carbon atoms are butyl (meth)-acrylate, amyl (meth)acrylate, hexyl (meth)acrylate, heptyl (meth)acrylate, octyl (meth)acrylate, nonyl (meth)acrylate, decyl (meth)acrylate, 2-ethylhexyl (meth)acrylate and the like. These adhesives may be used alone or in 2 or more combination.

As stated above, the plaster comprising the film layer specified in the present invention and the adhesive layer of a specified thickness containing transdermally absorbable drugs is an extremely thin laminated product and desires careful handling in some cases so that film damage, blocking between the adhesive layers (a) and (a) or the like may not occur.

In the plaster of the present invention, a backing sheet can be laminated via the adhesive layer (b) onto said film layer by adhering the sheet partially or entirely to the one face of the film layer opposite to the other surface on which the adhesive layer (a) is laminated, with an adhesion force of higher than 3 g/12 mm.

Such backing sheet may be left on the plaster as it is, but can be also used for leaving the film layer and the adhesive layer (a) on human skin by applying the plaster, then removing the sheet therefrom.

The lamination of such a backing sheet decreases the curling of the plaster and the damages and facilitates the application by patients themselves.

The backing sheet which can be used in the present invention is films, nonwoven fabrics, paper-like substance and/or cloth such as woven or knitted fabrics or their combination. In the case where the backing sheet of the present invention is removed after application of the plaster, there is no specific limitation to these materials, but in the case where the material remains laminated after application, the sheet is preferably flexible and suitably stretchable without disturbance of moisture permeation of the film layer so that the plaster can prevent skin rash and follow the expansion and contraction of the skin.

When the backing sheet of the present invention is film, the base material for such film are, for example, polyolefins such as polyethylene or polypropylene; polyesters such as polyethylene terephthalate or polyethylene naphthalate; polyamides such as nylon 6 or nylon 66; ethylene-vinyl acetate copolymer, polyvinyl alcohol and the like. Among the backing sheet materials made of these films, microporous films are preferred because the moisture permeability of the film layer of the invention is not disturbed.

Particularly, the films having the thickness, strength and elongation which are specified in the present invention are preferred, further the polyester films containing the above-defined amount of solid fine particles of the above-defined particle sizes are more particularly preferred.

US006156335A

United States Patent [19]

Rovati et al.

[11] Patent Number: 6,156,335

[45] Date of Patent: Dec. 5, 2000

[54] **PREPARATION WITH AN ACRYLIC-BASED, ADHESIVE COPOLYMERIC MATRIX FOR THE TRANSDERMAL DELIVERY OF ESTRADIOL**

[75] Inventors: **Luigi Rovati; Lucio Rovati; Francesco Makovec,** all of Monza, Italy; **Günter Cordes,** *Leichlingen; Wilfried Fischer,* Bad Tölz, both of Germany

[73] Assignee: **Rotta Research Laboratorium S.p.A.,** Monza, Italy

[21] Appl. No.: **08/244,132**

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PCT Pub. Date: **Jun. 10, 1993**

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[51] **Int. Cl.**[7] **A61F 13/02**

[52] **U.S. Cl.** **424/448**; 424/449

[58] **Field of Search** 424/448, 449

[56] **References Cited**

U.S. PATENT DOCUMENTS

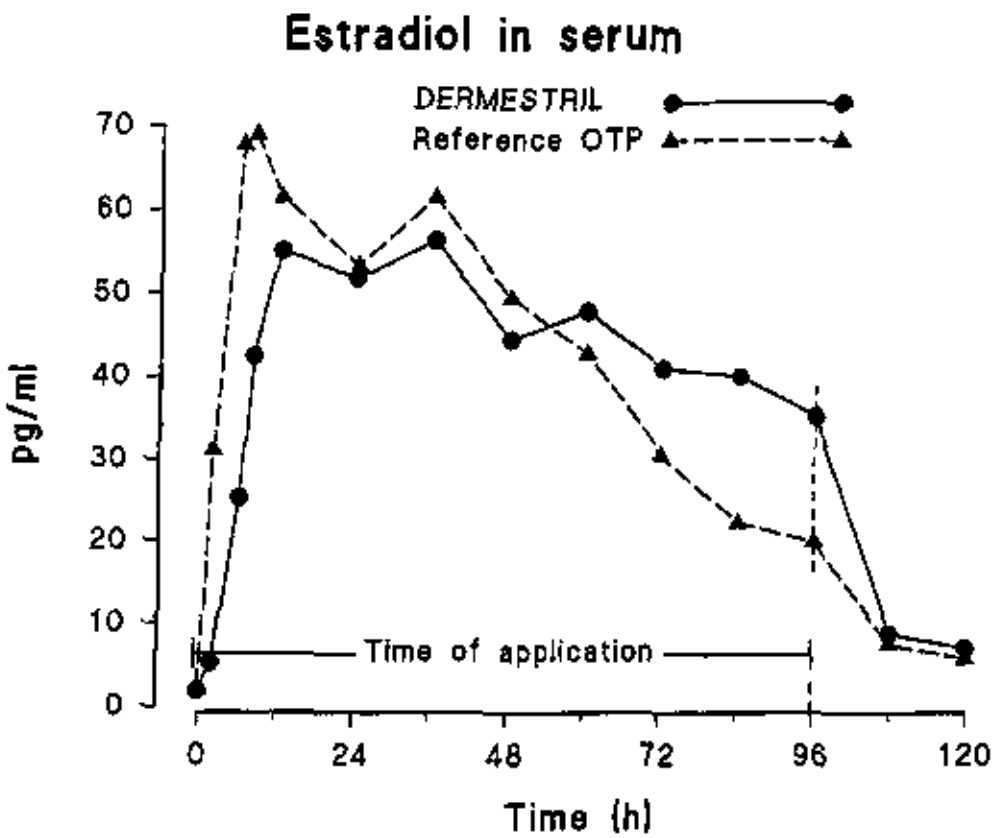
4,906,475	3/1990	Kim	424/449
4,994,267	2/1991	Sablotsky	424/78

Primary Examiner—Thurman K. Page
Assistant Examiner—Isis Ghali
Attorney, Agent, or Firm—Pitney, Hardin, Kipp & Szuch, LLP

[57] **ABSTRACT**

The invention is represented by a transdermal medicated patch for the extended release of 17β-estradiol to the skin. The transdermal patch is formed by an outer covering, a matrix containing from 1% to 5% (w/w) 17β-estradiol, and a protective liner which is removed before use. The matrix is formed of pressure-sensitive adhesive acrylic copolymers, in which the active ingredient is dissolved or dispersed. The acrylic copolymers are obtained by radical copolymerization of 2-ethylhexyl acrylate, methyl acrylate, acrylic acid, vinyl acetate, hydroxyethyl acrylate or a mixture thereof. Optionally quantities of less than 0.5% (w/w) of other substances may be added.

8 Claims, 1 Drawing Sheet



PREPARATION WITH AN ACRYLIC-BASED, ADHESIVE COPOLYMERIC MATRIX FOR THE TRANSDERMAL DELIVERY OF ESTRADIOL

This application is a 371 of PCT/EP92/02704 filed Nov. 24, 1992.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to pharmaceutical delivery systems and more particularly to preparations for transdermal administration of estradiol.

2. Brief Description of Related Art

Introduction

Ovarian secretion of 17β-estradiol is lacking in postmenopausal women. In many women this physiological phenomenon induces progressive hypotrophy of the urogenital system as well as characteristic vasomotor symptoms, often followed by osteoporosis affecting particularly the vertebral column.

These *climacteric symptoms* can be prevented by an exogenous estrogen-based hormone replacement therapy. However, the oral administration of 17β-estradiol (hereinafter referred to as "estradiol") has problems, since the hormone is modified in the intestine and in the liver and produces high blood levels of its metabolites, such as estradiol sulfate, estrone and estrone sulfate which may accumulate in the organism, *if the administration is prolonged*. One of the undesired effects of the oral administration of estradiol is the increased synthesis by the liver of proteins, including the substrate of renin, with a possible consequent increase in arterial pressure.

The oral route can be bypassed by the transdermal administration of estradiol, which delivers the active ingredient directly into the systemic circulation. However, the diffusion of estradiol through the skin is difficult. To improve it, a special transdermal systems must be developed that can enhance the absorption of estradiol, such as an especially designed, estradiol containing, pressure sensitive adhesive patch, i.e. an Estradiol Transdermal Patch (hereinafter *referred to as "OTP"*).

The OTP represents a considerable therapeutic progress, over the conventional oral administration, since it avoids the "first pass effect" and delivers estradiol directly into the systemic circulation in quantities comparable to those which are physiologically produced by the ovaries.

A widely used OTP is represented by a reservoir in which estradiol is dissolved in ethanol gelatinised with, for example, hydroxypropyl cellulose. The reservoir is contained by a membrane, through which estradiol diffuses to the skin. In this system the membrane becomes the diffusion-rate limiting component of the OTP, as it is the case of an OTP already on the market.

Various patents have been applied for in connection with OTPs provided with diffusion-rate limiting membranes and the use of solvents such as ethanol, alone or in mixture, for dissolving or dispersing estradiol in the drug reservoir, and for improving its absorption through the skin. Thus, for example, GB patent 2158 355 describes the use of a combination of propylene glycol and glycerol in variable ratios; U.S. Pat. No. 4,658,343 described the use of polyethylene glycol monolaurate as agent for improving the skin-penetration of estradiol ("enhancer"), and EP patent 0 147 146 describes the use of methanol for the same purpose.

The transdermal systems based on a diffusion-rate limiting membranes involve various problems. For instance any small hole in the membrane causes inevitably the breakdown of the whole transdermal system.

These systems often require the use of absorption enhancers, which ultimately act by disrupting the intercellular connections of the superficial layers of the skin. This effect increase the permeability of the skin to the active ingredient but often causes skin irritation or sensitisation. The absorption enhancers may also be absorbed through the skin causing unwanted systemic side effects.

In general the systems with diffusion-rate limiting membranes do not allow to achieve constant release rates of the active ingredient, which is disadvantageous since usually the therapeutic treatments require that the active ingredient is released over a prolonged period of time.

Another possible structure of transdermal systems is that of the so-called "monolithic" systems. In these systems the active ingredient is dissolved or dispersed in a "matrix", which becomes the drug reservoir and contains also the pressure sensitive adhesives which assure the adhesion of the transdermal system to the skin. In these systems the release of the active ingredient from the matrix takes place by diffusion, which is driven by the chemical potential of the active ingredient resulting from the concentration gradient and the thermodynamic properties of the components of the matrix.

Many patents have recently been published on OTP based on matrix systems.

Thus, for example, EP patent 0 379 045 describes an OTP in which the system contains 2% estradiol dispersed in a matrix constituted by an acrylic polymer, an ethylene/vinyl acetate copolymer, gums and adhesives. Lecithin, butylene diglycol and propylene diglycol are used as absorption enhancers.

EP patent 0 371 496 describes an OTP in which estradiol is dispersed in a matrix constituted by acrylic polymers, vinyl acetate, gums and silicone, containing also various enhancers such as oleic acid, ethanol and glycols.

JP patent 02 196 714 described the use of a matrix constituted by a copolymer based on 2-ethylhexyl acrylate and vinyl pyrrolidone, and absorption enhancers consisting of lactic esters formed by C_2–C_{20} alcohols.

EP patent 0 341 202 describes the use of methyl pyrrolidone and eucalyptol as enhancers.

A last example is EP-A-88 394.3, which describes a transdermal patch containing as enhancers polysorbate 80, polyoxyethylene ethers and aliphatic alcohols with high molecular weight.

The use of enhancers to improve the absorption of estradiol through the skin is clear from the quoted patent literature.

In order to avoid the drawbacks connected with the enhancers (skin irritation, systemic side effects) the absorption of the active ingredient can be improved by increasing its thermodynamic activity in the matrix, for example by increasing its concentration. This, however, often leads to supersaturated matrices due to the limited solubility of the active ingredients. In order to stabilise the supersaturation, additives must be included in the matrix (cfr. for example, DE-C-3 933 460). Nevertheless the systems remain in *metastable conditions and the incorporated active ingredi*ents may crystallise during time, decreasing their thermodynamic activity, which is the driving force for diffusion through the skin. The physical stability of these systems is

therefore not predictable. The crystallisation of the active ingredients may also change the adhesive properties of the transdermal patch, jeopardising the adhesion of the matrix to the skin and the reliable drug absorption.

The matrix of "monolithic" transdermal patches must therefore comply with several prerequisites. In fact the active ingredient must be provided by a notable thermodynamic potential and nevertheless it must be stable in time. Since the matrix contains also the pressure sensitive adhesives which stick the patch to the skin, it must have good "tack" properties.

Nevertheless the patch must be easily removable from the skin after use, and during this procedure the matrix must remain attached to the outer covering and not to the skin. The adhesives must not "creep", because in this case the patch would stick to the container. As already pointed out, the matrix should not contain absorption enhancers, in order to prevent skin irritation or sensitisation. In addition, obviously, all the components of the matrix must be well tolerated by the skin, even after repeated and prolonged applications of the patches.

SUMMARY OF THE INVENTION

Several formulations were investigated in order to optimize the matrix of the OTP described in this invention. Most formulations were based on acrylic copolymers, to which different substances were added in order to improve the adhesive quality of the matrix, for example hydroabiethylalochol, glycerylester of hydrated collophonium, pentaester of hydrated collophonium, methylester of partially hydrated collophonium, or α-methylstyrol/styrol copolymers. All these formulations had to be discarded because of crystallisation of the active ingredient or impairment of its release rate.

Based on this experience a monolithic matrix was developed which represents a definite improvement over the present state of the art, since it eliminates or reduces to a minimum the main disadvantages of the transdermal patches known up to now and previously described. In fact the new invention provides a system for the transdermal administration of estradiol which is well tolerated, is stable, is effective, prevents the crystallisation of the active ingredient in the matrix, ensures adequate and extended levels of the active ingredient in blood, and has very good tack and adhesive properties.

BRIEF DESCRIPTION OF THE DRAWING

The accompanying drawing is a graph showing a comparison of the averages of serum estradiol levels in 20 postmenopausal women during the application for 96 hours of an OTP of the invention (Dermestril) or a reference OTP.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

According to the invention the above mentioned features were provided by a transdermal patch for the extended release of 17β-estradiol onto the skin consisting of:

a) an outer covering (backing foil);

b) pressure-sensitive adhesive copolymers constituting the matrix in which the active ingredient is dissolved or dispersed (drug reservoir);

c) a protective liner which is removed at the time of use;

The invention describes a new transdermal patch for the extended release of estradiol to the skin, in which the active ingredient is dissolved or dispersed in a suitable pressure-sensitive adhesive copolymeric matrix, and which surprisingly avoids the need of substances to improve the absorption of the drug through the skin (enhancers), or of supersaturated solutions of the active ingredient, thus preventing problems of skin compatibility and of stability of the whole system.

A specific embodiment concerns a transdermal medicated patch which is characterised in that the components of the adhesive copolymers are obtained by radical polymerization of 2-ethylhexyl acrylate, methyl acrylate, acrylic acid, vinyl acetate, hydroxyethyl acrylate or mixtures thereof, possibly with quantities of less than 0.5% (w/w) of other additives in the adhesive copolymers.

A specific embodiment of the invention concerns a transdermal medicated patch in which the adhesive copolymers of the matrix are obtained by radical polymerization of (w/w of the matrix) about 50% to 70% (preferably 55% to 65% and especially 61% to 64%) 2-ethylhexyl acrylate, about 20% to 40% (preferably 24% to 32% and especially 25% to 28%) methyl acrylate, about 2% to 8% (preferably 3% to 5% and especially 4% to 5%) acrylic acid, about 2% to 10% (preferably 3% to 7% and especially 4% to 5%) vinyl acetate, and about 0.5% to 3% (preferably 0.7% to 1.5% and especially about 1%) hydroxyethyl acrylate.

Small quantities of less than 0.5% of other substances may also be used to improve the adhesive properties and the strength of the matrix.

According to the invention no cross-linker is used in the adhesive copolymer, such as titanium acetylacetonate, as it is suggested by the prior art, in order to avoid creeping of the adhesives onto the removable protective liner and therefore sticking of the patch to its container. The problem of creeping is surprisingly avoided in the invention by using the described copolymers obtained by radical polymerization.

The OTP according to the invention is characterized by a content of 17β-estradiol from 1% to 5%, preferably 2.0% to 2.5%, (w/w) of the weight of the adhesive copolymers.

A specific embodiment of the invention concerns a transdermal patch which contains about 4 mg 17β-estradiol per 18 to 20 cm^2 of patch area.

A specific embodiment of the invention of the transdermal patch comprises an outer covering of suitable protective materials, which forms the external backing foil of the patch and is constituted by a foil of thin, flexible and water-impermeable material, preferably selected from the group of polyester, polyurethane, polyethylene and/or polyvinyl chloride. Finally, the transdermal patch according to the invention comprises a removable protective liner, preferably constituted by a foil of paper or polyester which is preferably silicone-coated on one or both sides and that is easily removed at the time of use without impairing the transdermal patch.

According to the additional embodiment of the invention, a process is described for the production of a transdermal patch for the extended release of 17β-estradiol to the skin, which is characterized in that pressure-sensitive adhesive copolymers containing 17β-estradiol as active ingredient are spread onto a removable protective liner and then covered by another liner which becomes the outer covering.

Alternatively the pressure-sensitive adhesive copolymers containing 17β-estradiol are spread on a water-impermeable foil which becomes the outer covering, and are then covered by the protected liner.

Still alternatively the pressure-sensitive adhesive copolymers containing 17β-estradiol are spread on an intermediate

The results clearly show that formulations No. 1 to 4 and particularly No. 1 exhibit the properties required for the matrix of a "monolithic" transdermal patch. Conversely other formulations, which are here listed as Comparative Examples 1 to 7, had disadvantages, for instance discolouration *(formulations No. 6 to 10), unacceptable skin compatibility* (formulation No. 5), or unacceptable tack properties (formulations No. 6, 7, 9 and 11).

TABLE 3

Percentage of monomers in the acrylic copolymers and other substances in different formulations. Properties of the matrix obtained with these copolymers.

	Examples				Comparative Examples						
Formulation No.	2 1	3 2	4 3	5 4	1 5	2 6	3 7	4 8	5 9	6 10	7 11
Substances											
2-EHA	62.6	61.5	63.4	57.6	66.9	62.2	63.1	64.0	59.2	56.6	64.2
HA	26.4	33.0	21.5	19.5	0.0	26.4	21.5	16.5	25.1	24.0	16.5
VA	5.6	0.0	9.8	8.9	28.0	5.6	9.8	14.0	5.3	5.1	14.0
AA	4.4	5.5	3.6	3.3	0.0	4.3	3.5	2.7	4.1	3.9	2.8
GMA	0.0	0.0	0.1	0.1	0.2	0.1	0.1	0.1	0.0	0.0	0.1
HEA	1.0	0.0	1.8	1.6	5.0	1.0	1.8	2.5	1.0	0.9	2.5
TA	0.0	0.0	0.0	0.0	0.0	0.4	0.3	0.3	0.4	0.4	0.0
HR	0.0	0.0	0.0	9.1	0.0	0.0	0.0	0.0	4.8	9.1	0.0
Features											
Extrud. solub.	G	G	G	G	G	G	G	G	G	G	G
Discoloration	–	–	–	–	–	+	+	+	+	+	–
Tack on skin	G	G	M	G	G	B	B	G	B	G	S
Skin compat.	G	M	M	M	B	G	G	M	G	M	G

Legends: B = Bad; M = Medium; G = Good; S = Too strong; + = Present; – = Absent
Substances:
2-EHA = 2-Ethylhexylacrylate
HA = Methylacrylate
VA = Vinyl acetate
AA = Acrylic acid
GMA = Glycidylmethacrylate
HEA = Hydroxyethylacrylate
TA = Titanium acetylacetonate
HR = Hydrocarbon resin

What is claimed is:

1. A transdermal medicated patch for the extended release of 17β-estradiol to the skin, consisting of pressure-sensitive adhesive copolymers in which the active ingredient is dissolved or dispersed, supported by a water-impermeable foil and covered by a protective liner which is removed at the time of use, wherein the pressure-sensitive adhesive copolymers are obtained by radical copolymerization of

55 to 65 weight %	2-ethylhexyl acrylate
24 to 32 weight %	methyl acrylate
3 to 5 weight %	acrylic acid
3 to 7 weight %	vinyl acetate and
0.7 to 1.5 weight %	hydroxyethyl acrylate.

2. A transdermal medicated patch according to claim 1, characterized by a content of 17β-estradiol from 1% to 5% by weight of the adhesive copolymers.

3. A transdermal medicated patch according to claim 1, characterized by a content of about 4 mg 17β-estradiol per 18 to 20 cm^2 of patch area.

4. A transdermal medicated patch according to claim 1 characterized in that the patch comprises a removable protective liner constituted by a sheet of paper.

5. A transdermal patch according to claim 1, characterized by an outer covering constituted by a foil of a water-impermeable material, selected from the group of polyester, polyurethane, polyethylene and/or polyvinyl chloride materials.

6. A process for the production of a transdermal medicated patch according to claim 1, characterized in that pressure-*sensitive adhesive copolymers containing* 17β-estradiol as active ingredient are spread onto a removable protective liner and then covered by an outer covering.

7. A process for the production of a transdermal medicated patch according to claim 6,, which comprises:

dissolving pressure-sensitive adhesive copolymers in an organic solvent to form an adhesive mixture;

dissolving - 17β-estradiol, in the adhesive mixture by stirring at a concentration from 1% to 5% by weight of the dry weight of the pressure-sensitive adhesive *copolymers; and*

spreading the solution onto a removable protective liner.

8. A transdermal medicated patch according to claim 1, wherein the pressure-sensitive adhesive copolymers are obtained by radical copolymerization of (w/w or the matrix)

61 to 64%	2-ethylhexyl acrylate
25 to 28%	methyl acrylate
4 to 5%	acrylic acid
4 to 5%	vinyl acetate and
about 1%	hydroxyethyl acrylate. ..

* * * * *

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
GERMÁN CASTILLO GRAU
(Apoderado)

ASUNTO	Radicación	05077560
	Trámite	002
	Evento	*001*
	Actuación	430
	Oficio	
	Folios	013 8736

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

Vía Nacional [ ]

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

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

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

1. Documentos estudiados:

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

1.2. Reivindicaciones: 1 a 29 (Folios: 36 a 39) como se radicó inicialmente. Modificadas 1 a 20 (Folios: *113 y 114*).

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

2. Análisis de la Prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. **Objeto de la invención:**

La presente solicitud se titula: "Granisetrón transdérmico".

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

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

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

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

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 20 (folios: 113 y 114): Un parche adhesivo apropiado para la administración en donde el adhesivo es un adhesivo acrílico que contiene moléculas no ácidas de hidroxilo, con una cantidad fisiológicamente efectiva de granisetrón cargada en el adhesivo.

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

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

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

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

No se presentaron oposiciones al objeto reivindicado.

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

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

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

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

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

Nº	Documento	Título	Fecha de Publicación
D1	WO 98/53815	Transdermal drug delivery device for the delivery of tropisetron or granisetron	3 de diciembre de 1998
D2	WO 98/37111	Transdermal pressure sensitive adhesive drug delivery system and pressure sensitive adhesive used therein	27 de agosto de 1998
D3	EP 0484543	Plaster	13 de mayo de 1992
D4	US 6156335	Preparation with an acrylic-based, adhesive copolymeric matrix for the transdermal delivery of estradiol	5 de diciembre de 2000

6. Análisis de patentabilidad (artículo 14 D486)

6.1. Nivel inventivo *(artículo18 D486)*

La presente Solicitud de Patente reivindica lo siguiente: Un parche adhesivo apropiado para la administración en donde el adhesivo es un adhesivo acrílico que contiene moléculas no ácidas de hidroxilo, con una cantidad fisiológicamente efectiva de granisetrón cargada en el adhesivo.

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

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

La anterioridad EP 0484543 (folios: 115 a 119) menciona una preparación transdérmica para administrar fármacos y que tiene un adhesivo acrílico como por ejemplo el metacrilato de 2-hexilo, y otros acrilatos relacionados. Este documento es del año 1992 y ya mostraba las ventajas de las formas transdérmicas para administración de fármacos.

El documento US 6156335 (folios: 120 a 123) se relaciona con un parche transdérmico para administración de 17β-estradiol. Este parche es de matriz y tiene adhesivo acrílico conformado por la copolimerización de acrílato de 2-etilhexilo, acrilato de metilo, ácido acrílico, acetato de vinilo y acrilato de hidroxietilo. En este documento también se explican las desventajas de emplear intensificadores de absorción (irritación en la piel, efectos colaterales, etc.).

Estos documentos revelan la existencia y amplio uso de formas transdérmicas tipo parches transdérmicos que emplean como adhesivo un polímero derivado de ácido acrílico como por ejemplo metacrilatos y acrilatos de hidroxipropilo, hidroxietilo e hidroximetilo, para la liberación de antieméticos tipo granisetrón o fármacos que también son antagonistas de $5HT_3$ como el tropisetrón. También se evidencia el uso de parches transdérmicos de matriz. También estos documentos sugieren que los parches transdérmicos son de liberación sostenida para fármacos que requieran que

se liberen durante periodos largos o tratamiento a largo plazo.

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

Las reivindicaciones 1 a 20 de esta solicitud no mencionan una característica que conceda un efecto inesperado o especial a los parches transdérmicos, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia.

Además, puesto que D1, D2, D3, D4 divulgaban previamente parches transdérmicos (folios: 84 a 93, 115 a 123), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto de esta solicitud parches transdérmicos de granisetrón; de manera que para una persona medianamente versada en la materia sería obvio emplear estos documentos. Por lo cual puede no haber Nivel Inventivo.

7. **Conclusión:**

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	EP 1044684	1 a 20	Nivel Inventivo
D2	US 6136807	1 a 20	Nivel Inventivo
D3	WO 98/53815	1 a 20	Nivel Inventivo
D4	WO 98/37111	1 a 20	Nivel Inventivo

D3

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

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

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

El anterior requerimiento fue notificado por fijación en lista, de fecha 31 JUL. 2009

CONCEPTO TÉCNICO No. 2544	**EXAMINADOR TÉCNICO** Código No. 202005