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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF. **Expediente 04-129-358**

TÍTULO SOLICITADO: **"UN AGENTE PARA HACER CÁPSULAS DE GELATINA BLANDA Y LAS CÁPSULAS ASÍ OBTENIDAS".**

PUBLICACIÓN: **Gaceta 557 de 31-16-2005, número de publicación 657**

PRIORIDAD: **JP 2002-167041 de 07-06-2002**

SOLICITANTE: **R. P. SCHERER TECHNOLOGIES INC.**

APODERADO: **LUIS FELIPE CASTILLO GIBSONE**

TRÁMITE: **SUSTENTACIÓN DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, identificado como aparece al pie de mi firma, reconocido apoderado del opositor en el trámite de la referencia, estando dentro de los términos de la prórroga solicitada, por medio del presente escrito me permito ratificar y sustentar los argumentos del escrito de oposición, también radicado dentro del plazo de ley ante esa entidad.

I. RATIFICACIÓN

Reitero a su Despacho la solicitud de negar el beneficio patentario para la totalidad de las reivindicaciones contenidas en el expediente en referencia, por los argumentos que fueron expuestos en el escrito de oposición del 27 de enero de 2006.

En efecto, es evidente que en el estado del arte ya se encontraban algunos documentos que demuestran la falta de nivel inventivo de la solicitud en trámite

puesto que la combinación de las anterioridades mencionadas y lo contenido en la solicitud colombiana revelan en ambos casos:

- Cápsulas de gelatina blanda masticables;
- Cápsulas que tienen una capa o cáscara que comprende gelatina, un plastificante como glicerina o Sorbitol y un agente adhesión que bien puede ser un almidón y que además contiene la cápsula de gelatina blanda que posee el material activo por llamarlo de alguna manera.

Además, de la lectura detallada de la materia revelada en las anterioridades mencionadas en el escrito de oposición podemos abstraer que, a través de los años se ha venido trabajando en el perfeccionamiento de la formulación y elaboración de cápsulas de gelatina blanda por lo que se han ido haciendo variaciones en la composición y se han incluido nuevos elementos a la misma, lo que demuestra que, las supuestas bondades ahora descritas en la solicitud colombiana en trámite como son: Textura excelente y gusto al ser masticadas, no presencia de residuos insolubles en la boca y excelentes características de almacenamiento, no son más que el producto de el trabajo que ejerce un formulador en su trabajo rutinario.

II. COMPLEMENTO DE INFORMACIÓN

Como adición a lo expuesto en el punto precedente y en el escrito inicial de oposición, ruego al Despacho se sirva tener en cuenta de igual manera lo consignado a continuación:

A. La patente americana **US 6,319,518 B1 "COLON SELECTIVE DRUG DELIVERY COMPOSITION"** publicada el 20 de noviembre de 2001 y con prioridad KR 97-30767 de 03-07-1997 revela una composición que comprende gelatina y un polisacárido el cual es degradable por unan enzima colónica y, opcionalmente, con un aldehído y/o un ión metálico polivalente y/o una polisacárido adicional que no se degrada o desintegra en el tracto gastrointestinal alto y que en consecuencia, permite que la sustancia activa pueda ser entregada selectivamente y liberada con eficacia en el colon.

Además, describe que:

a) esta composición puede ser presentada en forma de cápsula blanda por o mediante la explotación del fenómeno de que la transición de sol-gel de gelatina ocurre en una temperatura en los límites de 40°C a 50°C.
b) La composición para la producción de una cápsula blanda contiene entre 50 y 99% de **gelatina**; entre 0.1 y 50% de pectinato (polisacárido) y, opcionalmente entre 0 y 45% de dextrano (Polisacárido); además contiene un exceso de gelatina cantidad suficiente para inducir la cambio de gel-sol que facilita el proceso de preparación y puede contener un **plastificante** en cantidades entre 5 y 100%.

Teniendo en cuenta esto y retomando lo revelado en la solicitud colombiana, es decir:

- Un agente de cápsula de gelatina blanda que comprende una gelatina que tiene una temperatura de transición sol-gel en una solución acuosa de 10% de no más de 22°C y una temperatura de transición sol-gel en una solución acuosa de 30% por peso de no más de 32°C, un plastificante y un agente antiadhesión.
- Una cápsula de gelatina blanda que comprende una concha de gelatina blanda que comprende entre 36 y 47% por peso de **gelatina**, aproximadamente 45% por peso de **plastificante** y entre 4 y 16% del agente antiadhesión.

Podemos ver de manera general que en las dos solicitudes se hace provecho del estado de transición sol-gel que puede tener la gelatina en la preparación de cápsulas blandas de gelatina a una temperatura dada y también es importante resaltar que en las dos solicitudes dichas cápsulas comprenden entre otros componentes Gelatina y un plastificante.

Si bien es cierto las temperaturas de transición y las proporciones de los ingredientes que conforman las cápsulas blandas reivindicadas en uno y otro documento no son los mismos, no lo es menos que la solicitud colombiana carece de nivel inventivo si se tiene en cuenta que la anterioridad mencionada revelaba cápsulas blandas fabricadas sobre la base del aprovechamiento de la transición de sol-gel de la gelatina junto con excipientes adecuados dentro de la formulación y cuyo objetivo no es más que el de proporcionar una composición de buenas características que permita la correcta entrega del fármaco en el sitio estipulado.

De esa forma queda demostrado que la combinación de las revelaciones mencionadas en el escrito de oposición con este nuevo documento permitirían a una persona medianamente versada en la materia técnica derivar el objeto reivindicado en esta solicitud.

Por lo todo lo expuesto, reitero mi solicitud para que sea negada la solicitud en cuestión y como consecuencia de ello, se ordene el archivo del expediente debido al evidente incumplimiento de lo dispuesto en los artículos 14 y 18 de la Decisión 486 de 2000.

III. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, la siguiente:

- Patente americana US 6,319,518 B1 publicada el 20 de noviembre de 2001, columnas 5 a 8.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR
C.C. 79'152.473 de Usaquén
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US006319518B1

(12) **United States Patent**
Lee et al.

(10) **Patent No.: US 6,319,518 B1**
(45) **Date of Patent: *Nov. 20, 2001**

(54) **COLON SELECTIVE DRUG DELIVERY COMPOSITION**

(75) Inventors: **Seung-Seo Lee; Sung-Bum La; Chang-Baeg Lim; Sujung Lee; Bo-Youn Seo; Chaul-Min Pai**, all of Taejeon (KR)

(73) Assignee: **Sunyang Corporation** (KR)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/919,957**

(22) Filed: **Aug. 29, 1997**

(30) **Foreign Application Priority Data**

Jul. 3, 1997 (KR) 97-30767

(51) **Int. Cl.**[7] **A61K 9/22**; A61K 9/26; A61K 9/36; A61K 9/64

(52) **U.S. Cl.** **424/468**; 424/469; 424/478; 424/479; 424/964; 424/965; 424/460, 424/451

(58) **Field of Search** 424/464, 451, 424/456, 460, 461, 468, 469, 478, 479, 964, 965

(56) **References Cited**

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* cited by examiner

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(57) **ABSTRACT**

A composition comprising gelatin and a polysaccharide which is degradable by a colonic enzyme and, optionally, with an aldehyde and/or a polyvalent metal ion and/or an additional polysaccharide, which is not degraded or disintegrated in the upper gastrointestinal tract, thereby rendering the active substance loaded therein to be selectively delivered to the colon and to be effectively released in the colon.

13 Claims, 4 Drawing Sheets

chondroitin sulfate, polygalacturonic acid, tragacanth gum, arabic gum, and a mixture thereof. The polysaccharide may be employed in an amount ranging from 0.01 to 99.99% by weight, preferably 1 to 99% by weight of the composition.

A colonic disease such as ulcerative colitis and Crohn's disease may occur at various sites on the colon. The composition of the present invention comprising gelatin and the polysaccharide may release all of the active substance at the ascending colon and, therefore, may not deliver the active substance to the downstream region of the colon. In order to retard the active substance release, the composition may further comprise an additional component to provide the composition with a semi-interpenetrating polymer network or an interpenetrating polymer network, thus controlling the targeting site in the colon.

As the additional component, the composition of the present invention may comprise an aldehyde which can crosslink gelatin. Representative examples of the aldehyde may include formaldehyde, gluteraldehyde, terpene, cinnamaldehyde, aldose, and a mixture thereof. The aldehyde must be employed in the present invention in an amount less than 1% by weight.

The aldehyde used in the present invention reacts with an amino group of gelatin, not with a hydroxyl group of the polysaccharide, to form a semi-interpenetrating polymer network (SIPN) structure into which the polysaccharide molecules penetrate. The SIPN structure retards disintegration of the crosslinked gelatin but easily breaks down once the polysaccharide begins to be degraded. Thus, a colon selective drug delivery composition comprising an aldehyde crosslinked gelatin penetrated by non-crosslinked polysaccharide is suitable for delivering the active substance to a deep site in the colon.

The composition of the present invention may further comprise a polyvalent metal ion. Representative examples of the polyvalent metal ion include calcium, magnesium, strontium, barium, ferrous or ferric, zinc, aluminum, bismuth and zirconium ions, and a mixture thereof. Preferred polyvalent metal ion is a calcium ion. The polyvalent metal ion may be employed in an amount ranging from 0.0001 to 50% by weight, preferably 0.0001 to 20% by weight of the composition.

The polyvalent metal ion may be reacted with the carboxylic group of the polysaccharide as a role of crosslinking agent to form a polymer network. In case the polyvalent metal ion is incorporated with the molecules of the polysaccharide penetrating into the network of gelatin, the polysaccharide molecules are crosslinked with the polyvalent metal ion to form another network, the two polymer networks being interpenetrated, not crosslinked. The interpenetrating polymer network (IPN) structure thus produced has a higher mechanical strength than that of the SIPN formed by the addition of the aldehyde compound alone, and therefore, is not easily disintegrated at the start site of the colon and has a longer lag time than that of the SIPN structure. Accordingly, the colon selective drug delivery composition comprising a gelatin, a polysaccharide, an aldehyde and a polyvalent metal ion is suitable for delivering the active substance loaded therein to a deeper site in the colon.

The composition of the present invention may further comprise an additional colon-degradable polysaccharide which does not form a complex with gelatin and is degradable by colonic enzymes. When the additional polysaccharide is incorporated with the SIPN or IPN structure of the present invention, it forms another polymer chain which is not crosslinked with, but penetrates into the network, thus increasing the mechanical strength of the composition by strengthened hydrogen bonding and other intermolecular forces. In addition, the additional polysaccharide contained in the composition can function as another barrier to drug diffusion and render the composition unable to release the drug in the upper gastrointestinal tract. However, the composition is easily degraded in the colon because the additional polysaccharide is easily degraded by the colonic enzymes present in the colon and functions to shorten the lag time of the active substance in the colon, contrary to the function of an aldehyde and a polyvalent metal ion.

The additional polysaccharide may be neutral and representative examples thereof may includes dextran, amylose, arabinogalactan, arabinoxylan, cellulose, guar gum, laminarin, locust bean gum, pectin, starch, xylan, or a mixture thereof. The preferred additional polysaccharide is dextran. The additional polysaccharide may be employed in an amount ranging from 0.0001 to 45% by weight of the composition.

The delivery composition of the present invention may further comprise a pharmaceutically acceptable additive. Examples of such an additive may include a plasticizer, a pigment, a sweetening agent and the like. Representative examples of the plasticizer which may be employed to facilitate the formulation of the composition may include glycerin, triacetin, sorbitol, polyethylene glycol, propylene glycol, citrate, phthalate, castor oil and the like. The preferred plasticizers are glycerin, triacetin and sorbitol. The plasticizer may be employed in an amount ranging from 0.1 to 100 parts by weight, preferably 35 to 100 parts by weight, per a part by weight of the total polymeric components (dry weight basis) in the composition.

With the composition containing gelatin and a polysaccharide, and, optionally, an aldehyde and/or a polyvalent metal ion and/or an additional polysaccharide, as described above, in accordance with the present invention, various pharmaceutical formulations including coated tablets, capsules, pills and so on may be easily manufactured, and an active substance is easily loaded in the formulation. Therefore, the colon selective drug delivery composition of the present invention satisfies all the conditions required for a composition for selectively delivering a drug to the colon: (1) the composition is not degraded or disintegrated at the upper gastrointestinal tract, (2) the composition does not release the drug loaded therein at the upper gastrointestinal tract; (3) the composition releases the drug effectively at the targeting site of the colon; and (4) the composition is easy to formulate in a form suitable for loading the drug. Further, the delivery composition of the present invention also has a good processing property.

The present invention also provides a colon selective pharmaceutical composition comprising a biologically active substance and the inventive colon selective drug delivery composition as mentioned above.

Representative examples of the active substance which may be employed in the pharmaceutical composition of the present invention may include topical active drugs for the treatment of colon diseases, e.g., ulcerative colitis, Crohn's disease, hypersensitive colon symptom, colon cancer and constipation. Specifically, the active substance may include mesalazine, sulfasalazine, ibuprofen, prednisolone, dexamethasone, budesonide, beclomethasone, fluticasone, thioxocortal, hydrocortisone, cyclosporins, methotrexate, domperidone, 5-fluorouracil, bisacodyl, a dietary fiber, bifidobacteria and a mixture thereof. Further, the active substance may include a systemic active drug such as peptide or

protein, or an agent for the treatment of asthma, rheumatism, arthritis, calcium antagonist and the like; specifically, insulin, vasopressin, a growth hormone, a growth factor, a colony stimulating factor, calcitonin, immunoglobulins, diltiazem, verapamil, nifedipin, captopril, theophylline, naproxen and a mixture thereof. Also, the pharmaceutical composition of the present invention may include diagnostic reagents and nutrients as active substances. The active substance which may be used in the pharmaceutical composition of the present invention is not limited to those mentioned above.

The pharmaceutical composition of the present invention may be prepared by inserting a biologically active substance into a capsule made of the inventive delivery composition, or by coating any known pharmaceutical formulation with the inventive drug delivery composition. The pharmaceutical composition may be in the form of a capsule, a coated tablet, a coated pill, a coated seed, or a coated capsule.

When the delivery composition of the present invention is coated on a known pharmaceutical formulation, the coating process may be conveniently conducted by spraying the colon selective drug delivery composition of the present invention. The coating amount of the delivery composition of the present invention may range from 1 to 100 mg/cm^2, preferably from 20 to 50 mg/cm^2, of the surface area of the formulation.

In a preferred embodiment, the inventive delivery composition to be coated on a known pharmaceutical formulation may contain 0.1 to 99.9%, preferably 5 to 50% by weight, of gelatin and 0.1 to 99.9%, preferably 50 to 95% by weight, of a pectinate and, optionally, 0 to 99.9%, preferably 0 to 45% by weight of dextran on the basis of the weight of the composition. The delivery composition may further comprise a plasticizer in an amount ranging from 10 to 100% by weight based on the weight of the polymeric components.

The aldehyde and/or polyvalent metal ion which may be employed in the present invention as an additional component, may be applied on a pharmaceutical formulation coated with a coating composition containing no such additional components. The additional components may be applied by dipping the previously coated formulation into a solution containing the aldehyde and/or the polyvalent metal ion. Formaldehyde and gluteraldehyde are preferred for such an application and they may be employed in the form of 0.01 to 50 wt %, preferably 0.01 to 20 wt %, of an alcohol solution. The dipping process of the aldehyde compound may be carried out with stirring for a period ranging from 1 second to 60 minutes, preferably from 1 to 30 min. The polyvalent metal ion, which is employed to cross-link the polysaccharide, may be used in the form of an aqueous solution having a concentration of 0.01 to 99.9 wt %, preferably 0.1 to 30 wt %, and the dipping process thereof may be conducted for a period ranging from 1 min. to 72 hrs, preferably from 10 min. to 2 hrs.

Although the coated formulation is preferably dried by drying slowly at a relative humidity of less than 20% for 48 hours or longer, other drying procedures may also be used.

Alternatively, the aldehyde and/or polyvalent metal ion may be employed directly in the composition to be coated on the formulation. The aldehyde which may be employed directly in the coating composition is preferably terpene, cinnamaldehyde, or aldose.

Besides a coated capsule formulation, a capsule formulation may be prepared by, shaping the drug delivery composition of the present invention into a capsule and filling a biologically active substance into the capsule. The capsule may be a hard or soft capsule and may be prepared by using a pin molder or a rotary die. The capsule formulation has the advantage that more drugs having widely varying properties can be formulated than possible with other forms of formulation.

In another embodiment, a soft capsule may be prepared using the delivery composition of the present invention by exploiting the phenomenon that the sol-gel transition of gelatin occurs at a temperature ranging from 40 to 50° C. An example of a composition for the production of a soft capsule is one containing 0.1 to 99.9%, preferably 50 to 99.9%, by weight of gelatin and 0.1 to 99.9%, preferably 0.1 to 50%, by weight of pectinate and, optionally, 0 to 45% by weight of dextran. Preferably, the soft capsule composition contains an excess amount of gelatin sufficient to induce the gel-sol phase change which facilitates the processing step for the preparation, e.g., a rotary die. Further, the inventive soft capsule composition may contain a plasticizer in an amount of 5 to 100% by weight based on the total weight of the polymeric components in the composition.

A biologically active substance may be filled into a capsule in the form of an oily dispersion, powder, granules or pellets.

The pharmaceutical composition of the present invention is not limited to the above mentioned embodiments and modification and change may be made thereto by a person skilled in the art.

The following examples are only provided for the purposes of illustrating certain aspects of the present invention; they are not to be construed as limiting the scope of the present invention in any way.

EXAMPLE 1

Preparation of colon selective film composition CSC-1

Pectin (USP/200, Copenhagen Pectin, Denmark) was dissolved in water and the pH was adjusted to 7 by adding sodium carbonate and sodium chloride, followed by adding water thereto to obtain a 10 wt % pectin solutions. Gelatin (Kyungki Gelatin, Korea) was then added to the above solution in an amount of 20 wt % based on the dry weight of pectin, and the resulting solution was homogenized at 50° C. Glycerol was added thereto in an amount of 80 wt % based on the combined amount of pectin and gelatin. The resulting mixture was homogenized at 50° C. and cast into a film having a thickness of 0.1 mm on a silicone plate by using a casting blade. The film was then air-dried by 48 hours to obtain a gelatin/pectinate film, which was designated CSC-1.

EXAMPLE 2

Preparation of colon selective film composition CSC-2

CSC-1 obtained in Example 1 was immersed in an ethanol solution containing 3 wt % formaldehyde for 3 min., air-dried for 48 hours and cut into 1 cm×1 cm pieces. This aldehyde crosslinked gelatin/pectinate film was designated CSC-2.

EXAMPLE 3

Preparation of colon selective film composition CSC-3

CSC-2 prepared in Example 2 was soaked in a 10 wt % $CaCl_2$ solution for 2 hours, washed with distilled water,

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2020
Bogotá, D.C.,

Doctor:
Luis Felipe Castillo Gibsone
Apoderado

Oficio Nº: 6343

ASUNTO:

Radicación PCT Nº	04-129358
Trámite	011
Evento	379
Actuación	440
Folios	022

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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

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

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

09 JUN. 2006

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

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Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
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2020
Bogotá, D.C.,

Doctor:
Luis Felipe Castillo Gibsone
Apoderado

Oficio Nº: 6344

ASUNTO:

Radicación PCT Nº	04-129358
Trámite	011
Evento	379
Actuación	440
Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor Reinaldo Pinilla Moreno, en su calidad de apoderado de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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

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

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

09 JUN. 2006

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

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