Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-162306- -00004-0000
Fecha: 2013-05-30 13:09:03 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 36

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

X Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
☐ Esquema de Trazado de Circuitos Integrados

Número de expediente: 12 162.306

Solicitante: GELITA AG

Apoderado: LUZ CLEMENCIA DE PAEZ

Título de la Nueva Creación: COMPOSICIÓN DE ENCAPSULAMIENTO DE LIBERACIÓN RAPIDA

Gaceta: 663

2. Datos del Opositor

☐ Persona Natural X Persona Jurídica

PROCAPS S.A.S

Nombre o denominación /Razón social completa

WALTER TANAKA TATEKAWA

Nombre del representante legal

Documento de identificación: C.C. ☐ C.E. ☐ NIT X Otro ☐ Cuál _____

Número 890106527-5

Dirección. CALLE 80 78B 201 Ciudad BARRANQUILLA

Teléfono 055 3719900 Fax: _____ Correo electrónico _____

☐ **Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico**

3. Datos del representante o apoderado:

MORENO BOHORQUEZ ELIANA ISAURA	51.975.664	83823
Apellidos y Nombre	**Documento de identificación**	**Tarjeta profesional**

Dirección del representante		
CRA 13 119-95 OFICINA 104		
Dirección electrónica negocios@optimum-co.com	No. Fax (571)6121979	Número telefónico (571)2131213

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general:

4. Fundamentos de la oposición

Causal: Art14, 16, 18,20 y 30 de la decisión 486 de la CAN no cumple con los requisitos De patentabilidad.

Justificación: La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capitulo "fundamento de hecho".

Prórroga: **SI** ☐ **NO** ☐

5. Anexos

- ☑ Comprobante de pago de la tasa.
- ☑ Poder, si fuera el caso.
- ☑ Fundamentos de la oposición. Se anexan 7 folios (obligatorios indicar cuántos).
- ☑ Anexo de fundamentos de la oposición. Se anexan 25 folios (obligatorios indicar cuántos)
- ☑ Copias para traslado.
- ☐ Copia de la solicitud y sus anexos en formato magnético.

6. Firma	
Nombre del Firmante ELIANA ISAURA MORENO BOHORQUEZ	Firma
CC. 51.975.664	Tarjeta Profesional: 83823

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0052574

Bogotá D.C., Mayo 30 de 2013 - 12:08:31

RECIBIDO DE : PROCAPS S.A. NI 890.106.527

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	505990111	28/05/2013	975.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	1632 OPOSICION NUEVA CRACION / PRESENTACION	325.000.00	325.000.00
				$325.000.00

SON: **TRESCIENTOS VEINTICINCO MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-***-
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-162306- -00004-0000
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Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señor Director,

DIRECCIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 12 162306
Asunto	: Oposición a la solicitud de patente de Invención titulada *"COMPOSICION DE ENCAPSULAMIENTO DE LIBERACION RAPIDA"*
Solicitante	: GELITA AG.
Opositora	: PROCAPS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 663 del 01 DE MARZO DE 2013

Yo, *ELIANA ISAURA MORENO BOHÓRQUEZ,* abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.S** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada *"COMPOSICION DE ENCAPSULAMIENTO DE LIBERACION RAPIDA",* cuyo titular **GELITA AG ,** y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés

de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular MELOXICAM. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 19 de septiembre de 2012, reivindicando prioridad bajo la solicitud US20100306744P del 2010-02-22; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **N° 663 del 01 DE MARZO DE 2013**, cuya publicación internacional corresponde a la WO2011103436 del 2011-08-25.

2.2. La solicitud colombiana **12 162306** objeto de la presente oposición se refiere a una composición de encapsulamiento de liberación rápida la cual incluye un agente hidrosoluble de liberación rápida y una gelatina, donde la composición de encapsulamiento de liberación rápida puede incluir además un hidrolizado de gelatina. Y se refiere también a una composición de encapsulamiento de liberación rápida que incluye carbonato de calcio y una gelatina en la cual la composición tiene una proporción de masa del carbonato de calcio a la gelatina en un rango desde cerca de 1:1 hasta cerca de 1:20. Y finalmente menciona el método para manufacturar una composición de encapsulamiento de liberación rápida que puede incluir además la adición de un plastificante.

2.3. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la

fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: US2008275140 publicada el 06 de noviembre de 2008.
- D2: US4681765 publicada el 21 de julio de 1987.

2.4.Ahora bien, el documento D1, que se refiere a un procedimiento para hacer composiciones de gelatina hidrolizada y de gelatina hidrolizada de bajo peso molecular, enseña una composición de encapsulación de liberación rápida (párrafos [0006), [0047), [0067) - [0068) - La "composición de encapsulamiento de liberación rápida" es la cápsula de gelatina dura o blanda que se desintegra rápidamente liberando de este modo un medicamento) que comprende un componente de gelatina en el que la composición de encapsulación de liberación rápida se utiliza en la fabricación de un producto farmacéutico de cápsula dura o blanda en donde las cápsulas de gelatina proporcionan un método conveniente y eficaz para administrar por vía oral un fármaco porque las cápsulas de gelatina se desintegran rápidamente después de la exposición al contenido de ácido del estómago, liberando así el fármaco en el cuerpo.

2.5.El documento D2, que se refiere a capsulas de gelatina de liberación rápida de Triamtereno para su uso antihipertensivo una vez al día, revela de manera especial una composición de encapsulación de liberación rápida que comprende un componente de gelatina en donde la composición de encapsulación de liberación rápida encapsula un agente de liberación rápida insoluble en agua. El mismo documento D2 revela de manera especial que el agente "insoluble en agua de liberación rápida es carbonato de calcio y enseña que la composición de encapsulación de liberación rápida se utiliza para hacer una dosificación farmacéutica en forma de cápsula. Así entonces como lo evidencian dichos documentos D1 y D2, la solicitud objeto de la presente oposición carece evidentemente de altura inventiva.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 en combinación con D2 carece evidentemente de ALTURA INVENTIVA.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **12 162306** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.9. **CARENCIA DE ALTURA INVENTIVA**. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."*. A la fecha de prioridad, 22 de febrero de 2010, a partir del documento D1, en combinación con D2 un experto en la materia puede llegar de manera evidente a una composición de encapsulamiento de liberación rápida la cual incluye un agente hidrosoluble de liberación rápida y una gelatina, donde la composición de encapsulamiento de liberación rápida puede incluir además un hidrolizado de gelatina, y a una composición de encapsulamiento de liberación rápida que incluye carbonato de calcio y una gelatina en la cual la composición tiene una proporción de masa del carbonato de calcio a la gelatina en un rango desde cerca de 1:1 hasta cerca de 1:20. Y finalmente a un método para manufacturar una composición de encapsulamiento de liberación rápida que puede incluir además la adición de un plastificante, sobre lo cual busca protección en el capítulo reivindicatorio.

2.10. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la

Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*. La solicitud pretendida no cumple con uno de los tres requisitos de patentabilidad.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada *"COMPOSICION DE ENCAPSULAMIENTO DE LIBERACION RAPIDA"*, cuyo titular **GELITA AG ,** solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial **N° 663 del 01 DE MARZO DE 2013.**

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US2008275140 publicada el 06 de noviembre de 2008.
- D2: US4681765 publicada el 21 de julio de 1987.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Artículo 45 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.2. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: US2008275140 publicada el 06 de noviembre de 2008.
- D2: US4681765 publicada el 21 de julio de 1987.

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

6. NOTIFICACIONES

Para efectos de notificaciones que debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 Nº 119-95, Of. 104 de esta ciudad de Bogotá.

Señor director,

ELIANA ISAURA MORENO BOHÓRQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

ANEXO

US 20080275140A1

(19) United States

(12) Patent Application Publication

Babel et al.

(10) Pub. No.: US 2008/0275140 A1

(43) Pub. Date: Nov. 6, 2008

(54) PROCESS FOR MAKING A LOW MOLECULAR WEIGHT GELATINE HYDROLYSATE AND GELATINE HYDROLYSATE COMPOSITIONS

(75) Inventors: Wilfried Babel, Heidelberg (DE); John M. Dalphin, Sioux City, IA (US); Jon Keenan, Sioux City, IA (US); Jason D. Russell, Sioux City, IA (US)

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WASHINGTON, DC 20005-3960 (US)

(73) Assignee: GELITA AG, Eberbach (DE)

(21) Appl. No.: 11/908,503

(22) PCT Filed: May 31, 2006

(86) PCT No.: PCT/EP06/05179

§ 371 (c)(1),
(2), (4) Date: Nov. 14, 2007

Related U.S. Application Data

(63) Continuation of application No. 11/140,863, filed on May 31, 2005.

Publication Classification

(51) Int. Cl.
A61K 47/42 (2006.01)
C12P 21/06 (2006.01)
C07K 4/00 (2006.01)

(52) U.S. Cl. 514/774; 435/68.1; 530/300

(57) ABSTRACT

The present invention provides a process to make a gelatine hydrolysate, a gelatine hydrolysate, and gelatine compositions including gelatine hydrolysates. More specifically, the invention provides gelatine compositions having a reduced tendency to cross-link and improved dissolution properties.

PROCESS FOR MAKING A LOW MOLECULAR WEIGHT GELATINE HYDROLYSATE AND GELATINE HYDROLYSATE COMPOSITIONS

[0001] This application claims priority of U.S. Ser. No. 11/140,863 filed on May 31, 2005, which application is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention generally relates to a gelatine hydrolysate, a process for making the gelatine hydrolysate, and a composition comprising the gelatine hydrolysate. More specifically, the present invention provides a low molecular weight gelatine hydrolysate having a high primary amine content, to a process for making the gelatine hydrolysate, and to a gelatine composition including gelatine hydrolysate.

BACKGROUND OF THE INVENTION

[0003] Gelatine is manufactured by the denaturation of collagen contained in materials such as pig skin, cattle skin or hide, and animal bones. Like its parent protein, collagen, gelatine is defined by a distinctive structure comprising a unique blend of amino acids. Native collagen is a scleroprotein based on a polypeptide chain comprising approximately 1050 amino acids. Three of these polypeptide chains come together to form a triple helix. Supercomposition of several of these triple helices produces fibrils of collagen that are stabilized by cross-linking, hence forming a three-dimensional network structure. This particular structure renders collagen insoluble; it is then brought into soluble form by partial hydrolysis as gelatine or gelatine hydrolysate. The amino acid content of collagen and hence of gelatine, is about one third glycine and a further 22% proline and 4-hydroxyproline; the remaining 45% comprise 17 different amino acids. Gelatine has a particularly high content of acidic and basic amino acids. Of the acidic amino acids (glutamic acid and aspartic acid), variable amounts are present in the amide form as glutamine and asparagine depending on the processing conditions used in the gelatine manufacturing process. Cysteine is completely absent, of the sulphur-containing amino acids, methionine is the only one present.

[0004] The data for poultry and fish collagen are somewhat different, but the present invention is applicable likewise to gelatine and/or gelatine hydrolysate derived from poultry and fish collagen.

[0005] Gelatine can be utilized in a wide array of applications depending upon its starting material and method of manufacture. This is because the physical and chemical behavioral of gelatine is determined on one hand by a combination of its amino acid content and the resulting spatial structure, and on another hand by a myriad of conditions such as pH, ionic strength and reactions with other molecules. For example, different kinds of gelatines are utilized in diverse applications such as food, photographic, cosmetic, and pharmaceutical.

[0006] In the pharmaceutical industry, gelatine is used inter alia in the manufacture of hard and soft capsules. Gelatine capsules provide a convenient and efficient method to orally administer a drug because the capsules disintegrate rapidly upon exposure to the acidic content of the stomach, thus releasing the drug into the body. While gelatine capsules provide a pharmaceutically elegant manner in which to administer a drug, there is, however, a risk that the gelatine capsule may suffer from retardation of disintegration and dissolution resulting from a process known as cross-linking. Cross-linking is believed to occur when carbonyl groups in gelatine, carbonyl-containing fill ingredients in capsules, or decomposition of fill ingredients into carbonyl groups, react with primary amines and other nitrogenous compounds present in gelatine to form cross-links.

[0007] Cross-linking, in particular, can have dire consequences on the performance of gelatine capsules upon extended storage and exposure to extremes of heat and humidity. Extensive gelatine cross-linking in capsule formulations may lead to the formation of a very thin, tough and water-insoluble film, usually referred to as a pellicle. The pellicle acts as a rubbery, water-insoluble layer that can restrict, or prevent release of the contents of the capsule.

[0008] One widely reported means to prevent cross-linking in gelatine capsules focuses on products that act as carbonyl scavengers, preventing the interaction of carbonyl groups, e.g., aldehyde groups, with the gelatine capsule shell, thus preventing gelatine cross-linking. These methods all generally suggest adding products to the pharmaceutical composition contained in the gelatine capsules. For example, it has been shown that adding the amino acid glycine and citric acid in combination to formulations encapsulated in gelatine hard capsules improved the dissolution profile of the hard capsules (3). Addition of the amino acid glycine alone was proven not to yield satisfactory results. But the addition of carbonyl scavengers such as glycine, and carboxylic acids such as citrate, in the amounts needed to reduce cross-linking in gelatine capsules is significantly cost prohibitive. As such, adding these products to gelatine is not a practical solution to reduce cross-linking in gelatine capsules.

SUMMARY OF THE INVENTION

[0009] The present invention provides a practical, cost-effective means to reduce cross-linking in gelatine. Briefly, the invention encompasses a low molecular weight gelatine hydrolysate that, when blended with higher molecular weight gelatine, reduces the gelatine's cross-linking and improves the dissolution properties by increasing the amounts of free glycine, other amino acids, and small peptides in the blended gelatine product. Advantageously, because the gelatine hydrolysate and blended gelatine composition of the invention have reduced cross-linking properties achieved without the addition of products such as glycine as an isolated compound admixed with citric acid, the gelatine may still be marketed as a natural product.

[0010] Among the several aspects of the invention, therefore, is a process for producing a gelatine hydrolysate having an average molecular weight of from about 100 to about 2000 Da, preferably about 1500 Da, and an average primary amine content from about 1.0×10^{-3} to about 1.0×10^{-2} μMol of primary amine per μg of gelatine hydrolysate. The process comprises combining a gelatine starting material with at least one proteolytic enzyme having endopeptidase activity to form an endopeptidase digested gelatine product. The endopeptidase digested gelatine product is then typically contacted with at least one proteolytic enzyme having exopeptidase activity. Generally, the endopeptidase and exopeptidase proteolytic digestions proceed for a sufficient length of time and are conducted under reaction conditions so as to form the gelatine hydrolysate.

[0011] Another aspect of the invention encompasses a process for making a gelatine hydrolysate. The process comprises contacting a gelatine starting material with a series of at least three proteolytic enzymes having endopeptidase activity to form an endopeptidase digested gelatine product. Typically, the three proteolytic enzymes consist of Endopeptidase from *Bacillus subtilis* (e.g. Corolase® 7089), Bromelain (e.g. Enzeco® Bromelain concentrate) and Papain (e.g. Papain 6000). The endopeptidase digested gelatine product is then contacted with a series of at least two proteolytic enzymes having exopeptidase activity. Generally, the two proteolytic enzymes consist of Exopeptidase from *Aspergillus oryzae* (e.g. Validase® HPH) and Exopeptidase from *Lactobacillus sakei* (e.g. Corolase® LAP).

[0012] Yet another aspect of the invention provides a gelatine hydrolysate. The gelatine hydrolysate will typically have an average molecular weight of from about 100 to about 2000 Da, preferably about 1500 Da and an average primary amine content from about 1.0×10^{-5} to about 1.0×10^{-4} μMol of primary amine per μg of gelatine hydrolysate. In one embodiment, the gelatine hydrolysate is made by a process comprising contacting a gelatine starting material with a series of at least three proteolytic enzymes having endopeptidase activity to form an endopeptidase digested gelatine product. Typically, the three proteolytic enzymes are selected from Endopeptidase from *Bacillus subtilis* (e.g. Corolase® 7089), Bromelain (e.g. Enzeco® Bromelain Concentrate), and Papain (e.g. Papain 6000). The endopeptidase digested gelatine product is then contacted with a series of at least two proteolytic enzymes having exopeptidase activity. Generally, the two proteolytic enzymes are selected from Exopeptidase from *Aspergillus oryzae* (e.g. Validase® HPH) and Exopeptidase from *Lactobacillus sakei* (e.g. Corolase® LAP).

[0013] An additional aspect of the invention is directed to a gelatine composition. The composition comprises a gelatine hydrolysate and solution. Typically, the composition will comprise from about 1% to about 20% by weight of the gelatine hydrolysate and from about 80% to about 99% by weight of the solution.

[0014] Other objects and features of the invention will be in part apparent and in part pointed out hereinafter.

BRIEF DESCRIPTION OF THE FIGURES

[0015] FIG. 1 shows the reduction in formaldehyde induced cross-linking of LHSH, a limed-hide gelatine, upon the addition of 2 different gelatine hydrolysates, type HH-3 and Type LHSH, as assessed by the Vortex Hardening procedure. Hydrolysate Type BH-3 is a low molecular weight limed-hide hydrolysate and Type LHSH is a limed-hide hydrolysate of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The present invention provides a novel gelatine hydrolysate, a process to make the gelatine hydrolysate and gelatine compositions containing the gelatine hydrolysate. It has been discovered that blending a low molecular weight gelatine hydrolysate and in particular, the gelatine hydrolysate of the present invention, with gelatine, reduces the gelatine's tendency to cross-link and improves dissolution properties by increasing the amounts of free glycine, other amino acids, and small peptides in the blended gelatine product. Advantageously, the present invention provides a cost effective means to reduce gelatine cross-linking with the benefit of maintaining the original amino acid composition of gelatine and without the need to add non-gelatine derived compounds like citric acid. As such, the gelatine hydrolysate compositions of the present invention can still be marketed as natural products.

I. Process for Making the Gelatine Hydrolysate

[0017] One aspect of the present invention encompasses a process to produce a gelatine hydrolysate having an average molecular weight of from about 100 to about 2000 Da, preferably about 1500 Da and an average primary amine content from about 1.0×10^{-5} to about 1.0×10^{-4} μMol of primary amine per μg of gelatine hydrolysate. The process comprises contacting a gelatine starting material with at least one proteolytic enzyme having endopeptidase activity to form an endopeptidase digested gelatine product. The endopeptidase digested gelatine product is then typically contacted with at least one proteolytic enzyme having exopeptidase activity. Generally, the endopeptidase and exopeptidase proteolytic digestions proceed for a sufficient length of time and are conducted under reaction conditions such to form the gelatine hydrolysate.

[0018] The gelatine starting material used in the process of the invention is typically derived from collagen or collagen rich tissue available from several suitable raw materials. Collagen rich tissues include the skin and bones from animals, such as from fish, poultry, pigs or cattle. There are generally two main types of gelatine derived from collagen, Type A and Type B that differ in their method of manufacture. In one embodiment, the gelatine starting material is Type A gelatine. Type A, with an isoionic point of 7 to 10.0, is derived from collagen with exclusively acid pretreatment by methods generally known in the art. In an alternative embodiment, the gelatine starting material is Type B gelatine. Type B, with an isoionic point of 4.8 to 5.8, is the result of an alkaline pre-treatment of collagen and is produced by methods generally known in the art.

[0019] In another alternative embodiment, the gelatine starting material is a mixture of Type A and Type B. The respective amounts of Type A and Type B gelatine may be greatly varied without detrimental effect on the properties of the gelatine hydrolysate produced.

[0020] In principle, any one of Type A and Type B gelatine could be exchanged completely or partially by enzymatically produced gelatine. However, the enzymatic process for manufacturing gelatine is up to present not widely used.

[0021] Irrespective of the embodiment, the gelatine starting material will normally contain from about 80% to about 90% by weight protein, from about 0.1% to about 2% by weight mineral salts (corresponding to the ash content) and from about 10% to 15% by weight water.

[0022] It is also contemplated that the physical properties of the gelatine starting material can and will vary depending upon the intended use of the gelatine hydrolysate. The gelatine starting material will typically have an average molecular weight of from about 50,000 Da to about 200,000 Da. In a particularly preferred embodiment, the gelatine starting material will have an average molecular weight of less than about 150,000 Da.

[0023] In one embodiment, the Bloom strength of the gelatine starting material will be from about 50 to about 300, the pH will be from about 3.8 to about 7.8, the isoelectric

point will be from about 4.7 to about 9.0, the viscosity will be from about 15 to about 45 mP, and the ash will be from about 0.1 to about 2.0%.

[0024] In an alternative embodiment, when the gelatine starting material is substantially Type A gelatine, the bloom strength will be from about 50 to about 300, the pH will be from about 3.8 to about 5.5, the isoelectric point will be from about 7.0 to about 9.0, the viscosity will be from about 15 to about 75 mP, and the ash will be from about 0.1 to about 2.0%.

[0025] In an alternative embodiment, when the gelatine starting material is substantially Type B gelatine, the bloom strength will be from about 50 to about 300, the pH will be from about 5.0 to about 7.5, the isoelectric point will be from about 4.7 to about 5.4, the viscosity will be from about 20 to about 75 mP, and the ash will be from about 0.5 to about 2.0%.

[0026] In one preferred embodiment, where the gelatine hydrolysate is used in the manufacture of soft elastic pharmaceutical products, the gelatine starting material will have a bloom strength from about 200 to about 300, a viscosity from about 40 to about 60 mP, and a pH from about 4.8 to about 6.5. In yet another preferred environment, where the gelatine hydrolysate is used in the manufacture of soft shell capsule pharmaceutical products, the gelatine starting material will have a bloom strength from about 125 to about 200, a viscosity from about 25 to about 45 mP, and a pH from about 4.5 to about 6.5.

[0027] In the process of the invention, the gelatine starting material is typically mixed or dissolved in water by a process known as swelling to form a solution comprising from about 10% to about 60% gelatine by weight. In one preferred embodiment, the solution has from about 40% to about 50% gelatine by weight.

[0028] In a further preferred embodiment, the solution has from about 20% to about 50% gelatine by weight. In a still more preferred embodiment, the solution has from about 35% to about 40% gelatine by weight.

[0029] It is contemplated that gelatines having varying particle sizes may be utilized in the invention as starting material. For example, the gelatine particle size may vary from about 0.1 mm to about 10 mm. In one embodiment, the gelatine particle size may be fine having an average particle size from about 0.1 to about 0.5 mm. In another embodiment, the gelatine particle size may be medium having an average particle size of from about 0.4 to about 0.8 mm. In still another embodiment, the gelatine particle size may be large having an average particle size of approximately greater than about 0.8 mm. Generally speaking, the particle size of the gelatine starting material will impact the amount of time needed for the gelatine to dissolve in solution. During the swelling process, the ability for gelatine to absorb up to ten times its weight in cold water is utilized. Generally speaking, a fine particle size will swell within a few minutes, gelatines having a medium particle size will swell within about 5 to about 12 minutes, and gelatines having a large particle size swell within about an hour. Typically, for concentrated gelatine solutions, solutions having for example, from about 10% to about 20% by weight gelatine, can be prepared using all particle sizes. For highly concentrated solutions, solutions having for example, from about 30% to about 35% gelatine by weight, coarse particles are typically used because they tend not to aggregate and produce fewer air bubbles when being processed.

[0030] After the gelatine has been brought in solution through the swelling process and is ready prior to the addition of the proteolytic enzymes, the pH, temperature and Redox State of the solution is typically adjusted to take care of minor amounts of residual peroxide present in the gelatine from its manufacturing process so as to optimize the hydrolysis reaction, and in particular, to ensure that the cysteine-containing proteolytic enzymes utilized in the hydrolysis reaction function near their optimum activity level. The pH of the gelatine solution is adjusted and maintained at from about 5 to about 7. In a particularly preferred embodiment, the pH of the gelatine solution is adjusted and maintained at from about 6.0 to about 6.5. At this pH, proteolytic enzymes detailed below are near their optimum activity level. The pH of the gelatine solution may be adjusted and monitored according to methods generally known in the art. For example, to decrease the pH of the gelatine solution an acid, such as hydrochloric acid, is typically added. Alternatively, to increase the pH of the gelatine solution a base, such as sodium hydroxide, is typically added. The temperature of the gelatine solution is preferably adjusted and maintained from about 40° C. to about 65° C. during the hydrolysis reaction in accordance with methods known in the art. In a particularly preferred embodiment, the temperature of the gelatine solution is adjusted and maintained from about 50° C. to about 60° C. during the hydrolysis reaction. In general, temperatures above this range may deactivate proteolytic enzymes, while temperatures below this range tend to slow the activity of the proteolytic enzymes. Depending upon the proteolytic enzyme used in the hydrolysis reaction, the Redox State of the gelatine solution typically should be adjusted and maintained as neutral to slightly on the reducing side. High levels of oxidants tend to inactivate some of the cysteine-containing proteolytic enzymes used in the hydrolysis reaction, while low levels of reductants may serve to keep some of the proteolytic enzymes, such as papain, active until they are deactivated.

[0031] In general, the hydrolysis reaction is conducted by adding proteolytic enzymes to the gelatine solution. Several proteolytic enzymes are suitable for use in the process of the invention. In a preferred embodiment, the proteolytic enzymes will be food grade enzymes having endopeptidase or exopeptidase activity at a pH from about 5 to about 7 and at a temperature from about 40° C. to about 65° C. In a particularly preferred embodiment, the proteolytic enzymes will be food grade enzymes having endopeptidase or exopeptidase activity at a pH from about 6 to about 6.5 and at a temperature from about 50° C. to about 60° C.

[0032] In one embodiment, the endopeptidase will be a food grade serine proteinase belonging to EC 3.4.21. In one alternative of this embodiment, the serine proteinase is a chymotrypsin proteinase. In a further alternative of this embodiment, the serine proteinase is a subtilisin proteinase. In another embodiment, the endopeptidase will be a food grade cysteine proteinase belonging to EC 3.4.22. In yet another embodiment, the endopeptidase will be a food grade aspartic proteinase belonging to EC 3.4.23. In an additional embodiment, the endopeptidase will be a food grade metalloproteinase belonging to EC 3.4.24. Exemplary non-limiting examples of food grade endopeptidases that may be utilized in the process of the invention include Validase® AFP, Validase® FP 500, Alkaline Protease Concentrate, Validase® 15L Enzeco® Bromelin Concentrate, Corolase® 7089, Papain 600T and Validase® Papain Concentrate Sulfite Free.

[0033] In a further embodiment, the exopeptidase will be a food grade amino peptidase belonging to EC 3.4.11. In

another embodiment, the exopeptidase will be a food grade dipeptidase belonging to EC 3.4.13. In still another embodiment, the exopeptidase will be a food grade peptidyldi or tripeptidase belonging to EC 3.4.14. In yet another embodiment, the exopeptidase will be a food grade peptidyldipeptidase belonging to EC 3.4.15. In an additional embodiment, the exopeptidase will be a food grade serine-type carboxy peptidase belonging to EC 3.4.16. In yet another embodiment, the exopeptidase will be a food grade metallo carboxy peptidase belonging to EC 3.4.17. In an additional embodiment, the exopeptidase will be a food grade cysteine-type carboxy peptidase belonging to EC 3.4.18. In still an another embodiment, the exopeptidase will be a food grade omega peptidase belonging to EC 3.4.19. An exemplary example of a food grade exopeptidase that may be utilized in the process of the invention includes Validase® FP II or Corolase® LAP®.

[0034] Another example of a food grade hydrolytic enzyme that may be used in the process of the invention is Validase® FPII Concentrate. Examples of other suitable proteolytic food grade enzymes are shown in Table A.

TABLE A

Proteolytic Enzyme	Source
Alcalase®	Novozymes
Flavourzyme®	Novozymes
Protamex®	Novozymes
Fungal Protease Concentrate	Genencor Enzymes
Fungal Protease 500,000	Genencor Enzymes
Protex™ 6L	Genencor Enzymes
Validase® FP 500	Genencor Enzymes
Multifect® Neutral	Genencor Enzymes
Corolase® 7089	AB Enzymes
Corolase® PP	AB Enzymes
Enzeco® Chymotrypsin [illegible]	Enzeco Development Corp.
Enzeco® Papain 125	Enzeco Development Corp.
Enzeco® Pepsin	Enzeco Development Corp.
Enzeco® Ficin	Enzeco Development Corp.
Enzeco® Fungal Acid Protease	Enzeco Development Corp.
Enzeco® Fungal Protease 100	Enzeco Development Corp.
Enzeco® Fungal Protease 180	Enzeco Development Corp.
Enzeco® Fungal Protease 400	Enzeco Development Corp.
Enzeco® Exo-Protease	Enzeco Development Corp.
Enzeco® Neutral Bacterial Protease [illegible]	Enzeco Development Corp.
Enzeco® Neutral Bacterial Protease 10X	Enzeco Development Corp.
Enzeco® Thermolysin 10X	Enzeco Development Corp.
Enzeco® Alkaline Protease L FG	Enzeco Development Corp.
Enzeco® Alkaline Protease 4000	Enzeco Development Corp.
Enzeco® Alkaline Protease 4.0L	Enzeco Development Corp.
HT Proteolytic	Deerland Enzymes
BC Papain 1000 [illegible]	Bio-Cat, Inc.
BC Papain 1000 [illegible]	Bio-Cat, Inc.
Promod™ 144GL	Biocatalysts
Promod™ [illegible]	Biocatalysts
Promod™ 144P	Biocatalysts
Promod™ [illegible]	Biocatalysts
Promod™ [illegible]	Biocatalysts
Promod™ [illegible]	Biocatalysts
Promod™ [illegible]	Biocatalysts
Promod™ [illegible]	Biocatalysts
Promod™ [illegible]	Biocatalysts
Promod™ [illegible]	Biocatalysts
Promod™ [illegible]	Biocatalysts

[0035] Typically, combinations of endopeptidases and exopeptidases will be used to catalyze the hydrolysis reaction. The proteolytic enzymes are preferably selected by considering the protease activity of the enzymes and selecting enzymes that will maximize the cleaving of peptide bonds in the gelatine starting material. In a preferred embodiment, enzymes with preferential endopeptidase activity are added to the gelatine solution first to form an endopeptidase digested gelatine product. The endopeptidase digested gelatine product is then contacted with enzymes having preferential exopeptidase activity without deactivating the endopeptidase(s). It is also contemplated that in certain embodiments enzymes having exopeptidase activity may be added before or at the same time as enzymes having endopeptidase activity.

[0036] In one preferred embodiment, the endopeptidase is selected from the group consisting of Corolase® 7089, Validase® AFP, Validase® FP 500, Alkaline Protease Concentrate, Validase® TSP, Enzeco® Bromelain Concentrate, Papain 6000L and Validase® Papain Concentrate Sulfite Free; and the exopeptidase is Validase® FP II or Corolase® LAP. In yet another embodiment, the endopeptidase is selected from the group consisting of Corolase® 7089, Enzeco® Bromelain Concentrate, and Papain 6000L; and the exopeptidase is selected from the group consisting of Validase® FPII and Corolase® LAP. In a preferred embodiment, each proteolytic enzyme is sequentially added to the gelatine starting material in the following order: Corolase® 7089, Enzeco® Bromelain Concentrate, Papain 6000L, Validase® FPII and Corolase® LAP. In one alternative of this embodiment, each proteolytic enzyme digests the gelatine starting material for approximately 0.5 to about 2 hours before addition of the subsequent proteolytic enzyme.

[0037] The amount of proteolytic enzyme added to the hydrolysis reaction can and will vary depending upon the desired degree of gelatine hydrolysis and the duration of the hydrolysis reaction. In general, about 0.0250% to about 0.150% (w/w) of the proteolytic enzyme having endopeptidase activity is added and from about 0.025% to about 0.15% (w/w) of the proteolytic enzyme having exopeptidase activity is added for a hydrolysis reaction lasting for a duration of from about 5 hours to about 24 hours. In a preferred embodiment, about 0.05% to about 0.15% (w/w) of Corolase® 7089, about 0.025% to about 0.075% (w/w) of Enzeco® Bromelain Concentrate, about 0.05% to about 0.15% (w/w) of Papain 6000L, about 0.025% to about 0.075% (w/w) of Validase® FPII, and about 0.05% to about 0.15% (w/w) of Corolase® LAP are added to the gelatine starting material.

[0038] The hydrolysis reaction will typically proceed for up to approximately 24 hours. Typically, after about 24 hours the quality of the gelatine hydrolysate, in terms of color and smell, will begin to noticeably diminish. In another embodiment, the hydrolysis reaction will proceed from about 1 hour to about 24 hours. In yet another embodiment, the hydrolysis reaction will proceed from about 3 hours to about 15 hours. In a still more preferred embodiment, the hydrolysis reaction will proceed from about 5 hours to about 12 hours. Within this time period, highly economic process conditions and constant quality of the gelatine hydrolysate are easily achievable. To end the hydrolysis reaction, the hydrolyzed gelatine solution may be heated to approximately 90° C. to deactivate the proteolytic enzymes. An additional step to deactivate the cysteine proteases may be required. If so required, the addition of hydrogen peroxide or other oxidizing agent may be added, generally not to exceed 1000 ppm. The gelatine hydrolysate may then be purified from the hydrolysis solution by any means generally known in the art, e.g., microfiltration.

[0039] Typically, the degree of hydrolysis (DH) of the starting gelatine material in the process of the invention is greater than about 13%. In certain embodiments, the DH is from about 10% to about 20%. In other embodiments, the DH is

from about 20% to about 50%. In another embodiment, the DH is from about 30% to about 40%. In yet another embodiment, the DH is from about 40% to about 80%. In still another embodiment, the DH is from about 50% to about 60%. In an additional embodiment, the DH is from about 60% to about 70%. In yet a further embodiment, the DH is from about 70% to about 80%. In still another embodiment, the DH is from about 80% to about 90%. In still another embodiment, the DH is greater than about 90%. The DH is the percentage of the total number of peptide bonds in the gelatine starting material that have been hydrolyzed by proteolytic enzymes. The DH may be calculated by methods generally known in the art, such as according to the Adler-Nissen method (19).

[0040] It has been surprisingly found that gelatine hydrolysates with a lower average molecular weight are more effective in preventing the cross-linking process. As a consequence, the amount of hydrolysate in the gelatine formulation may be reduced which optimizes costs.

II. Gelatine Hydrolysate

[0041] Yet another aspect of the invention encompasses a gelatine hydrolysate made by the process of the invention. Generally speaking, the gelatine hydrolysate, compared to the gelatine starting material, will comprise a mixture of peptide of different lengths has a net increase in the amounts of free glycine, other amino acids, and small peptides. The gelatine hydrolysate will also have a lower average molecular weight and higher primary amine content compared to the gelatine starting material.

[0042] The gelatine hydrolysate will typically have an average molecular weight of at least about 100 Da. In other embodiments, the gelatine hydrolysate will typically have an average molecular weight not exceeding about 2000 Da. In some embodiments, the gelatine hydrolysate will have an average molecular weight of from about 100 Da to about 2,000 Da. In other embodiments, the gelatine hydrolysate will have an average molecular weight of about 700 Da to about 1800 Da. In another embodiment, the gelatine hydrolysate will have an average molecular weight of about 700 Da to about 1500 Da. In still other embodiments, the gelatine hydrolysate will have an average molecular weight of from about 800 Da to about 1200 Da.

[0043] The average molecular weight is the weight of a gelatine hydrolysate as measured by electrospray ionization liquid chromatography mass spectrometry (ESI-LCMS). For example, a gelatine hydrolysate has a high average molecular weight of approximately 1200 Da, may have a molecular weight range from about 75 Da to 5000 Da.

[0044] In general, the gelatine hydrolysate will have an average primary amine content of no less than about 1.0×10^{-5} pMol of primary amine per µg of gelatine hydrolysate. In another embodiment, the gelatine hydrolysate will have an average primary amine content of no less than about 1.5×10^{-5} pMol of primary amine per µg of gelatine hydrolysate. In still another embodiment, the gelatine hydrolysate will have an average primary amine content of no less than about 2.0×10^{-5} pMol of primary amine per µg of gelatine hydrolysate. In an additional embodiment, the gelatine hydrolysate will have an average primary amine content of from about from about 1.0×10^{-5} to about 1.0×10^{-3} pMol of primary amine per µg of gelatine hydrolysate. The primary amine content of the gelatine hydrolysate is measured through derivatization and subsequent UV absorption (280 nm) as illustrated in the Examples.

[0045] The gelatine hydrolysate of the present invention comprises polypeptides typically of up to about 25 amino acids in length, preferably up to 80 amino acids in length. In one embodiment, the average polypeptide comprising the gelatine hydrolysate is from about 6 to about 18 amino acids in length. In another embodiment, the average polypeptide contained in the gelatine hydrolysate of the present invention is from about 9 to about 20 amino acids in length. The length of a polypeptide chain may be determined indirectly by size-exclusion chromatography/high performance liquid chromatography (SEC/HPLC).

[0046] In one embodiment, the gelatine hydrolysate will have an average molecular weight from about 100 Da to about 2,000 Da, an average primary amine content from about 1.0×10^{-5} to about 1.0×10^{-3} pMol of primary amine per µg of gelatine hydrolysate, and an average polypeptide length of up to about 20 amino acids. In still another embodiment, the gelatine hydrolysate will have an average molecular weight from about 700 Da to about 1500 Da, an average primary amine content from about 1.0×10^{-5} to about 2.0×10^{-3} pMol of primary amine per µg of gelatine hydrolysate, and an average polypeptide length of up to about 18 amino acids. In another embodiment, the gelatine hydrolysate will have an average molecular weight from about 800 Da to about 1200 Da, an average primary amine content from about 1.0×10^{-5} to about 2.0×10^{-3} pMol of primary amine per µg of gelatine hydrolysate, and an average polypeptide length of from about 4 to about 18 amino acids.

III. Gelatine Compositions

[0047] Another aspect of the invention encompasses a gelatine composition comprising a low molecular weight gelatine hydrolysate and gelatine. Surprisingly it has been found that when a low molecular weight gelatine hydrolysate is blended with higher molecular weight gelatine, it reduces the gelatine's cross-linking and improves the dissolution properties by increasing the amount of free glycine, other amino acids, and small peptides in the blended gelatine product, as shown in the Examples.

[0048] A number of different gelatine hydrolysates are suitable for use in the gelatine composition. In one embodiment, the gelatine hydrolysate will be an enzymatically-digested hydrolysate. By way of non-limiting example, the gelatine hydrolysate of the present invention is produced via an enzymatic hydrolysis procedure, as detailed above. In another embodiment, the gelatine hydrolysate will be an acid-digested hydrolysate. For example, acid hydrolysis may be conducted by digesting a gelatine starting material with approximately 6 N hydrochloric acid for about 24 hours at a reaction temperature of approximately 110° C. In yet another embodiment, the gelatine hydrolysate will be a base-digested hydrolysate. By way of non-limiting example, base hydrolysis may be conducted by digesting a gelatine starting material with a strong base, such as sodium hydroxide. Acid and base hydrolysis will typically result in a hydrolysate having free amino acids. In each embodiment (i.e., enzymatic, acid and base hydrolysis), suitable gelatine starting materials are detailed in section I above, which delineates structural and functional properties for gelatine starting materials to be used in the process of the invention.

[0049] Typically, gelatine hydrolysates will have a low molecular weight. In one embodiment, the average molecular weight will be from about 400 Da to about 2000 Da. In another embodiment, the gelatine hydrolysate will have an average molecular weight from about 700 Da to about 1500 Da. In addition, the gelatine hydrolysate will also have an average primary amine content ranging from about 1.0×10[illegible] to about 1.0×10[illegible] μMol of primary amine per μg of gelatine hydrolysate.

[0050] In another embodiment, the average primary amine content may range from about 1.0×10[illegible] to about 2.0×10[illegible] μMol of primary amine per μg of gelatine hydrolysate.

[0051] In still another embodiment, the average primary amine content may range from about 2.0×10[illegible] to about 4.0×10[illegible] μMol of primary amine per μg of gelatine hydrolysate. In still a further embodiment, the average primary amine content may range from about 4.0×10[illegible] to about 6.0×10[illegible] μMol of primary amine per μg of gelatine hydrolysate. In yet an additional embodiment, the average primary amine content may range from about 6.0×10[illegible] to about 1.0×10[illegible] μMol of primary amine per μg of gelatine hydrolysate.

[0052] The gelatine hydrolysate will also generally have an average polypeptide chain length of from about 4 to about 30 amino acids. In one embodiment, the average polypeptide comprising the gelatine hydrolysate is up to about 30 amino acids in length. In another embodiment, the average polypeptide comprising the gelatine hydrolysate is from about 9 to about 20 amino acids in length. The average molecular weight, average primary amine content and average polypeptide chain length are determined as detailed in section II.

[0053] In a preferred embodiment, the gelatine hydrolysate used in the composition will be the hydrolysate of the present invention as detailed in section II. Examples of other exemplary gelatine hydrolysates that may be used in the composition are delineated in Table B. Mixtures of the afore-described gelatine hydrolysates may also be used.

TABLE B

GELITA Gelatine Hydrolysates	GELITA Location Where Manufactured	Raw Material	Molecular Weight	Viscosity
Type A-1	Europe	porcine skin	2.0 – 3 kDa	30-60 mP (15% @ 25° C.)
Type A-2	Chicago	porcine skin	2.0 – 3 kDa	40-60 mP (15% @ 25° C.)
Type BH-1	Europe	bovine hide	2.0 – 3 kDa	30-40 mP (15% @ 25° C.)
Type BH-2	Europe	bovine hide	2.0 – 3 kDa	[illegible] mP (15% @ 25° C.)
Type A-5	Sioux City	porcine skin	2.0 – 3 kDa	42-51 mP (20% @ 25° C.)
Type BB-1	Sioux City	bovine bone	2.0 – 3 kDa	42-50 mP (20% @ 25° C.)
Type BB-2	Sioux City	bovine bone	2.0 – 3 kDa	20-40 mP (15% @ 25° C.)
Type BBH-1	Europe	bovine bone/hide	2.0 – 3 kDa	32-50 mP (15% @ 25° C.)
Type BB-3	Chicago	bovine bone	2.0 – 3 kDa	30-50 mP (20% @ 25° C.)
Type BB-4	Chicago	bovine bone	2.0 – 3 kDa	30-50 mP (15% @ 25° C.)
Type BB-5	Chicago	bovine bone	2.0 – 3 kDa	40-60 mP (20% @ 25° C.)
Type BB-6	Chicago	bovine bone	2.0 – 3 kDa	40-50 mP (15% @ 25° C.)
Type A-3	Chicago	porcine skin	2.0 – 3 kDa	30-60 mP (20% @ 25° C.)
Type A-4	Chicago	porcine skin	2.0 – 3 kDa	30-60 mP (15% @ 25° C.)
Type A-6	South America	porcine skin	2.0 – 3 kDa	30-60 mP (20% @ 25° C.)
Type BH-3	South America	bovine hide	2.0 – 3 kDa	30-40 mP (15% @ 25° C.)

[0054] The gelatine hydrolysate may be blended with several types of gelatine having a broad range of physical and functional properties. The choice of a particular gelatine can and will vary greatly depending upon the intended use of the gelatine composition. Generally speaking, irrespective of the embodiment or intended use, the gelatine is typically derived from collagen or collagen rich tissue available from several suitable raw materials such as from the skin and bones of animals. In one embodiment, the gelatine is Type A gelatine. In another embodiment, the gelatine is Type B gelatine. In still another embodiment, the gelatine is a mixture of Type A and Type B gelatine. Again, gelatine prepared in an enzymatic process may be used to substitute Type A and/or Type B gelatine.

[0055] The gelatine, irrespective of the embodiment, will preferably contain from about 80% to about 90% by weight protein, from about 0.1% to about 2% by weight mineral salts (ash content) and from about 10% to 15% by weight water.

[0056] The gelatine will typically have a high average molecular weight. In one embodiment, the gelatine will have an average molecular weight of greater than about 200,000 Da. In another embodiment, the gelatine will have an average molecular weight greater than about 150,000 Da. In still

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[0127] 17. Digenis, G. A., Gold, T. B., Shah, V. P., "Cross-Linking of Gelatin Capsules and its Relevance to Their in Vitro-in Vivo Performance", *J. Pharm. Sci.*, July 1994, 83(7):915-921.

[0128] 18. Nagaraj, R. H., Shipanova, I. N., Faust, F. M., "Protein Cross-Linking by the Maillard Reaction", *J. Biol. Chem.*, August 1996, 271(32):19338-19345.

[0129] 19. "Enzymic Hydrolysis of Food Proteins", Elsevier Applied Science Publishers Ltd. (1986), page 122.

1. A process for making a gelatine hydrolysate, the process comprising:

a) contacting a gelatine starting material with at least one proteolytic enzyme having endopeptidase activity to form an endopeptidase digested gelatine product; and

b) contacting the endopeptidase digested gelatine product with at least one proteolytic enzyme having exopeptidase activity, wherein the endopeptidase and exopeptidase proteolytic digestions form the gelatine hydrolysate, the gelatine hydrolysate having an average molecular weight of from about 100 to about 2000 Da and an average primary amine content from about 1.0×10^{-3} to about 1.0×10^{-2} μMol of primary amine per μg of gelatine hydrolysate.

2. The process of claim 1, wherein the proteolytic enzymes are food grade enzymes having endopeptidase or exopeptidase activity at a pH from about 5 to about 7 and at a temperature from about 40° C. to about 65° C.

3. The process of claim 1, wherein the proteolytic enzymes are selected from the group consisting of Endopeptidase from *Bacillus subtilis*, Bromelain, Papain, Exopeptidase from *Aspergillus oryzae* and Exopeptidase from *Aspergillus sojae*.

4. The process according to claim 1, wherein about 0.025% to about 0.15% (w/w) of the proteolytic enzyme having endopeptidase activity is contacted with the gelatine starting material and about 0.025% to about 0.15% (w/w) of the proteolytic enzyme having exopeptidase activity is contacted with the endopeptidase digested gelatine product.

5. A process for making a gelatine hydrolysate, the process comprising:

a) contacting a gelatine starting material with a series of at least three proteolytic enzymes having endopeptidase activity to form an endopeptidase digested gelatine product, the three proteolytic enzymes consisting of Endopeptidase from *Bacillus subtilis*, Bromelain, and Papain; and

b) contacting the endopeptidase digested gelatine product with a series of at least two proteolytic enzymes having exopeptidase activity, the two proteolytic enzymes consisting of Exopeptidase from *Aspergillus oryzae* and Exopeptidase from *Aspergillus sojae*.

6. The process of claim 5, wherein each proteolytic enzyme is sequentially added to the gelatine starting material in the following order: Endopeptidase from *Bacillus subtilis*, Bromelain, Papain, Exopeptidase from *Aspergillus oryzae* and Exopeptidase from *Aspergillus sojae*, and wherein each proteolytic enzyme digests the gelatine starting material for approximately 0.5 to about 2 hours before addition of the subsequent proteolytic enzyme.

7. The process according to claim 1, wherein the proteolytic digestion is allowed to proceed for about 5 to about 12 hours.

8. (canceled)

9. The process according to claim 1, wherein an aqueous solution containing about 10% to about 50% (w/w) of the gelatine starting material is contacted with the proteolytic enzymes.

10. The process according to claim 1, wherein the gelatine starting material is a pharmaceutical grade gelatine.

11. (canceled)

12. The process according to claim 1, wherein the proteolytic digestions are conducted at a pH of about 5 to about 7 and at a temperature of about 40° C. to about 65° C.

13. (canceled)

14. (canceled)

15. A gelatine hydrolysate having an average molecular weight of from about 100 to about 2000 Da and an average primary amine content from about 1.0×10^{-3} to about 1.0×10^{-2} μMol of primary amine per μg of gelatine hydrolysate.

16. The gelatine hydrolysate of claim 15, wherein the gelatine hydrolysate has a degree of hydrolysis of greater than about 13%.

17. The gelatine hydrolysate of claim 15, wherein the average molecular weight of the gelatine hydrolysate is in the range of from about 100 to about 1500 Da.

18. The gelatine hydrolysate of claim 17, wherein the average molecular weight is between about 700 to about 1200 Da.

19. The gelatine hydrolysate according to claim 15, wherein the average polypeptide in the gelatine hydrolysate is from about 4 to about 13 amino acids in length.

20. (canceled)

21. A gelatine composition comprising from about 1% to about 20% by weight of a gelatine hydrolysate and from about 80% to about 99% by weight of gelatine.

22. The gelatine composition of claim 21, wherein the composition comprises from about 5% to about 10% by weight of the gelatine hydrolysate and from about 90% to about 95% by weight of the gelatine.

23. The gelatine composition of claim 21, wherein the composition comprises a ratio of gelatine hydrolysate to gelatine from about 1:4 to about 1:99 (w/w).

24. The gelatine composition according to claim 21, wherein the gelatine has an average molecular weight of greater than about 150,000 Da.

25. The gelatine composition according to claim 21, wherein the gelatine has an average molecular weight of from about 100,000 to about 150,000.

26-28. (canceled)

29. The gelatine composition according to claim 21, wherein the gelatine hydrolysate has an average molecular weight of about 100 to about 2000 Da.

30. The gelatine composition of claim 29, wherein the gelatine hydrolysate has an average molecular weight between about 100 and about 1500 Da and an average primary amine content from about 1.0×10^{-3} to about 1.0×10^{-2} μMol of primary amine per μg of gelatine hydrolysate.

31. (canceled)

32. The gelatine composition according to claim 21, wherein the gelatine hydrolysate is an acidic hydrolyzed gelatine.

33. The gelatine composition according to claim 21, further comprising glycine.

34. The gelatine composition of claim 33, wherein the amount of glycerine is from about 0.5% to about 5% by weight.

35. The gelatine composition of claim 33, further comprising citric acid.

36. The gelatine composition of claim 35, wherein the amount of citric acid is from about 0.5% to about 5% by weight.

37. The gelatine composition of claim 33, wherein the amount of glycine is from about 1.5% to about 2.5% by weight and the amount of citric acid is from about 0.5% to about 1.5% by weight.

38. (canceled)

39. (canceled)

40. The gelatine composition according to claim 21, wherein the composition has an average viscosity of from about 10 to about 15 cP and wherein after the addition of about 0.5% by weight of [2-(4-dimethylcarbamoyl-pyridino)-ethane-1-sulfonate] to the composition and reacting the same for about two hours at a reaction temperature of about 60° C., the composition has an average viscosity of from about 15 to about 50 cP.

* * * * *

ANEXO 2

United States Patent [19]

Guley

[11] Patent Number: 4,681,765

[45] Date of Patent: Jul. 21, 1987

[54] RAPID RELEASING TRIAMTERENE CONTAINING GELATIN CAPSULE DOSAGE FORMS FOR ONCE DAILY ANTIHYPERTENSIVE USE

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[58] Field of Search 514/869, 960, 962, 778, 514/781; 424/37, 156, 21

[56] References Cited

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4,248,856	2/1981	Guley et al.	424/19
4,256,413	3/1981	Ratte et al.	424/37
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Primary Examiner—Ronald W. Griffin
Attorney, Agent, or Firm—Walter Patton

[57] ABSTRACT

A gelatin capsule dosage form containing triamterene, 2,4,7-triamino-6-phenylpteridine, which results in rapid dissolution of the active ingredient. The dosage form comprises the pharmaceutical binder methylcellulose in combination with low doses of a surfactant or a carbonate salt as disintegrants.

11 Claims, No Drawings

RAPID RELEASING TRIAMTERENE CONTAINING GELATIN CAPSULE DOSAGE FORMS FOR ONCE DAILY ANTIHYPERTENSIVE USE

This invention relates to gelatin capsule dosage forms containing a combination of medicaments which includes triamterene as an active ingredient. Specifically, propranolol long acting spheroids and a hydrophobic hydrochlorothiazide-triamterene formulated powder were dual encapsulated in tandem into a hard gelatin capsule shell for once-a-day administration.

The utility of this capsule combination relates to the pharmacological action of each medicament. Propranolol hydrochloride, a known beta receptor blocker, has utility as an antihypertensive agent in that it reduces renin secretion by the kidney. Renin, via the renin-angiotensin system, stimulates aldosterone secretion that conserves sodium and which in turn conserves water to raise and maintain blood pressure.

Beta blockade of renin by propranolol hydrochloride is one pharmacological drug action to lower blood pressure.

Hydrochlorothiazide, a nonmercurial orally effective sulfonamide diuretic, potentiates the antihypertensive effect of propranolol hydrochloride by sodium, potassium, and water diuresis.

Triamterene, another nonmercurial orally effective diuretic, has additional utility in that it potentiates the action of other diuretics and in combination minimizes potassium diuresis. This is important due to the very narrow therapeutic index of the potassium ion and its relation to the sodium ion for normal biological activity.

Thus the utility of this triple combination dosage form lies in enhanced antihypertensive activity with potassium conservation in a convenient once-a-day capsule.

The formulation of a poorly soluble hydrophobic medicament such as triamterene in a gelatin capsule presents several problems. Due to the low solubility and hydrophobicity of triamterene, it is necessary to add excipients to lessen the hydrophobic character of the medicament. A disadvantage of formulation is that hydrophobic lubricants are necessary for machine encapsulation. These hydrophobic lubricants (e.g.: magnesium stearate) additionally interfere with triamterene release from the capsule shell.

The interference of triamterene release is caused by the dry coating of the inner gelatin capsule wall by the hydrophobic ingredients (e.g.: triamterene, hydrochlorothiazide, magnesium stearate, and talc) during encapsulation. On hydration in artifical gastric media, a hydrophobic gelatin interface forms that entraps the encapsulated dry powders and prevents rapid dispersion and dissolution of the active powder ingredients. Instead of obtaining a maximum surface area for the dissolving drug, which is a necessary requirement for a increased rate of solution, a minimum surface area is obtained. This results in erratic and slow rates of drug dissolution, dependent on the degree of hydrophobic dry coating within the gelatin capsule shell.

U.S. Pat. No. 4,256,413 discloses that the combination of a surfactant and carbonate or bicarbonate salt as diluents in a triamterene gelatin capsule dosage form overcomes the above stated problems.

A capsule dosage form containing propranolol hydrochloride film coated spheroids and a blended hydrochlorothiazide and triamterene powder was prepared that overcomes the hydrophobic gelatin interface problem that occurs on hydration. In addition, compression of these hydrophobic powders into one or two tablets further minimizes the hydrophobic gelatin barrier effect. This is very evident after high temperature dissolution comparison of dry powder and tablet encapsulated dosage forms.

Formulation of the blended hydrochlorothiazide and triamterene powder was completed using either a direct compression or mixed granulation method.

In the direct compression method, two disintegrants and a surfactant (sodium starch glycolate, calcium carbonate and sodium lauryl sulfate) were required to overcome the poor dissolution of triamterene. At least 17% by weight of the capsule contents consisted of disintegrants in order to increase the triamterene dissolution to an acceptable rate of not less than 60 percent in 30 minutes for in vitro capsule dissolution.

The mixed granulation method consists of granulating and drying the water stable formulation components. The water sensitive materials are sequentially added as a dry blend to the dried granulation. When the mixed granulation method was applied to this same formula, only 7 percent triamterene was released in 30 minutes (Formula I below).

Addition of 0.25 percent PEG 8000 increased the release rate of triamterene to more than 60 percent in 30 minutes, but this formulation was not stable under exaggerated high temperature stability conditions.

It has been unexpectedly discovered that in the presence of either a surfactant or calcium carbonate the addition of methylcellulose, a binder, increased the release of triamterene to more than 60 percent in 30 minutes. This formula displayed satisfactory stability after 5 weeks under exaggerated high temperature stability conditions.

It is therefore the object of this invention to provide a gelatin capsule dosage form of triamterene which provides a significantly better dispersion and faster dissolution of the medicament resulting in better absorption and bioavailability.

The compositions of this invention, as described above, are advantageously used in conjunction with beta blockers such as atenolol, nartolol, pindolol, timolol, metoprolol, alprenolol, labetalol, cetamolol, and propranolol hydrochloride. The preferred beta blocker is propranolol hydrochloride.

The compositions of this invention as described above are also advantageously used in conjunction with other non-pteridine diuretics, particularly with a thiazide diuretic. Exemplary of such thiazide diuretics are chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, benzylhydroflumethiazide, trichloromethiazide or benzthiazide.

Advantageously the triamterene will be present in the capsule in an amount offrom about 5 mg. to about 100 mg. and the hydrochlorothiazide of from about 2 mg. to about 250 mg and long acting propranolol hydrochloride from about 60 mg to 320 mg.

Following are triamterene in-vitro test results comparing the dissolution rate of capsule dosage forms containing long acting propranolol spheroids and quick release hydrochlorothiazide, triamterene with a variety of diluents.

TABLE I

	Gram Quantities per 1000 Capsules					
	I	II	III	IV	V	VI
Propranolol L.A. Spheroid Strength (55% w/w)	160.0	160.0	160.0	160.0	160	160
Triamterene, USP	50.0	50.0	50.0	50.0	50	50
Hydrochlorothiazide, USP	50.0	50.0	50.0	50.0	50	50
Lactose, spray dried USP	68.25	62.25	34.0	59.5	40	45.5
Microcrystalline Cellulose, PH, NF	27.0	27.0	37.0	27.0	27	27
Sodium Starch Glycolate, NF	27.0	27.0	27.0	27.0	27	27
Calcium Carbonate, ppt	16.0	16.0	20.0	—	20	—
Sodium Lauryl Sulfate	0.25	0.25	—	0.5	—	0.5
Sodium Croscarmellose, Type A	—	—	4.5	4.5	4.5	4.5
Methylcellulose, 15 cps	—	6.0	6.0	6.0	6.0	6.0
Talc	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate, USP	1.0	1.0	1.0	1.0	1.0	1.0
Theoretical Capsule Content Wt. "Powder only"	240 mg.	240 mg.	220 mg.	226 mg.	220 mg.	212 mg.

[illegible]

TABLE II

	Percent Triamterene Dissolved				
Formula	7 minutes	15 minutes	30 minutes	60 minutes	90 minutes
I	2	3	7	11	16
II	21	83	91	94	95
III	68	79	91	98	99
IV	29	58	87	94	95
V	—	44	68	87	95
VI	—	31	71	93	97

The above dissolution rate studies were performed in the USP Apparatus I (basket) in 900 ml. of artificial gastric fluid without enzyme at 37° C. and 100 RPM. This test is detailed under Dissolution, Apparatus I, United States Pharmacopeia XX, National Formulary XV, page 959, released July 1, 1980.

Referring to the above Table I, it can be seen that Formula I and II containing long acting propranolol spheroids, and triamterene with hydrochlorothiazide both contain a surfactant, sodium lauryl sulfate, and calcium carbonate. It will be noted from Table II that in the case of Formula I, prepared by the mixed granulation method, only 7% of the triamterene dissolves over a 30 minute period.

When methylcellulose, a pharmaceutical binder, is added in Formula II, a very dramatic increase in dissolution of the triamterene results, i.e. from 7% to 91% in *30 minutes.*

According to the present invention, it has been found that the presence of both a surfactant and calcium carbonate are not required to achieve a rapid release of triamterene provided that methylcellulose is present in the formula, to the extent of at least 1% of the formula weight.

Reference to Formula III shows that in the absence of the surfactant, sodium lauryl sulfate, addition of 2.7% by weight of methylcellulose results in a rapid release of triamterene, i.e. 91% in 30 minutes. Reference to Formula IV shows that in the absence of the carbonate, calcium carbonate, addition of 2.7% by weight of methylcellulose results in a rapid increase of triamterene, i.e. 87% in 30 minutes.

In addition to calcium carbonate, it will be evident to one skilled in the pharmaceutical art that any nontoxic ammonium or alkali metal or amino acid metal, carbonate or bicarbonate salt may also be employed as an effervescent disintegrant in Formula II, III, and V of this invention. Exemplary of such carbonates or bicarbonates are magnesium carbonate, calcium carbonate, ammonium carbonate, sodium carbonate, sodium glycine carbonate, potassium carbonate, or sodium bicarbonate. The salts will be present from about 4% to about 40% by weight of the capsule formulation. Preferably the salts will be present at about 9% of the capsule formulation.

Exemplary of surfactants other than sodium lauryl sulfate which may be employed in Formula IV and VI of this invention are polysorbate derivatives such as polysorbate 80, cetyldimethylpyridinium chloride, and dioctyl sodium sulfosuccinate. The surfactant may be present in an amount of from about 0.05% to about 2.0% of the composition. Preferably the surfactant will be present at about 0.2% of the capsule formulation.

In addition, adjunctive disintegrant aids such as sodium croscarmellose, Type A, starch, calcium carboxy methyl cellulose, polypiasdone XL, alginic acid which are standard pharmaceutical excipients commonly used in capsule manufacturing may also be employed in the normal ranges commonly used preferably in the range of 2% to 15% by weight of the ingredients in the formula. The other ingredients are not an essential aspect of this invention, and those amounts can be varied.

Propranolol Hydrochloride L.A. Spheroid Preparation Procedure

The procedure for the preparation of propranolol hydrochloride long acting spheroids is set forth in U.S. *Pat. No. 4,138,475, Feb. 6, 1979, which is herein incorporated by reference.*

Triamterene and Hydrochlorothiazide Mixed Granulation Procedure

1. Triamterene, methylcellulose 15 cps, lactose, sodium starch glycolate, microcrystalline cellulose, talc and sodium lauryl sulfate, if desired, was added to a suitable mixer and dry mixed till blended.

2. Water was added in Step 1 and mixed till granulated.

3. The wet granulation was Fitzmilled using a #4 screen and dried to theoretical weight using a forced air oven (temperature not greater than 50° C. for drying) overnight.

4. The dried granulation was returned to a suitable mixer for blending and the water sensitive materials: the hydrochlorothiazide, calcium carbonate, sodium croscarmellose, and magnesium stearate was added to the same mixer and mixed till blended.

5. The total blended powder formula (Step #4) was passed through a Fitzmill at #2 screen and the Fitzmilled formula was blended in suitable mixer till uniform and than encapsulated.

In human bioavailability studies Formula III containing calcium carbonate, sodium starch glycolate, sodium croscarmellose type A, and methylcellulose but no sodium lauryl sulfate surfactant was found to be 93% bioavailable when compared to triamterene suspension reference standard. Statistically Formula III is bioequivalent to the suspension reference.

Formula IV containing sodium lauryl sulfate surfactant, sodium starch glycolate, sodium croscarmellose type A, and methylcellulose without calcium carbonate was found to be 74% bioavailable when compared to the triamterene suspension reference standard.

These relative triamterene bioavailability percents demonstrate the relative effectiveness of the carbonate Formula III and the surfactant Formula IV in providing a bioequivalent rapid releasing triamterene dosage form. It is clear from these results that "a rapid dissolution and dispersing amount of a combination of a surfactant and carbonate" are not solely necessary for bioequivalent triamterene absorption, in that the presence of carbonate and adjunctive excipients without a surfactant provides bioequivalent triamterene absorption when compared to the triamterene suspension reference standard. In contrast, the absence of a carbonate in the presence of a surfactant with the same other adjunctive excipients provides a lesser bioavailability that may be statistically bioequivalent for rapid releasing triamterene.

What is claimed is:

1. Method of producing triamterene and hydrochlorothiazide capsules by mixed granulation comprising the steps:

(1) blending triamterene, methylcellulose, lactose, sodium starch glycolate, microcrystalline cellulose, and talc

(2) adding water to the blend of step 1 and mixing till granulated

(3) milling and drying the wet granulation of step 2

(4) blending the dried granulation of step 3 with hydrochlorothiazide, calcium carbonate, sodium croscarmellose and magnesium stearate and

(5) milling, and blending the blend of step 4 and encapsulating.

2. Method of treating hypertension by the administration of a gelatin capsule dosage unit comprising triamterene, propranolol long acting spheres, hydrochlorothiazide, and

(a) a rapid dispersing amount of a calcium, magnesium, ammonium, aminoacid, or alkali metal nontoxic carbonate or bicarbonate salt in the presence of adjunctive disintegrant aids selected from the group consisting of sodium starch glycolate, sodium croscarmellose and methylcellulose in the absence of a surfactant.

3. An improved rapid dispersing gelatin capsule dosage unit comprising triamterene in the presence of adjunctive disintegrant aids selected from the group consisting of sodium starch glycolate, sodium croscarmellose, and methylcellulose, wherein the improvement comprises the addition of a rapid dispersing amount of a calcium, magnesium, ammonium, aminoacid, or alkali metal nontoxic carbonate or bicarbonate salt in the absence of a surfactant.

4. The gelatin capsule of claim 3 in which the carbonate salt is calcium carbonate.

5. The gelatin capsule of claim 4 in which the triamterene is present in an amount of from 5 mg. to 100 mg., the carbonate salt is present in an amount of from about 4% to about 40% and the adjunctive disintegrant aids are present in an amount of from about 2% to about 15% by weight of the ingredients in the formula.

6. An improved rapid dispersing gelatin capsule dosage unit comprising triamterene and hydrochlorothiazide in the presence of adjunctive disintegrant aids selected from the group consisting of sodium starch glycolate, sodium croscarmellose, and methylcellulose, wherein the improvement comprises the addition of a rapid dispersing amount of a calcium, magnesium, ammonium, aminoacid, or alkali metal nontoxic carbonate or bicarbonate salt in the absence of a surfactant.

7. The gelatin capsule of claim 6 in which the carbonate salt is calcium carbonate.

8. The gelatin capsule of claim 6 in which the triamterene is present in an amount of from 5 mg. to 100 mg. and the hydrochlorothiazide is present in an amount of from 2 mg. to 250 mg., the carbonate salt is present in an amount of from about 4% to about 40% and the adjunctive ingredient aids are present in an amount of from about 2% to about 15% by weight of the ingredients in the formula.

9. An improved rapid dispersing gelatin capsule dosage unit comprising triamterene, hydrochlorothiazide and propranolol hydrochloride in the presence of adjunctive disintegrant aids selected from the group consisting of sodium starch glycolate, sodium croscarmellose, and methylcellulose, wherein the improvement comprises the addition of a rapid dispersing amount of a calcium, magnesium, ammonium, aminoacid, or alkali metal nontoxic carbonate or bicarbonate salt in the absence of a surfactant.

10. The gelatin capsule of claim 9 in which the carbonate salt is calcium carbonate.

11. The gelatin capsule of claim 9 in which the triamterene is present in an amount of from about 5 mg. to about 100 mg. and the hydrochlorothiazide is present in an amount of from about 2 mg. to about 250 mg., and the propranolol long acting spheroids are present in an amount from 60 mg. to 320 mg., the carbonate salt is present in an amount of from about 4% to about 40% and the adjunctive disintegrant aids are present in an amount of from about 2% to about 15% by weight of the ingredients in the formula.

* * * * *

PROCAPS

PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA,** mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.S** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 **del C.S. de la J.**, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **12 162306,** titulada **"COMPOSICIÓN DE ENCAPSULAMIENTO DE LIBERACIÓN RAPIDA",** cuyo titular es **GELITA AG.** publicada en la gaceta No. 663 del 3 de marzo de 2013.

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