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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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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: COMPOSICION DE ENCAPSULAMIENTO DE LIBERACION RAPIDA.

Gaceta: 663 de 1 de marzo de 2013, No. de publicación 89 .

2. Datos del Opositor

[ ] Persona Natural [X] Persona Jurídica

TECNOQUIMICAS S.A.

Nombre o denominación /Razón social completa

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

Número 890 300 466-5 .

Dirección Calle 23 No. 7-39 .Ciudad Cali

Teléfono (092) 882.55.55 Fax: (092) 883.88.59 .E-mail: _____

[ ] 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:

REYES VILLAMIZAR JOSE LUIS	**79`152.473**	**44655**
Apellidos y Nombre	**Documento de identificación**	**T.P. No.**

Dirección del representante		
Cra 17 No. 88-23 Of.205		
Dirección electrónica	No. Fax	Número telefónico
info@reyes-abogados.com	621.25.42	621.26.31

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

6. Fundamentos de la oposición

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000)

Justificación: VER ANEXO

Prórroga: **SI** [X] **NO** [ ]

7. Anexos

- [X] Comprobante de pago de la tasa para la presentación de la solicitud No. _____ Fecha: _____
- [X] Poder, si fuera el caso con el que se acredita la representación.
- [X] Pruebas de los fundamentos de la oposición
- [X] Copias para traslado

8. Firma

JOSÉ LUIS REYES VILLAMIZAR

Nombre y apellidos

Firma

79.152.473 **C.C.**

44655 **T.P.**

REYES & REYES
A B O G A D O S

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF:	**Expediente 12-162-306**
TÍTULO SOLICITADO:	**COMPOSICIÓN DE ENCAPSULAMIENTO DE LIBERACIÓN RÁPIDA.**
PUBLICACIÓN:	**Gaceta 663 de 01/03/2013, Nº de publicación 89**
PRIORIDAD:	**US 61/306,744 de 22/02/2010**
SOLICITANTE:	**GELITA AG**
APODERADO:	**LUZ CLEMENCIA DE PAEZ.**
TRÁMITE:	**PRESENTACION DE OPOSICION**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente:

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **12-162-306,** por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUIMICAS S.A.**, legítimo interés para remitir esta información, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTOS DE LA OPOSICION

La solicitud colombiana en trámite **12-162-306,** que se refiere a una composición de encapsulamiento de liberación rápida la cual incluye un agente hidrosoluble de liberación rápida y una gelatina o incluso un hidrolizado de gelatina y carbonato de calcio y un método para manufacturar una composición de encapsulamiento de liberación rápida que puede incluir además la adición de un plastificante, no reúne los requisitos necesarios para otorgársele el privilegio de patente de invención, como se demuestra a través de los siguientes argumentos:

En primer lugar, es necesario resaltar que las reivindicaciones 2, 5 – 8, 12 – 18, 20, 24 – 25, 27 – 31, 35 – 37, 49 - 54 se encuentran dirigidas a aspectos tales como pesos moleculares, proporciones, solubilidades, velocidades de disolución, u otras especificaciones del producto terminado, que no tienen por sí mismos naturaleza inventiva, en tanto se encuentran relacionados con ensayos rutinarios de laboratorio de control de calidad, que todo experto medianamente versado en la materia debe conocer y por tal razón no hacen parte de las actividades industriales.

En otro aspecto, y esta vez en relación con el análisis de requerimientos de patentabilidad para la solicitud en trámite, específicamente en cuanto a novedad y nivel inventivo, encontramos que en la misma es evidente la ausencia de novedad y para tal efecto, mencionamos a continuación algunos documentos en los cuales se sugiere cada una de sus características técnicas esenciales tal y como se

pretende proteger en la solicitud colombiana en trámite en su reivindicación independiente 1, veamos:

1) **una composición** de **encapsulamiento** de **liberación rápida** que comprende:
   (a) un **agente hidro - insoluble** de liberación rápida y
   (b) un componente de **gelatina**

Encontramos que lo contenido en ella no es nuevo ya que dicha composición se revelaba previamente en la patente americana **US 4,681,765** "**Rapid releasing triamterene containing gelatin capsule dosage forms for one daily antihypertensive use**":

[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.

El documento americano enseña composiciones medicamentosas que como puede observarse a simple vista, contiene todas las características esenciales que se pretenden proteger en la reivindicación independiente, es decir, una **cápsula de gelatina** de **rápida disolución** que comprende surfactantes o **sales de carbonato como desintegrantes**.

CARACTERÍSTICAS DE LA REIVINDICACION 1 CO 12-162-306	US 4,681,785
Composición de encapsulamiento	Abstract
Liberación rápida	Abstract
Agente hidrosoluble	Abstract, Col 2 ln 15 – 16 Col 3 ln 65 - 66
Gelatina	Abstract, col 1, ln 7 - 10

De esta forma, la composición de la reivindicación 1 **no es nueva** ya que no hay características técnicas esenciales que la diferencien de las enseñanzas divulgadas en la patente americana mencionada.

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. (...)

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 disintegrent 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 bicar- (...)

La patente en mención, muestra además, ejemplos de posibles sales de carbonato hidro–insoluble de liberación rápida tales como: el carbonato de calcio o el carbonato de magnesio que pretende protegerse en la reivindicación 3, 34, 38 de la solicitud en trámite.

En consecuencia, mediante dicha anterioridad y la composición sugerida allí, queda demostrado que la solicitud colombiana en trámite y lo contenido en ella ya era absolutamente conocido lo que hace que carezca de novedad y a su vez de nivel inventivo frente al arte anterior.

* Por su parte, la publicación **US 2008/0275140** de 06/11/2008 "**Process for making a low molecular weight gelatine hydrolysate and gelatine hydrolysate compositions**" expone un proceso para elaborar un hidrolizado de gelatina y composiciones encapsuladas que lo contienen logrando así disoluciones mejoradas:

(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.

Claramente se evidencia que la realización de composiciones de encapsulamiento de liberación rápida con **gelatina** y además un **hidrolizado de gelatina**, tal como

pretende protegerse en la reivindicación 2 de la presente solicitud colombiana en trámite es una práctica ampliamente reconocida en el estado de la técnica.

> **[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

Como puede observarse, la publicación americana enseña inclusive los mismos pesos moleculares elegidos por la solicitud en trámite en su reivindicación 2, es decir 100 Dalton hasta 2000 Dalton, el cual es resultado de su proceso de elaboración del hidrolizado de gelatina.

Dicha anterioridad había solucionado el problema técnico previamente al enseñar que la gelatina era usada en la industria farmacéutica para la manufactura de composiciones en cápsulas de gelatina tanto duras como blandas, las cuales son de rápida liberación y que contienen gelatina, y un hidrolizado de gelatina tal como se pretende proteger en las reivindicaciones 1, 2, 14, 30, 26 y 48 de la presente solicitud colombiana en trámite, veamos:

> **[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

> 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 amounts of free glycine, other amino acids, and small peptides in the blended gelatine product, as shown in the Examples.

La publicación en mención, sugiere además el uso de **plastificantes** para la fabricación de cápsulas de gelatina blandas, tales como el **sorbitol** de la misma manera que aparece indicado en las reivindicaciones 9, 10, 11, 21, 22, 33, 40, 46, 47 de la presente solicitud colombiana en trámite:

(pág 7 [0068])

> from about 20% to about 45% by weight of water. The soft gelatine capsules may be made according to any method generally known in the art. Typical examples for plasticizers are glycerol (usually used in the form of a 85 weight % aqueous solution) and sorbitol (usually used in the form of a 70 weight % aqueous solution) and mixtures thereof.

Como se puede observar en los recuadros siguientes, también encontramos cómo la publicación americana enseña que el material de inicio dentro de sus procesos de producción es la **gelatina** la cual se disuelve en **agua** siendo así, procesos de elaboración de cápsulas plenamente conocidos en el arte de tal forma que el método de manufactura que se pretende proteger en la reivindicación 43 no es inventivo toda vez que se caracteriza de la misma manera, es decir, disolviendo gelatina en un medio acuoso para adicionar un agente hidro – insoluble (tal y como lo sugiere el documento US 2008/0275140 tantas veces mencionado).

> **[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 10% to about 50% gelatine by weight. (...)

> **[0067]** In one preferred embodiment, the gelatine composition is used in the manufacture of hard gelatine capsules. As detailed above, when the gelatine composition is used in the manufacture of hard capsule pharmaceutical products, the gelatine 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 4.5 to about 6.5. A typical hard capsule formulation will comprise approximately 30% by weight of the gelatine composition of the invention, approximately 65% by weight water, approximately 5% by weight of a suitable dye, and will contain a pigment as needed. The hard gelatine capsules may be made according to any method generally known in the art. (...)

[0092] The gelatine hydrolysate of the invention may be made according to the following process. A solution containing 34% by weight gelatine (limed-bone gelatine Type B. Bloom=100) was made by adding 1.94 kg of water to 1.0 kg of de-ionized processed gelatine. The gelatine was left to hydrate for 1 hour and then placed into a 55° C. water bath to dissolve. Once completely dissolved, the pH of the gelatine

En conclusión, la solicitud colombiana en trámite incumple con los requisitos fundamentales de novedad y nivel inventivo para merecer el privilegio de patente de invención, ya que la composición y las características técnicas esenciales que se pretenden proteger se describían ampliamente en el estado de la técnica, bien sea por medio de la patente americana **US 4,681,765** como documento único o combinado con la publicación **US 2008/0275140**.

De esta forma una persona medianamente versada en la materia a partir de al menos uno de los dos documentos que aquí se mencionan, lograría fácilmente y sin mucho esfuerzo, solucionar el mismo problema técnico, es decir, obtener una rápida velocidad de disolución encapsulando composiciones con principios activos, mediante gelatina y un agente de liberación o desintegración rápida con el fin de que se degrade ágilmente en el medio ácido de la cavidad gástrica pero con el medio acuoso de pH neutro de la cavidad oral y el esófago y que a su vez no degraden la estructura del encapsulante durante la producción.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente solicito que su Despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para

sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- Patente americana US 4,681,765 publicada el 21 de julio de 1987, todo el documento.
- Publicación americana US 2008/0275140 publicada el 6 de noviembre de 2008, abstract, pág 1, 3, 5, 6, 7, 8.

VII. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de TECNOQUIMICAS S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. Las mencionadas en el acápite de pruebas

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A. las recibirá en sus oficinas localizadas en la Calle 23 N° 7-39 de Cali.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.

- 3C MOLDE GRAFICAS LTDA • 2000 •

AA 3286577

ESCRITURA NUMERO CUATRO MIL QUINIENTOS - TREINTA Y NUEVE (No.4.539) -------------- En la ciudad de Cali, Capital del Departamento del Valle del Cauca, República de Colombia, a los VEINTITRES (23) días - del mes de OCTUBRE del año DOS MIL UNO -- (2.001), ante mi, JORGE ENRIQUE CAICEDO ZAMORANO, Notario TERCERO (3o.) del Círculo de Cali, -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali, identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: ----

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y representación de TECNOQUIMICAS S.A.. sociedad comercial organizada y existente conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de junio de 1957, reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali --

SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de Bogotá, identificado con C.C. # 79.152.473 de Usaquén, abogado en ejercicio, portador de la T.P 44655 del C.S.de la J., domiciliado en Bogotá, D.C., República de Colombia con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos u otros de diferente naturaleza; acciones y procesos que promovamos o se nos promuevan; y c) para

Como Notario Veintitres de este Circulo hago constar que esta fotocopia coincide con su fotocopia auténtica que he tenido a la vista.
13 AGO 2007
WILLY VALEK MORA
NOTARIO VEINTITRES
Bogotá D.C., Colombia

4539
OCT 23

LUZ MERY CORREA
ELABORACION DE ESCRITURAS
Notaria 3 de Cali

que en todos los asuntos arriba determinados, , tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos y ceder a titulo gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.----------

Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.----------

Se agregan comprobantes. Derechos $30.000.oo Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

Como Notario Veintitrés de este Círculo hago constar que esta fotocopia coincide con su fotocopia auténtica que he tenido a la vista.
13 AGO 2007
WILLY VALEK MORA
NOTARIO VEINTITRES
Bogotá D.C., Colombia

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.

REPUBLICA DE COLOMBIA
NOTARIO TERCERO
JORGE CAICEDO

El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO

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

[75] Inventor: Paul C. Guley, Clinton, N.Y.

[73] Assignee: American Home Products Corporation, New York, N.Y.

[21] Appl. No.: 650,035

[22] Filed: Sep. 13, 1984

[51] Int. Cl.[4] A61K 9/22; A61K 9/40

[52] U.S. Cl. 424/456; 514/869; 514/960; 514/962; 514/778; 514/781; 424/455

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

[56] References Cited

U.S. PATENT DOCUMENTS

2,883,327	4/1959	Dale	424/156
4,138,475	2/1979	McAinsh et al.	424/19
4,248,856	2/1981	Guley et al.	424/19
4,255,413	3/1981	Rattie et al.	424/37
4,444,769	4/1984	Blume et al.	424/20

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 diurectics 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. 4,255,413 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, nadolol, 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, 101, NF	27.0	27.0	27.0	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.	226 mg.	212 mg.

#O Grey H.G.C. Formulae were machine encapsulated on a suitable capsule filler.

TABLE II

	Percent Triamterene Dissolved				
Formula	7 minutes	15 minutes	30 minutes	60 minutes	90 minutes
I	2	3	7	11	16
II	71	83	91	94	95
III	68	79	91	98	99
IV	28	58	87	94	95
V	—	45	68	87	95
VI	—	33	71	94	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 1, 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 ¼% 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 disintegrent 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, polyplasdone 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.

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

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(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. Superimposition 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 amido 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 behavior 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 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 so as to form the gelatine hydrolysate.

point will be from about 4.7 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%.

[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 hard capsule 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 4.5 to about 6.5. In yet another preferred embodiment 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 10% 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 0.3 mm. In another embodiment, the gelatine particle size may be medium having an average particle size of from about 0.3 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. Gelatines having a fine particle size swell within a few minutes, gelatines having a medium particle size swell within about 8 to about 12 minutes, and gelatines having a large particle size swell within about an hour. Typically, low 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 typically 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® TSP, Enzeco® Bromelain Concentrate, Corolase® 7089, Papain 600L 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

from about 20% to about 30%. In another embodiment, the DH is from about 30% to about 40%. In yet another embodiment, the DH is from about 40% to about 50%. 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 observed 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 having an 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 electro-spray ionization liquid chromatography mass spectrometry (ESI-LC/MS). For example, a gelatine hydrolysate having an average molecular weight of approximately 1200 Da may have a molecular weight range from about 75 Da to 8000 Da.

[0044] In general, the gelatine hydrolysate will have an average primary amine content of not less than about 1.0×10^{-3} μMol of primary amine per μg of gelatine hydrolysate. In another embodiment, the gelatine hydrolysate will have an average primary amine content of not less than about 1.5×10^{-3} μMol of primary amine per μg of gelatine hydrolysate. In still another embodiment, the gelatine hydrolysate will have an average primary amine content of not less than about 2.0×10^{-3} μMol 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^{-3} to about 1.0×10^{-2} μMol of primary amine per μg of gelatine hydrolysate. The primary amine content of the gelatine hydrolysate is measured through derivatization and subsequent UV absorption (6-8) as illustrated in the Examples.

[0045] The gelatine hydrolysate of the present invention comprises polypeptides typically of up to about 75 amino acids in length, preferably up to 50 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^{-3} to about 1.0×10^{-2} μMol 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^{-3} to about 2.0×10^{-3} μMol 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^{-3} to about 2.0×10^{-3} μMol 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 amounts 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^{-3} to about 1.0×10^{-2} 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^{-3} to about 2.0×10^{-3} 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^{-3} to about 4.0×10^{-3} 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^{-3} to about 6.0×10^{-3} 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^{-3} to about 1.0×10^{-2}. Mol of primary amine per μg of gelatine hydrolysate.

[0052] The gelatine hydrolysate will also generally have an average polypeptide chain length from about 4 to about 50 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-2	Europe	porcine skin	2.5-4.5 kDa	30-60 mP (25%@20° C.)
Type A-3	Chicago	porcine skin	2.5-3.0 kDa	40-60 mP (25%@25° C.)
Type BH-1	Europe	bovine hide	2.0-4.0 kDa	32-47 mP (20%@25° C.)
Type BH-2	Europe	bovine hide	2.0-4.0 kDa	32-47 mP (20%@25° C.)
Type A-5	Sioux City	porcine skin	2.0-4.0 kDa	42-71 mP (20%@25° C.)
Type BB-1	Sioux City	bovine bone	2.0-4.0 kDa	42-90 mP (20%@25° C.)
Type BB-2	Sioux City	bovine bone	2.0-4.0 kDa	20-40 mP (20%@25° C.)
Type BBH-1	Europe	bovine bone/hide	2.0-4.0 kDa	32-50 mP (20%@25° C.)
Type BB-3	Chicago	bovine bone	2.0-4.0 kDa	30-50 mP (20%@25° C.)
Type BB-4	Chicago	bovine bone	2.0-4.0 kDa	30-50 mP (20%@25° C.)
Type BB-5	Chicago	bovine bone	2.0-4.0 kDa	42-90 mP (20%@25° C.)
Type BB-6	Chicago	bovine bone	2.0-4.0 kDa	42-90 mP (20%@25° C.)
Type A-6	Chicago	porcine skin	2.0-4.0 kDa	30-60 mP (20%@25° C.)
Type A-7	Chicago	porcine skin	2.0-4.0 kDa	30-60 mP (20%@25° C.)
Type A-8	South America	porcine skin	2.0-4.0 kDa	30-60 mP (20%@25° C.)
Type BH-3	South America	bovine hide	2.0-4.0 kDa	30-60 mP (20%@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

another embodiment, the gelatine will have an average molecular weight from about 100,000 Da to about 200,000 Da.

[0057] In one embodiment, the bloom strength of the gelatine will be from about 50 to about 300, the pH will be from about 3.8 to about 7.5, the isoelectric point will be from about 4.7 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%.

[0058] In an alternative embodiment when the gelatine 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 10.0, the viscosity will be from about 15 to about 75 mP and the ash will be from about 0.1 to about 2.0%.

[0059] In an alternative embodiment when the gelatine 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 4.8 to about 5.8, the viscosity will be from about 20 to about 75 mP and the ash will be from about 0.5 to about 2.0%.

[0060] In one preferred embodiment where the gelatine composition is used in the manufacture of hard capsule pharmaceutical products, the gelatine 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 4.5 to about 6.5.

[0061] In yet another preferred embodiment where the gelatine composition is used in the manufacture of soft shell capsule pharmaceutical products, the gelatine 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.

[0062] The gelatine composition of the invention will generally comprise from about 1% to about 20% by weight of the gelatine hydrolysate and from about 80% to about 99% by weight of the gelatine. In another embodiment, the gelatine composition will comprise from about 1% to about 5% by weight of the gelatine hydrolysate and from about 95% to about 99% by weight of the gelatine. In yet another embodiment, the gelatine composition will comprise from about 5% to about 10% by weight of the gelatine hydrolysate and from about 90% to about 95% by weight of the gelatine. In another embodiment, the gelatine composition will comprise from about 10% to about 15% by weight of the gelatine hydrolysate and from about 85% to about 90% by weight of the gelatine. In an additional embodiment, the gelatine composition will comprise from about 15% to about 20% by weight of the gelatine hydrolysate and from about 80% to about 85% by weight of the gelatine. In a typical embodiment, the gelatine composition will comprise a ratio of gelatine hydrolysate to gelatine from about 1:4 to about 1:99 (w/w).

[0063] In a preferred embodiment, the gelatine composition will comprise the gelatine hydrolysate of the present invention and a higher molecular weight pharmaceutical grade gelatine. In one embodiment, the gelatine composition will comprise from about 5% to about 10% by weight of the gelatine hydrolysate and from about 90% to about 95% by weight of the pharmaceutical grade gelatine. In another embodiment, the gelatine composition will comprise from about 10% to about 15% by weight of the gelatine hydrolysate and from about 85% to about 90% by weight of the pharmaceutical grade gelatine.

[0064] Advantageously, gelatine compositions of the present invention and of this embodiment typically have reduced cross-linking as measured by the vortex hardening test and viscosity test. Gelatine compositions of this embodiment typically have a vortex hardening time of about 200 to about 300 seconds. In another embodiment, the vortex hardening time is greater than about 300 seconds. The procedure for determining the vortex hardening time is described in the Examples. Gelatine compositions of this embodiment typically also have an average initial viscosity of from about 10 to about 15 cP and after the addition of less than about 0.5% by weight of [2-(4-dimethyl-carbamoyl-pyridino)-ethane-1-sulfonate] (OB1207® of H.W. Sands Corporation) to the gelatine composition for about two hours at a reaction temperature of about 60° C., the gelatine composition has an average viscosity of from about 15 to about 50 cP. The procedure for measuring viscosity is described in the examples.

[0065] In one embodiment, glycine as a separate compound may be added to the gelatine composition of the invention. The glycine may be added to the gelatine composition in an amount of from about 0.5% to about 5% by weight. In a more typical embodiment, the amount of glycine will be from about 1.5% to about 2.5% by weight. In yet another embodiment, citric acid may be added to the gelatine composition. The citric acid may be added in an amount of from about 0.5% to about 5% by weight. In a more typical embodiment, citric acid is added to the gelatine composition in an amount of from about 0.5% to about 1.5%.

[0066] The gelatine composition of the invention may be employed in several applications including as a food ingredient, as a cosmetic ingredient and as a photographic ingredient. Because of the gelatine composition's reduced tendency to cross-link and improved dissolution properties, in a preferred embodiment, the gelatine composition is used in the manufacture of pharmaceutical products.

[0067] In one preferred embodiment, the gelatine composition is used in the manufacture of hard gelatine capsules. As detailed above, when the gelatine composition is used in the manufacture of hard capsule pharmaceutical products, the gelatine 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 4.5 to about 6.5. A typical hard capsule formulation will comprise approximately 30% by weight of the gelatine composition of the invention, approximately 65% by weight water, approximately 5% by weight of a suitable dye, and will contain a pigment as needed. The hard gelatine capsules may be made according to any method generally known in the art.

[0068] In yet another preferred embodiment, the gelatine composition is used in the manufacture of soft capsule gelatine. As detailed above, when the gelatine composition is used in the manufacture of soft shell capsule pharmaceutical products, the gelatine 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. A typical soft capsule gelatine formulation will comprise from about 40% to about 45% by weight of the gelatine composition of the invention, from about 15% to about 35% by weight of plasticizer and from about 20% to about 45% by weight of water. The soft gelatine capsules may be made according to any method generally known in the art. Typical examples for plasticizers are glycerol (usually used in the form of a 85 weight % aqueous solution) and sorbitol (usually used in the form of a 70 weight % aqueous solution) and mixtures thereof.

[0069] All publications, patents, patent applications and other references cited in this application are herein incorporated by reference in their entirety as if each individual pub-

lication, patent, patent application or other reference were specifically and individually indicated to be incorporated by reference.

DEFINITIONS

[0070] "Amphoteric" is a substance that can be both cationic and anionic in character, such as a protein.

[0071] "Bloom value" is the degree of firmness of a gel measured in grams. The bloom value is the force required for a punch of defined form and dimension to penetrate 4 mm deep into the surface of a 6.7% by weight gelatine solution. The bloom values of commercially available gelatines are between 80 and 280.

[0072] "Bone chip" is chipped, degreased and dried bone from which, subsequent to demineralization (see maceration), gelatine is produced.

[0073] "Cross-linking" refers to the mechanism by which, e.g., a pellicle is formed on a pharmaceutical soft capsule. Typically, cross-linking decreases the dissolution properties of the capsule.

[0074] "Da" is an abbreviation for Dalton.

[0075] "EC" is an abbreviation for Enzyme Classification. It is typically used as a prefix in the numerical designation of an enzyme.

[0076] "Endopeptidase" is an enzyme typically belonging within subclass EC 3.4, peptide hydrolases, that hydrolyses nonterminal peptide linkages in oligopeptides or polypeptides and comprising any enzyme subclasses EC 3.4.21-99.

[0077] "Exopeptidase" is an enzyme of a group of peptide hydrolases within subclass EC 3.4 that catalyzes the hydrolysis of peptide bonds adjacent to the terminal amino or carboxyl group of an oligopeptide or polypeptide. The group typically encompasses enzyme subclasses 3.4.11-3.4.19.

[0078] "Food Grade Enzyme" is an enzyme that is typically free of genetically modified organisms and is safe when consumed by an organism, such as a human being. Typically, the enzyme and the product from which the enzyme may be derived are produced in accordance with applicable FDA guidelines.

[0079] "Hard capsules" are hollow capsules of various sizes made of pure gelatine with or without the addition of dye. They comprise an upper and lower part; these are joined together once filling is completed.

[0080] "Instant gelatine" is powder gelatine capable of swelling in cold water.

[0081] "Microgel" is considered to be gelatine with a molecular weight greater than 300,000 Da.

[0082] "Scleroproteins" are those proteins providing a support function within the body. They are insoluble in water and possess a fibrous structure. These proteins include e.g. keratin that occurs in hair and nails, the elastins and the collagens that occur in support and connective tissue, skin, bone and cartilage.

[0083] "Soft capsules" are elastic capsule made of gelatine for filling with active ingredient/excipient mixture. They can be produced with different wall thicknesses and either with or without a seam.

[0084] "Split" is a gelatine raw material: mid-layer of the connective tissue of cattle hide.

[0085] "Triple helix" is a basic structure of collagen consisting of 3 protein chains. These often possess somewhat different amino acid sequences.

[0086] "Type A gelatine" is acid digested gelatine.

[0087] "Type B gelatine" is alkali (basic) digested gelatine.

[0088] "Type LBSH" is a limed-bone hydrolysate of the present invention produced by proteolytic digestion of gelatine.

[0089] "Type LHSH" is a limed-hide hydrolysate of the present invention produced by proteolytic digestion of gelatine.

[0090] As various changes could be made in the above compounds, products and methods without departing from the scope of the invention, it is intended that all matter contained in the above description and in the examples given below, shall be interpreted as illustrative and not in a limiting sense.

EXAMPLES

[0091] The following examples illustrate the invention.

Example 1

[0092] The gelatine hydrolysate of the invention may be made according to the following process. A solution containing 34% by weight gelatine (limed-bone gelatine Type B, Bloom=100) was made by adding 1.94 kg of water to 1.0 kg of de-ionized processed gelatine. The gelatine was left to hydrate for 1 hour and then placed into a 55° C. water bath to dissolve. Once completely dissolved, the pH of the gelatine solution was adjusted to 6.0-6.5 with aqueous sodium hydroxide. Calcium Chloride was added to the gelatine solution in the amount of 0.0370% w/w with the amount of gelatine in solution (CDG—Commercial Dry Gelatine (having a moisture content of about 10% by weight), all additions in this procedure were based on this amount). An aliquot was taken and was diluted to 5% by weight in order to test the Redox State of the solution. Peroxide testing strips (EM Science) were used to quickly measure the amount of peroxide. If peroxide was present, Fermcolase® 1000F (Genencor International Inc.) was added in 0.5 ml increments. After each addition, the solution was left to react for 30 minutes before repeating the peroxide measurement. Fermcolase® 1000F additions were repeated until the peroxide level approached zero.

[0093] Corolase® 7089 (AB Enzymes) was added to the solution in the amount of 0.1% w/w. Near the end of the 1-hour reaction time and before the addition of the next enzyme, a small sample was taken and the molecular weight was analyzed. This process was repeated for each of the enzyme additions. After a 1-hour reaction time, 0.050% w/w of Enzeco® Bromelain Concentrate (Enzyme Development Corp.) was added and the solution was left to react for an additional hour. Liquid Papain 6000L (Valley Research) was then added 0.1% w/w. After 1 hour, 0.05% w/w of Validase® FPII (Valley Research) was added to the solution and was reacted for another hour. The final enzyme addition was 0.1% w/w of Corolase® LAP (AB Enzymes). After 1 hour, the solution was heated to 90° C. to deactivate the remaining functional enzymes. In some instances, an additional 30-40 ppm of hydrogen peroxide was added to be certain the Papain 6000L was deactivated. No proof of enzymatic activity after heat deactivation was seen. A summary listing the details of the five enzymes used during hydrolysis is given in Table 1.

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CONSIGNACION	BANCO DE BOGOTA	062754387	559955023	30/05/2013	856.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 OPOSICION POR CADA CLASE-MARCAS Y LEMAS COMERCIALES	325.000.00	325.000.00
				$325.000.00

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

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CONSIGNACION	BANCO DE BOGOTA	062754387	559955023	30/05/2013	856.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	1608 N CREACION PRORROGA DE TERMINOS O PLAZO ADICIONAL	103.000.00	103.000.00
				$103.000.00

SON: **CIENTO TRES MIL PESOS MONEDA CORRIENTE***

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