



Señor

SUPERINTENDENTE DE INDUSTRIA Y COM

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REF:

EXPEDIENTE 12-156-938

TÍTULO SOLICITADO:

“PELÍCULA DE ÉTER DE CELULOSA QUE TIENE
UNA BAJA OPACIDAD AÚN CON UNA ELEVADA
CONCENTRACIÓN DE CLORURO SÓDICO Y
MÉTODO DE PREPARACIÓN DE LA MISMA”

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SOLICITANTE:

SAMSUNG FINE CHEMICALS CO., LTD.

APODERADO:

JUAN PABLO CADENA SARMIENTO

TRÁMITE:

SUSTENTO DE OPOSICIÓN

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 **FARMACÁPSULAS 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. RATIFICACIÓN

Mediante el presente escrito ratifico que la solicitud 12-156-938, referida a películas para cápsulas duras, películas para alimentos, películas médicas, o películas industriales y un método para producirlas; no cumple con los requisitos de patentabilidad y no puede ser objeto de patente.

En la oposición presentada el 31 de mayo 2013, se demostró que la solicitud en trámite no cumple con los requisitos para ser aceptada, debido a que carece de claridad, concisión y soporte en la descripción. Entre otros aspectos se observó que dicha solicitud se refiere al uso de la película, lo cual no es patentable en el marco de la D. 486.

También, se mencionó que la anterioridad **US6294008** pertenece al mismo campo técnico de la materia reclamada (C08), identifica el mismo problema técnico y anticipa el mecanismo mediante el cual se resuelve el problema. Específicamente, **US6294008** revela composiciones que contienen éter de celulosa y cloruro de sodio en una cantidad de 0,3 % en peso (Col 1, ln. 45 a 55) al igual que la materia reclamada por la solicitud 12-156-938 en trámite.

Además se mencionó que la anterioridad **EP1045000** se relaciona con composiciones para formar películas para fabricar cápsulas farmacéuticas con la ventaja de mantener una apariencia favorable exterior durante un largo almacenaje, incorporando plastificantes como la hidroxipropilcelulosa e hidroxietilmetilcelulosa, por lo que se observa que el objeto de la solicitud ya había sido evaluado y demostrado su efecto técnico.

De lo allí divulgado, es evidente que los documentos **US6294008** y **EP1045000** anticipaban la composición reclamada en la solicitud en trámite, lo que hace que la misma carezca de Novedad y resulte, por ello, inaceptable como materia patentable.

II. COMPLEMENTO DE INFORMACIÓN

En adición a lo mencionado en el numeral precedente, debo anotar que la solicitud en curso, referida, reitero, a una película de éter celulosa más cloruro de sodio, y a un método de preparar una película disolviendo éter de celulosa que se irradia con ondas ultrasónicas, para luego impregnar la solución sobre un sustrato y secar la solución, incumple los requisitos materiales de patentabilidad en los términos que se precisarán en el presente documento:

2.1. Concisión, claridad y soporte en la descripción

- Reivindicación por “Resultados a Alcanzar”

En la reivindicación 2 se observa que se reclama la composición en función de una reducción esperada en la transmisión de luz alrededor de 2% o menos.

En primer término se estima inaceptable la pretensión de reivindicación en función de resultados esperados y no de propiedades intrínsecas de la materia revelada. De igual manera, se considera que el parámetro transcrito carece de claridad, en tanto, además de no divulgar las características estructurales de la composición, mediante las cuales se lograría dicho parámetro de transmisión de la luz, hace uso de una expresión amplia e indeterminada como “o menos”, término que carece de claridad y concisión, y que por ello resulta inaceptable como parámetro de reivindicación.

Ahora bien, en lo referido a la reivindicación 4, ésta reclama una película que tiene una transmisión de luz de alrededor de 80% o mayor. Como se puede ver, esta reivindicación reclama una película muy diferente a la de revelada en la reivindicación 2, pues su “transmisión de luz” no solo es mucho más alta que la reclamada anteriormente, sino habida cuenta de que dicho parámetro no permite comprender cuáles son las características técnicas de la película que permite esperar dichos resultados en materia de transmisión de luz, circunstancia que ratifica la carencia de concisión y claridad en las reivindicaciones mencionadas.

Por su parte, la reivindicación 6 se refiere a la película que tiene un índice de transmisión de vapor de agua (WVTR) de alrededor de 160g/m²/día o menos. Se observa nuevamente que se pretende proteger la película mediante un parámetro de resultados esperados, lo cual le resta claridad y concisión a la materia reclamada en esta reivindicación.

Así las cosas, y de acuerdo con lo mencionado anteriormente, se concluye que las reivindicaciones 2 a 6 no son claras ni concisas, y que por ello las mismas deberán ser rechazadas por el Despacho al resolver sobre el fondo de la solicitud que nos ocupa.

Ahora bien, en lo referido a las reivindicaciones 9 y 12, se observan expresiones que no hacen referencia a un rango conciso de cloruro de sodio, y que por el contrario, resultan inaceptablemente amplias e indeterminadas:

9. El método de la reivindicación 8, en donde el éter de celulosa comprende cloruro de sodio, en donde una cantidad del cloruro de sodio es mayor que alrededor de 0,3% en peso e igual a o menor que 0,6% en peso, basado en el peso total del éter de celulosa.

12. El método de la reivindicación 8, en donde la solución de éter de celulosa no tratada tiene una concentración de éter de celulosa de desde alrededor de 5% en peso a alrededor de 25% en peso.

En la misma línea argumentativa, la reivindicación 10 no especifica cual es el disolvente acuoso, lo cual le resta claridad y concisión:

10. El método de la reivindicación 8, en donde el éter de celulosa es soluble en agua, y el disolvente es un disolvente acuoso.

Por su parte, en la reivindicación 8 se menciona un sustrato, pero no hay indicios de cuál podría ser dicho sustrato:

impregnar la solución de éter de celulosa tratada sobre un sustrato; y

Finalmente, se observa que las reivindicaciones que reclaman el método se centran más en los ingredientes de la composición que en los pasos propios de dicho método. Por lo tanto, se considera que las reivindicaciones relativas a un método no son claras ni concisas.

En cuanto a la Descripción

Ahora bien, en lo referido a este aparte de la solicitud que nos ocupa, anotamos que la descripción no revela la forma de aplicación de la película, mientras en el capítulo reivindicatorio se dice que la misma puede ser usada en cápsulas duras, alimentos, médicas y películas industriales:

7. La película de la reivindicación 1, en donde la película se utiliza para cápsulas duras, películas para alimentos, películas médicas, o películas industriales.

Según el artículo 28 de la Decisión 486, la descripción debe revelar claramente el sector tecnológico al cual se aplica la invención y una realización de la invención; sin embargo, de acuerdo con lo presentado en la solicitud en estudio, la descripción no revela la mejor forma de llevar a la práctica la materia reclamada:

*Artículo 28- La **descripción** deberá divulgar la invención de manera suficientemente **clara y completa** para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla. La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información:*

- a) **el sector tecnológico al que se refiere o al cual se aplica la invención;***
- b) la tecnología anterior conocida por el solicitante que fuese útil para la comprensión y el examen de la invención, y las referencias a los documentos y publicaciones anteriores relativas a dicha tecnología;*
- c) una descripción de la invención en términos que permitan la comprensión del problema técnico y de la solución aportada por la invención, exponiendo las diferencias y eventuales ventajas con respecto a la tecnología anterior;*
- d) una reseña sobre los dibujos, cuando los hubiera;*
- e) **una descripción de la mejor manera conocida por el solicitante para ejecutar o llevar a la práctica la invención, utilizando ejemplos y referencias a los dibujos, de ser éstos pertinentes; y,***
- f) una indicación de la manera en que la invención satisface la condición de ser susceptible de aplicación industrial, si ello no fuese evidente de la descripción o de la naturaleza de la invención.*

Por lo anterior, se considera que no hay soporte en la descripción para la materia reclamada en la solicitud en trámite, y que la solicitud (descripción y reivindicaciones) carece de claridad.

Clasificación de la invención

Se pone de presente que la solicitud en trámite ha sido presentada en el campo técnico de la ingeniería química; sin embargo, en el campo técnico de farmacia existen anterioridades y conocimientos anteriores que permitirían acercarse a lo aquí reclamado, circunstancia que permitiría suponer una incorrecta clasificación de la solicitud que nos ocupa.

Nótese cómo, en efecto, la anterioridad, EP1045000 clasifica este tipo de películas en el campo de **farmacia** inclusive:

(51) Int Cl.7: **C08J 5/18**, C08L 1/28,
A61K 9/48

Lo propio ocurre con la anterioridad US 4,993,137, como se ve a continuación:

Current International Class: A61J 3/07 (20060101); A61K 9/48 (20060101);
Current CPC Class: A61J 3/077 (20130101); A61K 9/4816 (20130101)

Se llama la atención del Despacho para tener en cuenta que la materia divulgada y el problema a resolver también están clasificados dentro de la clase **A61**, al poder ser usadas dichas películas en el ámbito farmacéutico (Reivindicación 7).

Unidad de invención

Ahora bien, en lo referido al requisito mencionado en el título, debe anotarse que acuerdo con la materia divulgada en las reivindicaciones 1 y 8, existen aquí dos conceptos inventivos involucrados en la materia reclamada:

- De una parte, una "película" (reivindicación principal);
- De otra, un "método de obtención de una película", que sin embargo, no está vinculado a la película de la reivindicación principal, en tanto no se establece relación con los contenidos de cloruro de sodio establecidos en aquélla (ver reivindicación 8)

2.2. Ausencia de Novedad y Nivel Inventivo de la Composición para preparar una película (Reivindicación principal)

Novedad

En primer término, debe reiterarse que la solicitud **12-156-938** busca amparar, en la reivindicación 1, películas que contienen éter de celulosa y cloruro de sodio en una cantidad comprendida entre el 0,25% y el 0,6% en peso, mientras que el documento **US 6,294,008** revela una composición para formar película que esta provista de éter de celulosa y cloruro de sodio en un **0.3 p/p** (Col. 1, ln. 45 a 55 y resumen):

ABSTRACT

Como se puede ver en el cuadro siguiente, las características técnicas esenciales de la reivindicación 1, ya habían sido reveladas por el documento **US6294008** pues en éste se divulgaba una cantidad de cloruro de sodio (0,3 p/p) que se encuentra claramente comprendida dentro del rango reclamado por la solicitud **12-156-938**, el cual está comprendido entre 0,25 y 0,6 p/p, razón por la cual la materia reclamada en la reivindicación 1 y sus dependientes de la solicitud que nos ocupa, carecen de novedad.

Se concluye, entonces, que la composición reclamada en la reivindicación principal de la solicitud en trámite carece de novedad a la luz de las características divulgadas en la anterioridad **US 6.294.008**.

De otro lado, y ahora en relación con el requisito de Nivel Inventivo, se llama la atención a que el problema técnico planteado y supuestamente resuelto en la solicitud **12-156-938**, ya encontraba solución en documentos del estado de la técnica publicados con anterioridad a su fecha de prioridad:

Exp. 12 156 938	
Problema (P.4)	Solución (Col. 2)
Descripción detallada de la invención - Problema técnico - La presente invención provee una película de éter de celulosa que contiene una elevada concentración de cloruro	De acuerdo con un aspecto de la presente invención, se provee una película que incluye <u>éter de celulosa y cloruro de sodio</u> , en donde una cantidad del cloruro de sodio es desde alrededor

de sodio y <u>tiene una opacidad baja</u>	de <u>0.25%</u> en peso a alrededor de <u>0.6%</u> en peso basado en un peso total de la película ...
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Nótese cómo el documento **US6294008** revela que las cápsulas de éter de celulosa tienden a formar turbidez en sus superficies (Col. 1, ln. 28 a 43) y menciona que para disminuir la formación de turbidez es necesario ajustar el contenido de cloruro de sodio en la composición (Col. 2):

US6294008	
Problema (Col 1)	Solución (Col. 2)
A problem commonly encountered in manufacturing cellulose ether capsules is haze formation at their inner surfaces. Haze formation is most noticeable in transparent capsules. 30 Haze causes cellulose ether capsules to exhibit less luster and gloss than they would otherwise. Due to haze, cellulose ether capsules typically do not have the same level of luster as gelatin capsules. This difference in appearance is discussed in "HPMC Capsules—An Alternative to Gelatin," <i>Pharmaceutical Technology Europe</i> 10(11) (1998). 35 It would be desirable to have cellulose ether capsules which are substantially free of haze formation at their interior surfaces and a process for making such capsules. It would also be desirable to have a process for making a cellulose ether composition useful in such capsules. 40	DETAILED DESCRIPTION 20 In the present invention, it was discovered that haze formation in cellulose ether capsules can be significantly reduced by limiting the amount of sodium chloride remain-

De lo expuesto puede concluirse que la composición revelada **carece de nivel inventivo**, pues la solución para el problema de la opacidad de las cápsulas de éter de celulosa, dada por el manejo de las cantidades de cloruro de sodio, y por la adición de este componente, ya se había divulgado en el documento **US 6,294,008**, lo que sin lugar a dudas motivaría a una persona medianamente versada en la materia, a derivar la posibilidad de emplear el cloruro de sodio para resolver el tema de la opacidad de las cápsulas, en una concentración de 0,3 p/p de la composición.

2.3. Ausencia de Nivel Inventivo del método para preparar una película (Reivindicación independiente 8)

Ahora bien, en adición a los argumentos ya expuestos en el escrito de oposición sobre la carencia de Nivel Inventivo de la composición reivindicada, me permito ahora demostrar que el método de la reivindicación 8 también había sido anticipado por documentos del estado de la técnica. En dicha reivindicación se presenta un proceso para lograr una solución de éter de celulosa en la cual se sumergen algunos sustratos y luego al secarlos se obtiene la película deseada.

Sin embargo, de la lectura de la descripción, se observa que la característica técnica esencial es la ultrasonificación para tratar la solución de éter de celulosa:

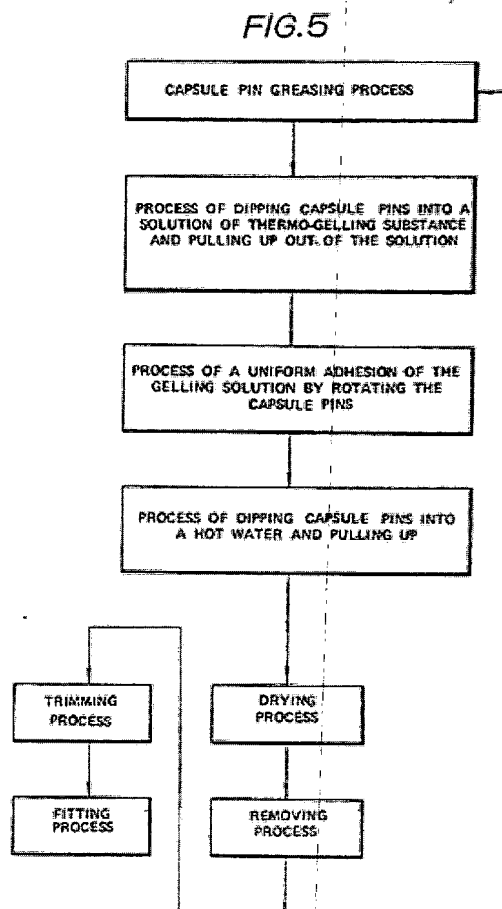
*8. Un método para preparar una película, método que comprende:
disolver éter de celulosa en un disolvente para obtener una solución de éter de celulosa no tratada;
irradiar con ondas ultrasónicas la solución de éter de celulosa no tratada para obtener una solución de éter de celulosa tratada;
impregnar la solución de éter de celulosa en un sustrato;
y secar la solución de éter de celulosa impregnada.*

En primer término, la tantas veces citada anterioridad **US 6,294,008** anticipaba parte del método reclamado, en el cual se disuelve el éter de celulosa para formar una solución y luego los sustratos “pins” son introducidos en ella, para ser posteriormente secados y obtener la película al remover los sustratos “pins” (Col. 2, ln. 5 a 17):

- 5 Further according to the present invention, there is a process for making cellulose ether capsules from the cellulose ether composition having low sodium chloride content. The cellulose ether is dissolved in water to form a dip coating solution. Metal pins are dipped into the coating
10 solution. The solution is allowed to gel and subsequently dry on the pins to form thin films of dried cellulose ether around the pins. The thin films takes the form of caps and/or bodies which are then removed from the pins. The caps and/or bodies can subsequently be mated to form whole capsules.
15 Both hot pin/cold solution and cold pin/hot solution processes are contemplated.

De otro lado, la anterioridad **US 4,993,137**, titulada “*Method of manufacturing hard capsules*”, publicada el **19 de febrero de 1991**, de Araume et al, presenta un método para obtener cápsulas que superan los problemas de las cápsulas de gelatina, que incluye **éter de celulosa**, la cual se calienta y se moldea, y en el cual los **sustratos** (pins) son hundidos en la solución del éter con un solvente acuoso (col. 1, líneas 20 a 25; fig. 5):

With an object to overcome the above described disadvantages of gelatin-made capsules, there have been proposed a methods in which cellulose ether substituted with alkyl groups or hydroxyalkyl groups is melted by heat and shaped, and in which molding pins are dipped in a solution of an organic solvent or in an aqueous solution and the solution is shaped by coating the pins with the solution.



Y la anterioridad **EP 1502588**, titulada "*Light-stabilized soft capsule formulations*", publicada en **mayo 6 de 2010**, de Perrie et al, presenta formulaciones de cápsulas blandas pequeñas con luz estabilizada, y el método para preparar la solución que forma las películas, en la cual se usa la irradiación de **ultrasonificación** "*ultrasonication*" (p.3):

[0019] According to another aspect, the present invention provides a method for preparing a shell-forming solution which is used to form a soft capsule shell containing a non-water-soluble light-shielding agent, said method comprising the step of dispersing the non-water-soluble light-shielding agent in a medium free from a gelling agent. Dispersion is preferably accomplished by ultrasonication.

[0020] According to yet another aspect, the present invention provides a method for manufacturing a soft capsule formulation containing a non-water-soluble light-shielding agent in its shell, comprising:

(i) the step of preparing a shell-forming solution, comprising the following steps (a) to (c):

(a) dissolving a gelling agent in Medium A;

(b) dispersing the non-water-soluble light-shielding agent in Medium B free from the gelling agent; and

(c) mixing Medium A containing the gelling agent dissolved therein with Medium B containing the non-water-soluble light-shielding agent dispersed therein; and

(ii) the step of forming a capsule shell for the soft capsule formulation using the shell-forming solution prepared in the step (i).

[0021] In the above step (i), the steps (a) and (b) may be performed in any order or simultaneously. Dispersion in the step (a) is preferably accomplished by ultrasonication.

En esta misma anterioridad, se revela que la **ultrasonicación** permite mejorar las propiedades de la solución del agente gelificante, pues permite alcanzar una dispersión más uniforme y el tratamiento de la solución de recubrimiento con la ultrasonicación hace que la dispersión sea exitosa hasta el final de la encapsulación (párr. [0057]):

[0057] To disperse a non-water-soluble light-shielding agent in a shell-forming solution, known mixers (e.g., a propeller mixer, a homomixer) can be used, but ultrasonication is preferred to achieve more uniform dispersion. For example, a commercially available ultrasonic cleaner can be used for this purpose. However, in a case where a non-water-soluble light-shielding agent is incorporated at a high content, as in the present invention, it has been found that it is difficult to ensure successful dispersion from beginning to end of encapsulation even when the non-water-soluble light-shielding agent is added to a solution of a gelling agent (e.g., gelatin) and then treated by ultrasonication. The inventors of the present invention made an attempt to disperse a non-water-soluble light-shielding agent in water, e.g., by ultrasonication before being added to a solution of a gelling agent. As a result, they have found that even in the case of incorporating a large amount of a non-water-soluble light-shielding agent, it is possible to ensure successful dispersion until the end of encapsulation and hence make soft capsule formulations having a good light-shielding property without any variation among capsules.

Como se puede observar, la materia reclamada por la reivindicación 8 y sus dependientes ya había sido revelada por las anterioridades **EP1502588**, **US4993137** y **US6294008**, por lo tanto, el método reclamado carece de nivel inventivo pues su característica técnica esencial - la ultrasonicación de la solución de éter - ya había sido divulgada previamente a la fecha de prioridad de la solicitud **12-156-938**.

En el cuadro a continuación, se enseña que los métodos de disolución del éter de celulosa en agua y la inmersión de sustratos o "pins" en ella para luego secarlos y obtener la película ya habían sido divulgadas por anterioridades como **US4993137** y **US6294008**; de igual manera, se ilustra que el documento **EP1502588** divulga que el proceso de **ultrasonicación** es recomendable para tratar la solución de éter (agente gelificante) en agua y obtener una solución de mayor calidad para el proceso de obtención de películas para cápsulas:

Exp. 12 156 938 Reivindicación 8	US6294008	US 4993137	EP 1502588
Un método para preparar una película, método que comprende:	Método para preparar cápsulas (Col. 2)	Método para preparar cápsulas (resumen)	Método para manufacturar formulaciones de cápsulas blandas (resumen)
disolver éter de celulosa en un disolvente para obtener una solución de éter de celulosa no tratada;	Éter de celulosa disuelto en agua (Col. 2, ln. 8 y 9) "The cellulose ether us dissolved in wáter to form a dip coating solution"	Primero, el éter de celulosa es disuelto en agua (col. 3, ln. 20-30) "the cellulose ether is first dissolved in wáter"	Disolver en agua el material gelificante para preparar la película (párr. [0063]) "Procedures for preparing the shell-forming solution are as follows. D-sorbitol (25 g) and gelatin (200 g) were dissolved in hot water at 80°C or more (500 mL) to prepare Solution A"
irradiar con ondas ultrasónicas la solución de éter de celulosa no tratada para obtener una solución de éter de celulosa tratada;	No se revela	No se revela	Irradiar la solución para tratarla "... ultrasonication is preferred to achieve more uniform dispersión..." (párr. [0052]) "..followed by ultrasonication at 47 kHz for 10 minutes (BRANSONIC ULTRASONIC CLEANER, Model 5210 J-DTH, Emerson Japan, Ltd.) while stirring by hand to prepare a suspension (Solution B)" (párr. [0063]) y
impregnar la solución de éter de celulosa en un sustrato;	Los sustratos son introducidos dentro de la solución de cubrimiento (col. 2, ln. 9 y 10) "Metal pins are dipped into the coating solution"	Impregnar unos sustratos "pins" con la solución de celulosa (Fig. 5) "molding pins are dipped in a solution of an organic solverl o ir a aqueous solution and the solution is shaped by coating the pins with the solution" (Col. 1, ln. 22 a 25)	Formar la cápsula (párr. [0010])
y secar la solución de éter de celulosa impregnada.	La solución se deja secar sobre los sustratos para luego retirarlos y obtener la película (Col. 2, ln. 10 a 12) "The solution is allowed to gel and subsequently dry on the pins to form thin films of dried cellulose ather around the pins"	Proceso de secado (Fig. 5) "Drying process"	Formar la cápsula (párr. [0010])

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Por lo tanto, el método de la reivindicación 8 carece de nivel inventivo pues una persona versada en la materia habría sido sugerida por **EP1502588** a utilizar el método de ultrasonicación para darle mejor calidad a la disolución de agua y éter de celulosa.

Adicionalmente, otros documentos presentan la utilidad de la ultrasonicación en métodos de obtención de películas de éter de celulosa: El documento **EP1547583**, titulado "*Capsule consisting essentially of low-substituted cellulose ether*" y publicado el 25 de junio de 2008, se refiere una cápsula de éter de celulosa con desintegración mejorada y métodos para prepararla (Párr. [0006]), y menciona que las dispersiones de éter de celulosa en el solvente puede ser homogenizadas para obtener mejores resultados (párr. [0031]):

homomixers and propeller-type homogenizers. The ho- 5
mogenizers may preferably include the homogenizer by
Sanwa Machine Co., Inc., which subjects the low-substi-
tuted cellulose ether to collisional friction by discharging
a treating liquid from a slit of a valve with high pressure;
the Ultimaizer System by Sugino Machine Limited; the 10
Microfluidizer by Mizuho Industrial Co., Ltd.; the Gaulin
high-pressure homogenizer; and an ultrasonic homoge-
nizer that utilizes vibration of ultrasonic waves such as
the ultrasonic homogenizer by Nippon Seiki Co., Ltd.
These homogenizers are preferably used for preparing 15
homogeneous dispersions. Furthermore, it is also pos-
sible to use dispersions that have been repeatedly treat-
ed by these apparatuses.

El documento **EP1591106**, titulado "*Film preparation and process for preparing the same*", publicado el 2 de noviembre de 2005, se refiere a hojas de gel para aplicaciones cosméticas y farmacéuticas (párr. [0001]) a base de éter de celulosa (párr. [0015]), y divulga que para su obtención es necesario preparar una dispersión de éter (párr.[0019]) que se homogeniza mediante un proceso de ultrasonicación (párr. [0021]) para mejorar los resultados obtenidos:

[0021] Examples of the wet-type pulverizer may include a vibratory ball mill, a colloid mill, a homomixer, a propeller-
type homogenizer, a high-pressure homogenizer, a ultrasonic homogenizer and a wet-type pulverizer of stone-mortar
form. The high-pressure homogenizer (e.g. "Ultimaizer", product of Sugino Machine Limited; "Nano-mizer", product of
20 Yoshida Kikai Co., Ltd.; "Microfluidizer", product of Mizuho Industrial Co., Ltd.) are advantageous for obtaining a uni-
formly shear-triturated product. The pressure for the treatment may be variable depending on a substance to be treated.

REYES & REYES

A B O G A D O S

Exp. 12 156 938	EP 1547583 – Cápsule consisting essentially of low-substituted cellulose ether – 25.06.2008	EP 1591106 - Film preparation and process for preparing the same – 02.11.2005
DESCRIPCIÓN: La presente invención ofrece asimismo un método de preparar una película, método que incluye irradiar ondas ultrasónicas sobre una solución de éter de celulosa (p.4) REIVINDICACIÓN N°8: Un método para preparar una película, método que comprende: disolver éter de celulosa en un disolvente para obtener una solución de éter de celulosa no tratada; irradiar con ondas ultrasónicas la solución de éter de celulosa no tratada para obtener una solución de éter de celulosa tratada; impregnar la solución de éter de celulosa en un sustrato; y secar la solución de éter de celulosa impregnada.	El documento revela homogenizadores ultrasónicos que utilizan la vibración de ondas ultrasónicas para homogenizar dispersiones de materiales como eter de celulsao en agua: <i>There is no particular limitation regarding the apparatus for preparing the cellulose ether dispersion obtained by collision of the low-substituted cellulose ether with each other, by collision of the low-substituted cellulose ether against a collision board, or by shear-triturating. Examples of the suitable apparatus may include vibration ball mills, colloid mills such as the Masscolloider or the Cerendipitor by Masuko Sangyo Co., Ltd., homomixers and propeller-type homogenizers. The homogenizers may preferably include the homogenizer by Sanwa Machine Co., Inc., which subjects the low-substituted cellulose ether to collisional friction by discharging a treating liquid from a slit of a valve with high pressure; the Ultimaizer System by Sugino Machine Limited; the Microfluidizer by Mizuho Industrial Co., Ltd.; the Gaulin high-pressure homogenizer; and an ultrasonic homogenizer that utilizes vibration of ultrasonic waves such as the ultrasonic homogenizer by Nippon Seiki Co., Ltd. These homogenizers are preferably used for preparing homogeneous dispersions. Furthermore, it is also possible to use dispersions that have been repeatedly treated by these apparatuses. (párr. [0031])</i>	Esta anterioridad revela que las dispersiones de eter de celulosa son tratadas mediante homogenizadores ultrasónicos: (párr. [0018]) <i>The aqueous dispersion of low-substituted cellulose ether can be prepared without any special agitator simply by placing the low-substituted cellulose ether in water, or by adding water to the low-substituted cellulose ether for absorption and expansion. The low-substituted cellulose ether can be shear-triturated directly by placing the low-substituted cellulose ether and water in a wet-type pulverizer.</i> (párr. [0019]) <i>Examples of the wet-type pulverizer may include a vibratory ball mill, a colloid mill, a homomixer, a propeller-type homogenizer, a high-pressure homogenizer, a ultrasonic homogenizer and a wet-type pulverizer of stone-mortar form. The high-pressure homogenizer (e.g. "Ultimaizer", product of Sugino Machine Limited; "Nano-mizer", product of Yoshida Kikai Co., Ltd.; "Microfluidizer", product of Mizuho Industrial Co., Ltd.) are advantageous for obtaining a uniformly shear-triturated product.</i>

Dado que todas las características de la composición de película ya habían sido divulgadas dicha composición carece de novedad y debido a que las características del método de obtención de película ya habían sido divulgadas por diferentes documentos del estado de la técnica, se considera que dicho método carece también de Nivel Inventivo, razón por la cual debe reiterarse la petición de negar la solicitud que nos ocupa en todas sus reivindicaciones.

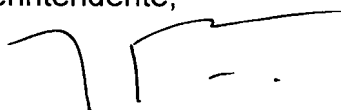
III. PRUEBAS

1. El documento **US4993137** titulado "*Method of manufacturing hard capsules*" publicada el 19 Febrero de 1991, de Araume et al, portada y página 1.
2. El documento **EP1502588** titulado "*Light-stabilized soft capsule formulations*" publicada el 6 Mayo de 2010, de Perrie et al, portada, p. 3.
3. El documento **EP1547583**, titulado "*Capsule consisting essentially of low-substituted cellulose ether*" y publicado el 25 de junio de 2008, de Hayakawa et al, portada, p. 2 y p. 5
4. El documento **EP1591106**, titulado "*Film preparation and process for preparing the same*" publicado el 02 de noviembre de 2005, de Maruyama et al, portada, p.2, p.3 y p.4.

IV. 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 FARMACÁPSULAS S.A., las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

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

[54] METHOD OF MANUFACTURING HARD CAPSULES

[75] Inventors: Hiroaki Muto, Joetu; Yuichi Nishiyama, Kubiki; Toru Chiba, Joetu; Kiyoshi Araume, Iwatsuki, all of Japan

[73] Assignee: Shin-Etsu Chemicals Co., Ltd., Tokyo, Japan

[21] Appl. No.: 449,354

[22] Filed: Dec. 13, 1989

1,831,212	11/1931	Voss et al.	264/304
1,870,775	8/1932	Gammeter	264/304 X
2,526,683	10/1950	Murphy	264/304 X
2,575,789	11/1951	Bogin	29/428
2,810,659	10/1957	Greminger, Jr. et al.	106/181
3,493,407	2/1970	Greminger, Jr. et al.	106/189
3,617,588	11/1971	Langman	264/301 X
3,794,453	2/1974	Padilla et al.	264/301 X
4,001,211	1/1977	Sarkar	536/84

FOREIGN PATENT DOCUMENTS

56825	8/1982	European Pat. Off.
180287	5/1986	European Pat. Off.

Primary Examiner—Jeffery Thurlow
Assistant Examiner—Leo B. Tentoni
Attorney, Agent, or Firm—Parkhurst, Wendel & Rossi

[57] ABSTRACT

A method for manufacturing capsules causes the solution of thermo-gelling material to gelatinize once, and then dries the gel. Therefore the process of manufacturing capsules is less affected by drying conditions, thus providing capsules of uniform wall thickness without wrinkle. In the apparatus, circulating capsule pins are dipped in the solution of thermo-gelling material, thus the solution adheres to the pins. The pins are rotated upside down, thus thickness of the solution adhering to the pins becoming uniform. Then the pins are retained in the vessel maintained at a higher temperature than the gelling temperature of the solution, and the solution adhering to the pins is gelatinized. The thus-formed gel is dried through a drying device, and the dried gel, i.e. capsules, is removed from capsule pins.

Related U.S. Application Data

[63] Continuation of Ser. No. 46,433, May 6, 1987, abandoned.

[30] Foreign Application Priority Data

May 12, 1986	[JP]	Japan	61-108275
Nov. 17, 1986	[JP]	Japan	61-274781

[51] Int. Cl.⁵ B29C 41/14

[52] U.S. Cl. 29/451; 106/170; 106/181; 106/189; 106/197.1; 106/197.2; 264/236; 264/297.8; 264/301; 264/303; 264/304; 264/306; 264/DIG. 37; 536/99

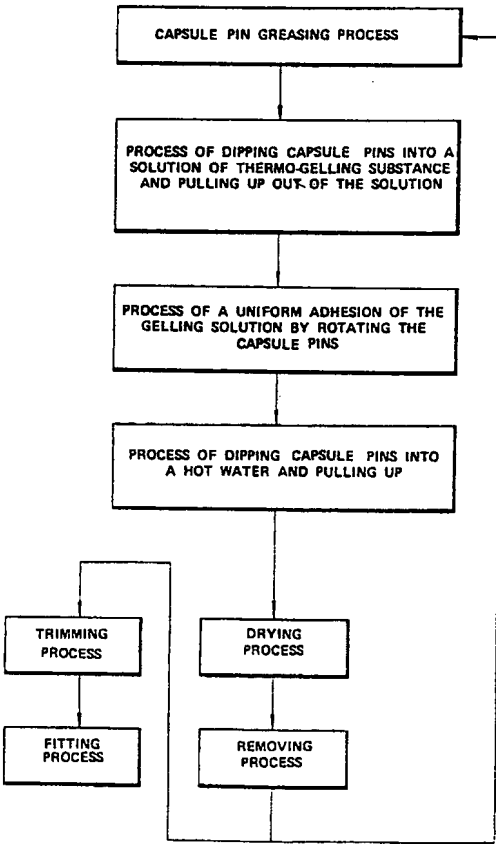
[58] Field of Search 264/232, 236, 297.8, 264/301, 303, 304, 306, 340, 345, 347, DIG. 37; 29/428, 451, 525, 899.1; 106/169, 170, 181, 189, 197.1, 197.2; 536/84, 99

[56] References Cited

U.S. PATENT DOCUMENTS

1,657,982	1/1928	Wilkie et al.	264/340
1,787,777	1/1931	Colton	425/96

2 Claims, 15 Drawing Sheets



METHOD OF MANUFACTURING HARD CAPSULES

This is a continuation of application Ser. No. 07/046,433 filed May 6, 1987, now abandoned.

BACKGROUND OF INVENTION

This invention relates to manufacturing equipment suitable for mass-production of hard capsules for medicament use.

Gelatin has been used as a thermo-gelling material of hard capsules for medicament use. However, the gelatin has problems in that it may interact with medicament ingredients and in that the control of the moisture content of capsules is troublesome for storage and handling thereof.

With an object to overcome the above described disadvantages of gelatin-made capsules, there have been proposed a methods in which cellulose ether substituted with alkyl groups or hydroxyalkyl groups is melted by heat and shaped, and in which molding pins are dipped in a solution of an organic solvent or in an aqueous solution and the solution is shaped by coating the pins with the solution.

The method of melt-shaping with heat has problems in that uniformity of the capsules can hardly be ensured and discoloration into yellow or brown may sometimes take place by the heat during shaping. The method of dipping in the organic solution has a disadvantage in that the solvent, which is toxic to humans, may remain in the capsules, in addition to the troublesome handling of the solvent. In the method of dipping in the aqueous solution, after pulling up the molding pins from the solution, the solution adhering to the pins sags down, so that it is difficult to prepare a capsule of uniform wall thickness. To improve this method it has been proposed to heat the molding pins in advance so that the solution adheres to the surface of the pin in a gelled form. But it is difficult to practice this method, because the effect is insufficient if the heating temperature is too low, while the capsule surface is often wrinkled in the course of drying if the temperature is too high.

The relation to the above-mentioned materials and methods is found in U.S. Pat. No. 3,493,407, U.S. Pat. No. 4,001,211, U.S. Pat. No. 2,810,659, U.S. Pat. No. 2,526,683 and U.S. Pat. No. 3,617,588.

Machines for making capsules are also found in U.S. Pat. No. 1,787,777.

SUMMARY OF THE INVENTION

The present invention is directed to a method of shaping hard capsules for medicament use having a uniform wall thickness without having wrinkle from an aqueous solution of a cellulose ether.

Therefore, an object of this invention is to provide an improved method of manufacturing hard capsules for medicament use that have a uniform wall thickness, no wrinkle and excellent properties.

Another object of this invention is to provide an improved apparatus for manufacturing hard capsules for medicament use that have a uniform wall thickness, no wrinkle and excellent properties.

A further object of this invention is to provide an improved apparatus which enables mass-production of hard capsules for medicament use.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and further objects and novel features of this invention will more fully appear from the following detailed description when the same is read in connection with the accompanying drawings. It is to be expressly understood, however, that the drawings are for purposes of illustration only and are not intended as a definition of the limits of the invention.

FIGS. 1A and 1B are partially sectional elevation views of a manufacturing apparatus embodying the present invention.

FIGS. 2A and 2B are partially sectional side elevation views of the above apparatus.

FIG. 3 is a partially sectional back side view of the above apparatus.

FIG. 4 is a sectional view taken in the direction of the arrows along the line IV—IV in FIGS. 1A and 3.

FIG. 5 is a flow chart of method of manufacturing hard capsules.

FIG. 6 is a perspective view of capsule pins.

FIG. 7 is a sectional view taken in the direction of the arrows along the line VII—VII in FIG. 1A.

FIG. 8 is an illustration of working condition of a part of the above apparatus.

FIG. 9 is a sectional view taken in the direction of the arrows along the line IX—IX in FIG. 8.

FIG. 10 is a perspective view of air nippers.

FIG. 11 is a top view of an air nippers.

FIG. 12 is a sectional view taken in the direction of the arrows along the line XII—XII in FIG. 9.

FIG. 13 is a drawing illustrating a working condition of a part of the above apparatus.

FIG. 14 is a drawing illustrating the process of coupling a pair of capsules.

FIG. 15 is a sectional view of a greasing device.

FIG. 16 is a schematic block diagram of a control system in the above apparatus.

FIGS. 17A, 17B and 17C are flow charts of a program of the control system.

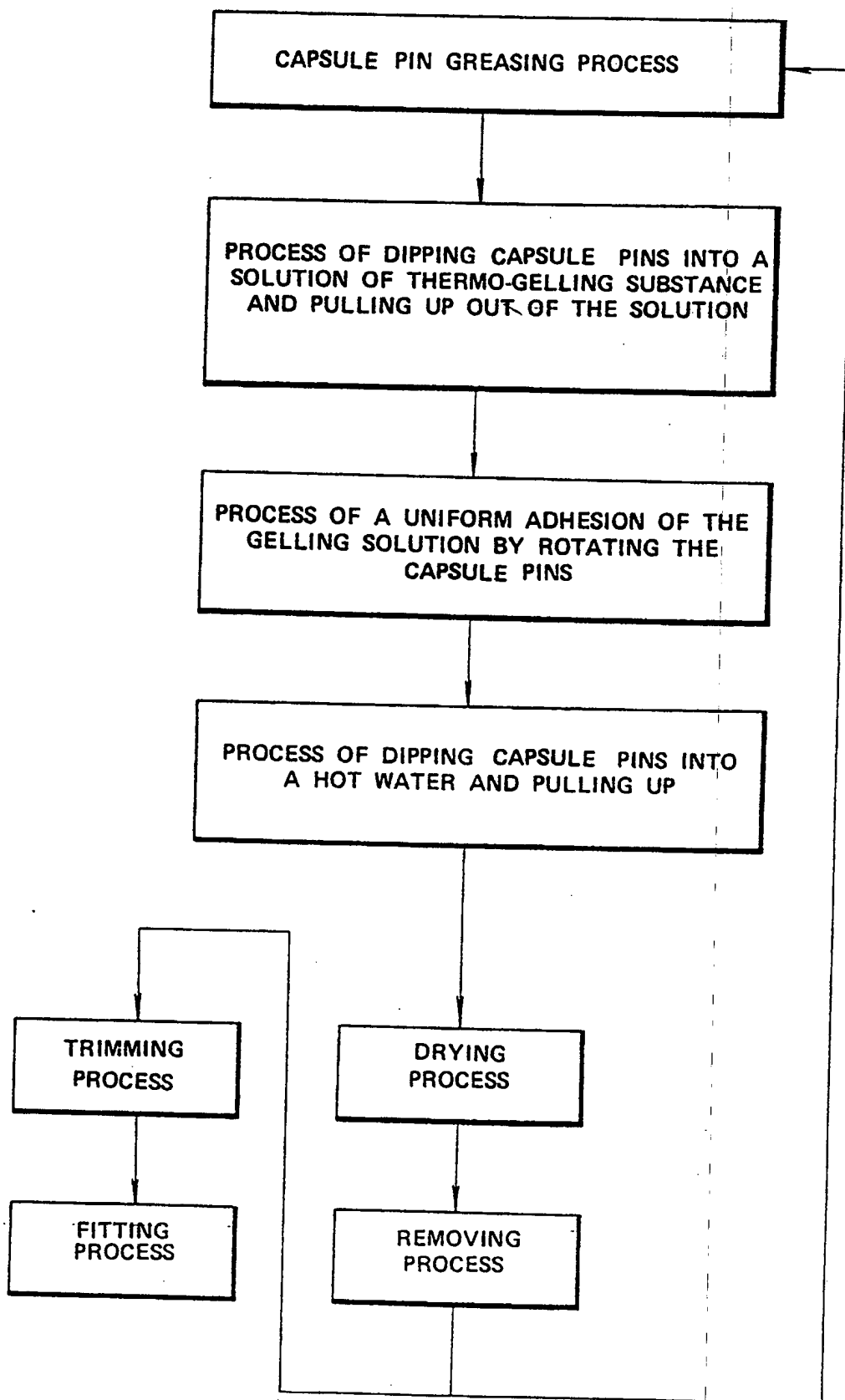
DESCRIPTION OF INVENTION

The method for manufacturing hard capsules in accordance with the present invention will be explained with reference to the flow.

FIG. 5 shows the following processes: 1. capsule pin greasing, 2. dipping the capsule pins into a solution of thermo-gelling material and pulling them up and out of the solution, 3. providing uniform adhesion of the gelling solution by rotating the capsule pins, 4. dipping the capsule pins into hot water and pulling them up and out of the hot water, 5. drying, 6. removing, 7. trimming and 8. fitting. The capsule pins pass through from processes 1. to 6. and return to process 1., thus repeatedly circulating through these processes. The manufacturing apparatus is provided with two lines that include processes 1. to 7., which manufacture capsules of different diameters, respectively. A pair of capsules of different diameter are fitted into each other to form a complete capsule.

The above-mentioned solution of the thermo-gelling material preferably provides an aqueous solution capable of being gelled by heating. Solutions such as alkyl-cellulose, hydroxyalkyl-cellulose and hydroxyalkyl-alkyl-cellulose exemplified by methyl-cellulose, hydroxypropyl-cellulose, hydroxyethyl-methyl-cellulose, hydroxypropyl-methyl-cellulose, hydroxybutyl-methyl-cellulose, hydroxyethyl-ethyl-cellulose, hydroxyethyl-

FIG. 5



(19)



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(84) Designated Contracting States: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR Designated Extension States: AL LT LV MK (30) Priority: 09.05.2002 JP 2002134070 (71) Applicant: CHUGAI SEIYAKU KABUSHIKI KAISHA Tokyo, 115-8543 (JP)	(72) Inventors: • MIZUTANI, Akihiko Chugai Seiyaku Kabushiki Kaisha Toshima-ku, Tokyo 171-8545 (JP) • KATSUKI, Hisakazu Chugai Seiyaku Kabushiki Kaisha Kita-ku, Tokyo 115-8543 (JP) • SAKAI, Ken-ichi Chugai Seiyaku Kabushiki Kaisha Gotenba-shi, Shizuoka 412-8513 (JP) (74) Representative: VOSSIUS & PARTNER Siebertstrasse 4 81675 München (DE)
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LIGHT-STABILIZED SOFT CAPSULE FOR FORMULATIONS

(57)

An object of the present invention is to provide a small-sized light-stabilized soft capsule formulation, which has a shell that ensures effective light shielding of an active ingredient encapsulated thereby.

The present invention provides a light-stabilized

soft capsule formulation comprising a shell containing a non-water-soluble light-shielding agent and having an average thickness of 200 μm or less, and a medicament encapsulated by the shell.

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Description

TECHNICAL FIELD

[0001] The present invention relates to light-stabilized soft capsule formulations having a shell that ensures effective light shielding of a medicament encapsulated thereby, as well as to a method for manufacturing the same. More particularly, the present invention relates to thin-shelled light-stabilized soft capsule formulations having a thin shell that ensures effective light shielding of a medicament encapsulated thereby.

BACKGROUND ART

[0002] Dosage forms conventionally used for the formulation of light-unstable substances include coated tablets, hard capsules, soft capsules, as well as oral solutions and powders filled in light-shielding containers. For example, JP 5-15691 B reports an example of soft capsule formulation whose shell is supplemented with 0.2 wt% of titanium oxide. Also, JP 57-4345 B reports an example of hard capsule formulation which contains 2 wt% or less of titanium oxide in combination with 0.5 wt% or less of iron oxide red. In certain cases such as where light-unstable substances are in a liquid form (e.g., oils, suspensions, emulsions) or are hardly soluble or easily oxidizable, dosage forms preferably used are soft capsules having a light-shielding shell.

[0003] Techniques known for manufacturing soft capsules include the plate method or the rotary method in which two sheet materials for shell formation are punched and shaped into capsules, as well as the in-liquid curing coating method (drop method) in which a solution to be encapsulated and a shell-forming solution are simultaneously dripped into a curing solution through a double nozzle. Soft capsules manufactured by the in-liquid curing coating method are also called seamless soft capsules because of their seamless shell.

[0004] When compared to the plate method and the rotary method, the in-liquid curing coating method enables the manufacture of soft capsule formulations having a smaller capsule size (e.g., 2 mm or less), thus also enabling the manufacture of granular soft capsule formulations which are readily taken by children, elderly people, or patients with reduced swallowing ability. Such formulations of smaller size are expected to have improved dispersibility of medicaments in the digestive tract and reduced variations in medicament absorption.

[0005] Commonly used soft capsule formulations have a capsule size of about 4 to 20 mm and a shell thickness of about 200 to 600 μm . It is therefore possible to achieve effective light shielding of the encapsulated active ingredient (s) when the shell is supplemented with about 0.1 to 2 wt% of a light-shielding agent, as stated above. However, in conventional techniques, it was inevitable that the shell thickness would be reduced as the capsule size decreased. For this reason, in the case of soft capsule formulations having a capsule size of 2 mm or less, conventional recipes for capsule shell could not ensure a shell thickness enough to provide sufficient light shielding of a light-unstable active ingredient.

[0006] As stated above, no soft capsule formulation has been developed for commercial use, which has a small capsule size and sufficiently prevents photodegradation of the encapsulated medicament by the action of a light-shielding shell.

DISCLOSURE OF THE INVENTION

[0007] An object of the present invention is to provide a light-stabilized soft capsule formulation, particularly a small-sized light-stabilized soft capsule formulation, which has a shell that ensures effective light shielding of an active ingredient encapsulated thereby.

[0008] Another object of the present invention is to provide a method for manufacturing such a light-stabilized soft capsule formulation.

[0009] As a result of extensive and intensive efforts directed to recipes for capsule shell of soft capsule formulations and methods for their manufacture, the inventors of the present invention have developed a recipe for capsule shell including a high content of a non-water-soluble light-shielding agent and a technique for its preparation. They also have found that this technique allows a sufficient reduction in light transmittance even for soft capsule shells less than 200 μm in thickness, thus enabling light stabilization of soft capsule formulations containing a light-unstable medicament even with a smaller capsule size. This finding led to the completion of the present invention.

[0010] Namely, the present invention provides a light-stabilized soft capsule formulation comprising:

a shell containing a non-water-soluble light-shielding agent and having an average thickness of 200 μm or less; and a medicament encapsulated by said shell.

[0011] In the light-stabilized soft capsule formulation of the present invention, the amount of the non-water-soluble

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light-shielding agent is preferably 5 to 30 wt%, based on the total amount of all components constituting the shell.

[0012] In the light-stabilized soft capsule formulation of the present invention, the non-water-soluble light-shielding agent is preferably titanium oxide.

[0013] In the light-stabilized soft capsule formulation of the present invention, the soft capsule formulation preferably has an average capsule size of 2 mm or less.

[0014] In the light-stabilized soft capsule formulation of the present invention, the shell is preferably seamless.

[0015] In the light-stabilized soft capsule formulation of the present invention, the medicament is preferably a light-unstable substance.

[0016] In the light-stabilized soft capsule formulation of the present invention, the medicament is preferably in a liquid form or the medicament is preferably dissolved or suspended in a liquid base.

[0017] In the light-stabilized soft capsule formulation of the present invention, the medicament is preferably a vitamin D derivative.

[0018] In the light-stabilized soft capsule formulation of the present invention, the major component of the shell is preferably gelatin.

[0019] According to another aspect, the present invention provides a method for preparing a shell-forming solution which is used to form a soft capsule shell containing a non-water-soluble light-shielding agent, said method comprising the step of dispersing the non-water-soluble light-shielding agent in a medium free from a gelling agent. Dispersion is preferably accomplished by ultrasonication.

[0020] According to yet another aspect, the present invention provides a method for manufacturing a soft capsule formulation containing a non-water-soluble light-shielding agent in its shell, comprising:

(i) the step of preparing a shell-forming solution, comprising the following steps (a) to (c):

(a) dissolving a gelling agent in Medium A;

(b) dispersing the non-water-soluble light-shielding agent in Medium B free from the gelling agent; and

(c) mixing Medium A containing the gelling agent dissolved therein with Medium B containing the non-water-soluble light-shielding agent dispersed therein; and

(ii) the step of forming a capsule shell for the soft capsule formulation using the shell-forming solution prepared in the step (i).

[0021] In the above step (i), the steps (a) and (b) may be performed in any order or simultaneously. Dispersion in the step (a) is preferably accomplished by ultrasonication.

[0022] In the method of the present invention for manufacturing a soft capsule formulation, the step of forming a capsule shell for the soft capsule formulation is preferably accomplished by the in-liquid curing coating method.

[0023] The light-stabilized soft capsule formulation of the present invention is preferably manufactured by the method of the present invention for manufacturing a soft capsule formulation.

[0024] According to yet another aspect, the present invention provides a unit dose package comprising the light-stabilized soft capsule formulation of the present invention (which is preferably manufactured by the method of the present invention for manufacturing a soft capsule formulation).

[0025] According to yet another aspect, the present invention provides a hard capsule, a tablet, an oral solution or an external preparation, which is prepared using the light-stabilized soft capsule formulation of the present invention (which is preferably manufactured by the method of the present invention for manufacturing a soft capsule formulation).

[0026] This application claims the priority of Japanese Patent Application No. 2002-134070, the disclosure of which is hereby incorporated by reference in its entirety.

BRIEF DESCRIPTION OF DRAWINGS

[0027]

Figure 1 is a top view of the mold used in Examples 1 and 2 for preparing a shell sample sheet.

Figure 2 is a side view of the mold shown in Figure 1 for preparing a shell sample sheet.

Figure 3 is a graph showing the results of light transmittance measured at each wavelength for the shell sample sheets obtained in Example 1. In the figure, the vertical axis represents the light transmittance of the shell and the horizontal axis represents the detection wavelength. The open diamond denotes a shell sample sheet obtained using a shell-forming solution immediately after its preparation by the in-gelatin dispersion method, the filled diamond denotes a shell sample sheet obtained using a shell-forming solution one hour after its preparation by the in-gelatin dispersion method, the open triangle denotes a shell sample sheet obtained using a shell-forming solution

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immediately after its preparation by the in-water dispersion method, and the filled triangle denotes a shell sample sheet obtained using a shell-forming solution one hour after its preparation by the in-water dispersion method.

Figure 4 is a graph showing the results of light transmittance measured at each wavelength for the shell sample sheets obtained in Example 2. In the figure, the vertical axis represents the light transmittance of the shell and the horizontal axis represents the detection wavelength. The filled diamond, filled square and filled triangle denote shell sample sheets obtained using shell-forming solutions containing 4%, 10% and 20% titanium oxide, respectively.

Figure 5 is a graph showing the relationship among titanium oxide content, sheet thickness and light transmittance at 500 nm of the shell sample sheets obtained in Example 2.

Figure 6 is a graph showing the results of accelerated irradiation test performed on the soft capsule formulations obtained in Example 3. The vertical axis represents the percentage of remaining 1 α -hydroxyvitamin D₃ and the horizontal axis represents the titanium oxide content in the shell. The filled diamond and filled square denote the results under accelerated conditions of 600,000 and 1,200,000 lux-h, respectively.

PREFERRED MODE FOR CARRYING OUT THE INVENTION

[0028] As used herein, the term "soft capsule formulation" is intended to mean an encapsulated formulation of a medicament, which is encapsulated either alone or in combination with an appropriate excipient, base or the like within a shell component containing an appropriate gelling agent (e.g., gelatin), if necessary together with polyhydric alcohols (e.g., glycerine, sorbitol) or other additives to increase its plasticity, and then shaped into a given form. This term encompasses soft capsule formulations defined in the Japanese Pharmacopoeia 13th revision (JP13) and soft capsule formulations found in USP24, as well as all other concepts such as so-called microcapsules. Such a soft capsule formulation is composed of a substance to be encapsulated (i.e., a medicament, either alone or in combination with a base or the like) and a shell encapsulating the same.

[0029] As used herein, the term "medicament" is used as a generic name for substances having specific effects, functions and efficacy. Examples include substances used for the purpose of treating, preventing or diagnosing human or animal diseases (i.e., human or animal drugs), as well as nutrients in foods with health claims and general foods, and animal feed. Other examples include deodorants, insecticides, antimicrobial agents, as well as dyes, pigments and colorants. Thus, the soft capsule formulation of the present invention can also be applied in the fields of pharmaceutical products, agricultural products, sanitary products, as well as office supplies, toys and other industrial products.

[0030] A soft capsule is a dosage form useful for obtaining oral formulations of liquid medicaments (e.g., in an oil or suspension form), hardly soluble medicaments, easily oxidizable medicaments, etc. Although soft capsules often encapsulate liquid medicaments, powder and solid medicaments can also be filled in soft capsules when using an appropriate instrument.

[0031] As used herein, the term "light-stabilized soft capsule formulation" is intended to mean a soft capsule formulation designed to encapsulate an inherently light-unstable medicament by a capsule shell having a high light-shielding property. Such a formulation is characterized by allowing the medicament encapsulated therein to have improved stability upon light irradiation when compared to the absence of such a light-shielding shell. By taking the form of light-stabilized soft capsule formulations, it is desirable to avoid, to the extent practically acceptable, photochemically induced changes and losses in the physical and chemical properties (e.g., activity, color, smell, taste) of inherently light-unstable medicaments during normal handling, shipping or storage. Light-stabilized soft capsule formulations encompass formulations in the dosage forms of light-stabilized soft capsules, light-stabilized seamless soft capsules, light-stabilized small-sized seamless soft capsules, light-stabilized microcapsules, etc.

[0032] Although any medicament can be encapsulated in the soft capsule formulation of the present invention, light-unstable medicaments can be filled to obtain effective light shielding. For example, effective light shielding can be achieved for dihydropyridine derivatives (e.g., nifedipine), antiviral HIV protease inhibitors (e.g., Ritonavir, Saquinavir), therapeutic agents for hyperlipidemia (e.g., clofibrate), iodine compounds (e.g., sodium iopodate, sodium iodide), polyunsaturated fatty acid derivatives (e.g., ethyl eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)), carotenoids (e.g., lycopene, bixin, β -carotene, xanthophyll, lutein), ubiquinones (coenzyme Q)(e.g., ubidecarenone used as a metabolizable cardiac stimulant), various vitamin derivatives, as well as indomethacin, colchicine, diazepam, syrosin-gopine, norethisterone, piretanide, propericyazine, perphenazine, mequitazine, medazepam, menatetrenone, indenolol hydrochloride, reserpine, sofalcone, bromocriptine mesilate, bufetolol hydrochloride and oxprenolol hydrochloride when they are filled into the soft capsule formulation of the present invention.

[0033] Among vitamin derivatives, fat-soluble ones are preferred for use. Examples include vitamin A derivatives (e.g., tretinoin, liver oil, retinol palmitate), vitamin A analogs (e.g., etretinate), vitamin D derivatives, vitamin E derivatives (e.g., tocopherol nicotinate, tocopherol acetate, tocopherol calcium succinate), and vitamin K derivatives (e.g., phytonadione (vitamin K1), menaquinone (vitamin K2), menadione (vitamin K3), menatetrenone, phytonadione).

[0034] The term "vitamin D derivative" refers to a compound having a 9, 10-secoandrostan skeleton, which may

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from easily settling out for a period during which a shell-forming solution is in a tank of an encapsulation machine. In manufacturing aspects, it is therefore preferred that a non-water-soluble light-shielding agent is kept from easily settling out and can be maintained in a dispersed state at least during encapsulation after preparation of a shell-forming solution. The time required for encapsulation will vary depending on the manner and the scale of encapsulation to be used, but it is desirable to maintain a given state of dispersion for at least 1 hour or more, preferably 3 hours or more, by taking into account the time required to adjust machine settings before encapsulation.

[0057] To disperse a non-water-soluble light-shielding agent in a shell-forming solution, known mixers (e.g., a propeller mixer, a homomixer) can be used, but ultrasonication is preferred to achieve more uniform dispersion. For example, a commercially available ultrasonic cleaner can be used for this purpose. However, in a case where a non-water-soluble light-shielding agent is incorporated at a high content, as in the present invention, it has been found that it is difficult to ensure successful dispersion from beginning to end of encapsulation even when the non-water-soluble light-shielding agent is added to a solution of a gelling agent (e.g., gelatin) and then treated by ultrasonication. The inventors of the present invention made an attempt to disperse a non-water-soluble light-shielding agent in water, e.g., by ultrasonication before being added to a solution of a gelling agent. As a result, they have found that even in the case of incorporating a large amount of a non-water-soluble light-shielding agent, it is possible to ensure successful dispersion until the end of encapsulation and hence make soft capsule formulations having a good light-shielding property without any variation among capsules.

[0058] In the present invention, such a method for preparing a shell-forming solution is referred to as the in-water dispersion method, which is characterized in that a non-water-soluble light-shielding agent is dispersed in water and then added to a solution of a gelling agent. A non-water-soluble light-shielding agent may be dispersed in water according to standard procedures, e.g., using a mixer, but ultrasonication is more preferred for this purpose. As used herein, the term "in-water" of the in-water dispersion method is intended to mean a medium free from a gelling agent, which includes cases where a non-water-soluble light-shielding agent is dispersed not only in pure water, but also in an aqueous solution supplemented with additives such as plasticizers, colorants, solvents, solvent aids, dispersants, solubilizers, stabilizers, correctives, sweeteners, adsorbents, abherents, antioxidants, antiseptics, preservatives, desiccants, flavors, perfumes, pH adjusters, binders, disintegrating agents, release-controlling agents, etc. These additives may be water-soluble or non-water-soluble. Examples of non-water-soluble additives include antiseptics such as methyl parahydroxybenzoate, ethyl parahydroxybenzoate, propyl parahydroxybenzoate, butyl parahydroxybenzoate, isobutyl parahydroxybenzoate, isopropyl parahydroxybenzoate, benzyl parahydroxybenzoate and sorbic acid.

[0059] Shell-forming solutions prepared using this in-water dispersion method can maintain a given state of dispersion during the time required for encapsulation, even when containing a high content of a non-water-soluble light-shielding agent. The amount of water or an aqueous solution required to disperse a non-water-soluble light-shielding agent therein is preferably at least 100 wt%, more preferably at least 300 wt%, based on the weight of the non-water-soluble light-shielding agent. It is also preferably 10000 wt% or less, and more preferably 5000 wt% or less. The amount of water used to dissolve a gelling agent will vary depending on the type of base to be used, but it is usually at least 80 wt%, more preferably at least 200 wt%, based on the weight of the gelling agent. It is also preferably 5000 wt% or less, and more preferably 1000 wt% or less. The frequency of ultrasonic waves to be used will vary depending on the type and amount of non-water-soluble light-shielding agent to be used, but it is usually at least 10 kHz, and more preferably at least 20 kHz. It is also 500 kHz or less, and more preferably 60 kHz or less. More specifically, it ranges from 10 kHz to 500 kHz, and preferably 20 kHz to 60 kHz. The time for ultrasonication is preferably at least 10 seconds, more preferably at least 30 seconds, and even more preferably at least 1 minute. It is also preferably 24 hours or less, more preferably 10 hours or less, and most preferably 30 minutes or less. More specifically, it ranges from 10 seconds to 24 hours, preferably 30 seconds to 10 hours, even more preferably 30 seconds to 1 hour, and most preferably 1 minute to 30 minutes.

[0060] The degree of dispersion of a non-water-soluble light-shielding agent in a shell-forming solution may be evaluated by measurement using a particle size distribution analyzer, sedimentation velocity measurement, microscopic observation, etc. In the case of aiming at light shielding, as in the present invention, the degree of dispersion may be evaluated by light transmittance measurement.

[0061] The light-stabilized soft capsule formulation of the present invention may be fabricated into various dosage forms. For example, the light-stabilized soft capsules of the present invention may further be treated to have some coating on it. Alternatively, the light-stabilized soft capsule formulation of the present invention may be filled into hard capsules. Moreover, the light-stabilized soft capsule formulation of the present invention may be compressed and molded into a certain dosage form together with an appropriate additive(s) or may be shaped and dried in a certain mold together with an additive(s) wetted with an appropriate medium, thereby giving tablets. Also, the light-stabilized soft capsule formulation of the present invention may be incorporated into oral solutions or external preparations. In each case of these fabrication examples, light-stable formulations can be obtained when using the light-stabilized soft capsule formulation of the present invention.

[0062] Moreover, in each case of these fabrication examples, it is possible to use one or more light-stabilized soft



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Capsule comprising low-substituted cellulose ether

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A capsule with good disintegration properties that can quickly display its content's efficacy as well as a method for preparing the same are provided. More specifically, provided is a capsule comprising a shell comprising low-substituted cellulose ether. Also, provided is a method for preparing a hard capsule comprising the low-substituted cellulose ether comprising a step of covering a pin for forming the hard capsule with the low-

substituted cellulose ether by immersing the pin in an alkaline solution of the low-substituted cellulose ether; a step of forming the low-substituted cellulose on a surface of the pin into a gel by further immersing the covered pin in an aqueous acid solution; a step of washing by immersing the pin whose surface has been covered with the gel in water; and a step of drying.

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Description**BACKGROUND OF THE INVENTION****1. Field of the Invention**

[0001] The present invention relates to a capsule with improved disintegration comprising low-substituted cellulose ether that is mainly used for food and pharmaceutical products and to a method for preparing the same.

2. Description of the Related Art

[0002] Generally, a shell of a hard or soft capsule comprises a water-soluble shell-forming component such as gelatin, agar, carrageenan, hydroxypropylmethylcellulose and the like. And a hard capsule is prepared, for example, by filling a content into a hard capsule shell formed by adhering an aqueous solution of gelatin onto a mold pin and drying the solution.

[0003] On the other hand, a soft capsule is prepared, for example, by encapsulating a content by a soft capsule shell that are obtained by forming a gel from a shell base substrate comprising gelatin, water and a plasticizer.

[0004] However, the conventional shell for the capsule described above has the following problems:

(1) Because eicosapentanoic acid (hereafter referred to as "EPA"), docosahexaenoic acid (hereafter referred to as "DHA"), β -carotene or the like, which is believed to be generally effective for the prevention of lifestyle diseases and the like, has many double bonds within the molecule, it is very easily oxidizable substance. Furthermore, because the substance has unpleasant taste and odor, it cannot be generally admixed to food as it is. Consequently, the substance is ordinarily used as health food sealed in a soft capsule. A method of adding the substance to food after sealing in a soft capsule is widely known (Japanese Patent Application Unexamined Publication No. 60-102138/1985, Japanese Patent Application Unexamined Publication No. 60-66935/1985, and Japanese Patent Application Unexamined Publication Nos. 2-203741/1990 and 5-65222/1993). However, although the methods can veil the unpleasant taste and odor, an oxidation of content cannot be completely prevented, so that the peroxide value increases as time passes, and the content turns yellow.

(2) Because the capsule used in pharmaceutical products or health food is generally required to have good intragastric dissolution after intake and the content's efficacy is displayed quickly, the improvement of the dissolution of a capsule has been an important problem to be solved. But nevertheless,

water-soluble polymers that are soluble in water but do not disintegrate and tend to form a thick gel film are presently used for the capsule base substrate.

5 SUMMARY OF THE INVENTION

[0005] In view of the above problems, it is an object of the present invention to provide a capsule that has good disintegration properties and that can quickly display its content's efficacy as well as a method for preparing the same.

[0006] As a result of intensive studies to attain this object, the inventors have focused on the various properties of low-substituted cellulose ether that does not dissolve but swells in water, and dissolves in an alkaline aqueous solution, and completed the present invention by finding that favorable disintegration properties are achieved and the content's efficacy can be quickly displayed and the drug does not undergo denaturation when using low-substituted cellulose ether as a base substrate for the capsule.

[0007] Therefore, the present invention provides a capsule comprising the following low-substituted cellulose ether and a method for preparing the same.

[0008] According to the present invention, provided is a capsule comprising a shell comprising low-substituted cellulose ether.

[0009] Moreover, according to the present invention, provided is a method for preparing a hard capsule comprising a low-substituted cellulose ether comprising a step of covering a pin for forming the hard capsule with the low-substituted cellulose ether by immersing the pin in an aqueous alkaline solution of the low-substituted cellulose ether; a step of forming the low-substituted cellulose on the surface of the pin into a gel by further immersing the covered pin in an aqueous acid solution; a step of washing by immersing in water the pin whose surface has been covered with the gel; and a step of drying.

[0010] According to the present invention, provided is a method for preparing a soft capsule comprising a low-substituted cellulose ether comprising a step of casting an aqueous alkaline solution of the low-substituted cellulose ether to obtain a sheet; a step of forming a gel sheet of the low-substituted cellulose by immersing the obtained sheet in an aqueous acid solution; a step of washing by immersing the gel sheet in water; a step of drying; and a step of molding by introducing the dried gel sheet into a film-introducing part of a gelatin soft capsule molding apparatus.

[0011] Furthermore, according to the present invention, provided is another method for preparing a hard capsule comprising a low-substituted cellulose ether comprising a step of preparing an aqueous solution by dispersing the low-substituted cellulose ether in water and further dispersing it by a shearing force; a step of covering a pin for forming the hard capsule with the low-substituted cellulose ether by immersing the pin in this

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and it may be preferable that the concentration corresponds to an amount that can stoichiometrically neutralize the concentration of the aqueous alkaline solution used.

[0026] In general, two methods described below can be given as examples of the methods for preparing a capsule comprising low-substituted cellulose ether of the present invention using the low-substituted cellulose ether described above.

[0027] In a first method, a pin for forming a hard capsule is immersed in an aqueous alkaline solution in which the low-substituted cellulose ether is dissolved, then the pin is lifted up and then immersed in an aqueous acid solution to cover the pin with a gel film of the low-substituted cellulose ether which contains the salt generated in the reaction of the aqueous acid solution and the aqueous alkaline solution. The pin covered with the gel film are then immersed in water for washing and later dried, thus obtaining a hard capsule-forming body.

[0028] It may be preferable that the concentration of the aqueous alkaline solution of the low-substituted cellulose ether is such that the solution is viscous enough that dripping of the solution is reduced to a minimum when the pin is drawn up from the solution. The concentration of 10 to 30% by weight may be particularly preferable. There is no particular limitation regarding the pin for forming the hard capsule and any pin as known in the art can be used. By immersion in the aqueous acid solution, the aqueous alkaline solution contained by the low-substituted cellulose ether which is present on the surface of the pin is neutralized. A gel film of the low-substituted cellulose ether is formed and the pin is covered with the gel film. At this time, the salt formed by the neutralization is present in the gel film, but the salt will be removed by washing in the subsequent step. There is no particular limitation regarding the drying and any of the drying methods known in the art can be used. The thickness of the capsule containing the low-substituted cellulose ether can be adjusted by the concentration of the aqueous alkaline solution of the low-substituted cellulose ether or the like, but the thickness may be preferably 10 to 50 μm .

[0029] In a method for preparing a soft capsule, the aqueous alkaline solution of the low-substituted cellulose ether may be cast on a substrate, then the cast portion is immersed in an aqueous acid solution, and while still containing the resulting salt, the gel sheet of low-substituted cellulose is formed. After immersing the gel film sheet in water for washing, it is washed and dried. The obtained gel sheet can be molded by introducing the gel sheet preferably into a film-introducing part of a gelatin capsule molding apparatus.

[0030] In this method for preparing a soft capsule, the concentration of the low-substituted cellulose ether in the aqueous alkaline solution may depend on the ease of the casting. It may be preferable that the concentration is 10 to 30% by weight. The casting may be performed by applying the low-substituted cellulose ether

on a known substrate of glass or synthetic resin such as polyethylene terephthalate, polypropylene or the like, and adjusting the thickness of the applied low-substituted cellulose ether with a doctor blade, thus obtaining a sheet of the low-substituted cellulose ether. The gel sheet is a sheet in which the surface of the low-substituted cellulose ether sheet has been formed into a gel. There is no particular limitation to the gelatin capsule molding apparatus and any apparatus known in the art can be used, such as the rotary soft capsule R&D model SSC-A3 by Sankyo Co., Ltd., for example. The thickness of the sheet before the introduction into the gelatin capsule forming apparatus may be preferably 0.05 to 0.20 μm , and the thickness of the sheet obtained after the molding with the gelatin capsule-forming apparatus may be preferably 0.03 to 0.15 mm.

[0031] After washing, the gel pin or the gel sheet may be immersed in a plasticizer solution containing glycerin, propylene glycol, ethylene glycol or their derivative or an aqueous solution containing the same, and may be impregnated with the plasticizer. With subsequent drying, it may be possible to obtain even a softer hard capsule or soft capsule. Instead of the plasticizer solution, it may be also possible to add an appropriate amount of starch, pullulan or chitin in order to adjust the disintegrating properties. The amount of plasticizer may be preferably 10 to 30% by weight and the concentration of the plasticizer solution may be preferably 10 to 50% by weight.

[0032] Another method for preparing the capsule comprising the low-substituted cellulose ether may comprise steps of dispersing the low-substituted cellulose ether in water, applying a shearing force to the dispersion, immersing a pin in the cellulose ether dispersion which has been subjected to the shearing force, washing and drying so as to obtain a hard capsule forming body.

[0033] The dispersion of the low-substituted cellulose ether can be prepared by using preferably 2 to 10 parts by weight of low-substituted cellulose ether in 100 parts by weight of water. Application of the shearing force may be performed by collision of the low-substituted cellulose ether against each other, collision of the cellulose ether against a collision board, shear-trituration, for example. However, there is no limitation to this, and as long as being dispersed by wet pulverization is done, any method can be applied. There is no particular limitation to the pin, and a pin similar to the pin described above may be used. The surface of the pin may be covered by immersing it in this dispersion. Drying may be performed by any known method. The thickness of the capsule comprising the low-substituted cellulose ether can be adjusted preferably in the range of 0.03 to 0.2 mm, more preferably in the range of 0.05 to 0.15 mm.

[0034] Another method for preparing a soft capsule can comprise steps of forming a cellulose ether dispersion, which has been obtained by applying a shearing force similarly as described above, into a sheet by cast-



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(54) Film preparation and process for preparing the same

(57) An object is to provide a film preparation comprising a polymer harmless to living bodies and being highly adhesive to the skin; and a film preparation further containing a pharmaceutically active oily ingredient and being highly adhesive to the skin. More specifically, provided is a film preparation comprising a drug, a wetly shear-triturated low-substituted cellulose ether having a

molar substitution of from 0.05 to 1.0 per anhydrous glucose unit, and a water-soluble cellulose ether, and having 100 minutes or greater of adhesion ability to the skin. The preparation becomes a skin-adhesive hydrous sheet having excellent skin adhesion after it is wet with water as it is used.

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Description**BACKGROUND OF THE INVENTION**

5 1. Field of the Invention

[0001] The present invention relates to a gel sheet used for cosmetics, pharmaceuticals and the other applications, particularly to a cosmetic sheet or percutaneous absorption preparation to be applied to the skin.

10 2. Description of the related art

[0002] Gel sheets mainly comprising agar or the like are conventionally known. Since the agar as a gel forming component forms a network structure in water, such gel sheets can be used for the purpose of moisture retention. The gel sheets made of agar however do not have a sufficient strength and in addition, there is a difficulty in incorporating an oily pharmaceutically active ingredient therein.

[0003] Gel sheets using an acrylic polymer gel are, on the other hand, not free from the fear of toxicity of the residual monomer and those with less irritation to the skin are requested. Many gel sheets need a crosslinking agent, the use of which complicates their preparation process. It is also impossible to incorporate a pharmaceutically active oily ingredient in such gels freely.

[0004] Many of cosmetic sheets to be applied to the skin such as face or hands contain therein a moisturizing agent and a polymer for supporting the moisturizing agent therewith, or are used after applying components containing a moisturizing agent to the sheet. For example, a cosmetic moisturizing sheet containing a moisturizing agent such as hyaluronic acid or collagen supported on a fiber sheet is disclosed in Japanese Patent Application Unexamined Publication No. 9-238738/1997. A cosmetic pack comprising chitosan and a medium paste, and a collagen-free moisturizing mask obtained by crosslinking a cationic biopolymer are disclosed in Japanese Patent Unexamined Application Nos. 6-48917/1994 and 2001-502678, respectively.

[0005] The above-described gel sheet is typically a paper sheet impregnated with a moisturizing agent. It does not have a sufficient water retention capacity and in addition, the paper sheet causes a sense of discomfort upon use. Gel polymers have improved adhesion to the skin, but are not sufficient. Another drawback of them is a complicated preparation process owing to the use of a crosslinking agent.

[0006] As a countermeasure against the above-described problems, a gel sheet of cellulose ether having a low molar substitution is disclosed in Japanese Patent Application Unexamined Publication No. 6-48197/1994. The gel sheet is free from the problem of a monomer which occurs upon use of an acrylic polymer, can be prepared without extra effort because a crosslinking agent is not necessary. The gel sheet has a sufficient water retaining capacity, and does not cause any sense of discomfort upon use. When such a sheet is applied to the body, however, it peels off the body before a drug such as a moisturizing agent, an anti-wrinkle agent, an anti-spot agent or a whitening cosmetic with which the sheet has been impregnated starts exhibition of its effect (about 20 minutes). It cannot keep its adhesion for at least 60 minutes, time at least necessary for the effective delivery of the chemical substance. Thus, the gel sheet has a drawback in skin adhesion. The above-described hydrous sheet of low-substituted cellulose ether can be prepared by casting an alkaline solution of low-substituted cellulose ether onto a supporting plate, neutralizing and coagulating the sheet with an acid and then washing off, from the sheet, the salt formed by neutralization. In order to produce a sheet containing a pharmaceutically active ingredient, the pharmaceutically active ingredient is added in advance upon preparation of an alkaline solution, or a sheet formed is dipped in a solution containing the pharmaceutically active ingredient. However, depending on a type of pharmaceutically active ingredient, production of sheet containing the pharmaceutically active ingredient has problems, for example, that the ingredient is decomposed in the alkaline solution, it does not dissolve in the solution smoothly, or a sufficient amount of the ingredient cannot be supported in the sheet even if the sheet is dipped in an aqueous solution of the ingredient. Moreover, an oily substance immiscible with water cannot be incorporated.

[0007] There is a process of preparing a hydrous gel sheet having improved skin adhesion, which comprises casting, on a supporting plate, a mixture of an alkaline solution of low-substituted cellulose ether and water-soluble and alkalisoluble cellulose ether having a substitution degree of 1.1 to 1.4, neutralizing and coagulating a sheet of the mixture on the plate with an acid, and washing off the salt in the sheet. By this process, however, it is impossible to prepare a hydrous sheet having a high content of water-soluble cellulose ether because a portion of the water-soluble cellulose ether leaks out during the washing step for removing the neutralization salt, leading to a reduction in the strength of the hydrous sheet. The higher the content of the water-soluble cellulose ether is, the better the skin adhesion of the sheet is. The sheet obtained by the above-described method therefore does not have sufficient skin adhesion.

[0008] As percutaneous absorption preparations, a nicotine-containing film preparation is disclosed in Japanese Patent Application Unexamined Publication No. 2003-95947. A skin adhesive film preparation obtained by incorporating

a water-soluble cellulose lower-alkyl ether in a fibroblast growth factor is disclosed in Japanese Patent Application Unexamined Publication No. 7-82171/1995. A membrane-attached adhesive multilayer film preparation comprising a water-soluble polymer layer containing a drug and an adhesive layer containing an adhesive substance is disclosed in Japanese Patent Application Unexamined Publication No. 9-235220/1997. Any of them does not relate to a hydrous sheet containing low-substituted cellulose ether.

SUMMARY OF THE INVENTION

[0009] With the foregoing in view, the present invention has been completed. An object of the present invention is to provide a hydrous gel sheet comprising a polymer harmless to the living body and being highly adhesive to the skin. Another object of the invention is to provide a hydrous gel sheet comprising a pharmaceutically-active oily ingredient and being highly adhesive to the skin.

[0010] The present inventors have carried out an extensive investigation with a view to attaining the above-described objects. As a result, it has been found that a film preparation containing a desired amount of drug can be prepared by casting a mixture onto a supporting plate wherein the mixture comprises a drug, wetly shear-triturated low-substituted cellulose ether having a molar substitution of 0.05 to 1.0 per anhydrous glucose unit ($C_6H_{10}O_5$) and an aqueous solution of water-soluble cellulose ether; and then drying the cast mixture. A hydrous gel sheet having excellent skin adhesion can be prepared only by wetting the film preparation when it is used, leading to the completion of the invention.

[0011] In one aspect of the present invention, there are thus provided a film preparation comprising a drug, wetly shear-triturated low-substituted cellulose ether having a molar substitution of 0.05 to 1.0 per anhydrous glucose unit and water-soluble cellulose ether and being capable of adhering to the skin for 100 minutes or greater; and a skin-adhesive hydrous sheet obtained by wetting said film preparation.

[0012] In another aspect of the present invention, there is also provided a preparation method of a film preparation, which comprises casting a mixture onto a supporting plate wherein the mixture comprises a drug, wetly shear-triturated low-substituted cellulose ether having a molar substitution of from 0.05 to 1.0 per anhydrous glucose unit and an aqueous solution of water-soluble cellulose ether; and then drying the cast mixture.

[0013] According to the present invention, a film preparation containing a desired amount of a drug is excellent in water retention. When the preparation is wetted with water, it has excellent sheet strength and elasticity. It is excellent in skin adhesion and feeling upon use. A skin adhesive hydrous sheet containing an oily substance can also be obtained according to the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0014] The present invention will hereinafter be described in details.

[0015] Low-substituted cellulose ether to be used in the present invention is insoluble in water but soluble in an alkaline solution. Cellulose is generally insoluble in water. However, when the hydrogen atom of the hydroxyl group on the glucose ring of the cellulose is substituted with an alkyl or hydroxyalkyl group, the cellulose becomes water-soluble, though depending on the degree of its substitution. When the substitution degree is low, the cellulose is not water-soluble and instead, tends to become soluble in an alkaline solution. In many cases, when low-substituted cellulose ether powder is dispersed in water, it becomes partially swelled with water. When it has a high molar substitution, it becomes water-soluble and loses alkaline solubility.

[0016] Low-substituted cellulose ether to be used in the present invention, which is insoluble in water but soluble in an alkali, preferably has a molar substitution of from 0.05 to 1.0. Examples of various low-substituted cellulose ethers (the number in parentheses means a molar substitution degree) may include low-substituted methyl cellulose having 3 to 15 wt% of a methoxyl group (from 0.16 to 0.85), low-substituted hydroxyethyl cellulose having 3 to 15 wt% of a hydroxyethoxyl group (from 0.08 to 0.45), low-substituted hydroxypropyl cellulose having 4 to 20 wt% of a hydroxypropoxyl group (from 0.09 to 0.51) and low-substituted hydroxypropyl methyl cellulose having 3 to 12 wt% of a methoxyl group and 4 to 20 wt% of a hydroxypropoxyl group (from 0.25 to 1.0 in total of both substituents). The substitution degree of a cellulose ether can be measured in accordance with the Japanese Pharmacopoeia.

[0017] Such low-substituted cellulose ether is insoluble in water but soluble in an aqueous alkaline solution. It absorbs water and swells. The typical example thereof may include low-substituted hydroxypropyl cellulose, which is commercially available now from Shin-Etsu Chemical Co., Ltd., under the trade name of "L-HPC". It is listed in the Japanese Pharmacopoeia and popularly used as a disintegrant to be incorporated in tablets, particularly in the field of pharmaceutical materials.

[0018] A preparation process of such low-substituted cellulose ether is known. For example, as described in Japanese Patent Application Unexamined Publication No. 57-53100/1982, alkali cellulose has to be prepared first. It may be obtained by immersing a starting pulp sheet in an aqueous alkaline solution such as sodium hydroxide; or mixing pulverized pulp directly with an alkaline solution; or adding an alkali to a pulp powder dispersed in an organic solvent.

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The alkali cellulose thus obtained is placed in a reactor, followed by the addition of an etherifying agent such as propylene oxide or ethylene oxide. The reaction mixture is then heated for the reaction to produce the cellulose ether. After completion of the reaction, the resulting crude cellulose ether is transferred into another tank, where the alkali is neutralized with an acid. The solid thus obtained is washed, dried and then pulverized to produce a powder as a final product. Alternatively, the final product may be prepared by completely or partially dissolving in water the crude cellulose ether just after the reaction, neutralizing the resulting solution, collecting the precipitated polymer, and washing, drying and pulverizing the polymer.

[0019] According to the method for producing a film preparation, the film preparation is produced by casting a mixture onto a supporting plate wherein the mixture comprises a drug, wetly shear-triturated low-substituted cellulose ether having a molar substitution of 0.05 to 1.0 per anhydrous glucose unit, and an aqueous solution of water-soluble cellulose ether; and drying the cast mixture. The wetly shear-triturated low-substituted cellulose ether can be obtained by shear-triturating an aqueous dispersion of low-substituted cellulose ether with a wet-type pulverizer.

[0020] The aqueous dispersion of low-substituted cellulose ether can be prepared without any special agitator simply by placing the low-substituted cellulose ether in water, or by adding water to the low-substituted cellulose ether for absorption and expansion. The low-substituted cellulose ether can be shear-triturated directly by placing the low-substituted cellulose ether and water in a wet-type pulverizer.

[0021] Examples of the wet-type pulverizer may include a vibratory ball mill, a colloid mill, a homomixer, a propeller-type homogenizer, a high-pressure homogenizer, a ultrasonic homogenizer and a wet-type pulverizer of stone-mortar form. The high-pressure homogenizer (e.g. "Ultimaizer", product of Sugino Machine Limited; "Nano-mizer", product of Yoshida Kikai Co., Ltd.; "Microfluidizer", product of Mizuho Industrial Co., Ltd.) are advantageous for obtaining a uniformly shear-triturated product. The pressure for the treatment may be variable depending on a substance to be treated. The pressure may be preferably from 100 to 250 MPa. When the pressure is less than 100 MPa, the satisfactory aqueous dispersion may not be obtained. When the pressure is more than 250 MPa, it may not be suited from the mechanical viewpoint.

[0022] According to Japanese Patent Application Unexamined Publication No. 2002-204951, there is a method for obtaining a uniformly shear-triturated product from an aqueous dispersion of low-substituted cellulose ether, the method comprising a step of adding an acid to an alkaline solution of low-substituted cellulose ether for neutralization and precipitation, while mixing the solution with a high speed stirrer. There is also a modified method comprising steps of adding an acid to an alkaline solution of low-substituted cellulose ether to form a gel product as a result of neutralization and precipitation, washing the gel product with hot water and then carrying out wet shear-trituration.

[0023] As the preparation of the alkaline solution of low-substituted hydroxypropyl cellulose, a low-substituted cellulose ether powder as a final product may be dissolved in an aqueous alkaline solution. This method can bring the same result as the method for dissolving in water an alkali-containing crude cellulose ether just after the reaction. In the latter case, the crude cellulose ether contains an alkali so that only water may be added, but an alkali may be added so as to ensure complete dissolution. Both methods are applicable to the present invention.

[0024] Examples of the alkali for dissolving the cellulose ether may include potassium hydroxide and sodium hydroxide. The concentration of alkali may vary depending on the kind or substitution degree of the substituent for the cellulose ether so that it may be determined accordingly. The alkali concentration may be preferably 2 to 25 wt%, particularly preferably 5 to 12 wt%. As a typical example, an aqueous 10 wt% sodium hydroxide solution can be used for low-substituted hydroxypropyl cellulose having a molar substitution of 0.2. The solution having the low-substituted hydroxypropyl cellulose dissolved may be transparent or may not be completely transparent, depending on the difference in the substituent distribution for the hydroxypropyl cellulose. Even if the solution is not completely transparent, it is regarded as a solution when the viscosity shows an apparent rise.

[0025] Examples of the acid used for neutralization may include organic acid such as acetic acid, formic acid and propionic acid; and inorganic acid such as hydrochloric acid and sulfuric acid. The acid concentration can be selected freely. The preferable acid concentration may be about 5 to 10 wt%.

[0026] The concentration of low-substituted cellulose ether which will be subjected to shear-trituration may be preferably from 2 to 20 wt%. When the concentration is less than 2 wt%, the burden for drying may become high. The shear-trituration treatment makes the slurry in the form of gel or sol thicken so that the concentration exceeding 20 wt% may disturb the treatment.

[0027] The average particle size of the shear-triturated low-substituted cellulose ether being in the swelling state containing water may be preferably 20 μm or less on basis of the volume as measured by the laser diffraction scattering method. It is known that the particle size of water-insoluble polymer in water has an influence on the film forming property after drying. This also applies to the shear-triturated low-substituted cellulose ether. As the particle size of the shear-triturated low-substituted cellulose ether is smaller, the particles will be packed most closely when the aqueous dispersion thereof is dried. The adjacent particles will coalesce each other, facilitating the formation of a transparent continuous film. The resulting continuous transparent film has high strength in a dry state, and becomes a gel sheet by absorbing water while maintaining its shape. Thus, a skin adhesive hydrous sheet can be obtained. On the other