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DIRECCION DE NUEVAS CREACIONES**

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Abogado: **EMILIO FERRERO**

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Patente de Invención ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☐ Cap.I ☐ Cap. II ☐

No. Solicitud Internacional PCT/EP2005/012978
Fecha de Presentación Internacional 2005-12-03

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

Documentos estudiados:

Descripción: Folios 39 a 64 como se radicó inicialmente.
Reivindicaciones: Folios 65 a 67 como se radicó inicialmente.
Dibujos: Folios 68 como se radicó inicialmente.

Prioridad: DE20041020040592209 (2004-12-09)
 DE20051020050553850 (2005-11-17)

Objeto de la Invención

Título de la invención: Medicamento para administración higiénica en el oído.

Problema Técnico Planteado: Necesidad de un medicamento que permita un tratamiento del oído con dosis exacta, higiénico y sencillo.

Solución: Medicamento para el tratamiento de enfermedades del oído en hombres y animales que contiene un agente anti infeccioso en una base fluida tixotrópica para una sola administración.

IPC: A61K009/000; A61K31/5395;

Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Dentro de las reivindicaciones 18 a 21 se establece una formulación que contiene un ácido, sin embargo dentro de la descripción no se evidencia como tal en la

formulación la presencia de un componente denominado “ácido”, aunque se describe que algunos componentes de la base oleosa o acuosa que conforma el medicamento pueden contener sustancias de tipo ácido como conservantes, antioxidantes (folio 52).

De igual manera en la reivindicación 19 delimita los posibles ácidos a utilizar (sorbico, esteárico, propiónico), sin embargo en la descripción solo se observan composiciones preferidas que utilizan ácido sorbico (folios 62-63) y no se presenta soporte del uso de ácido esteárico u ácido propiónico. Debido a lo anterior es necesario que el solicitante aclare a que tipo de ácidos se refiere, si tiene alguna propiedad específica dentro de la composición y delimitar los que presentan soporte en la descripción.

La reivindicación 20 expresa una formulación de medicamento que contiene hasta 30% en peso de ácido. Teniendo en cuenta la descripción proporcionada por el solicitante, las formulaciones que presentan como uno de sus componentes ácido sorbico solo tiene un porcentaje de 0,1% por tal razón se debe limitar el objeto de la solicitud en cuanto a la cantidad de ácido en la formulación.

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de solicitud prioritaria 2004-12-09 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO9724128	<i>Otic Microbial Combinations</i>	1997-07-10
D2	WO2004050021	<i>Methods And Compositions For Applying Pharmacologic Agents To The Ear</i>	2004-06-17
D3	EP1384478	<i>Antibiotic Compositions Containing Moxifloxacin For Treatment Of The Eye</i>	2004-01-28

D1- Se divulga una composición ótica útil en tratar las infecciones óticas dichas composiciones abarcan un agente antimicrobiano que puede ser quinolona o sus sales y sulfadiazina de plata en una combinación eficaz para tratar infecciones óticas en animales.

D2- Se describen los métodos y los materiales útiles para aplicar agentes farmacológicos al oído. Los métodos implican: entregar una composición que contenga por lo menos un agente viscosante y por lo menos un agente farmacológico a la superficie epidérmica de la membrana timpánica.

D3- Se divulgan composiciones oftálmicas, óticas y nasales que contienen una nueva clase de antibióticos (e.j., moxifloxacina). Estas composiciones también contienen uno o más agentes antiinflamatorios. Las composiciones se pueden utilizar para tratar condiciones oftálmicas, óticas y nasales tópico aplicando las composiciones a los tejidos afectados.

Análisis de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

Respecto a la solicitud en estudio:

1. **La reivindicación 1 dice:** “Un medicamento para el tratamiento de enfermedades del oído en hombres o animales, que contiene:
(a) Un agente antiinfeccioso,

(b) en una base líquida
 envasado en un medio de envasado primario para una sola administración.”.

Respecto al estado de la Técnica:

D1 da a conocer un medicamento para el tratamiento de enfermedades del oído en hombres o animales (página 2, línea 8 a 10 y 22), que contiene:

- (c) **Un agente antiinfeccioso** (página 2, línea 11 a 12 y 23 a 25; reivindicaciones 1, 6 7),
- (d) **en una base líquida** (Página 2, línea 8 a 14; Reivindicación 1, 0)
 envasado en un medio de envasado primario para una sola administración.

Los agentes antibacteriales divulgados dentro de D1 para la composición involucran una **fluoroquinolona** especialmente **enrofloxacino y marbofloxacino** (Página 3, Línea 1 a 15); y **sulfadiazina de plata** (Página 2, línea 12 y 25) en concentraciones dentro de la composición que proveen efecto terapéutico de **0.005 a 1.5%** para la fluoroquinilona (Página 3, línea 20 a 22) y de **0,05 a 2%** para la sulfadiazina de plata (Página 3, línea 23 a 25).

Adicionalmente D1 describe la posible combinación de Enrofloxacina con un **agente antimicótico** como **clotrimazol** para generar actividad tanto en bacterias como en hongos del tipo *Candida*. (Página 8, Línea 17 a 19).

A partir de lo anterior, D1 divulga las características esenciales de la invención en cuanto a la reivindicación independiente 1 y a las reivindicaciones dependientes 2 a 8 por lo cual el objeto de la solicitud **no es nuevo**.

2. La reivindicación 15 dice: “Formulación de medicamento que contiene:

- a. un agente anti infeccioso
- b. un agente antimicótico
- c. un corticoide
- d. una base líquida

Respecto al estado de la Técnica:

D2 da a conocer una composición útil para el tratamiento de afecciones del oído medio, dicha composición esta compuesta por una combinación de:

- **Agentes farmacológicos** (Página 4, línea 21,22) como **antibióticos**, anestésicos, antiinflamatorios, **corticosteroides**, **antimicóticos**, entre otros. (Página 28, línea 7 a 15), en un
- **Vehículo líquido con uno o más agentes viscosantes** que dan buenas características de aplicación a la superficie epidermal del tímpano. (Página 4, línea 23 a 29).

Así mismo D2 establece que la cantidad en la formulación de cada uno de dichos agentes depende de las características y de las dosis efectivas de estos (Página 28, línea 4 a 6). Y que los agentes pueden ser: quinolonas (Página 9, línea 7 a 8); clotrimazol, fluconazol, miconazol, etc (Página 9, línea 28 a 30); y betametasona, cortisona, dexametasona, etc. (Página 8, línea 23).

D2 divulga las características esenciales de la invención en cuanto a la reivindicación independiente 15 por lo cual el objeto de la solicitud junto con sus reivindicaciones dependientes **no es nuevo**.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO9724128	1-8	Novedad
D2	WO2004050021	1-17	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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



ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____ 18 2 NOV. 2010

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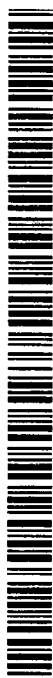


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- (51) International Patent Classification⁷: **A61K** [GB/US]; 2531 Wexford Court, New Brighton, MN 55112 (US).
- (21) International Application Number: PCT/US2003/037819 (74) Agent: **ELLINGER, Mark, S.**; Fish & Richardson P.C., P.A., 60 South Sixth Street, Suite 3300, Minneapolis, MN 55402-1104 (US).
- (22) International Filing Date: 25 November 2003 (25.11.2003) (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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WO 2004/050021 A2

(54) Title: METHODS AND COMPOSITIONS FOR APPLYING PHARMACOLOGIC AGENTS TO THE EAR

(57) Abstract: Methods and materials useful for applying pharmacologic agents to the ear are described. The methods involve delivering a composition that contains at least one viscogenic agent and at least one pharmacologic agent to the epidermal surface of the tympanic membrane via the ear canal. The composition is delivered to the tympanic membrane in a flowable form and, after delivery to the tympanic membrane, becomes sufficiently viscous such that the pharmacologic agent is localized against the tympanic membrane. Such compositions can be used to prophylactically and/or therapeutically treat middle and inner ear conditions, including otitis media.

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In one aspect, the invention features a method for administering a pharmacologic agent to a mammal (e.g., a rodent or a human). The method includes applying a formulation to the epidermal surface of a tympanic membrane of the mammal, wherein the formulation includes a viscogenic agent and at least one pharmacologic agent, 5 wherein the formulation has a viscosity less than 100,000 cps, and wherein the formulation, after application to the tympanic membrane, has a yield stress sufficient to maintain the formulation against the tympanic membrane. The viscogenic agent can be gellan, N-isopropyl acrylamide with sodium acrylate and n-N-alkylacrylamide, polyacrylic acid with polyethylene glycol, polymethacrylic acid with polyethylene glycol, 10 carbopol with hydroxypropylmethylcellulose, cellulose acetate hydrogen phthalate latex, sodium alginate, or a reverse thermosetting gel such as a poloxamer or a poloxamine. The pharmacologic agent can be an antibiotic, an anti-fungal, or an anti-viral agent. The pharmacologic agent can transfer across the tympanic membrane into the middle ear space. The antibiotic can be a penicillin, e.g., amoxicillin or amoxicillin-clavulanate. 15 The antibiotic can be a sulfa-based combination, e.g., erythromycin-sulfisoxazole or trimethoprim-sulfamethoxazole. The antibiotic can be a macrolide/azide, e.g., azithromycin or clarithromycin. The antibiotic can be a cephalosporin, e.g., cefaclor, cefprozil, cefuroxime axetil, loracarbef, cefdinir, cefixime, cefpodoxime proxetil, ceftibuten, or ceftriaxone. The at least one pharmacologic agent can include an antibiotic and an anti-inflammatory agent, and further can include an anesthetic. The formulation 20 further can include an adhesion facilitator, a permeability enhancer, a bioadhesive, a hygroscopic agent, an ear wax softener, or a preservative.

In another aspect, the invention features a kit that includes a formulation and instructions indicating that the formulation is to be applied to a tympanic membrane, 25 wherein the formulation includes a viscogenic agent and at least one pharmacologic agent, wherein the formulation has a viscosity less than 100,000 cps, and wherein the formulation has a yield stress sufficient, after application to the tympanic membrane, to maintain the formulation against the tympanic membrane.

The invention also features a rodent (e.g., a chinchilla) that includes a formulation 30 applied to the epidermal surface of its tympanic membrane, wherein the formulation includes a viscogenic agent and at least one pharmacologic agent, wherein the

more effective way to treat middle and inner ear disorders (e.g., OM). Suitable compositions also can contain other constituents, e.g., to facilitate the adhesion of the formulation to the tympanic membrane and/or to increase the permeability of the tympanic membrane to a pharmacologic agent.

5 Compositions of the invention have a viscosity of less than 100,000 centipoise (cps) at 25°C. Viscosity refers to the composition's resistance to flow. Compositions having a volume of 0.5 mL that can pass through a 19-gauge needle attached to a 1-mL tuberculin syringe in less than 1 minute at 25°C, by reasonable force and without aid of mechanical devices, typically have a viscosity of less than 100,000 cps. Viscosity of a
10 composition can be determined using a viscometer (e.g., from Brookfield) calibrated with commercially available viscosity standards.

 Compositions of the invention also have a minimum yield stress that is sufficient for maintaining the formulation against the tympanic membrane. Yield stress refers to the amount of force that, when applied to a solid material, causes the solid material to exhibit
15 liquid-like behavior in that it continues to deform with no further increase in stress. Minimum yield stress of compositions of the invention is dependent on the thickness of the applied gel, but is independent of the geometry of the gel and the temperature of the environment. As used herein, minimum yield stress of the composition is in reference to an applied gel that has a thickness of 4 mm and a density of 1 g/L. Yield stress (σ_0) is
20 represented as $\sigma_0 = \rho gh$, where ρ is the density, g is the acceleration due to gravity, and h is the layer thickness. Typically, minimum yield stress is about 39 pascals (Pa). Methods described herein also can be used to estimate if a composition has sufficient yield stress to be maintained against the tympanic membrane. For example, a test composition can be administered to the ear of an animal such as a chinchilla and the ear of the animal can be
25 monitored to determine if the composition transforms to a more solid-like state and is maintained against the tympanic membrane. See Example 1.

Viscogenic Agents

 As used herein, viscogenic agent refers to a polymer or other chemical moiety that
30 increases the viscosity of a fluid. Suitable viscogenic agents, when included in a composition of the invention, allow the composition to transform from a liquid-like state

Nonionic Surfactants such as poloxamers and poloxamines are particularly useful. Poloxamers are well known in the pharmaceutical arts and are described, for example, by Irving R. Schmolka in *Poloxamers in the Pharmaceutical Industry*, in *Polymers for Controlled Drug Delivery*, Chapter 10 (Peter J. Tarcha ed., 1990). Poloxamers are triblock copolymers because they are composed of two different polymer blocks (i.e., hydrophilic poly(oxyethylene) blocks and hydrophobic poly(oxypropylene) blocks) configured as a triblock of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene). Poloxamers are one class of block copolymer surfactants having a propylene oxide block hydrophobe and an ethylene oxide hydrophile. Poloxamers are commercially available (e.g., Pluronic[®] polyols are available from BASF Corporation). Alternatively, poloxamers can be synthesized by known techniques.

Poloxamers previously have been thought to lack utility for administering pharmacologic agents, given their non-biodegradability, their water solubility and their relatively rapid drug release kinetics (see e.g., U.S. Patent No. 6,201,072). Nonetheless, as described herein, poloxamers share a property that is advantageous for applying formulations to the tympanic membrane: aqueous formulations of poloxamers exhibit reverse thermal gelation, or reverse thermosetting. When an aqueous poloxamer formulation is heated over its gelation temperature, its viscosity increases and it transforms into a gel. When an aqueous poloxamer formulation is cooled below its gelation temperature, its viscosity decreases and it transforms into a liquid. The transition between gel and liquid does not involve a change in the chemical composition of the formulation, and is reversible and repeatable. The gel-liquid transition temperature of an aqueous poloxamer formulation can be adjusted by one of ordinary skill in the art using routine experimentation (e.g., by manipulating poloxamer concentration, pH and presence of other ingredients in the formulation). In some embodiments, compositions have a gelation temperature that is greater than the ambient temperature and less than or equal to the temperature of the tympanic membrane. Such compositions can be conveniently applied via an individual's ear canal as a liquid and then can transform into a gel against the tympanic membrane, thereby maintaining the drug in the formulation in close proximity to the tympanic membrane.

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WO 03/022254 A1

(54) Title: OILY THIXOTROPIC FORMULATIONS

(57) **Abstract:** The present invention relates to a novel thixotropic oily vehicle comprising from 0.2% to 5% (w/w) of a colloidal silica and from 0.2% to 5% (w/w) of a hydrophilic polymer in an edible oil. The interaction between the hydrophilic polymer and the colloidal silicon dioxide in the above concentration ranges enables to keep the amount of the latter component at a low concentration, by nevertheless conferring on the solution enough thixotropy and a low viscosity under shear. The invention also relates to capsules filled with the above fill mass.

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It is advantageous that solidification or gelling of the fill mass occurs since, in this way, a final sealing step of the capsule shell can be avoided. For suspensions, a gelification with a relatively high yield point (i.e. the critical stress to induce plastic deformation of the material, measured in Pa) is even vital to prevent re-liquefaction by accidental shaking of the capsules during e.g. transportation. Accidental re-liquefaction of the fill mass after encapsulation would in fact cause settling and caking of the suspended e.g. drug particles, thus decreasing dissolution and possibly also the bioavailability.

Such an ideal flow performance can be obtained by melting a waxy formulation during filling or by providing a so-called thixotropic system. The thixotropy is the property of certain solids or gels, which liquefy when subjected to shear forces and then solidify again when left standing. Thixotropic systems do not involve heat treatments and are therefore especially suitable for thermolabile active pharmaceutical substances. The absence of a heating phase is also favorable for suspensions where increased drug solubility may result to a precipitation upon cooling.

The particular characteristics of the thixotropic systems in the context of pharmaceutical fill masses are e.g. highlighted in "The filling of molten and thixotropic formulations into hard gelatin capsules", S.E. Walker, J.A. Ganley, K. Bedford and T. Eaves, J. Pharm.Pharmacol. 32, 1980, pp. 389-393.

On the other hand, many substances obtained from modern drug discovery are problematic in view of a sufficient bioavailability and often exhibit a very low aqueous solubility so that they have to be formulated in oily (apolar) vehicles.

Unfortunately, there are only few excipients originating thixotropy in oily systems, whereby the most significant is silicon dioxide. These colloidal silica display thixotropy and a convenient yield point ($> 2-4$ Pa) at concentrations of about 4 - 10% (w/w) depending on the polarity of the oil.

The viscosity under shear of the thixotropic vehicle, which is measured at a defined shear rate, must be enough low (< 300 mPa s) to also enable the filling of high concentrated suspensions where the viscosity is often the limiting factor of the technical feasibility. However, suspensions with a high amount of solid phase have to be processed to guarantee the possibility of widely varying the drug load range of the final dosage form.

It is furthermore necessary to keep the concentration of silicon dioxide in the fill mass as low as possible since this colloidal powder is exceptionally bulky (density is ≈ 0.03 g/cm³) and potentially harmful upon inhalation. The use of this material on an industrial

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scale may raise several practical problems and may endanger the health of the technicians who work with it.

The problem at the root of the present invention is therefore to provide a thixotropic oily vehicle containing as little silicon dioxide as possible but showing both a high yield
5 point (> 4 Pa) and a low viscosity under shear (< 300 mPa s).

This problem is solved, according to the present invention, by providing a
thixotropic oily vehicle comprising from 0.2% to 5% (w/w) of a colloidal silica and from
0.2% to 5% (w/w) of a hydrophilic polymer.

The oily vehicle according to the present invention contains a reduced amount of
10 silicon dioxide, while showing a relatively elevated yield point, a high thixotropy and a low viscosity under shear. The decrease of silicon dioxide quantities is meaningful regarding the reduction of the bulk volume when it is processed on a production scale.

The interaction between the hydrophylic polymer and the colloidal silicon dioxide in the above concentration ranges enables to keep the amount of the latter component at a
15 low concentration, by nevertheless conferring on the solution enough thixotropy and a low viscosity under shear.

The positive effects of this interaction are quite surprising and unexpected. In fact, although it is known that additives may improve the thickening performance of the colloidal silica dioxide (see e.g. Degussa's Technical Bulletin No. 23: "Aerosil[®] as a
20 Thickening Agent for Liquid Systems", 1989, pp. 22-24) it is to be expected that the addition of a hydrophilic polymer leads to a phase separation in the apolar oily environment, rather than to a homogenous colloidal system. In the claimed concentrations, however, the interaction of the silica surface with the hydrophilic polymer builds a coherent structure meeting the desired flow performance for liquid-fill systems.

25 When left standing, the composition of the present invention has preferably the visual aspect of a transparent oily gel.

According to a preferred embodiment of this invention, the colloidal silica is chosen from the group consisting of Aerosil[®] 200, Aerosil[®] 300 and Aerosil[®] R812 (Degussa AG, Frankfurt) whereby the most preferred colloidal silica is Aerosil[®] 200. The colloidal silica is
30 preferably used in a concentration varying from 0.5% to 3% (w/w) and, still more preferably, in a concentration varying from 1% to 2% (w/w).

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The hydrophilic polymer used according to the present invention can be chosen from the group of polyethers and polyalcohols. Examples thereof are the polyethylene glycols, the polypropylen polyethylene glycols and the polyvinylalcohols. Preferred are the polyethylene glycols having a molecular weight equal to or smaller than 400 g/mol.

- 5 Examples thereof are polyethylene glycol 200, polyethylene glycol 300 and polyethylene glycol 400. Most preferred is the polyethylene glycol 300.

The hydrophilic polymer is advantageously present in a concentration varying from 0.5% to 4% (w/w) and, still more advantageously, in a concentration varying from 1% to 3% (w/w).

- 10 As stated above, the oily vehicle of the present invention is suitable for the preparation of liquid-filled capsules which are intended for oral drug delivery. It is particularly suitable for active compounds whose oral bioavailability and/or chemical stability can be improved by a lipidic formulation rather than by a conventional dosage form. The special pharmacokinetic profile of a certain active compound can be a further
15 reason to use a lipidic vehicle as dispersing medium. Examples of such active compounds can be found among esters, lactones, retinoids, steroids, dihydropyridins and 4-phenylpyridin derivatives. Particularly, the present composition is used for active compounds selected among the group of the 4-phenylpyridine derivatives such as:

20 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide;

2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide; and

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide.

- 25 The above three compounds, whose synthesis may be found in EP-A-1035115, are characterized by valuable therapeutic properties. They are highly selective antagonists of the Neurokinin 1 (NK-1, substance P) receptor. Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue.

- 30 The oily component of the vehicle according to the present invention consists in an edible oil which can be chosen from the natural and semi-synthetic vegetable mono-, di- or triglycerides. Preferred are pharmaceutical grade triglycerides oils such as corn oil, peanut

oil, olive oil, castor oil, or middle chain triglyceride oil (Miglyol) or mixtures thereof. Most preferred is the middle chain triglyceride oil (Miglyol).

The present invention is also directed to a process for preparing a thixotropic oily vehicle as described above, which process comprises mixing, in an edible oil as defined above, from 0.2% to 5% (w/w) of a colloidal silica with from 0.2% to 5% (w/w) of a hydrophilic polymer.

A further aspect of the present invention consists in providing a fill mass comprising a thixotropic oily vehicle as described above and one or more pharmaceutically active ingredients.

A still further aspect of the present invention is directed to pharmaceutical unit dose wherein a fill mass as described above is encapsulated in an edible capsule. According to a preferred embodiment, the capsule is made of gelatin and, still more preferably, of hard gelatin.

The present invention is further described by the following non-limiting examples. Table 1 shows the viscosity under shear and the yield point of the exemplified oily vehicles, as well as of comparative oily vehicles which do not include a hydrophilic polymer.

The rheological characterization was performed using a controlled stress instrument Carri-Med CSL 500 equipped with a cone and plate system (6 cm diameter and 2° angle). The viscosity was determined at a shear rate of 100 s⁻¹ and a temperature of 25 °C on the "down-curve" of the hysteresis flow curve. On the other hand, the "up-curve" was used to extrapolate the yield point according to the Casson model ("Das Rheologie Handbuch für Anwender von Rotations- und Oszillations-Rheometern", T. Mezger, Vincentz, 2000, p.54).

PREPARATIONS OF THE COMPOSITION

Example 1

2.0 g Aerosil® 200 were exactly weighted and dispersed with a mixer (Type Bamix® (Switzerland), level 2 during 30 seconds) in 96.0 g of Miglyol 812 (middle chain triglyceride). 2.0 g of fluid polyethylene glycol 400 were added to and mixed with the above suspension (Bamix, level 2 during 45 seconds). The so obtained thixotropic vehicle was finally put under vacuum to remove the incorporated air.