

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-128769- -00002-0000
Fec: 2007-02-13 17:57:56 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII
Ere: 379 FASENACIONALII
Act 538 PETICION Folios: 2

Ref: Expediente No. 05-128.769

Solicitud de patente de invención titulada:

“COMPOSICION FARMACEUTICA DISPERSABLE PARA EL TRATAMIENTO DE
MASTITIS Y TRASTORNOS OTICOS”.

Solicitante: PHARMACIA & UPJOHN COMPANY LLC.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 571

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de \$202.000 pesos para cubrir la tasa correspondiente, según la Resolución 36155 del año 2006.

Atentamente,



CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$202.000 pesos

LMB/P2005/000158 070213

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Rad: 05-128769- -00002-0000
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FECHA : FEBRERO 6 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	57477377	05/02/2007	10,365,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		114 PTC CAP-II EXAMEN DE PATENTIBILID	202,000.00
		TOTAL :	\$ 202,000.00

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE : _____



DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-128769

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **571** DE

FECHA **29 DE DICIEMBRE DE 2006** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **28 DE MARZO DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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(19) **United States**

(12) **Patent Application Publication**

Hendl et al.

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(43) **Pub. Date: Jun. 6, 2002**

(54) **PHARMACEUTICAL COMPOSITION
HAVING SPECIFIC WATER ACTIVITY**

Publication Classification

(76) Inventors: **Ondrej Hendl**, Portage, MI (US);
Nancy J. Britten, Portage, MI (US)

(51) **Int. Cl.⁷** **A61K 39/38**; A61K 39/12;
A61K 39/00; A61K 31/545

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514/206

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(57) **ABSTRACT**

A composition comprising:

(a) one or more bioactive agents; and

(b) a non-aqueous liquid carrier;

wherein immediately after manufacture of the composition,
said composition can be administered to a host such that the
one or more bioactive agents is released to the host and
wherein said composition has been adjusted to have a water
activity of between about 0.2 and about 0.5 is provided.

(21) Appl. No.: **09/949,171**

(22) Filed: **Sep. 7, 2001**

Related U.S. Application Data

(63) Non-provisional of provisional application No.
60/231,868, filed on Sep. 12, 2000.

PHARMACEUTICAL COMPOSITION HAVING SPECIFIC WATER ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of US provisional application Serial No. 60/231,868, filed Sep. 12, 2000, under USC § 119(e)(1).

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention relates to pharmaceutical compositions. More specifically, it relates to the use of more chemically stable pharmaceutical formulations comprising one or more bioactive substance in a non-aqueous liquid carrier, where said improved chemical stability is achieved by the adjustment of formulation water activity from about 0.2 to about 0.5.

[0004] 2. Background of the Invention

[0005] In the pharmaceutical arts, drug delivery is an element as significant as drug activity. Many drugs or bioactive agents with apparent in vitro activity fail at the clinical level due to the inability to prepare, store, or deliver the bioactive agent to the site of action in effective concentrations over a sufficient period of time.

[0006] A vehicle for the stable storage and effective delivery profile of a bioactive agent is of great utility. Those skilled in the art will understand that storage stability and effective delivery profile are, to some extent, specific to bioactive agents, the condition for which the bioactive agent is administered, and the presenting condition of the subject.

[0007] The chemical stability and the improvement of chemical stability of pharmaceutical preparations are of great importance to the drug industry. Of particular concern has been the chemical stability of formulations where the pharmaceutical carrier and/or a component of the composition is an oxidizable oil or contains ingredient(s) capable of undergoing lipid oxidation during formulation manufacture and/or product storage. It is well known that lipid oxidation in a pharmaceutical composition can lead to reduced chemical stability of the product and a shorter shelf life. In addition to the oxidative tendencies of many commonly used oils and lipid containing excipients at room temperature, the preparation of pharmaceutical compositions often requires the heating or administration of radiation to the oil vehicles and/or excipients to adequately dissolve ingredients in the carrier or to sterilize the formulation. This heat stressing or radiation exposure promotes even more rapid rates of lipid oxidation in the compositions, thus frequently causing a decline in chemical stability. In the past, various methods have been employed in an attempt to enhance the chemical stability of such systems, including the addition of antioxidants, various stabilizers, etc.

[0008] Sustained release or oil based preparations are considered in WO97/49402 (Vlaminck); WO94/00105 (Sabater); U.S. Pat. No. 4,297,353 (Hawkins); U.S. Pat. No. 5,019,395 (Mahjour); U.S. Pat. No. 5,739,159 (Wolf); U.S. Pat. No. 5,162,057 (Akiyama); WO96/20698 (Levy) the teachings of which are incorporated herein by reference.

Also incorporated by reference is WO98/41207 (Brown) addressing subcutaneous (S.C.) administration of antibiotic into the ear of an animal.

[0009] U.S. Pat. No. 5,721,359 discloses the molecule crystalline ceftiofur free acid (CCFA), which is a cephalosporin antibiotic intended for use in mammals, and in particular food animals (e.g., cattle, sheep, goats and swine). The patent suggests that oil suspensions of CCFA can be produced for administration to food animals where the oils are vegetable oils. The oils as disclosed in the patent are intended to be used in their natural form. An advantage touted by this molecule over other antibiotics, particularly those in the ceftiofur family is the ability for CCFA to yield a sustained release pharmaceutical composition. It has now been discovered that the sustained release profile is not readily predictable and reproducible in immediate post-production product that uses natural vegetable oils

[0010] U.S. Pat. No. 5,736,151 "Antibiotic Oil Suspensions" describes the inclusion of small amounts of water in oil suspensions of active drug, such as ceftiofur hydrochloride. The resulting suspensions have improved resuspendability so less shaking is required before dosing.

[0011] A section of the book Lipid Oxidation by Edwin N. Frankel (pages 195-197) discusses the use of water activity as a predictor of food quality. The article states that water activity is a key factor affecting the lipid oxidation in foods during storage and describes how lipid oxidation in foods is high at low water activity (0.1-0.2) but decreases as water activity increases to a value of 0.2-0.4, then increases again above 0.4, reaching a maximum in the range of 0.6-0.8. Mechanisms to explain the effect of water activity on lipid oxidation in foods are suggested.

[0012] Despite the above teachings, there still exists a need in the art for pharmaceutical compositions that can be administered on a controlled release or immediate release basis and wherein the release performance is predictable and reproducible immediately after manufacture of the product, as well as a need for a means for improving the stability of formulations otherwise prone to lipid oxidation.

BRIEF SUMMARY OF THE INVENTION

[0013] In accordance with the present invention a novel pharmaceutical composition that can be administered on a sustained release or immediate release basis and wherein the release performance is predictable immediately after manufacture of the product is provided. More specifically, formulations of this invention have water activity levels of from about 0.2 to about 0.5.

[0014] One embodiment of the invention provides a pharmaceutical composition comprising:

[0015] (a) one or more bioactive agents; and

[0016] (b) a non-aqueous liquid carrier;

[0017] wherein immediately after manufacture of the composition, said composition can be administered to a host such that the one or more bioactive agents are released to the host and wherein said composition has been prepared such that the water activity of the composition is between about 0.2 and about 0.5.

[0018] In preferred embodiments, component (a) comprises CCFA and component (b) must include at least one of the following:

[0019] (1) a mixture of a modified or non-modified oxidizable oil with either a non-modified non-oxidizable oil or a non-modified non-oxidizing vehicle;

[0020] (2) a modified or non-modified oxidizable oil;

[0021] (3) a mixture of a non-modified or oxidizable oil with either a modified non-oxidizable oil or a modified non-oxidizing vehicle;

[0022] (4) a modified or non-modified non-oxidizable oil or non-oxidizing vehicle;

[0023] (5) a modified or non-modified non-oil;

[0024] (6) a vehicle containing oxidizable lipid components.

[0025] In particularly preferred embodiments component (b) is a mixture of modified oxidizable oil with a natural fully non-oxidizable oil, and even more preferably a mixture of modified cottonseed oil with saturated coconut oil.

[0026] Another embodiment of the present invention provides a method for producing a pharmaceutical composition comprising the steps of combining a non-aqueous liquid carrier with a bioactive substance and adjusting the resulting composition such that it has a formulation water activity of between 0.2 to about 0.5. The adjustment comprises the addition of water either prior to, during or after the combining step, and/or manufacturing the formulation under conditions of high humidity, and/or selecting hydrated bioactive substances, vehicles, and/or excipients containing water—such that the water activity of the final formulation is about 0.2 to about 0.5. In preferred embodiments, the liquid carrier is additionally modified by the use of chemical, physical or mechanical means to produce a carrier that has a higher level of oxidation products as compared to its original, or non-modified form. Particularly preferred embodiments comprise the use of a combination of heat and gamma radiation. In addition, the modification step of this process may occur either prior to, after or both prior to and after the combining step.

[0027] A more specific aspect of this method comprises the steps of:

[0028] (a) heating natural cottonseed oil to increase its oxidation products and yield a modified cottonseed oil;

[0029] (b) combining said modified cottonseed oil with saturated coconut oil or saturated coconut oil products to yield a carrier vehicle; and

[0030] (c) adding crystalline ceftiofur free acid to said carrier vehicle;

[0031] (d) adjusting the water activity of the resulting composition to between about 0.2 and about 0.5 and, optionally, thereafter;

[0032] (e) heating said pharmaceutical composition;

[0033] (f) cooling said composition;

[0034] (g) filling one or more vials with said composition; and

[0035] (h) exposing said one or more vials to gamma radiation.

[0036] A further embodiment of the present invention provides the composition of the present invention for use in medical treatment.

[0037] An additional embodiment of the present invention provides the use of the inventive composition to prepare a medicament for treating or preventing a disease in a mammal.

[0038] A final embodiment of the present invention provides a method of treating or preventing a disease comprising administering to a mammal in need of such treatment an effective amount of the inventive composition. A preferred aspect of this invention is to treat bacterial infections in food animals or companion animals with an inventive CCFA composition.

[0039] An objective of the present invention is to provide more chemically stable pharmaceutical formulations where such formulations would otherwise be subject to undesirable effects from lipid oxidation.

[0040] Another object of the present invention is to provide a novel sustained release composition.

[0041] Still another object of the present invention is to provide a method for producing a novel sustained release composition.

[0042] An additional objective of the present invention is to provide a novel immediate release composition.

[0043] Yet another object of the present invention is to provide a method for producing a novel immediate release composition.

[0044] A further object of the present invention is to provide a method for treating a disease or condition in a mammal.

[0045] These, and other objects, will readily be apparent to those skilled in the art as reference is made to the drawings and detailed description of the preferred embodiment.

DETAILED DESCRIPTION OF THE INVENTION

[0046] In describing the preferred embodiment, certain terminology will be utilized for the sake of clarity. Such terminology is intended to encompass the recited embodiment, as well as all technical equivalents which operate in a similar manner for a similar purpose to achieve a similar result.

[0047] 1. Terminology Definitions

[0048] This invention will be better understood with reference to the following definitions:

[0049] "Bioactive substances" shall be broadly understood to mean pharmaceuticals, immunogenic and immunomodulator compositions (including adjuvants), vectors such as liposomes and live vectors such as plasmids, viruses, prions, spores, nutritional supplements and bacteria and mixtures thereof.

[0050] These include, but are not limited to nutritional supplements, anti-infectives (e.g., antibiotics, antifungals, anti-virals), antineoplastics (e.g., anticancer agents, such as cis-platinum compounds), immunomodulators (e.g., antihistamines, immunoenhancers and immunosuppressors), laxa-

tives, vitamins, decongestants, gastrointestinal sedatives, antacids, anti-inflammatory substances (e.g., selective cox-2 inhibitors), anti-manics, vasodilators (coronary, cerebral and peripheral), psychotropics, stimulants, anti-diarrheal preparations, anti-anginal drugs, analgesics, anti-pyretics, hypnotics, sedatives, anti-emetics, growth promoters, anti-nauseants, anti-convulsants, neuro-muscular drugs, hyper and hypo glycaemic agents, thyroid and anti-thyroid preparations, diuretics, cytotoxic compounds, anti-spasmodics, antiarthritics, uterine relaxants, anti-obesity drugs, anthelmintics, hormones, vaccines, mineral and nutritional additives, CNS agents not disclosed in this listing and any mixtures thereof. Specifically preferred bioactive agents include, but are not limited to, crystalline ceftiofur free acid (CCFA), platinum compounds (e.g., cis-platinum), ibuprofen, piroxicam, 1-[2-(4-fluorobenzoyl)aminoethyl]-4-(7-methoxynaphthyl) piperazine hydrochloride (FAMP), camptothecin, paclitaxel, flucytosine, and quinine.

[0051] "Sustained delivery or Sustained release" as used in relation to bioactive substances shall mean continued release or distribution of the bioactive substance such that the amount of bioactive remains in the patient's blood levels at a concentration of greater than a certain value (that value being one that produces therapeutically effective blood levels of active substance) over an extended period of time. The effective sustained release blood levels desired would, of course, differ depending on the bioactive substance, the disease being treated, the patient, and the like, is considered to be known to the skilled artisan and can be determined by routine experimentation. More specifically, a sustained delivery vehicle differs from an immediate delivery vehicle in that the immediate delivery vehicle releases its bioactive material at faster rate than the sustained delivery vehicle, potentially requiring more administrations of bioactive per treatment regimen. For example, if the bioactive substance is ceftiofur crystalline free acid (CCFA), the desired level of ceftiofur metabolites in the patient's blood plasma is noted to be about 0.2 $\mu\text{g/ml}$. In one embodiment of the invention, a single dose of sustaining-vehicle CCFA maintains a ceftiofur metabolite level in the blood plasma of at or above about 0.2 $\mu\text{g/ml}$ for at least three and preferably at least about four and more preferably at least about five days post-administration (sustained delivery of CCFA). Comparisons as to the degree of sustained delivery are made with equivalent bioactive agents. That is, sodium salts to sodium salts and free bases to free bases. Sustained delivery as used in this document is to be specifically reconciled with the regulatory definition for the same term that requires that the concentration versus time profile have three distinct phases (i.e., an increasing concentration phase, a plateau phase and a concentration depletion phase). While the term sustained delivery as used in this document may encompass the above regulatory definition it is not intended to be limited to it as compositions which are sustained delivery as defined herein need not possess the three distinct phases (e.g., the composition may have an increasing concentration phase and an extended concentration depletion phase).

[0052] "Liquid carriers" include triglyceride fats and oils, including those derived from vegetable, animal, and marine sources. The liquid carrier is non-aqueous and preferably comprises an oxidizable oil or a liquid vehicle containing oxidizable lipid components. The liquid carrier may be fully saturated, partially or fully unsaturated and may be deemed an "oil" (which may be naturally occurring or synthetic) or

a "non-oil". Examples of liquid carriers which are partially or fully unsaturated hydrocarbons include, but are not limited to naturally occurring oils such as castor oil, safflower oil, cottonseed oil, corn oil, olive oil, cod liver oil, almond oil, avocado oil, palm oil, sesame oil, peanut oil, calendula oil and soybean oil. By way of example cottonseed oil is available in a preparation of 70% unsaturated fatty acids (Sigma, St. Louis, Mo.). Examples of fully saturated liquid carriers include, but are not limited to, esters of medium to large chain fatty acids (e.g., fatty acid triglycerides with a chain length of about C6 to about C24). Mixtures of fatty acids are split from the natural oil (e.g., coconut oil, palm kernel oil, babassu oil, etc.) and are refined. In some embodiments, about C8 to about C12 fatty acid medium chain triglycerides (MCT) are useful. These saturated vehicles are comprised of capric acid (about 20 to about 45%) and caprylic acid (about 45 to about 80%). Other oils include, but are not limited to glyceride vehicles comprising a glycerol ester, or propylene glycol di-esters, of a saturated or/and unsaturated fatty acid. Fully saturated liquid carriers include, but are not limited to, saturated coconut oil (which typically includes a mixture of lauric, myristic, palmitic, capric and caprylic acids), including those sold under the MIGLYOL trademark from Huls and bearing trade designations 810, 812, 829 and 840. Also noted are the NeoBeeRTM products sold by Drew Chemicals. Isopropyl myristate is another example of a non-oxidizing vehicle of the current invention. Examples of synthetic oils include tri-glycerides, or propylene glycol di-esters of saturated or unsaturated fatty acids having from 6 to 24 carbon atoms. Such carboxylic acids are meant to comprise those carboxylic acids having from 6 to 24 carbon atoms such as, for example hexanoic acid, octanoic (caprylic), nonanoic (pelargonic), decanoic (capric), undecanoic, lauric, tridecanoic, tetradecanoic (myristic), pentadecanoic, hexadecanoic (palmitic), heptadecanoic, tetracosanoic, nonadecanoic, hexadecanoic (palmitic), heptadecanoic, ocatadecanoic (stearic) nonadecanoic, eicosanoic, heneicosanoic, docosanoic and lignoceric acid. Examples of unsaturated carboxylic acids include oleic, linoleic, linolenic acid and the like. It is understood that the tri-glyceride vehicle may include the mono-, di-, or triglyceryl ester of the fatty acids or mixed glycerides and/or propylene glycol di-esters wherein at least one molecule of glycerol has been esterified with fatty acids of varying carbon atom length, preferably carbon lengths of between about 6 to about 24 carbon atoms, more preferably between about 8 and about 18. Some non-limiting examples of "non-oils" include polyethylene glycol (PEG).

[0053] Oxidizable lipid components of water activity adjusted formulations of the present invention include any excipient capable of undergoing lipid oxidation. These oxidizable excipients may contain aliphatic unsaturated straight or substituted fatty acids with one or more double bonds. Phospholipons are a non-limiting example of such an excipient. If water activity adjusted formulations of the current invention contain one or more oxidizable lipid excipients, as described above, the pharmaceutical carrier may be comprised of an oxidizable oil vehicle, a non-oxidizable vehicle, or a combination of both oxidizable and non-oxidizable vehicles.

[0054] "Lipid" shall be broadly understood to mean any group of fats or fat like substances including fatty acids,

neutral fats, waxes, and steroids; all contain aliphatic hydrocarbons, are water insoluble, and are easily stored in the body.

[0055] "Modified" and "modification" as to the vehicles of this invention and as used in the claims shall be understood to define a vehicle which, through physical, chemical or mechanical means, has been altered as compared to its natural (or "non-modified" in the case of synthetic liquid carriers) form such that the modified vehicle has an increased level of oxidation products and, when combined with the bioactive substance, yields a composition having a water activity of between about 0.2 and about 0.5. Modification can be accomplished by heat modification, irradiation (e.g., gamma or microwave radiation), addition of catalysts (i.e., t-butyl peroxide), the incorporation of specific triglycerides and their hydroperoxides, incorporation of polymeric species, incorporation of crosslinkers or of polymerization causing agents, oxidation regimens and combinations of these methods. These steps can be taken before or after addition of the drug to the vehicle, or both before and after addition of drug to the vehicle. In accordance with preferred embodiments of the present invention, the modification takes place in connection with the pharmaceutically acceptable liquid carriers which are either partially or fully unsaturated, although it is specifically contemplated that modification of the fully saturated liquid carriers or non-oils is also possible. Where modification relates to adjusting the water activity of the resulting composition, the adjustment can take place via the addition of water to the ultimate composition either before, during or after the combining of the bioactive substance with the modified liquid carrier, and/or conducting any of the processing steps under conditions of high environmental humidity, and/or by selecting hydrated bioactive substances, vehicles, and/or excipients containing water—such that the water activity of the resulting final formulation is from about 0.2 to about 0.5. Moreover, the liquid carrier, per se, need not be specifically modified to a given water activity; it is the resulting composition which is modified as such.

[0056] "Substantially peroxidized oxidizable oil vehicle" shall refer to a modified liquid carrier having a peroxide value of between about 0.1 and about 600, and in some embodiments about 10, about 20, about 40, or about 80 or any value in between. As used herein, peroxide values are expressed as milliequivalents (mEq) of peroxide per 1000 grams of oil sample. Peroxide value is conveniently measured by American Oil Chemists' Society (AOCS) (Official Method Cd 8-53) (Official Monographs, Soybean Oil, page 1434) manual titration, the teachings of which are incorporated herein by reference.

[0057] "Water activity" (WA) in heterogeneous systems determines the distribution of water between different components (i.e. bioactive agent and oil phase or non-oil phase or their mixture). The WA is defined as $WA = p/p_o$, where p = partial pressure of water in formulation, p_o = vapor pressure of water. From the literature is known the effect of water activity on lipid oxidation in food. Lipid oxidation is high at low water activity (0.1-0.2) but decreases as water activity is increased to a minimum, up to 0.2-0.4, and then increases again above 0.4, reaching maximum in the range 0.6-0.8. In accordance with the present invention, the desired water activity of the inventive composition is between about 0.2 and about 0.5.

[0058] 2. The Invention

[0059] The present invention comprises a composition comprising:

[0060] (a) one or more bioactive agents; and

[0061] (b) a non-aqueous liquid carrier;

[0062] wherein immediately after manufacture of the composition, said composition can be administered to a host such that the one or more bioactive agents is released to the host and wherein said composition has been adjusted to have a resulting water activity of between about 0.2 to about 0.5.

[0063] It is a substantial advantage to identify a dosage form and method of preparation of a dosage form that provides a desired release profile either a sustained release or immediate release immediately upon production and maintains that release profile during a substantial storage period. In the present invention, a combination of preparatory steps and vehicle compositions are defined which yield desired release formulations upon processing. Water activity adjusted formulations may be obtained by the use of, a modified or non-modified liquid carrier, which can be in the form of an oxidizable oil, a liquid vehicle containing oxidizable lipid components, a non-oxidizable oil, a non-oxidizing vehicle, a non-oil or any mixture thereof in combination with the bioactive agent. In certain embodiments where a modified liquid carrier is utilized, in addition to the modified component, the liquid carrier can also optionally include a non-modified oxidizable oil, a non-modified non-oxidizable oil, a non-modified non-oxidizing vehicle, a non-modified non-oil or any mixture thereof. In all preferred embodiments, a key feature is that of the formulation has been adjusted either before, after or both before and after it has been combined with the bioactive agent and that the resulting composition has been prepared to have a water activity ranging from about 0.2 to about 0.5.

[0064] The bioactive agents for use are as defined above. A preferred bioactive agent is crystalline ceftiofur free acid (CCFA) which is useful as an antibiotic drug compound in pharmaceutical dosage forms for treating valuable mammalian animals and humans suffering from bacterial infections. In particular embodiments, sustained release ceftiofur free acid is useful as a veterinary antibiotic drug to treat animals such as cattle, swine, horses, sheep, goats, dogs, poultry and cats. Such treatment fights the effects of bacterial infections caused by susceptible organisms, such as *Pasteurella haemolytica*, *Pasteurella multocida*, *Salmonella typhimurium*, *Salmonella choleraesuis*, *Actinobacillus pleuropneumoniae*, *Streptococcus suis*, *Haemophilus somnus*, *Escherichia coli*, *Staphylococcus aureus* and the like, as well as applicable anaerobic infections. These types of infections are commonly associated with diseases in animals, such as bovine respiratory disease and swine respiratory disease.

[0065] In specific embodiments, the following are used as the carrier vehicles of the instant invention:

[0066] (1) a mixture of a modified or non-modified oxidizable oil with either a non-modified non-oxidizable oil or a non-modified non-oxidizing vehicle;

[0067] (2) a modified or non-modified oxidizable oil;

[0068] (3) a mixture of a non-modified or oxidizable oil with either a modified non-oxidizable oil or a modified non-oxidizing vehicle;

189 D2

United States Patent [19]

Patil et al.

[11] 4,299,501

[45] Nov. 10, 1981

[54] CONTINUOUS PROCESS FOR THE PREPARATION OF SEMISOLID DISPERSIONS

[75] Inventors: Deepak R. Patil, Livingston; Glenn A. VanBuskirk, Bernardsville, both of N.J.

[73] Assignee: Ortho Pharmaceutical Corporation, Raritan, N.J.

[21] Appl. No.: 65,665

[22] Filed: Aug. 10, 1979

[51] Int. Cl.³ B01F 13/00; B01F 15/02; B01F 15/06

[52] U.S. Cl. 366/349; 366/136; 366/144; 366/159

[58] Field of Search 366/349, 341, 22, 23, 366/24, 76, 91, 96, 136, 159, 144, 145, 149, 336

[56]

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Primary Examiner—Edward J. McCarthy

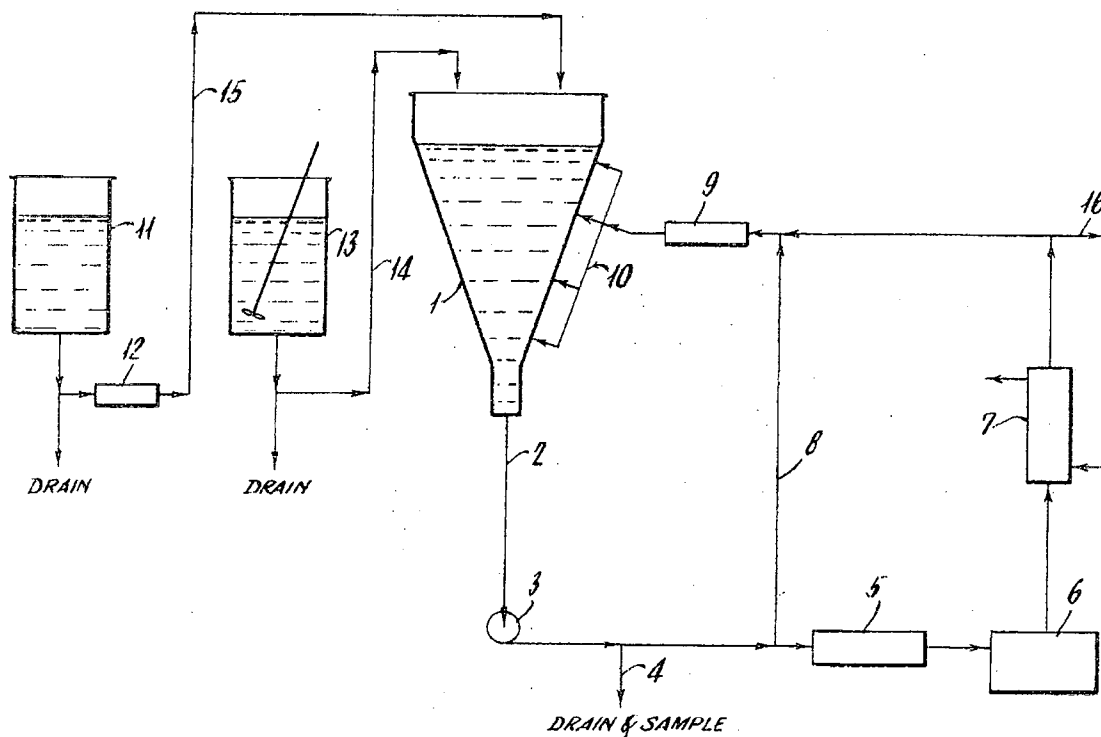
Attorney, Agent, or Firm—Benjamin F. Lambert

[57]

ABSTRACT

A semicontinuous or continuous process for preparing semisolid dispersions is provided wherein oil and water phases are circulated from a single vessel through a system of mixers and homogenizers until a dispersion is obtained.

4 Claims, 3 Drawing Figures



of the ingredients are not soluble in either phase, they can be suspended in the finished emulsion.

The aqueous phase generally includes about 70 to about 90% by weight of water and from about 10 to about 30% by weight of emulsifiers, emollients and/or preservatives. Other ingredients which can be present in the aqueous phase include antifoam agents, pharmaceutical materials, perfumes and dyes, for example.

An emulsifier can be included in the aqueous phase and/or the oil phase separately or mixed with the two phases. Emulsifiers suitable for use in the present process include those of the anionic, cationic and nonionic types, all of which are well known to those skilled in the art.

Other ingredients which can be included in either or both phases separately or mixed with the two phases include film-forming agents, astringents, deodorants, dyes, perfume, opacifiers, antifoam agents and solvents.

The advantages of the present invention over the prior art inventions include the elimination of extraneous tanks and agitation systems, elimination of transfer time required for mixing the oil and water phases, increased process control and greater process latitude. The latter two advantages are obtainable through subdivision of a complex manufacturing process into a series of unit operations which can be easily defined and controlled. The process described above is essentially a semicontinuous process, however, the process can be made continuous by adding to the main vessel an amount of the mixture of aqueous and oil phases equal to the amount of product withdrawn.

The following examples illustrate how the invention is carried into effect but is not meant to be limiting on the invention since it will be obvious to those skilled in the art how various changes can be made.

EXAMPLE 1

	% (w/w)
<u>Aqueous Phase</u>	
Purified Water	73.8
Benzoic Acid	0.2
<u>Oil Phase</u>	
Pegoxyl 7 Stearate	20.0
Peglicol 5 Oleate	3.0
Heavy Mineral Oil	3.0

Procedure

The pegoxyl 7 stearate, peglicol 5 oleate and heavy mineral oil are mixed while being melted and heated to 140° F. Hot purified water (120° F.) is transferred to the main vessel and circulated through the homogenizer. The benzoic acid is added to the water and the mixture is circulated until the benzoic acid is completely dissolved. The temperature of the solution stays at 120° F. The oil phase is added to the water phase and the temperature in the main vessel upon completion of the addition rises to 123° F. The two phases are circulated through the homogenizer until an emulsion is formed. The emulsion is withdrawn from the circulation system through a heat exchanger at a temperature of 90° F. Samples of the product are taken periodically from the batch as it passes through the heat exchanger.

EXAMPLE 2

Lubricating Jelly Ingredients	% (w/w)
CMC Type 7HF	1.85
Kelgin LV	1.08
Methylparaben	0.15
Propylene Glycol	3.75
Glycerin	11.25
Potassium Hydroxide	0.03
Boric Acid	3.00
Water	78.89

Procedure

The water (at 75° C.) and the boric acid are added into the main vessel. The mixture is circulated through the bypass loop until a solution is formed. To this solution, Kelgin LV is added and the mixture is circulated again until the Kelgin is completely dissolved.

In the slurry tank, a slurry of propylene glycol, glycerin, CMC and methylparaben is prepared. While the mixture is circulated through the homogenizer, the slurry is transferred to the main vessel and the circulation is maintained until a solution is formed. During this circulation period, the temperature of the jelly is maintained at 70° to 75° C. until all the solids are in solution.

This solution, with the aid of the heat exchanger, is cooled to 30° to 35° C. to form the lubricating jelly.

EXAMPLE 3

	% (w/w)
<u>Aqueous Phase</u>	
Purified Water	73.8
Benzoic Acid	0.2
<u>Oil Phase</u>	
Pegoxyl 7 Stearate	20.0
Peglicol 5 Oleate	3.0
Heavy Mineral Oil	3.0

Procedure

The pegoxyl 7 stearate, peglicol 5 oleate and heavy mineral oil are mixed while being melted and heated to 180° F. Hot purified water (180° F.) is transferred to the main vessel and circulated through the homogenizer. The benzoic acid is added to the water and the mixture is circulated until the benzoic acid is completely dissolved. The temperature of the solution drops to 165° F. The oil phase is added to the water phase and the temperature in the main vessel upon completion of the addition rises to 167° F. The two phases are circulated through the homogenizer until an emulsion is formed. The emulsion is withdrawn from the circulation system through a heat exchanger at a temperature of 110° F. Samples of the product are taken periodically from the batch as it passes through the heat exchanger.

EXAMPLE 4

A.	% (w/w)
<u>Oil Phase</u>	
Mineral Oil	25.0
Microcrystalline Wax	10.0
Cetyl Alcohol	5.0
Mixed Lanolin Alcohols	10.0
Sorbitan Sesquioleate	3.0

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.

Abogado
CARLOS R. OLARTE

ASUNTO	Radicación	05128769
	Trámite	011
	Evento	379
	Actuación	411
	Oficio	9921
	Folios	011

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐ Cap. II ☒
No. Sol. Internacional		PCT/IB2005/002474	
Fecha de Presentación Internal.		Julio 19 de 2004.	

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 le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 65 a 133 como se radicó inicialmente
- 1.2. Reivindicaciones: Folios: 134 a 147 como se radicó inicialmente
- 1.3. Prioridad: Julio 31 de 2003; US; 60/492,178

2. Objeto de la invención

Título de la invención: COMPOSICIÓN FARMACEUTICA DISPERSABLE PARA EL TRATAMIENTO DE MASTITIS Y TRASTORNOS OTICOS.

Problema Técnico Planteado: Necesidad de composiciones eficaces para la prevención y tratamiento de trastornos óticos y complicaciones relacionadas con los mismos.

Solución: Una composición conforme a la reivindicación 27 (folio 140 pg 76).

IPC: A61K47/00; A61P27/16.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

La reivindicación 27, no es concisa dado que no caracteriza a la composición por sus componentes, al no nombrar claramente cual es el aceite anfipático, ni el vehículo no acuoso, el agente antibacteriano, el anestésico, el bloqueador de canales de sodio, ni el agente antiedémico. Se definen los principios activos por su perfil farmacológico lo cual no es una característica esencial.

4. Unidad de invención (artículo 25 D 486)

Dado que el artículo puede estar conformado por diversos grupos de invención como la composición con el o los principios activos, el recipiente o dispositivo de suministro, se considera que el artículo no presenta unidad de invención.

En consecuencia esta Oficina recomienda que las reivindicaciones 61 a 63 que no guardan unidad de invención en si mismas sean eliminadas del alcance de la invención.

5. Excepción a la patentabilidad (artículo 20 D486 literal a)-d)

Las reivindicaciones 1-26 se reclaman un procedimiento para el tratamiento de una afección, lo cual no es patentable.

6. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria: Julio 31 de 2003.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	US20020068065	Pharmaceutical composition having specific water activity	Junio 6 de 2002
D2	US4299501	Continuous process for the preparation of semisolid dispersions	Noviembre 10 de 1981

D1 (folios 184-188); D2 (folios 189-190)

7. Análisis de patentabilidad (artículo 14 D486)

7.1 Nivel inventivo (artículo 18 D486)

Respecto a la solicitud en estudio:

La reivindicación 27 dice: Una composición farmacéutica que comprende un vehículo a) aceite anfipático que es dispersable en agua e insoluble en etanol, b) cera microcristalina, c) un vehículo no acuoso farmacéuticamente aceptable; teniendo dicho vehículo disperso de forma estable en el mismo una agente antibacteriano en cantidad eficaz y un segundo agente seleccionado entre el grupo constituido por anestésicos, bloqueantes de los canales de sodio y agentes antiedémicos.

A continuación se procede a comparar las características técnicas de la solicitud con las de las anterioridades **D1** y **D2**,

Solicitud Reivindicación 27		
	D1	D2
Una composición (suspensión uniforme) que contiene:	Una composición folios: 184, abstract; folio 185, pg 1, párrafo 0003)	Una composición (dispersión semisólida) folios: 189, abstract
a) aceite anfipático (5 oleato de peglicol)		Folio 190, colum 3, ejemplo 1.
b) cera microcristalina		Folio 190, colum 4, ejemplo 4.
c) vehiculo no acuoso	Folio 187, pg 3, párrafo 0052	
d) un agente antibacteriano en cantidad eficaz y un segundo agente seleccionado entre el grupo constituido por anestésicos, bloqueantes de los canales de sodio y agentes antiedémicos.	Folio 186, pg 2, párrafo 0050; Folio 187, pg 3, párrafo 0050.	

El documento del Estado de la Técnica más próximo es **D1**, que enseña composiciones farmacéuticas estables, para administrar por vía tópica entre otras, que contienen una o mas sustancias bioactivas en un vehículo no acuoso y otros excipientes como antioxidantes (Ver folios: 184, abstrat; 185, pg 1, párrafo 0003, 190,pg 6 párrafos 0079,0081, 0084; folio 187, pg 3, párrafos 0052, 0053 y 0054).

La diferencia entre la materia reclamada y **D1**, es que la solicitud reivindica otras composiciones que mencionan, específicamente la cera microcristalina y un aceite anfipático (5 oleato de peglicol)

El Efecto Técnico logrado es: Suspensiones (composiciones) uniformes.

El Problema Objetivo de esta solicitud es como obtener otras composiciones estables, de un antibacteriano y otro principio activo seleccionado entre el grupo constituido por anestésicos, bloqueantes de los canales de sodio y agentes antiedémicos, en un vehículo no acuoso, como alternativas a las ya divulgadas.

D2, divulga preparaciones (dispersiones semisólidas tales como cremas, geles y ungüentos, las cuales contienen ingredientes como material farmacéutico

(principios activos) y excipientes como la cera microcristalina y el 5 oleato de peglicol (folio 194 columna 3 y 4, ejemplo 3 y ejemplo 4), lo que hubiese sugerido a un experto en la materia las composiciones reivindicadas.

Por esta razón se considera que la inclusión de cera microcristalina y el 5 oleato de peglicol en la composición reivindicada, es evidente para una persona medianamente versada en la materia combinando la solución propuesta por **D2** con las composiciones divulgadas del **D1**; llegando de tal manera a las suspensiones (composiciones) de esta solicitud.

El análisis anterior, convierte a las composiciones reclamadas en una alternativa frente a las ya conocidas en D1.

Por lo anterior las composiciones reclamadas en las reivindicaciones 27- 60 no tienen nivel inventivo.

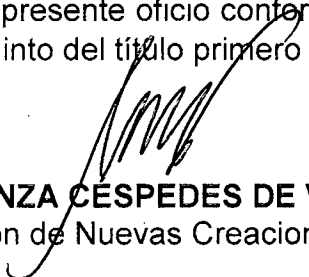
8. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	US20020068065	27-60	Nivel Inventivo
D2	US4299501	27-60	Nivel Inventivo

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 sesenta 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 Nº 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

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

20 AGO. 2009

CONCEPTO TÉCNICO No.2744	EXAMINADOR TÉCNICO Código No.202078
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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 009024

Por la cual se niega una patente de invención

Rad. PCT/05-128769

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

En ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 3, numeral 30 del decreto 3523 de 2009, y

CONSIDERANDO:

PRIMERO: Que la solicitud de patente de invención titulada "COMPOSICION FARMACEUTICA DISPERSABLE PARA EL TRATAMIENTO DE MASTITIS Y TRANSTORNOS OTICOS", que corresponde a la solicitud internacional PCT/IB2005/002474 de fecha 19 de julio del 2004, fue radicada en esta Superintendencia el 22 de diciembre del 2005 bajo el número 05-128769 -00000-0000, para que se iniciara la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un período de treinta días adicionales.(...) Si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente"*.

CUARTO: Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 184 a 194 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del solicitante, por lo cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 009024

Por la cual se niega una patente de invención

Rad. PCT/05-128769

RESUELVE:

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPOSICION FARMACEUTICA DISPERSABLE PARA EL TRATAMIENTO DE MASTITIS Y TRANSTORNOS OTICOS", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente al doctor Carlos Reinaldo Olarte García, en su calidad de apoderado de PHARMACIA & UPJOHN COMPANY LLC., o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los

18 FEB. 2010

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E),



GIANCARLO MARCENARO JIMENEZ

Doctor

CARLOS REINALDO OLARTE GARCIA

Diagonal 34 No. 5-28

Bogotá D.C.