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(54) Paste formulations comprising silica

Pastenformulierungen enthaltend Silica

Formulations pateuses comprenant de la silice

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Description

FIELD OF THE INVENTION

[0001] This invention provides for improved paste formulations suitable for pharmaceutical and veterinary use as well as the use of these formulations in the preparation of a medicament for treating various disease states. This invention also provides for an improved method for manufacturing paste formulations.

BRIEF DESCRIPTION OF THE DRAWINGS

[0002]

Fig. 1 depicts the change of viscosity as a function of increased CAB.O.SIL content wherein no viscosity modifier was added.
Fig. 2 depicts the impact of the viscosity modifier, PEG 300, on the paste viscosity of initial and after storage for 6 days at 60°C.
Fig. 3 depicts the schematic representation of the competition of excess PEG molecules with the crosslinking PEG molecules.
Fig. 4 depicts the sheer sensitivity study of the intermediate product at low sheer.
Fig. 5 depicts the sheer sensitivity study of the end product at high sheer.
Fig. 6 depicts the powder X-ray diffraction (XRPD) pattern of form A.
Fig. 7 depicts the XRPD pattern of form B.

BACKGROUND OF THE INVENTION

[0003] Therapeutic agents are administered to animals and humans by a variety of routes. These routes include, for example, oral ingestion, topical application or parental administration. The particular route selected by the practitioner depends upon factor such as the physiochemical properties of the therapeutic agent, the condition of the host, and economics.

[0004] One method of formulating a therapeutic agent for oral, topical, dermal or subdermal administration is to formulate the therapeutic agent as a paste.

[0005] EP 0181525 relates to antelminthic paste compositions containing resonated L-tetramisole or resonated DL-tetramisole, heavy mineral oil, a non-ionic surfactant, a second active ingredient, an agent to increase the density of the composition and fumed or participated silica. US 5,122,377 relates to a veterinary drug delivery system suitable for oral administration which comprises a therapeutic agent, a non-volatile oil, silicon dioxide, capric/caprylic triglyceride and/or capric/caprylic stearic triglyceride. US 3,746,490 relates to a veterinary paste for horses comprising dimethyldichlorovinylphosphate. US 5,708,017 relates to an oral paste composition suitable for the delivery of a proton pump inhibitor to horses. The paste comprises a thickening agent, a basifying agent and a hydrophobic oily liquid vehicle. US 4,891,211 relates to a stable, palatable and safe hydrogen peroxide releasing toothpaste or gel dentrifrice comprising sodium bicarbonate and sodium percabonate in a polyethylene glycol base. Thickening agents, surfactants, flavouring agents, sweeteners, fluoridating agents and other conventional adjuvants may also be included in the formulation. US 4,605,563 relates to compositions comprising 0.1% to 10% by weight of a high melting glyceride of saturated fatty acids melting above 50°C and 0.2% to 10% by weight of a highly dispersed pyrogenic silica. The ratio of component is adjusted to obtain a paste consistency. US 6,017,520 relates to topical compositions containing vitamin E as a penetration enhancing agent and a solvent selected from the group consisting of mineral oil, water, ethanol, triacetin, glycerin and propylene glycol, together with a cohesion agent selected from polyisobutylene, polyvinyl acetate and polyvinyl alcohol. The composition further comprises a thickening agent. Finally, WO 00/56346 relates to a stable oil in glycerin emulsion containing at least one oil, at least one emulsifier and glycerin.

[0006] Pastes have the advantage of being relatively easy to use. The disadvantage associated with their use is that often these products typically do not retain good chemical and physical stability over the shelf-life of the product. Hence, there is a need for improved paste formulations which do not exhibit these undesirable properties.

[0007] One of the causes of these disadvantages is the inclusion of fumed silica as a viscosity agent. Fumed silica is commercially available and sold, for example, under the trade names of CAB-O-SIL (Cabot, TD11) and AEROSIL (Degussa, Technical Bulletin Pigments, No. 11 and No. 49). Fumed silica is an extremely light material (density 0.04 g/ml), which makes its handling and processing difficult. Moreover, because of its light density, fumed silica, when mixed with a vehicle, introduces a significant amount of air into the product. This occurs even at the relatively small amounts (6 to 8%) typically used to make pastes (6 to 8%). Unless the paste is processed under vacuum or a deareation step is added at the end of the process, it is not possible to remove such large amounts of air bubbles from the paste.

[0008] In order to demonstrate the problems associated with using fumed silica such as CAB-O-SIL, the viscosity of a paste as a function of CAB-O-SIL, content was measured. Fig. 1 depicts the change of viscosity of the paste where no viscosity modifier was added. Triacetin was used as the vehicle in this study. When the CAB-O-SIT content was less than 5%, the paste remained thin as a free flow liquid and entrapped air could easily escape. After 5%, the viscosity increased dramatically and the additional air brought into the paste by the CAB-O-SIL could not escape and stayed in the paste. When about 7% of CAB-O-SIL was added, the paste had a penetration value of 35 mm. This amount is comparable with the initial penetration value of other commercially known pastes such as GASTROGARD (20-40 mm). Hence, in the absence of a viscosity modifier, at least 7% of CAB-O-SIL was needed to make pastes with useful viscosity. Because of the low density of CAB-O-SIL (0.04 g/ml), the amount of entrapped air is significant. Thus, unless processing under vacuum or adding a deaeration step at the end, it is impossible to remove such large amounts of air in the paste and cannot control the accuracy of the dose.

[0009] Viscosity modifiers include compounds that have two or more functional groups which are capable of forming hydrogen bonds with the silanols on the surface of the fumed silica particles. Compounds which function as viscosity modifiers include, for example, the polyethylene glycols ("PEGs"). These compounds are liquid and solid polymers which correspond to the general formula $H(OCH_2CH_2)_nOH$, where n is greater than or equal to 4, and are described in "The Merck Index", 10th ed., M. Windholz and S. Budavari eds., p. 1092, Merck & Co., Inc., Rahway, NJ (1983).

[0010] While not wishing to be bound by theory, in order to understand the mechanism of the viscosity modifiers, it is necessary to understand how CAB-O-SIL thickens a formulation. The hydrogen bonds between the silanol groups on the surface of the CAB-O-SIL particles are responsible for its thickening effect. CAB-O-SIL particles are connected through these hydrogen bonds to form a three-dimension network. The viscosity modifiers have two or more functional groups (e.g., -OH or $-NH_2$). These groups form hydrogen bonds with the silanols on the surface of CAB-O-SIL particles. These viscosity modifiers act as crosslinkers to extend the network structure and also increase the crosslinking density. This is why the addition of a small amount of the viscosity modifiers dramatically increased the viscosity of the pastes.

[0011] In order to demonstrate this, placebo pastes containing 4% CAB-O-SIL and 0.1-3.0% polyethylene glycol ("PEG") 300 in triacetin were prepared and their viscosity values were measured using penetrometer (Fig. 2). Before the addition of PEG 300, the viscosity was too low to be tested on penetrometer (>65 mm). The viscosity jumped dramatically with just the addition of only 0.1% PEG 300. The viscosity increased further when more PEG 300 was added. After the PEG level reached 0.5%, the viscosity increase plateaued. From 0.5-3.0%, the viscosity remained about the same, although a slight decrease in viscosity was seen when more than 2% PEG was added.

[0012] Fig. 3 depicts what is believed to be happening at the molecular level. Fig. 3 depicts the competition of excess PEG molecules with the crosslinking PEG molecules at the molecular level. The figure indicates that the silanol groups on the surface of CAB-O-SIL particles were saturated when more than 0.5% PEG was added. The extra PEG molecules could no longer increase the viscosity because it could not find two free silanol groups on two different particles to increase further the viscosity. On the contrary, the free PEG molecules actually compete with the bonded PEG molecules that crosslinks two particles (Fig. 3). As a result, some of the crosslinks dissociate and the viscosity decreases slightly. Based on Fig. 2, the ideal range of PEG 300 is about 0.2% to about 1.5% for this particular paste.

[0013] Thus, as depicted in Fig. 1, the prior pastes use a relatively high amount of fumed silica to achieve the proper viscosity. The effect of this is that a large amount of air will be entrapped into the paste, which causes, for example, dose inaccuracy, shrinkage, liquid separation (whipping) and discoloration of the paste. Further, the therapeutic agent may also oxidize. Moreover, when a large amount of fumed silica is used in an oral paste, the paste imparts a sandy feel to the mouth. This sandy feel causes the product to be less palatable. Furthermore, the manufacturing costs to prepare the pastes are expensive because the process must occur under vacuum or a subsequent deaeration step at the end of the process is required. Additional manufacturing costs are incurred because fumed silica is relatively expensive and very difficult to handle due to its extremely low density. The present invention overcomes these as well as other disadvantages.

SUMMARY OF THE INVENTION

[0014] The present invention provides for a stable paste formulation for a wide range of veterinary and pharmaceutical products. The present invention also provides for an improved process to make the inventive paste products. The formulations of the present invention exhibit good chemical and physical stability over the shelf life and maintain the chemical integrity, texture, consistency and viscosity over a wide temperature range. The inventive manufacturing process provides for a simple, fast and economical process for preparing the inventive paste formulations that avoids heating and cooling during manufacturing and entrapment of air, a common problem in the manufacturing of paste dosage forms.

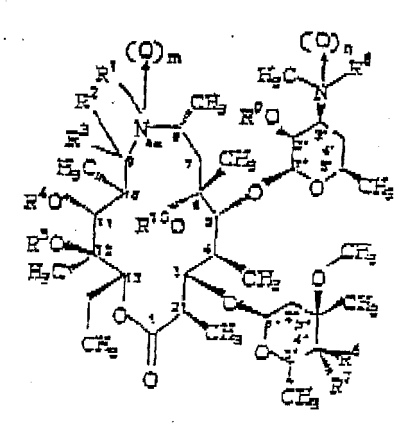
[0015] These and other embodiments are disclosed or are obvious, from and encompassed by, the following Detailed Description.

DETAILED DESCRIPTION

[0016] The present invention provides for a pharmaceutical or veterinary paste formulation comprising:

(a) an effective amount of a therapeutic agent selected from an 8a-azalide, azithromycin or erythromycin;
(b) fumed silica;
(c) a viscosity modifier selected from PEG 200, PEG 300, PEG 400, PEG 600, monoethanolamine, triethanolamine, glycerol, propylene glycol, polyoxylene sorbitan monoleate and poloxamers;
(d) a carrier;
(e) optionally, an absorbent selected from magnesium carbonate, calcium carbonate, starch and cellulose and its derivatives; and
(f) optionally, a stabilizer, surfactant, preservative or colorant selected from titanium dioxide, dye and lake;

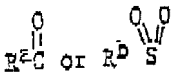
wherein the 8a-azalide is of formula I



wherein

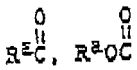
R^1 is hydrogen;
hydroxy;
C_{1-4} alkoxy;
formyl;
C_{1-10} alkylcarbonyl, C_{1-10} alkoxycarbonyl, aryloxycarbonyl, C_{1-10} aralkoxycarbonyl, C_{1-10} alkylsulfonyl, or arylsulfonyl wherein said C_{1-10} alkyl group or aryl group is unsubstituted or substituted by 1-3 halo (F, Cl, Br), hydroxy, amino, C_{1-5} acylamino or C_{1-4} alkyl groups; or
unsubstituted or substituted C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl wherein said substituents are independently 1-3 of

(a) aryl or heteroaryl optionally substituted by 1-3 halo (F, Cl, Br, I), C_{1-4} alkyl, C_{1-3} alkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl) amino or hydroxy,
(b) heterocyclyl optionally substituted by hydroxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkylcarbonyloxy or C_{1-4} alkylcarbonylamino,
(c) halo (F, Cl, Br or I),
(d) hydroxy optionally, acylated by a group



wherein
R^2 is hydrogen, C_{1-6} alkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl and

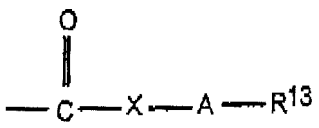
R^b is C_{1-6} alkyl or aryl,
(e) C_{1-10} alkoxy.
(f) aryloxy or heterocaryloxy optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl group,
(g) amino or C_{1-10} alkylamino optionally acylared by a group



or R^bSO_2, wherein
R^2 and
R^b are as defined above,
(g) di(C_{1-10} alkyl)amino,
(h) arylamino, heteroarylamino, aralkylamino or heteroarylakylamino wherein said aryl or heteroaryl groups is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,
(i) mercapto,
(j) C_{1-10} alkylthio, alkylsulfinyl or alkylsulfonyl, arylthio, arylsulfinyl or arylsulfonyl wherein said aryl group is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,
(k) formyl,
(l) C_{1-10} alkylcarbonyl,
(m)arylcarbonyl, heteroarylcarbonyl, aralkylcarbonyl or heteroarylalkylcarbonyl wherein said aryl or heteroaryl group is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,
(n) carboy,
(o) C_{1-10} alkoxycarbonyl,
(p) aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl or heteroarylalkoxycarbonyl wherein said aryl or heteroaryl group is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,
(q) carbamoyl or sulfamoyl wherein the N-atom is optionally substituted by 1-2 C_{1-6} alkyl groups or by a C_{4-6} alkylene chain,
(r) cyano,
(s) isonitrilo,
(t) nitro,
(u) azido,
(v) iminomethyl optionally substituted on nitrogen or carbon with C_{1-10} alkyl,
(w) oxo, or
(x) thiono;

wherein said alkyl chain, if more than two carbons in length, can be optionally interrupted by 1-2 oxa, thia or aza (-NR-wherein R is hydrogen or C_{1-3} alkyl) groups.

R^{10}	is hydrogen or
R^1 and R^{10}	together are C_1-C_3 alkylene optionally substituted by an oxo group;
R^1 and R^4	together are C_1-C_3 alkylene optionally, substituted by an oxo, group
R^2 and R^3	are hydrogen, C_{1-10} alkyl, aryl
R^2 and R^3	together are oxo and thiono;
R^4 and R^5	are independently hydrogen and alkylcarbonyl;
R^4 and R^5	are together carbonyl;
R^6 and R^7	are both hydrogen or one of R^6 and R^7 is hydrogen and the other is hydroxy, an acyloxy derivative taken from the group consisting of formyloxy, C_{1-10} alkylcarbonyloxy, arylcarbonyloxy and aralkylcarbonyloxy, or -NHR^{12} wherein R^{13} is hydrogen, arylsulfonyl or heteroarylsulfonyl optionally substituted by is halo or C_{1-3} alkyl groups, alkylsulfonyl, or



where
X is a connecting bond, O or NH,
A is connecting bond or C_1-C_3 alkylene
R^{13} is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, heteroaryl, heterocyclyl, or C_3-C_7 cycloalkyl, any of which R^{13} groups other than hydrogen can be substituted by one or more of halogen, hydroxyl, C_1-C_3 alkoxy, cyano, isonitrilo, nitro, amino, mono- or di-(C_1-C_3)alkylamino, mercapto, C_1-C_3 alkylthio, C_1-C_3 alkylsulfinyl, C_1-C_3 alkylsulfonyl, arylthio, arylsulfinyl, sulfamoyl, arylsulfonyl, carboxy, carbamoyl, C_1-C_3 alkylcarbonyl, or C_1-C_3 alkoxycarbonyl;
R^6 and R^7 are together oxo, hydroxyimino, alkoxyimino, aralkoxyimino or aminoimino;
R^8 is methyl, aralkoxycarbonyl, and arylsulfonyl;
R^9 is hydrogen, formyl, $C_{1\text{-}10}$ alkylcabonyl, $C_{1\text{-}10}$ alkoxycarbonyl, and arylalkoxycarbonyl;

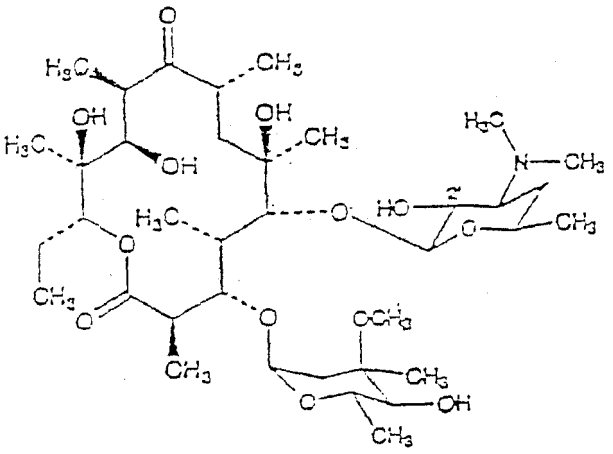
m and n are independently integers of zero or one; and said metal complex is taken from the group consisting of copper, zinc, cobalt, nickel and cadmium or a pharmaceutically acceptable salt, ester or metal complex thereof.

[0017] The invention further relates to the use of a paste as described above in the preparation of a medicament for treating a bacterial infection in a host in need thereof.

[0018] Additionally, the compounds can be administered in combination with other insecticides, parasiticides, and acaricides. Such combinations include anthelmintic agents, which include ivermectin, avermectin, and emamectin, as well as other agents such as thiabendazole, febantel or morantel; phenylpyrazoles such as fipronil; and insect growth regulators such as lufenuron. Such combinations are also contemplated in the present invention.

[0019] In one preferred embodiment, the therapeutic agent is erythromycin.

[0020] Erythromycin (MW 733.94 daltons) is the common name for a macrolide antibiotic produced by the growth of a strain of Streptomyces erythreous. It is a mixture of three erythromycins. A. B and C consisting largely of erythromycin A which is represented by the formula:



[0021] Its chemical name is (3R*,4S*,5S*,6R*,7R*,9R*,11R*,12R*, 13S*,14R*)-4-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexapyranosyl]oxy]oxacyclotetradecane-2,10-dione, ($C_{37}H_{67}NO_{13}$).

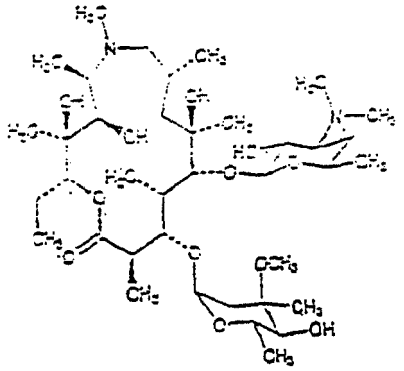
[0022] Erythromycin has a broad and essentially bacteriostatic action against many Gram-positive and some Gram-negative bacteria as well as other organisms including mycoplasmas, spirochetes, chlamydiae and rickettsiae. In humans, it finds usefulness in the treatment of a wide variety of infections. It finds wide application in veterinary practice in the treatment of infectious diseases such as pneumonias, mastitis, metritis, rhinitis, and bronchitis in, for example, cattle, swine and sheep.

[0023] Other derivatives of erythromycins include carbomycin, clarithromycin, josamycin, leucomycins, midecamycins, mikamycin, miokamycin, oleandomycin, pristinamycin, rokitamycin, rosaramicin, roxithromycin, spiramycin, tylosin, troleandomycin, and virginiamycin. As with the erythromycins, many of these derivatives exist as component mixtures. For example, carbomycin is a mixture of carbomycin A and carbomycin B. Leucomycin exists as a mixture of components A_1, A_2, A_3, A_9, B_1-B_4, U and V in various proportions. Component A_3 is also known as josamycin and leucomycin V is also known as miokomycin. The major components of the midecamycins is midecamycin A and the minor components are midecamycins A_2, A_3 and A_4. Likewise, mikamycin is a mixture of several components, mikamycin A and B. Mikamycin A is also known as virginiamycin M_1. Pristinamycin is composed of pristinamycins I_A, I_B, and I_C, which are identical to virginiamycins B_2, B_{13} and B_2 respectively, and pristinamycin II_A and II_B, which are identical to virginiamycin M_1 and

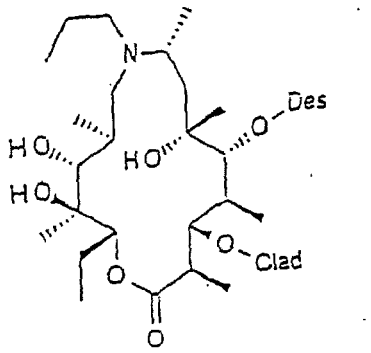
26,27-dihydrovirginiamycin M_1. Spiramycin consists of three components, spiromycin I, II, and III. Virginiamycin is composed of virginiamycin S_1 and virginiamycin M_1. All these components may be used in this invention. Sources of these macrolides are well known to the practitioner and are described in the literature in references such as "The Merck Index," 12th ed., S. Budarari, ed., Merck & Co., Inc., Whitehouse Station, NJ (1996).

[0024] These compounds are disclosed in EP 568 699. Azalides as a class of components is well-known in the art and further derivatives are described, for example, in U.S. Patent Nos. 5,869,629; 5,629,296; 5,434,140; 5,332,807; U.S. 5,250,518; 5,215,890; and 5,210,235, all incorporated herein by reference.

[0025] In one preferred embodiment, the therapeutic agent is azithromycin. The structure of azithromycin is

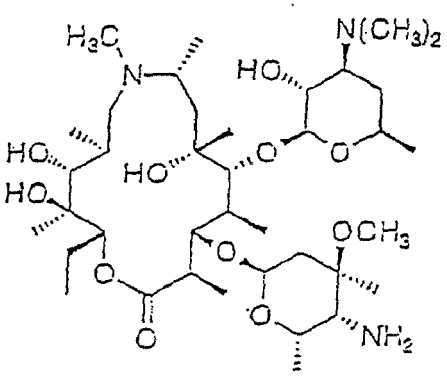


[0026] In another preferred embodiment, the therapeutic agent is an 8a-azalide selected from a compound of formula I,



I

wherein Des is desosomine and Clad is cladinose, and a compound of formula II,



II

[0027] The compound of formula II are also known as 8a-azalide. These compounds are disclosed in EP 508 699.

The corresponding basic and acid addition salts and ester derivatives of the macrolides, including the azalides compounds, are also contemplated. These salts are formed from the corresponding organic or inorganic acids or bases. These derivatives include the customary hydrochloride and phosphate salts as well as the acetate, propionate and butyrate esters. These derivatives may have different names. For example, the phosphate salt of oleandomycin is matromycin and the triaceyl derivative is troleandomycin. Rokitamycin is leucomycin V 4-B-butanoate, 3B-propionate.

[0028] The term "therapeutic agent," also includes the pharmaceutically or veterinary acceptable acid or base salts, where applicable, of these compounds. The term "acid" contemplates all pharmaceutically or veterinary acceptable inorganic or organic acids. Inorganic acids include mineral acids such as hydrohalic acids, such as hydrobromic and hydrochloric acids, sulfuric acids, phosphoric acids and nitric acids. Organic acids include all pharmaceutically or veterinary acceptable aliphatic, alicyclic and aromatic carboxylic acids, dicarboxylic acids tricarboxylic acids and fatty acids. Preferred acids are straight chain or branched, saturated or unsaturated C_1-C_{20} aliphatic carboxylic acids, which are optionally substituted by halogen or by hydroxyl groups, or C_6-C_{12} aromatic carboxylic acids. Examples of such acids are carbonic acid, formic acid, fumaric acid, acetic acid, propionic acid, isopropionic acid, valeric acid, α-hydroxy acids, such as glycolic acid and lactic acid, chloroacetic acid, benzoic acid, methane sulfonic acid, and salicylic acid. Examples of dicarboxylic acids include oxalic acid, malic acid, succinic acid, tataric acid and maleic acid An example of a tricarboxylic acid is citric acid. Fatty acids include all pharmaceutically or veterinary acceptable saturated or unsaturated aliphatic or aromatic carboxylic acids having 4 to 24 carbon atoms. Example include butyric acid, isobutyric acid, see-butyric acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, and phenylsteric acid, Other acids include gluconic acid, glycoheptonic acid and lactobionic acid.

[0029] The term "base" contemplates all pharmaceutically or veterinary acceptable inorganic or organic bases. Such bases include, for example, the alkali metal and alkaline earth metal salts, such as the lithium, sodium, potassium, magnesium or calcium salts. Organic bases include the common hydrocarbyl and heterocyclic amine salts, which include, for example, the morpholine and piperidine salts.

[0030] The ester and amide derivatives of these compounds, where applicable, are also contemplated. Specific compounds which belong to these classes of therapeutic agents are well known to the practitioner of this art.

[0031] An important feature of the present invention is the combustion of a viscosity modifier to the formulation. The addition of the viscosity modifier provides for a paste formulation which contains less fumed silica than the amount normally used in a conventional paste. The inventive formulation allows for all the air that is introduced into the formulation by the fumed silica to escape when the viscosity is low. The viscosity modifier is then added to bring the viscosity of the paste to the desired level without the introduction of more air into the final product. While not wishing to be bound by theory, it is believed that because of their functional groups, the viscosity modifiers act as crosslinkers and extend the three-dimensional network formed by the interaction of the silica and the hydrophobic carrier. The viscosity modifiers also extend the crosslinking density in the formulation.

[0032] Especially preferred hydroxy-containing viscosity modifiers include PEG 200, PEG 300, PEG 400, and PEG 600. Other hydroxyl-containing viscosity modifiers include block copolymer mixtures of polyoxyalkylene compounds, i.e., poloxamers including ethylene oxide and propylene oxide poloxamer mixtures, such as those described in U.S. Patent Nos. 4,343,785; 4,465,663; 4,511,563; and 4,476,107. Commercial versions of these nonionic poloxamer surfactants are available from BASF - Wyandotte Co., Wyandotte, Mich. and include various Pluronics such as Pluronic L81, Pluronic F108, and F127 and those Pluronics described in "Pluronic & Tetronic Surfactants", BASF Corp., 1987, as well as in "The Merck Index", 10th ed. on page 1090 and in Remington Pharmaceutical Science. Other suitable density modifiers useful as of the present invention include: polyoxyethylene sorbit in monoleate (Polysorbate 80); polyethylene glycols (Pluracols); nonylphenol ethoxylates (Surfonics); and linear alcohol ethoxylates polyethyleneglycol paraisooctyphenyl/ethers (Tritons's).

[0033] Propylene glycol mono- and di-fatty acid esters are also provided for in the inventive formulations. These esters include for example, propylene glycol dicaprylate; propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, and propylene glycol stearate, most preferably propylene glycol caprylic-capric acid diester as is available under the Trade Name MIGLYOL 840.

[0034] Other compounds which function as viscosity modifiers are those which contain both hydroxy and amino function groups. Such compounds include, for example, monoethanolamine, diethanolamine and triethanolamine. These compounds, as well as their use, are well known to a practitioner in the pharmaceutical and veterinary arts.

[0035] The amount of viscosity modifier varies from formulation to formulation and the determination of the amount required is well within the routine skill of a practitioner in the formulation an. Preferred is about 0.01 to about 20% of viscosity modifier, based upon total weight of the composition. An especially preferred amount is about 0.05 to about 5%, with about 0.1 to about 2% being most preferred.

[0036] Fumed silica is used as the thickening agent. In the pastes according to this invention, the amount of fumed silica is very low. This allows an intermediate with a low viscosity, which in turn allows for a quick escape of the air by buoyancy. After letting the intermediate settle for about 10 minute, no air was detected in the intermediate. Preferred pastes comprise from about 1 to about 20%, based upon total weight of solution, with from about 1% to about 6% being

preferred. Amounts of about 0.02% to about 20%, about 1% to 6.5% or about 1 to about 4% or 5% are also preferred. A paste where the amount of silica is about 4.25% is especially preferred.

[0037] The carrier is another important component of the formulation. It is the liquid phase that dissolves the active drug to give an excellent content uniformity and bioavailability. Compounds which act as carriers include solvents that are suitable for pharmaceutical applications, such as triacetin, short to medium chain mono-, di-, or tri-glycerides, glycerin, water, propylene glycol, N-methyl pyrrolidinone, glycerol formal, polyethylene glycol, polyethylene glycol-polypropylene glycol polyethylene glycol tri-block copolymers, vegetable oil, sesame oil, soybean oil, corn oil, mineral oil, peanut oil, castor oil, cotton oil, transcutol, benzyl alcohol, N,N-dimethylformamide, dimethylsulfoxide, or the like. These compounds may be used alone or as mixtures. Triacetin is especially preferred as it has some water solubility that allows an easy cleaning of the manufacturing equipment. Unlike some aqueous based pastes, triacetin does not support microbial growth, which eliminates the need for a preservative. Mixtures of other carriers with triacetin are also preferred. The amount and type of hydrophobic carrier for a particular formulation is well within the skill level of the practitioner.

[0038] When present, any of the conventional pharmaceutical or veterinary colorants may be used. Such colorants include, for example, dyes, aluminum lakes, colorants based upon iron oxide, caramel or combinations of various colorants. Preferably up to about 20%, by weight of total composition, may be present with about 0.001 or 0.01% to about 10% and 0.001 to about 4% being most preferred.

[0039] Absorbents may also be added to the paste formulation. Such compounds are well known in the art to the practitioner as well as their use in pastes. These compounds effectively prevent or alleviate the phase separation of the product during storage. Preferred absorbents include magnesium carbonate, calcium carbonate, starch, cellulose and its derivatives, or mixtures of absorbents with magnesium carbonate being especially preferred. The inclusion of these compounds is optional with amounts of 0% to about 30%, 0 to about 15% or about 1% to about 15% or about 1% to about 10%, based on total weight of the composition being especially preferred.

[0040] In addition to the therapeutic agent, the viscosity modifier, and the carrier, the formulation can contain other inert ingredients such as antioxidants, preservatives, stabilizers or surfactants. These compounds are well known in the formulation art. Antioxidants such as an alpha tocopheral, ascorbic acid, ascrobyl palmitate, fumeric acid, malic acid, sodium ascorbate, sodium metabisulfate, n-propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene) monothioglycerol and the like, may be added to the present formulation. The antioxidants are generally added to the formulation in amounts of from about 0.01 to about 2.0%, based upon total weight of the formulation. Preservatives such as the parabens (methylparaben and/or propylparaben) are suitably used in the formulation in amounts ranging from about 0.01 to about 2.0%. Other preservatives include benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, bronopol, butylparaben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben, imidurea, methylparaben, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid, thimerosal, and the like.

[0041] Surfactants can also be added to help solubilize the active drug, to prevent crystallization, and to prevent phase separation. Some examples of the surfactants are: glyceryl monooleate, polyoxyethylene sorbitan fatty acid esters, sorbitan esters, polyvinyl alcohol, Pluronics, sodium lauryl sulfate, etc. Again, these compounds, as well as their amounts are well known in the art.

[0042] In one highly preferred embodiment, the paste formulation of the invention, based upon total weight of composition, comprises:

(a) about 0.01 to about 50% of the therapeutic agent;
(b) about 0.02 to about 20% of fumed silica;
(c) about 0.01 to about 20% of a viscosity modifier;
(d) 0% to about 30% of an absorbent;
(e) 0% to about 20% of a colorant; and
(f) Q.S. a carrier.

[0043] The instant formulation is equally applicable to other compounds used for pastes as long as such compounds are soluble in the carrier. Additional compounds that can be used in this formulation are other antiparasitic agents and antibiotics, therapeutic vitamin and mineral supplements, and other agents that are assisted in their therapeutic effect by having improved stability over a prolonged period of time. Again, such compounds would be well know to the practitioner.

[0044] The pastes are administered to warm-blooded animals, such as humans, cattle, sheep, pigs, cats, dogs, horses, and the like, by oral, topical, dermal and subdermal administration. The inventive pastes may also be administered to humans. The amount of therapeutic agent depends on the individual therapeutic agent, the animal being treated, the disease state, and the severity of the disease state. The determination of those factors is well within the skill level of the practitioner. Generally, such preparation normally contain about 0.0005 to about 50% of therapeutic agent by total weight of composition. Preferred formulations are those containing about 0.01 to 10% of therapeutic agent and especially

preferred 2.5 to about 5% w/v. However depending upon the activity of the compound and the animal being treated, doses as low as about 0.3% of the active ingredient are usable. For nodulisporic acid and its derivatives, a formulation containing about 0.0005 to about 5% of the active compound is preferred.

[0045] The present invention also provides for a process to prepare paste formulations which is easier and relatively inexpensive. Because fumed silica is a relatively expensive and difficult to handle material, the use of a density modifier reduces the overall cost of the product and minimizes the material handling issue. The manufacturing process is described as follows:

1. In a proper mixer, charge all or a portion of the carrier. Add the active drug and mix it until all of the drug is dissolved.
2. Add the colorant and magnesium carbonate, if necessary. Apply appropriate mixing action to uniformly disperse the titanium dioxide and magnesium carbonate.
3. Add fumed silica to the mixer in a single charge or in portions. Apply appropriate mixing action to uniformly disperse the fumed silica.
4. Add the remaining portion of the triacetin to the mixer. Apply appropriate mixing action to produce a uniform intermediate.
5. Let the intermediate settle for a proper amount of time to let the air that was entrapped with the addition of fumed silica to escape.
6. Add the viscosity modifier and mix until a uniform paste product is produced.

[0046] In comparison, with the process to prepare prior paste products, such as EQVALAN paste and GASTROGARD paste, which are manufactured using different formulations and processes, this invention has the following advantages - First, the process is much simpler. A 300 kg batch can be made in less than 2 hours, while 5 hours or more are needed for EQVALAN and GASTROGARD pastes. Second, no heating or cooling is required during the manufacturing of this product, which lowers the equipment demand and cost. Many other paste products require heating and/or cooling. Third, this product is not very shear-sensitive. During manufacturing, over mixing of the inventive pastes, to a certain extent, has little effect on the final consistency of the product. This robustness provides for a forgiving manufacturing process. Many other paste products are shear sensitive and careful manufacturing parameter must be maintained to assure product quality. Fourth, the inventive pastes exhibit little temperature sensitivity. Extended storage under accelerated storage condition showed little physical or chemical change. While many other paste products change the viscosity, and/or dry out, and/or separate significantly when stored under high (e.g. 60°C)/or low (e.g. -20°C) temperature conditions.

[0047] The inventive paste formulations may be used to treat a number of disease states by administering to the host in need thereof an effective amount of the paste containing the therapeutic agent. The determining of a treatment protocol of a specific indication would he well within the skill level of a practitioner in the pharmaceutical or veterinary arts. Disease states which may be treated by the inventive formulations include, for example, treating inflammation, treating osteoarthritis and rheumatoid arthritis pain or fever, treating or preventing insect or parasitic infestations, treating or preventing bacterial infections: or inhibiting excess acid secretions in the stomach for treating stomach ulcers. The hosts include all animals. e.g. cats, dogs, cattle, sheep, horses, pigs, and humans.

EXAMPLES

[0048] A better understanding of the present invention and of its many advantages will be had from the following examples, given by way of illustration.

Example 1

[0049] The penetration value of placebo pastes were determined in order to demonstrate the ability of the viscosity modifier to increase the viscosity of the paste at low values of fumed silica. Penetration pastes containing 4% CAB-O-SIL and 0.25% to 2% of a viscosity modifier were prepared in a mixed vehicle (triacetin: miglyol 840). The penetration values of the resulting composition are listed below.

Table 4 Penetration value of placebo paste (mm)

Viscosity modifier	Initial	10 days at 50°C	1 month at 50°C
MEA 0.25%	23.4	22.7	23.7
MEA 0.5%	25.2	25.8	25.3
MEA 1.0%	24.3	22.7	21.9

(continued)

Viscosity modifier	Initial	10 days at 50°C	1 month at 50°C
MEA 1.5%	28.1	23.8	26.2
TEA 0.5%	25.6	21.9	20.7
Tween 80 1%	32.0	20.5	21.2
PEG 300 1%	33.4	26.6	26.5
PEG 300 2%	38.4	26.1	29.1
Pluronic L81 1%	43.9	27.0	27.0
None	Too thin to be tested (>65)	38.9	42.2
After two months storage at room temperature pastes changed to pale yellow when MEA was added. Degree of yellowish: MEA 1.5%> MEA 1.0%> MEA 0.5%> MEA 0.25%. No significant color change in pastes with other additives. Also paste with MEA had an acidic small, while other pastes did not have.			

[0050] In the table. MEA is the abbreviation for monoethanolamine and TEA is the abbreviation for triethanolamine. The results demonstrate that the viscosity modifiers have the ability to increase dramatically the viscosity of the placebo paste at low CAB-O-SIL levels. The results in Table 6 also demonstrate that the viscosity of all the pastes increased slightly over time. This result is consistent with the data presented in Fig. 2 which demonstrate that after storage for 6 days at 60°C the viscosity increased slightly. From this data, one would expect that this increase would stop after a few days.

Example 2

[0051] The physical stabilities of three pastes according to the present invention were prepared and placed into a 6.1 ml white syringe. The formulations were as fellows:

Table 5 Paste formulation containing the COX-2 inhibitor, formula III (not within the scope of the claims)

	Formula A	Formula B	Formula C
Cox-2 inhibitor[a]	1.16%	11.16%	1.16%
CAB-O-SIL	3.5%	4.0%	4.0%
PEG 300	----	1.0%	1.0%
Monoethanolamine	0.2%%	----	----
Titanium Dioxide	----	2.0%	----
Triacetin	QS	QS	QS
[a] 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one.			

a. Chemical Stability

[0052] The chemical stability of these formulations was tested over accelerated storage conditions. The results of these tests are provided below in Table 4.

Table 6 Chemical stability of paste formulation containing the Cox-2 inhibitor. 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one.

	% of initial after 10 days at 60°C	% of initial after 4 weeks at 60°C	% of initial after 4 weeks at 40°C	% of initial after 4 weeks at 40°C/75% RH
Formula A	99.3%	101%		
Formula B	98.3%	99.4%	99.0%	99.0%

(continued)

	% of initial after 10 days at 60°C	% of initial after 4 weeks at 60°C	% of initial after 4 weeks at 40°C	% of initial after 4 weeks at 40°C/75% RH
Formula C	99.4%	99.4%		

From these data one may conclude that the inventive formulations would be stable for a shelf life of two years.

b. Viscosity

[0053] Most semi-solie products change viscosity over storage. A useful product viscosity needs to be maintained throughout the shelf-life of a product to ensure animal acceptance and ease of use. Since the viscosity usually changes more and faster under higher temperature, the viscosity change of Formulation A and B was studied at 60°C (Table 7).

Table 7 Viscosity change of Formulation A and B under accelerated storage conditions.

	Initial	1 wk 60°C	4 wk 60°C	4 wk 40°C	4 wk 40°C/75% RH
Formulation A	22.8	22.9	22.9		
Formulation B	23.7	17.7	15.2	18.5	18.7

[0054] Formulation A used MEA as the viscosity modifier and showed almost no change in viscosity after even 4 weeks at 60°C. Formulation B used PEG 300 as the viscosity modifier and had a slight increase in viscosity after 4 weeks at 60°C and this increase is expected to stop after longer storage. The viscosity change under 40°C/75% RH was similar to that of 40°C. indicating that the humidity had no impact on paste viscosity. In contrast to Eqvalan or Gastrogard pastes, where Thixcin R was used as the thickener and their viscosity increased from 20-40 mm to 6 mm after 4 weeks at 60°C. the viscosity increase in these formulations is insignificant.

[0055] The viscosity of these pastes at extreme use temperature has not been measured. But based on visual observation, these pastes had good consistency at a wide temperature range.

c. Whipping

[0056] Slight phase separation: comparable to that of GASTROGARD, was observed in all three formulations, with Formulation B having slightly less separation.

d. Shrinkage and Discoloration

[0057] Discoloration was not seen in pastes except those using MEA as the viscosity modifier. Formulation A (containing 0.20% MEA) changed to slightly yellow but still clear. This slight discoloration is known for MEA and it has no impact on the drug.

[0058] No shrinkage occurred to all three formulations.

e. Air Entrapment

[0059] No air entrapment was noticed in the pastes.

Example 3.

[0060] Table 8 lists the concentrations of placebo pastes prepared in order to investigate whipping:

Table 8 Placebo Pastes

Formula D	Formula E	Formula F
4% CAB-O-SIL	4.5% CAB-O-SIL	5% CAB-O-SIL
1% PEG 300	1% PEG 300	1% PEG

(continued)

Formula D	Formula E	Formula F
1% $MgCO_2$	--	--
94% Triacetin	94.5% Triacetin	94% Triacetin

Whipping (phase separation) in all these pastes was reduced with whipping almost unnoticeable in formula D.

Example 4

[0061] The viscosity change of these two pastes under accelerated conditions is shown in Table 9

Table 9 Viscosity change of placebo pastes containing 1% PEG 300 and different amounts of CAB-O-SIL under accelerated storage condition.

Formulation	CAB-O-SIL content	Initial (mm)	6 days at 60°C	14 days at 60°C
D	4.0%	34.2	27.4	----
E	4.5%	23.9	18.4	18.8
F	5.0%	21.1	13.0	11.9

The paste of Formula F with 5% CAB-O-SIL seemed to be unnecessarily over-thickened. The paste of Formula E with 4.5% CAB-O-SIL was better balanced with respect to viscosity and whipping. Moreover, Formula E seemed to provide the best viscosity over storage.

Example 5

[0062] The following paste was prepared according to the process of the present invention.

Table 10 formulation example with a COX-2 inhibitor (not within the scope of the claims)

Ingredient	Composition in the specific example
COX-2 inhibitor[a]	0.82%
Titanium dioxide	10.2%
Magnesium carbonate	12%
Fumed silica	4.25%
Polyethylene Glycol (PEG) 300	0.4%
Triacetin	QS
[a] 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one.	

[0063] A portion of the triacetin was charged into a mixer followed by the addition of the COX-2 inhibitor. The compounds were mixed until all the drug was dissolved. Next, titanium dioxide and magnesium carbonate were added. Mixing continued until the titanium dioxide and magnesium carbonate were uniformly dispersed. Subsequent to this fumed silica was added to the mixer and mixing occurred until the fumed silica was uniformly dispersed. The remaining portion of the triacetin to the mixer. Mixing occurred until a uniform intermediate was obtained. The intermediate was allowed to settle for 10 minutes until the air that was entrapped with the addition of fumed silica escaped. PEG was added and mixing occurred until a uniform paste product was produced.

Example 6

[0064] The following paste was prepared using a process similar to that of Example 5. A uniform paste was obtained.

Table 11 Formulation example with a COX-2 inhibitor (not within the scope of the claims)

Ingredient	Composition in the specific example
COX-2 Inhibitor[a]	1.64%
FD&C Blue #1. aluminum lake	0.005%
Magnesium carbonate	2%
Fumed silica	4.25%
Polyethylene Glycol (PEG) 300	0.4%
Triacetin	QS
[a]3-(cyclopropylmethoxy)-3,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one.	

Example 7

[0065] The following paste was prepared using a process similar to that in Example 6. A uniform paste was obtained.

Table 12 Formulation example with a COX-2 inhibitor (not within the scope of the claims)

Ingredient	Composition in the specific example
COX-2 inhibitor[a]	2.5%
Titanium dioxide	1%
Fumed silica	4%
Monoethanolamine	1.0%
Triacetin	50%
Miglyol 840	QS.
[a] 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one.	

Example 8

[0066] In order to test the robustness of the paste obtained by the inventive process a placebo paste was prepared by the following process:

1. Charge triacetin. Turn on the mixing screw and chopper until the drug is completely dissolved.
2. Stop mixer, add titanium dioxide and turn on the chopper to disperse.
3. Stop the mixer, add CAB-O-SIL in several portions to the mixer. After each portion is added, turn on the mixer to wet the powder.
4. After all CAB-O-SIL is added, mix until uniform.
5. Stop mixer and wait for 10 minutes to let air escape.
6. Add magnesium carbonate. Add the remaining triacetin and PEG 300 to the mixer. Turn on mixing screw to mix until uniform.

[0067] To determine the robustness of the paste obtained by the inventive process, the intermediate sample (4% CAB-O-SIL in triacetin) at step 5 was tested with Brookfield viscometer (Fig. 4). Its viscosity seems to be not very sensitive to the low shear testing condition. As shown in Fig. 4, the viscosity remained almost constant throughout the course of a 5 minute measuring in the testing container. To evaluate the shear sensitivity of the end product, the final paste at step 6 was subjected to high shear using a homogenizer at 2500 rpm. Samples were collected at different time intervals and tested using Brookfield viscometer and penetrometer (Fig. 5). Both the Brookfield testing and penetrometer testing of the initial end product and the aged end product at 60°C demonstrated that the paste at step 6 were only a little sensitive to shear. Based on these data, we conclude that over-mixing during production should not have much impact on the paste viscosity.

Example 9 : Conversion of polymorph A to polymorph B by stirring in methanol without seeding

[0068] To a 5 ml flask was added 1 g of methanol and 1.5 g of polymorph A.

[0069] The agitation was maintained at room temperature for 50 minutes. All polymorph A had converted to polymorph B after this time. The results on the polymorphic form were confirmed by X-Ray diffraction.

[0070] The polymorphic B form may be formulated as described in examples 5-7.

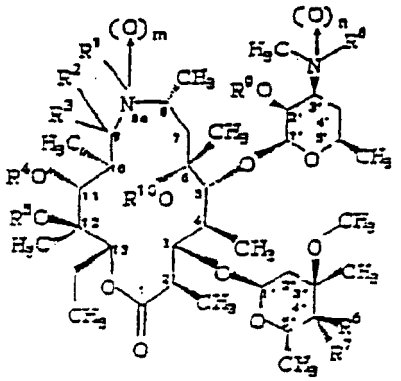
[0071] The above description of the invention is intended to be illustrative and not limiting. Various changes or modifications in the embodiment described may occur to those skilled in the art. These can be made without departing from the scope of the claims.

Claims

1. A pharmaceutical or veterinary paste formulation comprising:

(a) an effective amount of a therapeutic agent selected from an 8a-azalide, azithromycin or erythromycin;
(b) fumed silica;
(c) a viscosity modifier selected from PEG 200, PEG 300, PEG 400, PEG 600, monoethanolamine, triethanolamine, glycerol, propylene glycol, polyoxylene sorbitan monoleate and poloxamers;
(d) a carrier;
(e) optionally, an absorbent selected from magnesium carbonate, calcium carbonate, starch and cellulose and its derivatives; and
(f) optionally, a stabilizer, surfactant, preservative or colorant selected from titanium dioxide, dye and lake;

wherein the 8a-azalide is of formula I

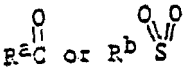


wherein

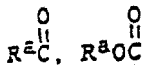
R^1 is hydrogen;
hydroxy;
C_{1-4} alkoxy;
formyl;
C_{1-10} alkylcarbonyl, C_{1-10} alkoxycarbonyl, aryloxycarbonyl, C_{1-10} aralkoxycarbonyl, C_{1-10} alkylsulfonyl, or arylsulfonyl wherein said C_{1-10} alkyl group or aryl group is unsubstituted or substituted by 1-3 halo (F, Cl, Br), hydroxy, amino, C_{1-5} acylamino or C_{1-4} alkyl groups; or
unsubstituted or substituted C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl wherein said substituents are independently 1-3 of

(a) aryl or heteroaryl optionally substituted by 1-3 halo (F, Cl, Br, I), C_{1-4} alkyl, C_{1-3} alkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl) amino or hydroxy,
(b) heterocyclyl optionally substituted by hydroxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkylcarbonyloxy or C_{1-4} alkylcarbonylamino,
(c) halo (F, Cl, Br or I),

(d) hydroxy optionally, acylated by a group



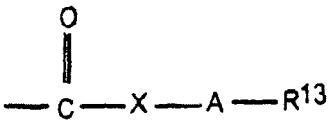
wherein
R^a is hydrogen, C_{1-6} alkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl and
R^b is C_{1-6} alkyl or aryl,
(e) C_{1-10} alkoxy.
(f) aryloxy or heteroaryloxy optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl group,
(g) amino or C_{1-10} alkylamino optionally acylared by a group



or R^bSO_2, wherein
R^a and
R^b are as defined above,
(g) di(C_{1-10} alkyl)amino,
(h) arylamino, heteroarylamino, aralkylamino or heteroarylalkylamino wherein said aryl or heteroaryl groups is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,
(i) mercapto,
(j) C_{1-10} alkylthio, alkylsulfinyl or alkylsulfonyl, arylthio, arylsulfinyl or arylsulfonyl wherein said aryl group is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,
(k) formyl,
(l) C_{1-10} alkylcarbonyl,
(m)arylcarbonyl, heteroarylcarbonyl, aralkylcarbonyl or heteroarylalkylcarbonyl wherein said aryl or heteroaryl group is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,
(n) carboxy,
(o) C_{1-10} alkoxycarbonyl,
(p) aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl or heteroarylalkoxycarbonyl wherein said aryl or heteroaryl group is optionally substituted by 1-3 halo, hydroxy, amino or C_{1-4} alkyl groups,
(q) carbamoyl or sulfamoyl wherein the N-atom is optionally substituted by 1-2 C_{1-6} alkyl groups or by a C_{4-6} alkylene chain,
(r) cyano,
(s) isonitrilo,
(t) nitro,
(u) azido,
(v) iminomethyl optionally substituted on nitrogen or carbon with C_{1-10} alkyl,
(w) oxo, or
(x) thiono;

wherein said alkyl chain, if more than two carbons in length, can be optionally interrupted by 1-2 oxa, thia or aza (-NR- wherein R is hydrogen or C_{1-3} alkyl) groups.
R^{10} is hydrogen or
R^1 and R^{10} together are C_1-C_3 alkylene optionally substituted by an oxo group;
R^1 and R^4 together are C_1-C_3 alkylene optionally, substituted by an oxo, group
R^2 and R^3 are hydrogen, C_{1-10} alkyl, aryl
R^2 and R^3 together are oxo and thiono;
R^4 and R^5 are independently hydrogen and alkylcarbonyl;
R^4 and R^5 are together carbonyl;
R^6 and R^7 are both hydrogen or one of R^6 and R^7 is hydrogen and the other is hydroxy, an acylox y derivative taken from the group consisting of formyloxy, C_{1-10} alkylcarbonyloxy, arylcarbonyloxy and aralkylcarbonyloxy, or -NHR^{12} wherein R^{12} is hydrogen, arylsulfonyl or heteroarylsulfonyl optionally substituted by 1-3 halo or C_{1-3}

alkyl groups, alkylsulfonyl, or



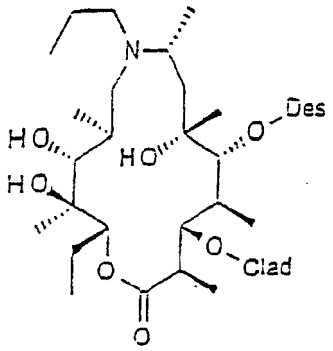
where
X is a connecting bond, O or NH,
A is a connecting bond or C_1-C_3 alkylene
R^6 and R^7 are together oxo, hydroxyimino, alkoxyimino, aralkoxyimino or aminoimino;
R^8 is methyl, aralkoxycarbonyl, and arylsulfonyl;
R^9 is hydrogen, formyl, C_{1-10} alkylcarbonyl, C_{1-10} alkoxycarbonyl, and arylalkoxycarbonyl;

m and n are independently integers of zero or one; and said metal complex is taken from the group consisting of copper, zinc, cobalt, nickel and cadmium or a pharmaceutically acceptable salt, ester or metal complex thereof.

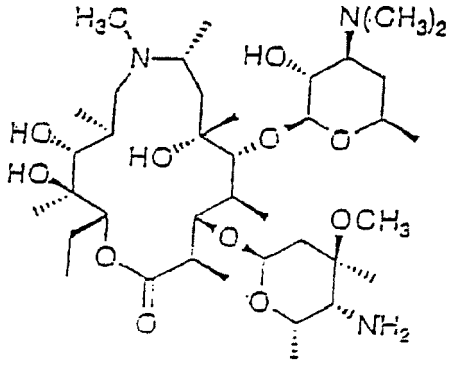
2. A paste according to claim 1 wherein the therapeutic agent is azithromycin.

3. A paste according to claim 1 wherein the therapeutic agent is erythromycin.

4. A paste according to claim 1 wherein the 8a-azalide is selected from a compound of formula I



wherein Des is desosomine and Clad is cladinose
and a compound of formula II



5. The paste formulation according to claim 1, which based upon total weight of composition, comprises:

(a) about 0.01 to about 50% of the therapeutic agent;
(b) about 0.02 to about 20% of fumed silica;
(c) about 0.01 to about 20% of a viscosity modifier;
(d) 0% to about 30% of an absorbent;
(e) 0% to about 20% of a colorant; and
(f) Q.S. a carrier.

6. The paste formulation according to claim 1, wherein the formulation is for oral administration.

7. The paste formulation according to claim 1, wherein the formulation is for topical, dermal or transdermal administration.

8. The paste formulation according to claim 1, which comprises an antioxidant and the antioxidant is selected from the group consisting of alpha tocopherol, ascorbic acid, ascrobyl palmitate, fumeric acid, malic acid, sodium ascorbate, sodium metabisulfate, n-propyl gallate, BHA, BHT and monothioglycerol.

9. The paste formulation according to claim 1 which comprises a preservative and the preservative is selected from the group consisting of the parabens, benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, bronopol, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid and thimerosal.

10. The paste formulation according to claim 1 wherein the carrier is selected from triacetin, short to medium chain mono-, di-, or tri-glycerides, glycerin, water, propylene glycol, N-methyl pyrrolidinone, glycerol formal, polyethylene glycol, polyethylene glycol-polypropylene glycol-polyethylene glycol tri-block copolymers, vegetable oil, sesame oil, soybean oil, corn oil, mineral oil, peanut oil, castor oil, cotton oil, transcutol, benzyl alcohol, N, N-dimethylformamide and dimethylsulfoxide.

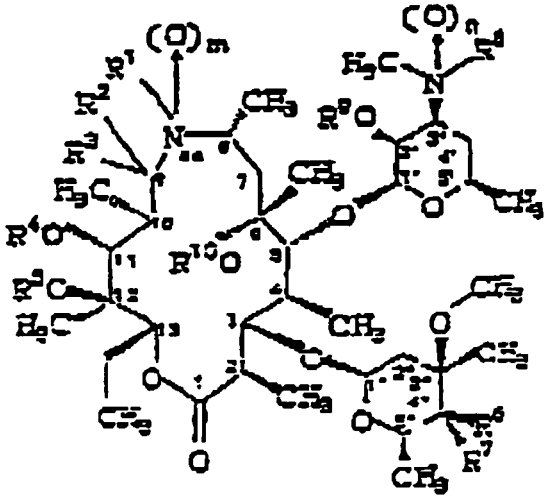
11. Use of a paste according to claim 1 in the preparation of a medicament for treating a bacterial infection in a host in need thereof.

Revendications

1. Formulation pâteuse pharmaceutique ou vétérinaire, comprenant :

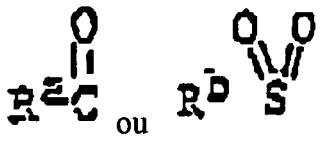
(a) une quantité efficace d'un agent thérapeutique choisi parmi un 8a-azalide, l'azithromycine, ou l'érythromycine,
(b) de la silice fumée ;
(c) un modificateur de viscosité choisi parmi le PEG 200, le PEG 300, le PEG 400, le PEG 600, la monoéthanolamine, la triéthanolamine, le glycérol, le propylène glycol, le polyoxylène sorbitane monoléate et les poloxamères ;
(d) un excipient ;
(e) éventuellement, un agent absorbant choisi parmi le carbonate de magnésium, le carbonate de calcium, l'amidon et la cellulose et ses dérivés ; et
(f) éventuellement, un stabilisateur, un tensio-actif, un conservateur ou un colorant choisi parmi le dioxyde de titane, une teinture et une laque ;

dans laquelle le 8a-azalide est de formule 1

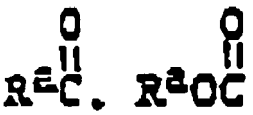


dans laquelle
R^1 est un hydrogène ;
un hydroxy ;
un alcoxy en C_{1-4} ;
un formyle ;
un alkylcarbonyle en C_{1-10}, un alcoxycarbonyle en C_{1-10}, un aryloxycarbonyle, un aralcoxycarbonyle en C_{1-10}, un alkylsulfonyle ou un arylsulfonyle en C_{1-10} dans lequel ledit groupe alkyle ou groupe aryle en C_{1-10} est non substitué ou substitué par des groupes 1-3 halo (F, Cl, Br), hydroxy, amino, acylamino en C_{1-5} ou alkyle en C_{1-4} ; ou
un alkyle en C_{1-10} non substitué ou substitué, un alcényle en C_{2-10} ou un alcynyle en C_{2-10} dans lequel lesdits substituants sont indépendamment 1-3 groupes parmi

(a) aryle ou hétéroaryle éventuellement substitué par 1-3 halo (F, Cl, Br, I), un alkyle en C_{1-4}, un alcoxy en C_{1-3}, un amino, un alkylamino en C_{1-4}, un di(alkyle en C_{1-4}) amino ou hydroxy,
(b) hétérocyclyle éventuellement substitué par un hydroxy, un amino, un alkylamino en C_{1-4}, un di(alkyle en C_{1-4})amino, un alkylcarbonyloxy en C_{1-4}, ou un alkylcarbonylamino en C_{1-4},
(c) halo (F, Cl, Br ou I),
(d) hydroxy éventuellement acylé par un groupe

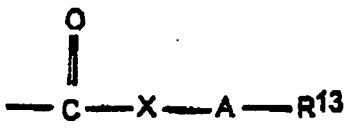


dans laquelle R^a est un hydrogène, un alkyle en C_{1-6}, un aryle, un hétéroaryle, un aralkyle ou un hétéroaralkyle, et
R^b est un alkyle en C_{1-6} ou aryle,
(e) un alcoxy en C_{1-10}
(f) un aryloxy ou hétéroaryloxy éventuellement substitué par un groupe halo 1-3, hydroxy, amino ou alkyle en C_{1-4};
(g) amino ou alkylamino en C_{1-10} éventuellement acylé par un groupe



ou R^bSO_2, dans lequel
R^a et
R^b sont comme définis ci-dessus,
(g) di(alkyle en C_{1-10}) amino,
(h) arylamino, hétéroarylamino, aralkylamino ou hétéroarylalkylamino dans lesquels ledit groupe aryle ou hétéroaryle est éventuellement substitué par des groupes 1-3 halo, hydroxy, amino ou alkyle en C_{1-4} ;
(i) mercapto,
(j) alkylthio en C_{1-10}, alkylsulfinyle ou alkylsulfonyle, arylthio, arylsulfinyle ou arylsulfonyle dans lesquels ledit groupe aryle est éventuellement substitué par des groupes 1-3 halo, hydroxy, amino ou alkyle en C_{1-4},
(k) formyle,
(l) alkylcarbonyle en C_{1-10},
(m) arylcarbonyle, hétéroarylcarbonyle, aralkylcarbonyle ou hétéroarylalkylcarbonyle dans lesquels ledit groupe aryle ou hétéroaryle est éventuellement substitué par des groupes 1-3 halo, hydroxy, amino ou alkyle en C_{1-4} ;
(n) carboxy ;
(o) alcoxycarbonyle en C_{1-10} ;
(p) aryloxycarbonyle, hétéroaryloxycarbonyle, aralcoxycarbonyle ou hétéroarylalcoxycarbonyle dans lesquels ledit groupe aryle ou hétéroaryle est éventuellement substitué par des groupes 1-3 halo, hydroxy, amino ou alkyle en C_{1-4} ;
(q) carbamoyle ou sulfamoyle dans lequel l'atome N est éventuellement substitué par 1-2 groupes alkyle en C_{1-6} ou par une chaîne d'alcylène en C_{4-6} ;
(r) cyano
(s) isonitrile,
(t) nitro,
(u) azido,
(v) iminométhyle éventuellement substitué sur l'azote ou le carbone avec un alkyle en C_{1-10},
(w) oxo ou
(x) thiono ;

dans lesquels ladite chaîne alkyle, si elle dépasse deux atomes de carbone en longueur, peut être éventuellement interrompue par des groupes 1-2 oxa, thia ou aza (-NR dans lesquels R est un hydrogène ou alkyle en C_{1-3}).
R^{10} est un hydrogène ou
R^1 et R^{10} sont ensemble un alcylène en C_1-C_3 éventuellement substitué par un groupe oxo ;
R^1 et R^4 sont ensemble un alcylène C_1-C_3 éventuellement substitué par un groupe oxo ;
R^2 et R^3 sont un hydrogène, un alkyl, en C_1-C_{10}, un aryl
R^2 et R^3 sont ensemble un oxo et thiono ;
R^4 et R^5 sont indépendamment un hydrogène et un alkylcarbonyle ;
R^4 et R^5 sont ensemble un carbonyle ;
R^6 et R^7 sont tous deux un hydrogène ou l'un de R^6 et R^7 est un hydrogène et l'autre est un hydroxy, un dérivé acyloxy pris dans le groupe constitué de formyloxy, d'alkylcarbonyloxy en C_{1-10}, un arylcarbonyloxy en C_1-C_{10} et un aralkylcarbonyloxy en C_{1-10} ou
-NHR^{12} dans lequel R^{12} est un hydrogène, un arylsulfonyle ou un hétéroarylsulfonyle éventuellement substitué par des groupes 1-3 halo ou alkyle en C_{1-3}, un alkylsulfonyle ou



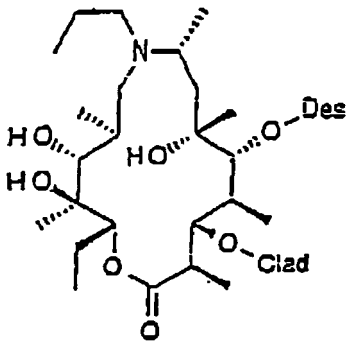
où
X est une liaison de connexion, O ou NH,
A est une liaison de connexion ou un alcylène en C_1-C_3
R^{13} est un hydrogène, un alkyle en C_1-C_{10}, un aryle, un aralkyle, un hétéroaryle, un hétérocyclyle, ou un cycloalkyle en C_3-C_7, dont l'un quelconque des groupes R^{13} autre que l'hydrogène peut être substitué par un ou plusieurs des groupes parmi un halogène, hydroxyle, alcoxy en C_1-C_3, cyano, isonitrilo, nitro, amino, mono- ou di-alkylamino (C_1-C_3), mercapto, alkylthio en C_1-C_3, alkylsulfinyle en C_1-C_3, arylthio, arylsulfinyle, sulfamoyle, arylsulfonyle, carboxy, carbamoyle, alkylcarbonyle en C_1-C_3 ou alcoxycarbonyle en C_1-C_3;

R^6 et R^7 sont ensemble un oxo, un hydroxyimino, alcoxyimino, aralcoxyimino ou aminoimino ;
R^8 est un méthyle, aralcoxycarbonyle et arylsulfonyle ;
R^9 est un hydrogène, formyle, alkylcarbonyle en C_{1-10}, alcoxycarbonyle en C_{1-10} et arylalcoxycarbonyle ;
m et n sont indépendamment des nombres entiers de zéro ou un ; et ledit complexe métallique est pris dans le groupe constitué de cuivre, zinc, cobalt, nickel et cadmium ou un sel, ester ou complexe métallique pharmaceutiquement acceptable de celui-ci.

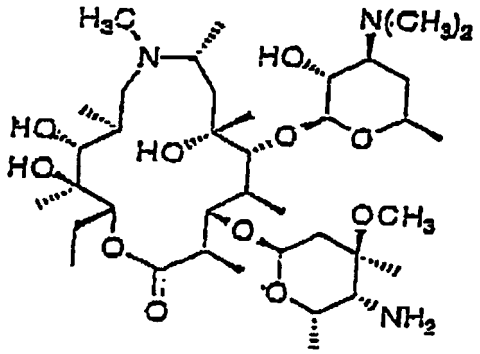
2. Pâte selon la revendication 1, dans laquelle l'agent thérapeutique est l'azithromycine.

3. Pâte selon la revendication 1 dans laquelle l'agent thérapeutique est l'érythromycine.

4. Pâte selon la revendication 1, dans laquelle le 8a-azalide est choisi à partir d'un composé de formule I



dans laquelle Des est la désosomine et Clad est la cladinose
et un composé de formule II



5. Formulation pâteuse selon la revendication 1, basée sur le poids total de la composition, comprenant :

(a) environ 0,01 à environ 50% de l'agent thérapeutique ;
(b) environ 0,02 à environ 20% de silice fumée ;
(c) environ 0,01 à environ 20% d'un modificateur de viscosité ;
(d) 0% à environ 30% d'un agent absorbant ;
(e) 0% à environ 20% d'un colorant ; et
(f) Q.S un excipient

6. Formulation pâteuse selon la revendication 1, dans laquelle la formulation est destinée à une administration par voie orale.

7. Formulation pâteuse selon la revendication 1, dans laquelle la formulation est destinée à une administration par

voie topique, dermique ou transdermique.

8. Formulation pâteuse selon la revendication 1, qui comprend un antioxydant et l'antioxydant est choisi dans le groupe constitué d'alpha-tocophérol, d'acide ascorbique, de palmitate d'ascorbyle, d'acide fumarique, d'acide malique, d'ascorbate de sodium, de métobisulfate de sodium, de n-propyl gallate, de BHA, de BHT et de monothioglycérol.

9. Formulation pâteuse selon la revendication 1 qui comprend un agent conservateur et l'agent conservateur est choisi dans le groupe constitué de parabènes, de chlorure de benzalkonium, de chlorure de benzéthonium, d'acide benzoïque, d'alcool de benzyle, de bronopol, de cétrimide, de chlorhexidine, de chlorobutanol, de chlorocrésol, de crésol, d'imidurée, de phénol, de phénoxyéthanol, d'alcool phényléthylique, d'acétate phénylmercurique, de borate phénylmercurique, de nitrate phénylmercurique, de sorbate de potassium, de benzoate de sodium, de propionate de sodium, d'acide sorbique et de thimérosal.

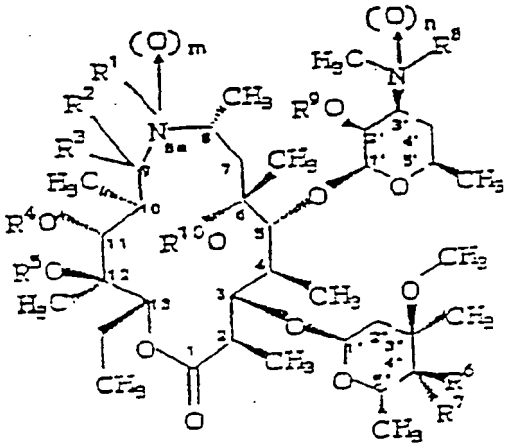
10. Formulation pâteuse selon la revendication 1, dans laquelle l'excipient est choisi dans le groupe constitué de triacétine, de mono-, di- ou triglycérides à chaîne courte à moyenne, de glycérine, d'eau, de propylène glycol, de N-méthyl pyrrolidinone, de glycérol formal, de polyéthylène glycol, de copolymères tri-blocs polyéthylène glycol-polypropylène glycol-polyéthylène glycol, d'huile végétale, d'huile de sésame, d'huile de soja, d'huile de maïs, d'huile minérale, d'huile d'arachide, d'huile de ricin, d'huile de coton, de transcutol, d'alcool benzylique, de N,N-diméthylformamide et de diméthylsulfoxyde.

11. Utilisation d'une pâte selon la revendication 1, dans la préparation d'un médicament pour traiter une infection bactérienne sur un hôte en ayant besoin.

Patentansprüche

1. Pharmazeutische oder veterinärmedizinische Pastenformulierung, umfassend:

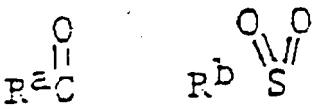
(a) eine wirksame Menge eines therapeutischen Mittels, ausgewählt aus einem 8a-Azalid, Azithromycin oder Erythromycin;
(b) Quarzstaub;
(c) einen Viskositätsmodifikator, ausgewählt aus PEG 200, PEG 300, PEG 400, PEG 600, Monoethanolamin, Triethanolamin, Glycerin, Propylenglycol, Polyoxylensorbitanmonooleat und Poloxameren;
(d) einen Träger;
(e) gegebenenfalls ein Absorbens, ausgewählt aus Magnesiumcarbonat, Calciumcarbonat, Stärke und Cellulose und ihren Derivaten; und
(f) gegebenenfalls einen Stabilisator, ein grenzflächenaktives Mittel, Konservierungsmittel oder ein Färbemittel, ausgewählt aus Titandioxid, Farbstoff und Pigmentfarbe,
wobei das 8a-Azalid eines der Formel I ist



wobei

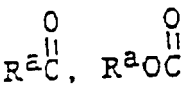
R^1 Wasserstoff;
Hydroxy;
C_{1-4}-Alkoxy;
Formyl,
C_{1-10}-Alkylcarbonyl, C_{1-10}-Alkoxycarbonyl, Aryloxycarbonyl, C_{1-10}-Aralkoxycarbonyl, C_{1-10}-Alkylsulfonyl oder Arylsulfonyl, wobei der C_{1-10}-Alkylrest oder Arylrest unsubstituiert oder mit 1 bis 3 Halogenatomen (F, Cl, Br), Hydroxy, Amino, C_{1-5}-Acylamino oder C_{1-4}-Alkylresten substituiert ist; oder
unsubstituiertes oder substituiertes C_{1-10}-Alkyl, C_{2-10}-Alkenyl oder C_{3-10}-Alkinyl ist, wobei die Substituenten unabhängig 1 bis 3 von

(a) Aryl oder Heteroaryl, gegebenenfalls substituiert mit 1 bis 3 Halogenatomen (F, Cl, Br, I), C_{1-4}-Alkyl, C_{1-3}-Alkoxy, Amino, C_{1-4}-Alkylamino, Di-(C_{1-4}-alkyl)amino oder Hydroxy,
(b) Heterocyclyl, gegebenenfalls substituiert mit Hydroxy, Amino, C_{1-4}-Alkylamino, Di-(C_{1-4}-alkyl)amino, C_{1-4}-Alkylcarbonyloxy oder C_{1-4}-Alkylcarbonylamino,
(c) Halogen (F, Cl, Br oder I),
(d) Hydroxy, gegebenenfalls acyliert mit einem Rest



oder

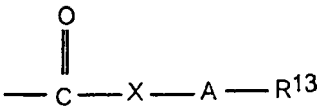
wobei
R^a Wasserstoff, C_{1-6}-Alkyl, Aryl, Heteroaryl, Aralkyl oder Heteroaralkyl ist
und
R^b C_{1-6}-Alkyl oder Aryl ist,
(e) C_{1-10}-Alkoxy,
(f) Aryloxy oder Heteroaryloxy, gegebenenfalls substituiert mit 1 bis 3 Halogenatomen, Hydroxy, Amino oder C_{1-4}-Alkylresten,
(g) Amino oder C_{1-10}-Alkylamino, gegebenenfalls acyliert mit einem Rest



oder R^bSO_2, wobei
R^a und
R^b wie vorstehend definiert sind,
(g) Di-(C_{1-10}-alkyl)amino,
(h) Arylamino, Heteroarylamino, Aralkylamino oder Heteroarylalkylamino, wobei der Aryl- oder Heteroarylrest gegebenenfalls mit 1 bis 3 Halogenatomen, Hydroxy, Amino oder C_{1-4}-Alkylresten substituiert ist,
(i) Mercapto,
(j) C_{1-10}-Alkylthio, Alkylsulfinyl oder Alkylsulfonyl, Arylthio, Arylsulfinyl oder Arylsulfonyl, wobei der Arylrest gegebenenfalls mit 1 bis 3 Halogenatomen, Hydroxy, Amino oder C_{1-4}-Alkylresten substituiert ist,
(k) Formyl,
(l) C_{1-10}-Alkylcarbonyl,
(m) Arylcarbonyl, Heteroarylcarbonyl, Aralkylcarbonyl oder Heteroarylalkylcarbonyl, wobei der Aryl- oder Heteroarylrest gegebenenfalls mit 1 bis 3 Halogenatomen, Hydroxy, Amino oder C_{1-4}-Alkylresten substituiert ist,
(n) Carboxy,
(o) C_{1-10}-Alkoxycarbonyl;
(p) Aryloxycarbonyl, Heteroaryloxycarbonyl, Aralkoxycarbonyl oder Heteroarylalkoxycarbonyl, wobei der Aryl- oder Heteroarylrest gegebenenfalls mit 1 bis 3 Halogenatomen, Hydroxy, Amino oder C_{1-4}-Alkylresten

substituiert ist,
(q) Carbamoyl oder Sulfamoyl, wobei das N-Atom gegebenenfalls mit 1 bis 2 C_{1-6}-Alkylresten oder mit einer C_{4-6}-Alkylenkette substituiert ist,
(r) Cyano,
(s) Isonitrilo,
(t) Nitro,
(u) Azido,
(v) Iminomethyl, gegebenenfalls an einem Stickstoff- oder Kohlenstoffatom mit C_{1-10}-Alkyl substituiert,
(w) Oxo, oder
(x) Thiono sind;

wobei die Alkylkette, wenn sie mehr als zwei Kohlenstoffatome in der Länge aufweist, gegebenenfalls durch 1 bis 2 Oxa-, Thia- oder Aza-(-NR-, wobei R Wasserstoff oder C_{1-3}-Alkyl ist)-Reste unterbrochen sein kann,
R^{10} Wasserstoff ist, oder
R^1 und R^{10} zusammen C_1-C_3-Alkylen, gegebenenfalls substituiert mit einem Oxorest, sind;
R^1 und R^4 zusammen C_1-C_3-Alkylen, gegebenenfalls substituiert mit einem Oxorest, sind;
R^2 und R^3 Wasserstoff, C_{1-10}-Alkyl, Aryl sind;
R^2 und R^3 zusammen Oxo und Thiono sind;
R^4 und R^5 unabhängig Wasserstoff und Alkylcarbonyl sind;
R^4 und R^5 zusammen Carbonyl sind;
R^6 und R^7 beide Wasserstoff sind oder eines von R^6 und R^7 Wasserstoff ist und das andere Hydroxy, ein Acyloxyderivat aus Formyloxy, C_{1-10}-Alkylcarbonyloxy, Arylcarbonyloxy und Aralkylcarbonyloxy ist, oder
-NHR^{12}, wobei R^{12} Wasserstoff, Arylsulfonyl oder Heteroarylsulfonyl, gegebenenfalls substituiert mit 1 bis 3 Halogenatomen oder C_{1-3}-Alkylresten, Alkylsulfonyl oder

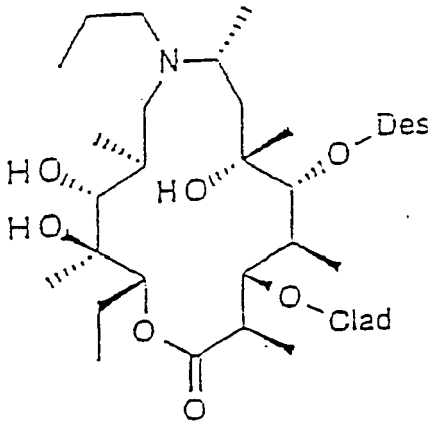


wobei
X eine verknüpfende Bindung, O oder NH ist,
A eine verknüpfende Bindung oder C_1-C_3-Alkylen ist,
R^{13} Wasserstoff, C_1-C_{10}-Alkyl, Aryl, Aralkyl, Heteroaryl, Heterocyclyl oder C_3-C_7-Cycloalkyl ist, wobei die Reste R^{13}, die von Wasserstoff verschieden sind, jeweils mit einem oder mehreren Halogenatomen, Hydroxyl, C_1-C_3-Alkoxy, Cyano, Isonitrilo, Nitro, Amino, Mono- oder Di-(C_1-C_3)-alkylamino, Mercapto, C_1-C_3-Alkylthio, C_1-C_3-Alkylsulfinyl, C_1-C_3-Alkylsulfonyl, Arylthio, Arylsulfinyl, Sulfamoyl, Arylsulfonyl, Carboxy, Carbamoyl, C_1-C_3-Alkylcarbonyl oder C_1-C_3-Alkoxycarbonyl substituiert sein können;
R^6 und R^7 zusammen Oxo, Hydroxyimino, Alkoxyimino, Aralkoxyimino oder Aminoimino sind;
R^8 Methyl, Aralkoxycarbonyl und Arylsulfonyl ist;
R^9 Wasserstoff, Formyl, C_{1-10}-Alkylcarbonyl, C_{1-10}-Alkoxycarbonyl und Arylalkoxycarbonyl ist;
m und n unabhängig ganze Zahlen von null oder eins sind; und der Metallkomplex ausgewählt ist aus Kupfer, Zink, Kobalt, Nickel und Cadmium; oder ein pharmazeutisch verträgliches/verträglicher Salz, Ester oder Metallkomplex davon.

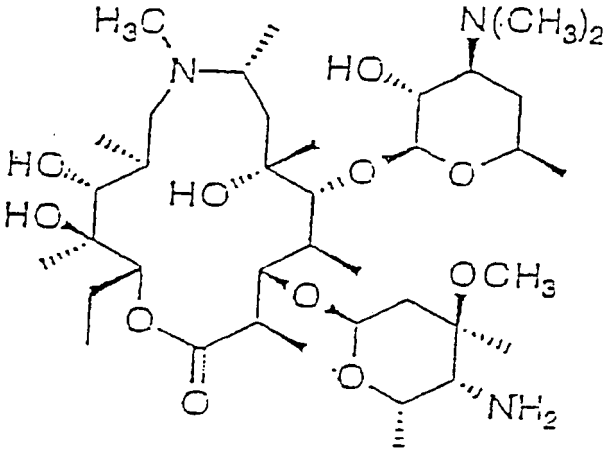
2. Paste gemäß Anspruch 1, wobei das therapeutische Mittel Azithromycin ist.

3. Paste gemäß Anspruch 1, wobei das therapeutische Mittel Erythromycin ist.

4. Paste gemäß Anspruch 1, wobei das 8a-Azalid ausgewählt ist aus einer Verbindung der Formel I



wobei Des Desosomin und Clad Cladinose ist,
und einer Verbindung der Formel II



5. Pastenformulierung nach Anspruch 1, welche, bezogen auf das Gesamtgewicht der Zusammensetzung:

(a) etwa 0,01 bis etwa 50% des therapeutischen Mittels;
(b) etwa 0,02 bis etwa 20% Quarzstaub;
(c) etwa 0,01 bis etwa 20% eines Viskositätsmodifikators;
(d) 0% bis etwa 30% eines Absorbens;
(e) 0% bis etwa 20% eines Färbemittels; und
(f) q.s. einen Träger,

umfasst.

6. Pastenformulierung gemäß Anspruch 1, wobei die Formulierung zur oralen Verabreichung bestimmt ist.

7. Pastenformulierung gemäß Anspruch 1, wobei die Formulierung zur topischen, dermalen oder transdermalen Verabreichung bestimmt ist.

8. Pastenformulierung gemäß Anspruch 1, welche ein Antioxidationsmittel umfasst und wobei das Antioxidationsmittel ausgewählt ist aus α-Tocopherol, Ascorbinsäure, Ascorbylpalmitat, Fumarsäure, Maleinsäure, Natriumascorbat, Natriummetabisulfat, n-Propylgallat, BHA, BHT und Monothioglycerin.

9. Pastenformulierung gemäß Anspruch 1, welche ein Konservierungsmittel umfasst und wobei das Konservierungsmittel ausgewählt ist aus Parabenen, Benzalkoniumchlorid, Benzethoniumchlorid, Benzoesäure, Benzylalkohol, Bronopol, Cetrimid, Chlorhexidin, Chlorbutanol, Chlorcresol, Cresol, Imidharnstoff, Phenol, Phenoxyethanol, Phenylethylalkohol, Phenylquecksilberacetat, Phenylquecksilberborat, Phenylquecksilbemitrat, Kaliumsorbat, Natriumbenzoat, Natriumpropionat, Sorbinsäure und Thimerosal.

10. Pastenformulierung gemäß Anspruch 1, wobei der Träger ausgewählt ist aus Triacetin, Mono-, Di- oder Triglyceriden mit kurzer bis mittlerer Kettenlänge, Glycerin, Wasser, Propylenglycol, N-Methylpyrrolidinon, Glycerinformal, Polyethylenglycol, Polyethylenglycol-Polypropylenglycol-Polyethylenglycol-Triblockcopolymeren, Pflanzenöl, Sesamöl, Sojaöl, Maisöl, Mineralöl, Erdnussöl, Rizinusöl, Baumwollöl, Transkutol, Benzylalkohol, N,N-Dimethylformamid und Dimethylsulfoxid.

11. Verwendung einer Paste gemäß Anspruch 1 bei der Herstellung eines Medikaments zur Behandlung einer bakteriellen Infektion in einem Wirt, der diese benötigt.

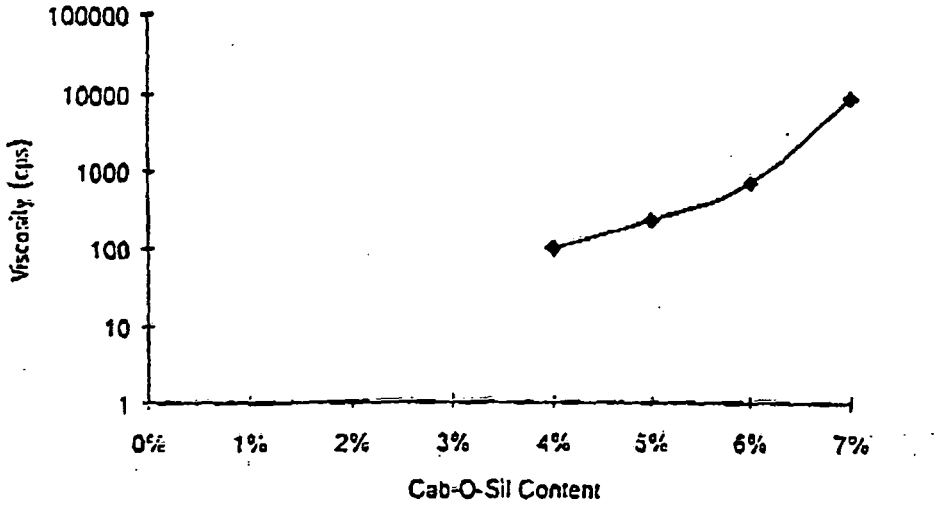

100000
10000
1000
100
10
1
Viscosity (cps)
0%
1%
2%
3%
4%
5%
6%
7%
Cab-O-Sil Content

FIG.1

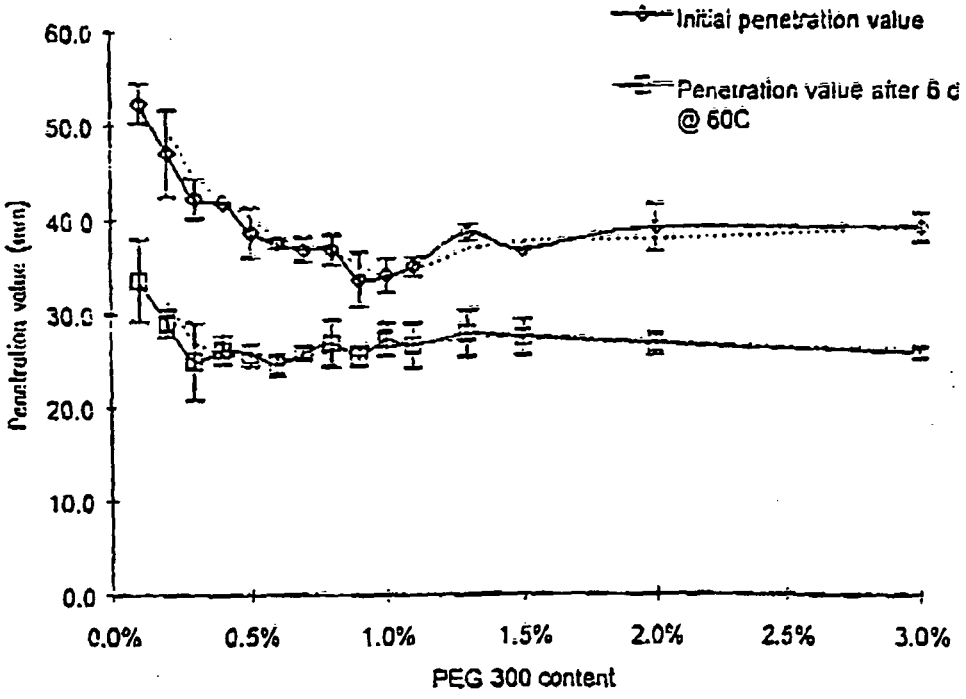

Initial penetration value
Penetration value after 5 d
@ 60C
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Penetration value (mm)
0.0%
0.5%
1.0%
1.5%
2.0%
2.5%
3.0%
PEG 300 content

FIG.2

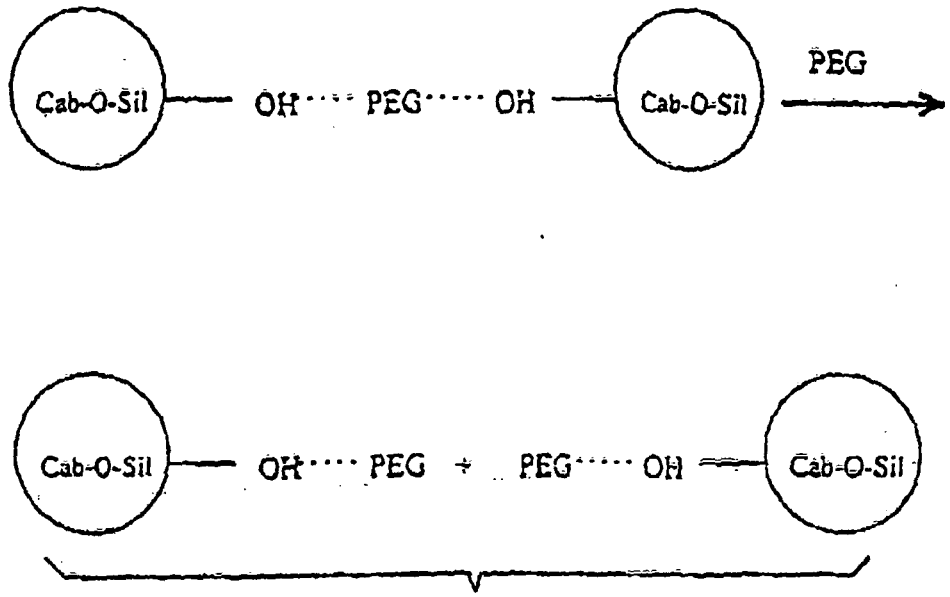

Cab-O-Sil
OH····· PEG····· OH
Cab-O-Sil
PEG
Cab-O-Sil
OH····· PEG + PEG····· OH
Cab-O-Sil

FIG.3

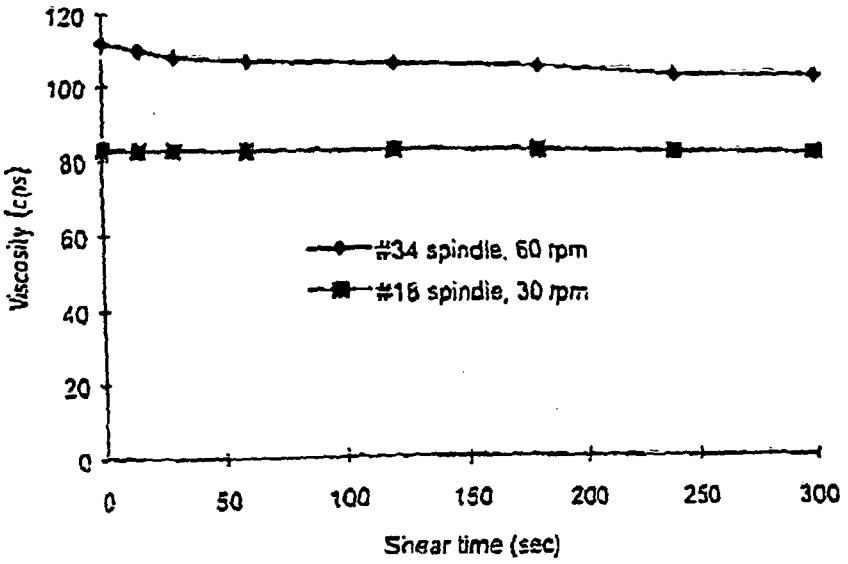

120
100
80
60
40
20
0
Viscosity (cps)
#34 spindle, 60 rpm
#18 spindle, 30 rpm
0
50
100
150
200
250
300
Shear time (sec)

FIG.4

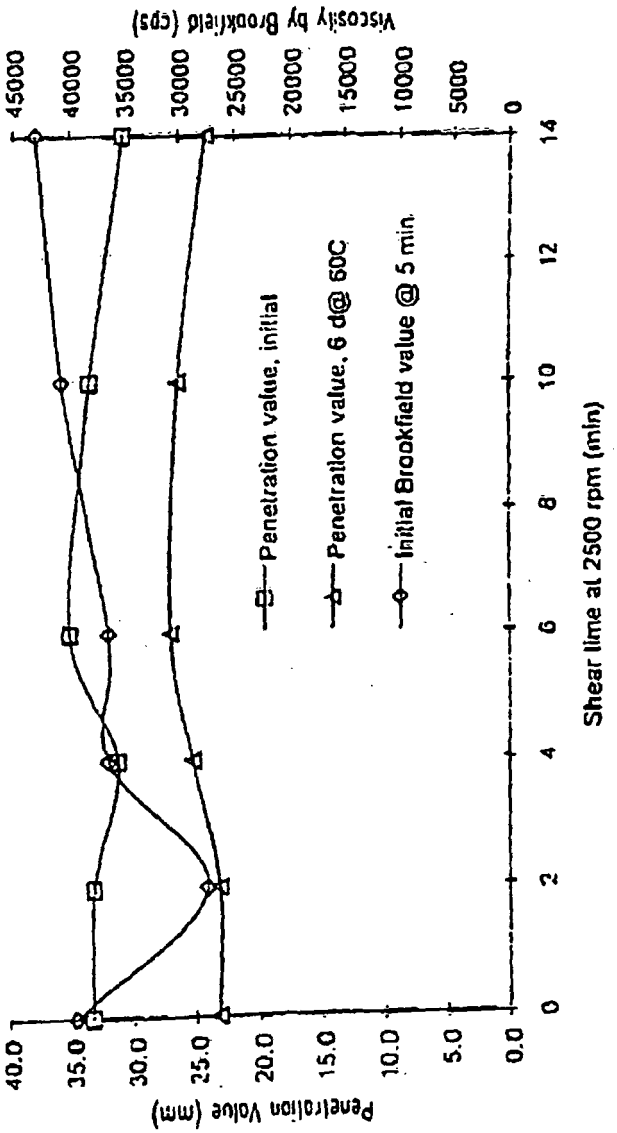

Viscosity by Brookfield (cps)
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
Penetration Value (mm)
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
0
2
4
6
8
10
12
14
Shear time at 2500 rpm (min)
Penetration value, initial
Penetration value, 6 d@ 60C
Initial Brookfield value @ 5 min.

FIG.5

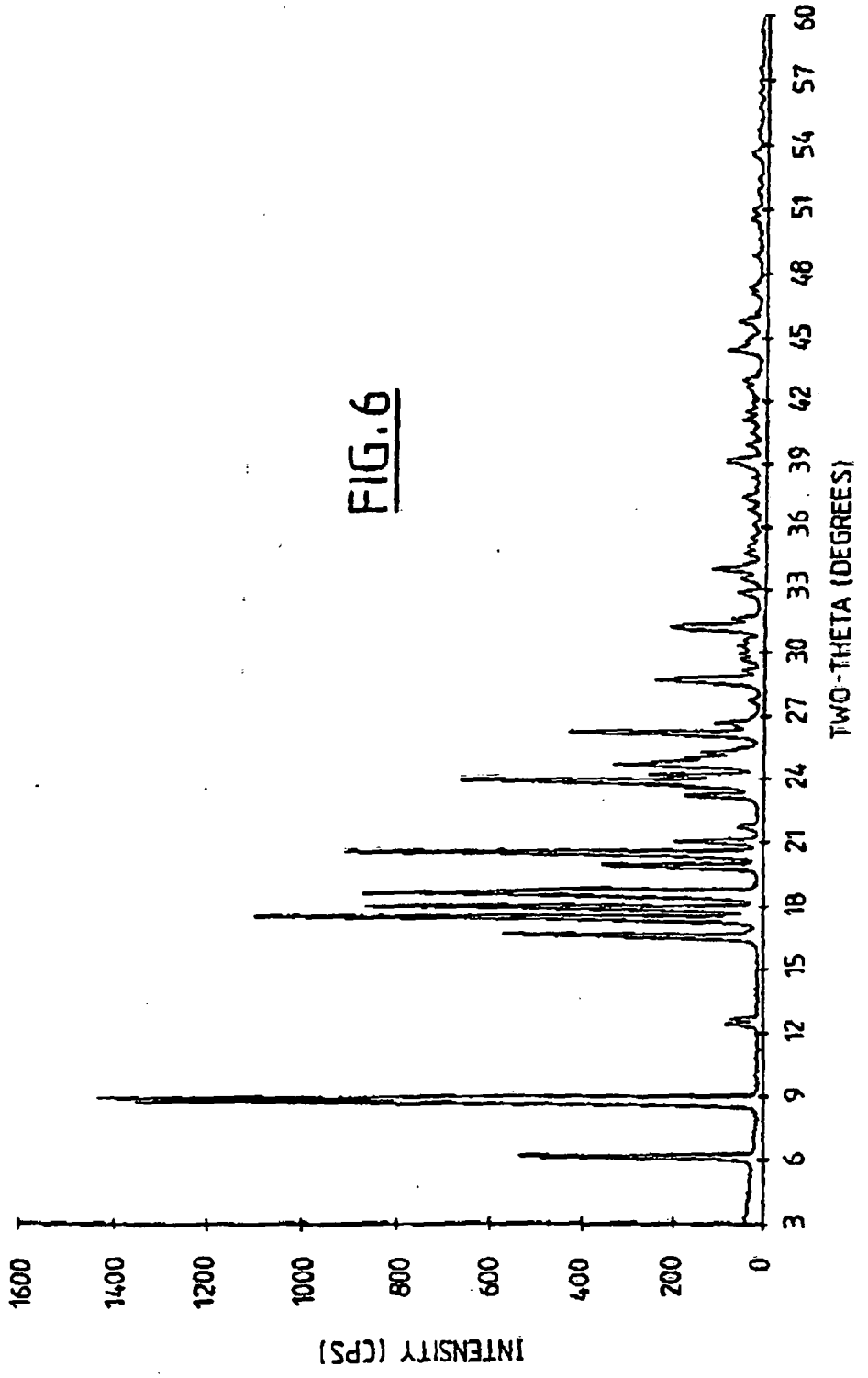
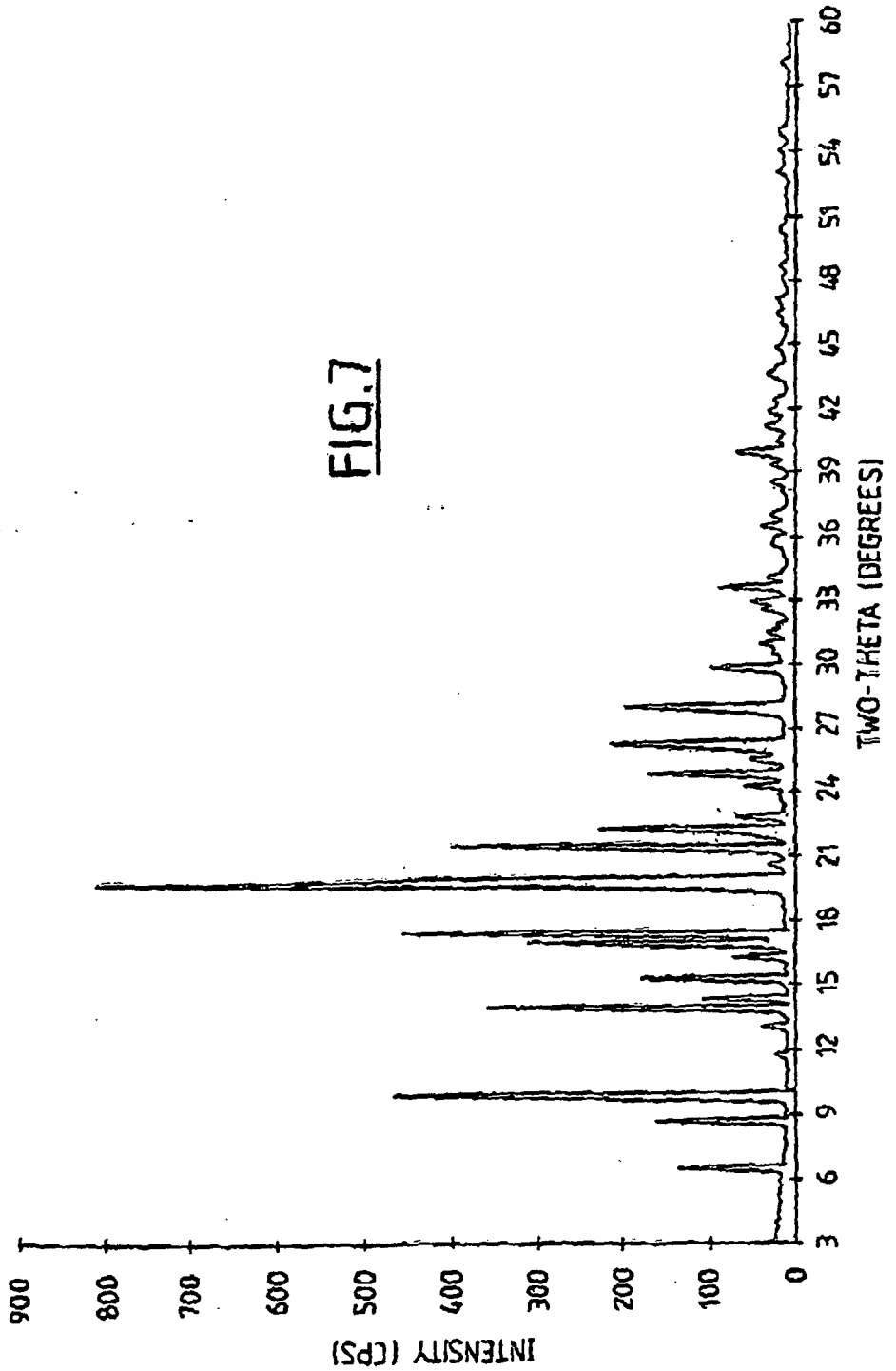

INTENSITY (CPS)
1600
1400
1200
1000
800
600
400
200
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
54
57
60
TWO-THETA (DEGREES)

FIG.6

FIG.7


INTENSITY (CPS)
900
800
700
600
500
400
300
200
100
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
54
57
60
TWO-THETA (DEGREES)

REFERENCES CITED IN THE DESCRIPTION

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