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(54) Title: STABLE POLYOL FORMULATIONS OF OXAZOLIDINONE ANTIBACTERIAL AGENTS

(57) Abstract: Stable gel formulations of oxazolidinone antibiotic drugs, such as linezolid, are provided which are suitable for topical administration. Gel formulations of the present invention comprise an oxazolidinone antibiotic drug solubilized in a polyol solvent system including a polyol solvent, a thickening agent, and water. The oxazolidinone drug remains solubilized in gel formulations of the present formulation for at least 3 hours at a temperature from 15°C to 30°C. Also provided are methods of topically administering gel formulations of the present invention to treat or prevent infection by gram-positive bacteria.

STABLE POLYOL FORMULATIONS OF OXAZOLIDINONE
ANTIBACTERIAL AGENTS

FIELD OF THE INVENTION

5 The present invention relates to stable polyol formulations of an oxazolidinone antibacterial agent, wherein the agent is solubilized in the formulation. The invention also relates to compositions, such as gels, hydrogels, soft elastic capsules, and films which include or contain such polyol formulations, and the use of such compositions in the delivery of the oxazolidinone antibacterial agent to a subject.

10

BACKGROUND

Numerous oxazolidinone compounds have been reported as being useful antibacterial agents. U.S. Patent No. 5,688,792 (Barbachyn et al.) discloses one set of such oxazolidinone antibacterial agents, including (S)-N-[[3-[3-fluoro-4-(4-
15 morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, referred to herein as "linezolid." Treatment of infections by administration to the skin of a mammal of a pharmaceutical formulation of an oxazolidinone antibacterial agent in the form of a solution, suspension, or emulsion is disclosed in WO 03/030906 (PHARMACIA & UPJOHN COMPANY).

20 Polyol gel formulations with various active agents solubilized therein have been developed to minimize irritation when applied to the skin of a mammal, while ensuring bioavailability of the agent in the formulation. For a good discussion of gel formulations, see Ofner III *et al.* "Gels and Jellies," pp. 1327-1344 of Encyclopedia of Pharmaceutical Technology, vol. 3 (ed. by Swarbrick, *et al.*, pub. by Marcel Dekker, 2002); or Pena, "Gel
25 Dosage Forms: Theory, Formulation, and Processing," pp. 381-388 of Topical Drug Delivery Formulations, (ed. by Osborne *et al.*, pub. by Marcel Dekker, Inc., 1990). For examples of polyol gel formulations of specific drugs, see WO 02/11698 (PHARMACIA AB), WO 89/07436 (THE UPJOHN COMPANY), and WO 88/01502 (THE UPJOHN COMPANY) for minoxidil, or WO 94/07478 (THE UPJOHN COMPANY) for
30 clindamycin.

Unfortunately, oxazolidinones, such as linezolid, tend to crystallize out of typical polyol formulations over time. (See Example 2, below). What is needed is a stable polyol formulation of an oxazolidinone antibacterial agent, suitable for topical delivery of the

agent to a subject.

SUMMARY OF THE INVENTION

5 The present invention relates to a gel formulation suitable for topical administration comprising: an oxazolidinone antibiotic drug solubilized in a polyol solvent system comprising a polyol solvent, a thickening agent, and water, in which the oxazolidinone drug remains solubilized in the solvent system for at least 3 hours at a temperature from 15°C to 30°C.

10 The present invention also relates to a method of treating an infection by gram-positive bacteria in a mammal in need of such treatment, comprising topically administering a therapeutically effective amount of the gel formulation of the present invention to such mammal.

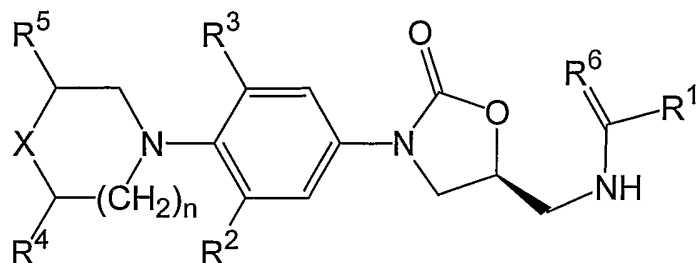
DETAILED DESCRIPTION OF THE INVENTION

15 The present invention, in one aspect, is a polyol formulation of an oxazolidinone antibacterial agent. The oxazolidinone antibacterial agent is suitably any one of a number of oxazolidinone compounds having therapeutically and/or prophylactically useful antibiotic activity. Among such compounds are those disclosed in the following patents, each of which is incorporated by reference herein: U.S. Patent No. 5,164,510 (Brickner);
20 U.S. Patent No. 5,231,188 (Brickner); U.S. Patent No. 5,565,571 (Barbachyn *et al.*); U.S. Patent No. 5,627,181 (Riedl *et al.*); U.S. Patent No. 5,652,238 (Barbachyn *et al.*); U.S. Patent No. 5,688,792 (Barbachyn *et al.*); U.S. Patent No. 5,698,574 (Riedl *et al.*); and U.S. Patent No. 6,069,145 (Betts).

25 Oxazolidinone antibacterial agents exhibit antibacterial activity against gram-positive organisms. The oxazolidinone antibacterial agent included in the formulations and used in the methods of the present invention preferably exhibit antibacterial activity against gram-positive organisms of at least one of the following genera: *Staphylococcus* (e.g., *Staphylococcus aureus*, *Staphylococcus epidermidis*), *Streptococcus* (e.g., *Streptococcus viridans*, *Streptococcus pneumoniae*), *Enterococcus* (e.g., *Enterococcus fecalis*, *Enterococcus faecium*), *Bacillus*, *Corynebacterium*, *Chlamydia* and *Neisseria*.
30 Many such gram-positive organisms have developed significant levels of resistance to other antibiotics. Oxazolidinone antibacterial agents are also generally effective against anaerobic organisms such as those of the genera *Bacteroides* and *Clostridia*, and against

acid-fast organisms such as those of the genus *Mycobacterium*.

In one embodiment of the formulation and method of the present invention, the oxazolidinone antibacterial agent is a compound of formula (I), below:



5

(I)

wherein:

R¹ is selected from (a) H, (b) C₁₋₈ alkyl optionally substituted with at least one substituent, preferably with from one to three substituents, independently selected from F, Cl, OH, C₁₋₈ alkoxy, C₁₋₈ acyloxy, C₁₋₈ benzyloxy, and C₃₋₆ cycloalkyl, (c) amino, (d) mono- and di(C₁₋₈ alkyl)amino and (e) C₁₋₈ alkoxy;

10

R² and R³ are each independently selected from H, F and Cl;

R⁴ is H or CH₃;

R⁵ is selected from H, CH₃, CN, CO₂R¹ and (CH₂)_mR⁶, where R¹ is as defined above, R⁶ is selected from H, OH, OR¹, OCOR¹, NHCOR¹, amino, mono- and di(C₁₋₈ alkyl)amino; and m is 1 or 2;

15

R⁶ is O or S;

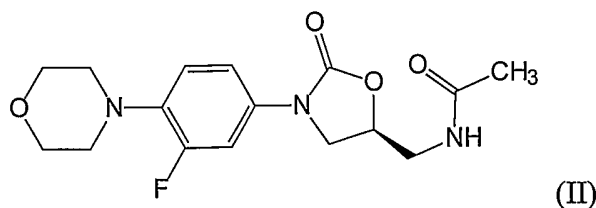
n is 0, 1 or 2; and

X is O, S, SO, SO₂, p-toluenesulfonyl, SNR⁷ or S(O)NR⁷, wherein R⁷ is selected from H and C₁₋₄ alkyl, wherein said C₁₋₄ alkyl is optionally substituted with one or more substituents, preferably with from one to three substituents, independently selected from F, Cl, OH, C₁₋₈ alkoxy, amino, and C₁₋₈ mono- or di(C₁₋₈ alkyl)amino group; or a pharmaceutically acceptable salt thereof.

20

The oxazolidinone antibacterial drug of Formula I is preferably (S)-N-[[3-[3-fluoro-4-(4-morpholinyl) phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide, also referred to herein by its generic name, "linezolid." Linezolid has the structure shown in formula (II):

25



and is in commercial use as a medicament under the trademark Zyvox® of Pharmacia and Upjohn Company. Linezolid exhibits strong antibacterial activity against gram-positive organisms of all of the genera of such organisms listed above.

5 The concentration of the oxazolidinone antibacterial agent in the gel formulation of the present invention is preferably high enough that it is capable of delivering an amount of the antibacterial agent above that is greater than or equal to the MIC₉₀ for the agent to target tissue, after being topically applied. The MIC₉₀ is the minimum inhibitory concentration for 90% of the target organisms, in this instance infective gram-positive
10 bacteria. For example, where the active agent is linezolid, the MIC₉₀ is about 4 µg/ml. The concentration of the oxazolidinone antibacterial agent in the gel formulation is also preferably low enough that the antibacterial agent does not crystallize out of the formulation within 3 hours, more preferably within 6 hours, more preferably within 12 hours, more preferably within 24 hours, even more preferably within 1 year, even more
15 preferably within 2 years of production of the formulation.

When the oxazolidinone antibacterial agent is linezolid, the concentration of oxazolidinone antibacterial agent in the gel formulation of the present invention is preferably 0.05% to 2%, more preferably 0.1% to 1%, even more preferably 0.1% to 0.5% by weight of the total weight of the gel formulation.

20 The polyol of the formulation of the present invention is preferably a polyol or polyol combination which does not cause irritation when applied to the skin of a mammal. Suitable polyols include glycerine, propylene glycol, dipropylene glycol, hexylene glycol, butylene glycol, and liquid polyethylene glycols, such as polyethylene glycol 200 to 600, and glycerol. The polyol is preferably selected from the group consisting of propylene
25 glycol, dipropylene glycol, butylene glycol, and polyethylene glycol. The polyol is more preferably propylene glycol or a combination of propylene glycol and a polyethylene glycol. When the polyol is polyethylene glycol, it is preferably polyethylene glycol 400.

The thickening agent of the polyol gel formulation of the present invention enhances the viscosity of the formulation. A wide variety of thickening agents are known
30 to those skilled in the art of the present invention, which are suitable for use as the

thickening agent in the formulations of the present invention. The thickening agent may be an organic thickening agent or an inorganic thickening agent, more preferably an organic thickening agent. When the thickening agent is an organic thickening agent, it is preferably a polymeric thickening agent. Polymeric thickening agents suitable for use in the present gel formulations include cellulose, cellulose derivatives, starches, gums, pectin, casein, gelatin, phycocolloids, and synthetic polymers. Examples of the foregoing materials include, but are not limited to, alginates and salts and derivatives thereof, including sodium alginate and propylene glycol alginate, acacia, carrageenan, guar gum, karaya gum, locust bean gum, tragacanth, and xanthan gum. Other suitable polymeric thickening agents for use in the present gel formulations include polymers of acrylic acid, such as crosslinked homopolymers of acrylic acid, crosslinked copolymers of acrylic acid, crosslinked interpolymers of acrylic acids, polyacrylic acid and salts thereof, acrylic/acrylate copolymers, dimethicone copolyols, polyacrylamide, ethylene/sodium acrylate copolymer, acrylamide/sodium acrylate copolymer, sodium acrylate/vinyl alcohol copolymer, sodium polymethacrylate, sodium polystyrene sulfonate, povidone and derivatives thereof, polyquaternium compounds, such as polyquaternium 10, polyvinyl alcohol, polyethylene oxide, and poloxamers. When the polymeric thickening agent is a polymer of acrylic acid, it is preferably a carbomer.

In one embodiment of the present invention, the thickening agent is a carbomer or a cellulose or a cellulose derivative, or a mixture of a carbomer and either cellulose or a cellulose derivative. When the thickening agent is cellulose or a cellulose derivative, it is preferably HPMC. The term "carbomer" as used herein refers to synthetic, high molecular weight crosslinked homopolymers of acrylic acid. Certain carbomers are particularly useful in formulations, such as the polyol gel formulations of the present invention, which contain high amounts of solvent, such as polyols or water. Examples of such carbomers include carbomer 910, 934, 940, 941, 980, 981, and 1343, and Carbopol® Ultrez™ 10, all of which are commercially available from Noveon (Cleveland, OH).

In an alternate preferred embodiment of the present invention, the polyol gel formulation includes an inorganic thickening agent. Suitable inorganic thickening agents include bentonite, magnesium aluminum silicate and colloidal silicon dioxide.

The amount of thickening agent included in the polyol gel formulations of the present invention may vary and depends, for example, on the particular thickening agent and polyol used, and on the quantity of oxazolidinone to be included in the formulation.

Generally speaking, the thickening agent is employed in an amount to provide a formulation with the desired viscosity. The thickening agent is preferably employed in an amount ranging from about 0.1% to about 20%, preferably about 0.1% to about 10%, more preferably from about 0.1% to about 3%, even more preferably from 0.15% to 1%.

5 In another embodiment, the polyol formulation of the present invention further comprises a crystallization inhibitor, preferably, a crystallization inhibitor which inhibits the crystallization of the oxazolidinone in the polyol gel formulation. The crystallization inhibitor preferably further acts as a thickening agent in the formulation. The crystallization inhibitor is preferably cellulose or a cellulose derivative, such as
10 carboxymethylcellulose ("CMC"), ethylcellulose, hydroxyethylcellulose, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose ("HPMC"), microcrystalline cellulose, and powdered cellulose, or a salt of a cellulose. The crystallization inhibitor is most preferably HPMC.

In another embodiment, the polyol formulation of the present invention further
15 comprises a neutralizing agent. The term "neutralizing agent", as used herein, refers to a material that may be used to modify the pH of a composition, for example, from an acidic pH to a more basic pH, or from a basic pH to a more acidic pH, to bring the pH of the formulation closer to a neutral pH. Components of the polyol formulations of the present invention, such as carbomeric thickening agents, tend to be acidic. Thus, suitable
20 neutralizing agents are preferably those which modify the pH of the polyol formulations of the present invention from an acidic to a more basic pH. A wide variety of suitable neutralizing agents are known to those skilled in the art for inclusion in this embodiment of the formulations of the present invention, including ammonium hydroxide, sodium hydroxide, potassium hydroxide, diethanolamine, diisopropanolamine, triethanolamine,
25 aminomethylpropanol, and TRIS. The neutralizing agent is preferably sodium hydroxide.

The pH of the polyol formulation is preferably a pH at which the oxazolidinone agent is stable, and at which the formulation does not cause pain or damage skin when applied thereto. The pH is preferably between 4 and 8, more preferably between 5 and 7, even more preferably between 5 and 6.

30 The amount of neutralizing agent included in this embodiment of the polyol formulations of the present invention will depend upon a number of different factors, including the particular neutralizing and thickening agents employed, the quantity of thickening agent to be neutralized, and the desired pH of the formulation.

In another embodiment, polyol formulations of the present invention further comprise a preservative. Suitable preservatives include benzyl alcohol, benzoic acid and salts thereof, quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride; imidazolidinyl urea; 5 parabens such as methylparaben, ethylparaben, propylparaben, and butylparaben, and salts thereof; phenoxyethanol; chlorophenoxyethanol; phenoxypropanol; chlorobutanol; chlorocresol; phenylethyl alcohol; disodium EDTA; and sorbic acid and salts thereof. The preservative is preferably a paraben or benzyl alcohol, most preferably methylparaben, propylparaben, or a combination of the above.

10 The quantity of preservative used in this embodiment of the polyol formulations of the present invention is preferably an amount sufficient to inhibit microbial growth in the formulation. The amount of preservative in the formulation is preferably 0.01% to 10%, more preferably 0.02% to 5%, even more preferably 0.02% to 1% of the total weight of the formulation.

15 Formulations and methods of the present invention are suitable for use in the treatment of skin infections. Specific types of skin infections that are suitably treated with formulations and methods of the present invention include acne and soft-tissue infections, such as infections caused by staphylococci or streptococci. Soft-tissue infections of the foot are particularly prevalent in individuals with diabetes. Diabetic foot infections are 20 typically treated by oral administration of antibiotics. However, individuals with late stage forms of diabetes tend to have very poor circulation, making delivery of orally administered drugs to infected extremities, such as feet, difficult. Topical delivery of oxazolidinone antibacterial agents through administration of formulations of the present invention to affected areas, such as to a diabetic foot, better ensures treatment of an 25 underlying infection than oral delivery. For a discussion of the advantages of topical delivery of oxazolidinone antibacterial agents in the treatment of acne and diabetic foot, see WO 03/030906.

The method of the present invention comprises topically administering the formulation of the present invention to a subject. The formulation is administered to the 30 subject in order to treat or prevent a gram-positive bacteria infection. The infection can be due to any gram-positive bacteria; but, is preferably due to an infection by one or more bacteria of a genus selected from the group consisting of: *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Bacillus*, *Corynebacterium*, *Chlamydia* and *Neisseria*. When the genus is

Staphylococcus, the species of bacteria is preferably *Staphylococcus aureus* or *Staphylococcus epidermidis*. When the genus is *Streptococcus*, the species of bacteria is preferably *Streptococcus viridans* or *Streptococcus pneumoniae*. When the genus is *Enterococcus*, the species is preferably *Enterococcus faecalis* or *Enterococcus faecium*.

5 Treatment of the infection according to the method of the present invention preferably comprises administering a sufficient amount of the oxazolidinone antibacterial drug to the affected area to either kill the gram-positive bacteria present therein and/ or to stop them from growing to a point where the subject's natural defense mechanism can reduce or eradicate the bacteria. Prevention according to the method of the present
10 invention preferably comprises preventing an infection by gram-positive bacteria, or preventing a minor infection of such bacteria from growing into a larger infection. Prevention of infection is a particularly important step in preparing a subject for surgery.

In the method of the present invention, the oxazolidinone antibacterial agent can be used either individually or in combination with another oxazolidinone antibacterial agent,
15 whether both agents are included in the same formulation or administered separately. Further, the oxazolidinone antibacterial agent can be used in combination with other antibacterial agents, whether administered separately or whether both are included in the formulation of the present invention. In addition, the formulation of the present invention can be used with non-antibacterial agents in treating infections, whether the non-
20 antibacterial agents are administered separately or included in the formulation.

The exact dosage and frequency of administration of the polyol gel formulations of the present invention depends upon the particular oxazolidinone antibiotic agent used, the particular condition being treated, the severity of the condition being treated; the age, weight, and general physical condition of the particular patient; and other medication the
25 particular patient may be taking. Such factors are well known to those skilled in the art and can be more accurately determined by the patient's response to the particular treatment administered.

The polyol gel formulations of the present application are preferably formulated for direct application to the skin, or incorporated into a matrix designed to be applied to
30 the skin, such as a hydrogel or other wound dressing matrix. Examples of such wound dressing matrices are described in various references, including US Pat. Nos. 6,476,104 (Nakamura *et al.*); 6,180,132 (Huang *et al.*); 6,333,054 (Rogozinski); 6,348,212 (Hymes *et al.*); 5,686,425 (Lee); 5,736,113 (Lee); 6,455,065 (Hymes); and EP 0 552 151 (THE DOW

CHEMICAL COMPANY).

The present invention is further illustrated by the following examples. These examples are intended to be illustrative of the invention and should not be used to limit or restrict its scope.

5

EXAMPLES

The following examples illustrate one or more of the embodiments of the invention described above.

EXAMPLE 1 - SOLUBILITY OF LINEZOLID IN SOLVENTS AND PROPYLENE GLYCOL SOLVENT SYSTEMS

10

The solubility of linezolid in the following solvents and solvent systems was tested at room temperature. Three samples of each solvent or solvent system were tested. The results of the solubility tests are shown in Table 1, below, where “%RSD” is the percent relative standard deviation.

15

TABLE 1

Solvent or Solvent System	Equilibrium Solubility	
	mg/mL	%RSD
Water	2.7	2.8
Ethanol	8.6	0.4
Isopropanol	5.0	1.1
Propylene Glycol	11.7	0.6
Polyethylene glycol (“PEG”) 400	28.2	0.4
5% propylene glycol, 10% PEG 400, 85% water	5.2	0.5
7% propylene glycol, 10% PEG 400, 83% water	5.6	0.4

As Table 1 shows, the solubility of linezolid in each of the individual solvents tested was highest in propylene glycol and in polyethylene glycol.

The two solvent systems of propylene glycol, polyethylene glycol 400, and water tested were identical to one another in composition, except that the two contained different concentrations of propylene glycol and water. Linezolid was slightly more soluble (5.6 mg/mL) in the solvent system with 7% propylene glycol than it was in the solvent system with 5% propylene glycol (5.2 mg/ml), although the difference did not appear to be statistically significant.

EXAMPLE 2 - PREPARATION AND TESTING OF A LINEZOLID GEL
FORMULATION

5 A 1% linezolid gel formulation with the composition shown in Table 2, below, was prepared as described below.

TABLE 2

Amount	%Wt/Wt	Material
35.0 g	1.0	Linezolid
10.5 g	0.3	Methylparben
350 g	10	Polyethylene Glycol 400
175 g	5.0	Propylene Glycol
26.25 g	0.75	Carbomer 934P
qs	qs	40% NaOH for pH of 5.4-5.7
qs	qs	Purified water
3,500 g	100%	(TOTAL)

- 10 1. The polyethylene glycol 400 and propylene glycol were added to 2.5 L of purified water and mixed.
2. Methylparaben was added, and mixing continued until the solution became clear.
3. Linezolid was added and the solution mixed until dissolved.
4. Carbomer was added and mixed into the solution until a substantially
15 homogenous dispersion was formed.
5. Sodium hydroxide was added until a uniform gel formed, at a pH of about 5.4-5.7.
6. Water was added for a final weigh of 3,500 g.

20 The resulting linezolid gel formulation was found to have a viscosity of 13,600 cps.

The linezolid in the gel formulation was found to retain its potency after 8 weeks at 30°C, 40°C, and even 50°C. However, after long term storage at room temperature (about 22°C), and at 25°C, 30°C, and 40°C, needle-like crystalline precipitates developed

in the gel formulation. A placebo gel formulation prepared as described above, without linezolid, and stored under the same conditions for the same length of time, remained clear through both the short term and long term stability studies.

5 EXAMPLE 3 - STABILITY STUDIES OF 0.5% AND 1% LINEZOLID GEL FORMULATIONS

Linezolid gel and placebo gel formulations were prepared according to the formulae in Table 3, below, using the procedure described below.

10

TABLE 3

% Wt/Wt			Material
Placebo	0.5% Linezolid	1% Linezolid	
0	0.5	1.0	Linezolid
0.3	0.3	0.3	Methylparben NF
10	10	10	Polyethylene Glycol 400 NF
7.0	7.0	7.0	Propylene Glycol USP
0.75	0.75	0.75	Carbomer 934 P NF
0.1	0.1	0.1	HPMC
qs	qs	qs	40% NaOH for pH of 5.3-5.7
qs	qs	qs	Purified water to 100% vol.

The same procedure was used to make the formulations as was used in Example 2, above, except that the temperature of the mixture produced in step 2 was elevated to 70°C before the addition of linezolid in step 3, and mixed at that temperature until the linezolid was dissolved. Hydroxypropylmethyl cellulose ("HPMC") was added to the resulting mixture, prior to step 4, and mixed until the solution became clear. The solution had cooled to 40°C by the time the carbomer was added in step 4.

The linezolid gel formulations prepared as described above were tested for short term and long term stability, as described in Example 2, above. The linezolid in the 0.5% and 1% gel formulations prepared as described in the present example was found to retain its potency after 3 months at 25°C and 50°C. All the gel formulations were also found to be physically stable at both temperatures. No precipitates or crystals were observed in the

placebo, or in the 0.5%, and 1.0% linezolid gel formulations, even after storage for over two years at room temperature.

EXAMPLE 4 - SKIN IRRITANCY STUDIES OF TOPICAL LINEZOLID GEL

5 FORMULATIONS

The placebo, 0.5% linezolid, and 1.0% linezolid gel formulations prepared as described in Example 3, above, were topically applied to the skin of female Harlan Sprague Dawley “fuzzy” rats. (HSD:fz). This particular type of rat was selected for use in the study because of the high sensitivity of the skin of such animals to irritation, and
10 because the skin condition is easier to observe than the skin of rats with more hair.

The three gel solutions were applied twice daily to the dorsal skin of 4 female fz rats for each formulation tested. The skin of each rat was inspected daily for irritancy (i.e., erythema and edema), and transepidermal water loss (“TEWL”), a measure of water efflux through the skin, was measured before and after the 4 day treatment regimens. Just after
15 the day 3 dose, the rats were fitted with a modified cardboard Elizabethan collar to prevent ingestion of the topical treatment. Blood samples were taken 3 hours after doses 5 (day 3) and 7 (day 4) for plasma drug analysis. Terminal skin biopsies were taken for histological examination. Assay results are shown in Table 4, below.

TABLE 4

Formulation	TEWL (mg/cm ² /hr)	Clinical Observation	Mean Drug Plasma Concentration (µg/mL)
Placebo	0.30 +/- 0.06	no signs	not applicable
0.5% Linezolid	0.19 +/- 0.04	no signs	0.5 +/- 0.1
1% Linezolid	0.19 +/- 0.03	minimal flaking/ possible drug residue	0.22 +/- 0.05

20

After four days of treatment, the rats appeared to have tolerated the placebo and linezolid gels well. There was very little indication of overt irritation in the skin of animals administered any of the gel formulations. A white residue, probably a drug residue, was observed on the skin of rats treated with the 1% linezolid gel, but, not on the
25 skin of rats administered the placebo or 0.5% linezolid gel.

The TEWL measurements, shown in Table 4, indicate no change relative to basal

levels, thus indicating no impact of the formulation on the integrity of the dermal membrane of any of the animals tested.

Histological examination of the skin biopsies revealed no differences between the control group and the treated groups. The epidermal thickness was similar, there was no increase in the number of mitoses in the epidermal cells in the basal layer, and there was
5 no evidence of edema or inflammation in the dermis.

Plasma levels indicated that the group of rats administered the 0.5% linezolid gel formulation absorbed nearly twice the dose of the 1% linezolid group.

Without being limited by theory, it is thought that the precipitate observed on the skin of rats administered the 1% linezolid gel formulation and the lower concentration of
10 linezolid found in the plasma of drugs administered the 1% linezolid gel compared to the 0.5% linezolid gel are interrelated, for the following reasons. It is likely that the precipitate which dropped out of the 1% linezolid gel formulation after the volatilization of other components in the formulation, after application to the skin of the test subjects, is
15 linezolid. An assay of the gel formulations verified that linezolid was present at the stated concentrations in both the 0.5% and 1% linezolid gel formulations. The linezolid only crystallized and dropped out of the 1% gel formulation when used *in vivo*. It appears that the amount of liquid volatilized from the 0.5% linezolid gel formulation after topical application was insufficient to result in drug crystal formation in that formulation.

20

EXAMPLE 5 - SOLUBILITY OF LINEZOLID IN BUTYLENE GLYCOL SOLVENT SYSTEMS AND IN A CONCENTRATED PROPYLENE GLYCOL SOLVENT SYSTEM

The solubility of linezolid in butylene glycol, and in additional solvent systems of
25 propylene glycol or butylene glycol was tested, as follows. Three samples of each solvent or solvent system were tested. An excess of linezolid was added to each solvent or co-solvent system listed in Table 5, below, and shaken overnight (about 16 hours) at room temperature. A portion of the resulting suspension was then centrifuged for 5 minutes at 11,000 rpm. An aliquot of the supernatant was diluted and assayed by HPLC, in order to
30 determine the amount of linezolid present. The solubility assay results are shown in Table 5, below.

TABLE 5

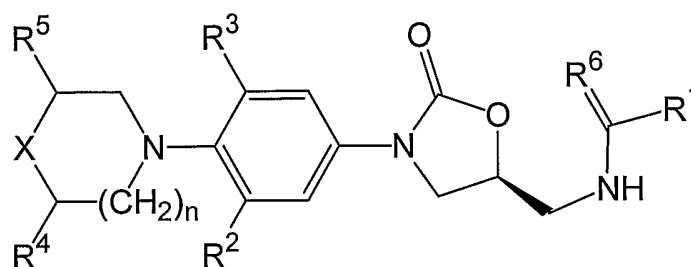
Solvent or Solvent System	Equilibrium Solubility	
	mg/mL	%RSD
100% water	2.7	
10% propylene glycol, 10% PEG 400, 80% water	4.7	1.2
5% butylene glycol, 10% PEG 400, 85% water	5.0	0.5
7% butylene glycol, 10% PEG 400, 83% water	4.8	0.9
15% PEG 400, 85% water	4.2	1.2
20% butylene glycol, 80% water	6.6	0.9
30% butylene glycol, 70% water	9.0	0.3
50% butylene glycol, 50% water	16	2.5
60% butylene glycol, 40% water	22	0.9
70% butylene glycol, 30% water	24	1.6
100% Butylene glycol	6.2	0.7

The solubility of linezolid in each of the 5% or 7% butylene glycol, 10 % PEG,
 5 and water solvent systems shown in Table 5, above (i.e., 5.0 and 4.8 mg/mL, respectively),
 was comparable to the solubility of linezolid in the 5% and 7% propylene glycol, 10%
 PEG, and water solvent systems of Example 1, above (i.e., 5.2 and 5.6 mg/mL,
 respectively). The solubility of linezolid in vehicles containing propylene glycol/PEG 400
 or butylene glycol/PEG 400 in combination with water resulted in solubilities ranging
 10 from 4 to 5 mg/mL, which is greater than the solubility of linezolid in 100 % water.
 Solubility of linezolid was significantly higher in the glycol and water systems containing
 30% or more butylene glycol, with the highest equilibrium solubility (24 mg/mL) found in
 the 70% butylene glycol, 30% water solvent system.

CLAIMS

We claim:

1. A gel formulation suitable for topical administration comprising: an oxazolidinone antibiotic drug solubilized in a polyol solvent system comprising a polyol solvent, a thickening agent, and water, wherein the drug remains solubilized in the solvent system for at least 3 hours at a temperature of 15°C to 30°C.
2. The formulation of claim 1 wherein the oxazolidinone antibiotic drug is a compound of formula (I)



(I)

10

wherein:

- R^1 is selected from (a) H, (b) C_{1-8} alkyl optionally substituted with at least one substituent, preferably with from one to three substituents, independently selected from F, Cl, OH, C_{1-8} alkoxy, C_{1-8} acyloxy, C_{1-8} benzyloxy, and C_{3-6} cycloalkyl, (c) amino, (d) mono- and di(C_{1-8} alkyl)amino and (e) C_{1-8} alkoxy;
- R^2 and R^3 are each independently selected from H, F and Cl;
- R^4 is H or CH_3 ;
- R^5 is selected from H, CH_3 , CN, CO_2R^1 and $(CH_2)_mR^6$, where R^1 is as defined above, R^6 is selected from H, OH, OR^1 , $OCOR^1$, $NHCOR^1$, amino, mono- and di(C_{1-8} alkyl)amino; and m is 1 or 2;
- R^6 is O or S;
- n is 0, 1 or 2; and
- X is O, S, SO, SO_2 , p-toluenesulfonyl, SNR^7 or $S(O)NR^7$, wherein R^7 is selected from H and C_{1-4} alkyl, wherein said C_{1-4} alkyl is optionally substituted with one or more substituents, preferably with from one to three substituents, independently selected from F, Cl, OH, C_{1-8} alkoxy, amino, and C_{1-8} mono- or di(C_{1-8} alkyl)amino group;

25

or a pharmaceutically acceptable salt thereof.

3. The formulation of claim 2 wherein, is CH₃; R² and R³ are independently selected from H and F but at least one of R² and R³ is F; R⁴ and R⁵ are each H; n is 1; and X is selected from O, S and SO₂.
- 5 4. The formulation of claim 1 wherein the oxazolidinone antibiotic drug is selected from the group consisting of:
- linezolid;
- N-((5*S*)-3-(3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide;
- 10 (*S*)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- (*S*)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride;
- N-[[5*S*)-3-[4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 N-[[5*S*)-3-[3-fluoro-4-tetrahydro-1,1-dioxido-2*H*-thiopyran-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]methyl]acetamide; and
- N-[[5*S*)-3-[3-fluoro-4-thiomorpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide.
5. The formulation of claim 1 wherein the oxazolidinone antibiotic drug is
- 20 linezolid.
6. The formulation of claim 5, wherein the concentration of linezolid in the formulation is about 0.05% to about 2% by weight of the gel formulation.
7. The formulation of claim 1, wherein the polyol solvent is selected from the group consisting of propylene glycol, dipropylene glycol, butylene glycol, and a polyethylene
- 25 glycol.
8. The formulation of claim 1, wherein the thickening agent is a carbomer.
9. The formulation of claim 1, further comprising a crystallization inhibitor.
10. The formulation of claim 9, wherein the crystallization inhibitor is

hydroxypropylmethyl cellulose.

11. The formulation of claim 1, further comprising a preservative.
12. The formulation of claim 11, wherein the preservative is selected from the group consisting of methylparaben and propylparaben.
- 5 13. The formulation of claim 1, further comprising at least one monomer which polymerizes to form a hydrogel.
14. The formulation of claim 1 incorporated into a polymeric matrix, thereby forming a hydrogel or film.
15. A method of treating an infection by gram-positive bacteria in a mammal in need
10 of such treatment, comprising topically administering a therapeutically effective amount of the gel formulation of claim 1 to such mammal.