(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19366 A1

(51) International Patent Classification[7]: A61K 31/422, 31/424, 9/00, 47/32

(21) International Application Number: PCT/US00/24914

(22) International Filing Date:
12 September 2000 (12.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

09/394,617	13 September 1999 (13.09.1999)	US
09/659,063	11 September 2000 (11.09.2000)	US

(71) Applicant: INSITE VISION INCORPORATED [US/US]; 965 Atlantic Avenue, Alameda, CA 94501 (US).

(72) Inventors: BOWMAN, Lyle, M.; 5135 Mount Tam Circle, Pleasanton, CA 94566 (US). SAMIR, Roy; 2844 Morgan Drive, San Ramon, CA 94583 (US). SHEN, Peng; 26967 Hemmingway Court, Hayward, CA 94542 (US).

(74) Agent: BRENC, Andrew, S.; Howrey Simon Arnold & White, LLP, 1299 Pennsylvania Avenue, N.W., Box 34, Washington, DC 20004-2402 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/19366 A1

(54) Title: TOPICAL TREATMENT FOR PREVENTION OF OCULAR INFECTIONS

(57) Abstract: The topical application of an oxazolidinone antibiotic in a polymeric suspension or aqueous composition to the eye is useful in treating or preventing ocular infections. Preferred oxazolidinone antibiotic compositions comprise the compound of formula (IV), and are represented by formula (IV), and the pharmaceutically acceptable salts thereof.

TOPICAL TREATMENT FOR PREVENTION OF OCULAR INFECTIONS

BACKGROUND OF THE INVENTION

1. Cross-reference to Related Application

This application is a continuation-in-part of Application Serial No. 09/394,617, which was filed September 13, 1999.

2. Field of the Invention

The present invention relates to a method for treating or preventing infections in the eye and to compositions useful therein.

3. Description of the Related Arts

The eye is susceptible to bacterial and parasitic infections arising from both traumatic and non-traumatic related events. Infections are a concern after ocular surgery and precautions are correspondingly taken to prevent the onset of infection. However, even without the invasive trauma of a surgical procedure, infections in the eye lids, conjunctiva, cornea, and other ocular tissues can arise.

Treating infections in ocular tissues can be challenging and/or problematic because of the difficulty in delivering an antibiotic to the affected tissue. In general, ocular infections are treated by local injection, systemic administration, or topical application of an antibiotic. The route of administration depends on the antibiotic selected, the location of the infection and the type of infection.

The simple and direct approach of topically applying the antibiotic to the exterior of the eye has several benefits, including the avoidance of side effects and the reduced chance of developing resistant strains of bacteria as compared to systemic administration. However, for a variety of reasons, many antibiotics are not amenable or suitable for topical application to the eye.

For example, in order for a topical application to be effective, the antibiotic must be able to penetrate the desired tissue. This may include penetrating the conjunctiva and the cornea. Also, the penetration rate must be sufficient to impart an effective dose. Many drugs do not possess a requisite penetration ability with regard to the tissues of the eye. It should be noted that the external layers of the eye are quite different from the tissues encountered in the stomach and intestinal tract. Thus, while a certain drug may be readily absorbed in the intestines and introduced into the blood supply for systemic

administration, the same drug may be incapable of being absorbed by, or of passing through, the substantially avascular outer layers of the conjunctiva or cornea at a minimally acceptable therapeutic concentration. The mechanism of transport or uptake of the drug is entirely different for topical administration than for oral administration.

Another concern is that the antibiotic will be toxic to the eye. A toxic response includes redness, swelling and/or discharge. Toxicity is especially problematic for topical administration because it is a concentration dependent phenomenon. The concentration ratio between tear fluid and ocular tissue in topical administration is generally in the range of about 1:500 to 1:1000, due to the penetration gradient. Thus, while a drug may be non-toxic at the minimum effective concentration, the 500% to 1000% increase in concentration associated with topical administration may well induce a toxic response. Again, the fact that oral or systemic administration shows the drug to be compatible with ocular tissue does not predict or address the toxicity issue associated with topical administration.

A further potential unsuitability of an antibiotic is the practicality of topical administration by the patient. Assuming that sufficiently high concentrations of the antibiotic can be used to achieve an effective dose within the target tissue without a toxic response, the application may nonetheless be irritating. An irritation response includes temporary burning, stinging and/or watering of the eye. Beyond whether the increased watering of the eyes washes away so much of the antibiotic composition that an effective dose is prevented, the patient may simply be resistant to complying with the dosage regimen because of the irritation. By failing to comply with the dosing regimen, the treatment efficacy is reduced or eliminated.

Some antibiotics have been found to sufficiently meet the above requirements so as to be applicable to topical administration. Examples of antibiotics that are reported to be useful in ocular topical administration include tobramycin, gentamycin, fluoroquinolone derivatives including norfloxacin, ofloxacin, and ciprofloxacin, naphthyridine, tetracyclines, and erythromycin. However, in view of the rise in resistant strains of bacteria, it would be desirable to find additional antibiotics that can be topically applied to the eye. It would be further desirable to provide an ophthalmic topical formulation that is effective against gram-positive aerobic bacteria as well as anaerobic organisms.

SUMMARY OF THE INVENTION

The present invention relates to a process for treating an eye that comprises topically applying an oxazolidinone antibiotic to an eye in an amount effective to treat or prevent infection in a tissue of the eye. Applicant has discovered that oxazolidinone antibiotics, which are class of known oral antibiotics, are suitable for topical administration to the eye. Preferably the oxazolidinone antibiotic is a phenyloxazolidinone, more preferably an oxazine or thiazine phenyloxazolidinone.

The invention also relates to a topical ophthalmic composition containing an oxazolidinone antibiotic. In one embodiment, the ophthalmic composition is a sustained release composition comprised of an aqueous suspension of the oxazolidinone antibiotic and a polymer suspending agent.

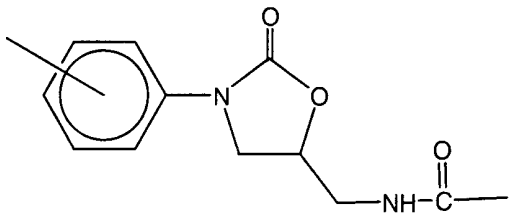
The present invention includes and provides an aqueous polymeric suspension comprising water, 0.05% to 5.0% of an oxazolidinone antibiotic, and 0.1 to 10% of a polymeric suspending agent, wherein said polymeric suspending agent comprises a water-swellable water-insoluble crosslinked carboxy-vinyl polymer.

The present invention includes and provides a composition comprising water, a polymeric suspending agent, and a compound of formula IV.

The present invention includes and provides a composition comprising water, an oxizolidinone, a polymeric suspending agent, and a solubility enhancer.

DETAILED DESCRIPTION OF THE INVENTION

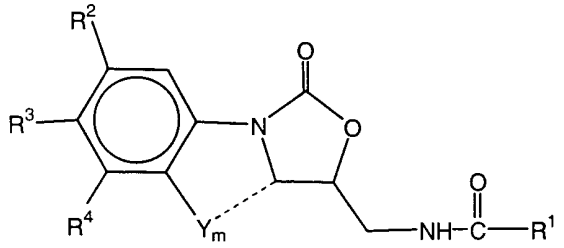
"Oxazolidinone antibiotic" as used herein means a compound having an oxazolidinone nucleus that exhibits antimicrobial activity. Typically the compound nucleus is substituted as shown in the following structure fragment:



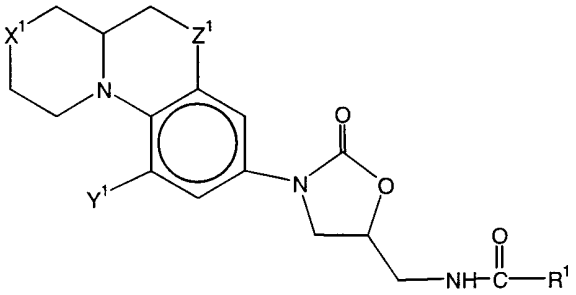
The phenyl ring can be substituted by a variety of groups as is well known in the oxazolidinone antibiotic art and can form a fused ring with the substituents and/or the oxazolidinone ring itself. The carbonyl moiety is bonded to one of a number of well

known terminal groups. An "phenyloxazolidinone" means a oxazolidinone ring with a phenyl group bonded to the ring nitrogen as shown in the above fragment, with or without the amidemethylene substituent.

More specifically, the oxazolidinone antibiotics used in the present invention can generally be represented by the following formulas I and II and the pharmaceutically acceptable salts thereof:



I



II

wherein:

R^1 is selected from the group consisting of (1) -H, (2) NH_3, (3) C_1-C_8 alkylamine, (4) C_1-C_8 dialkylamine, (5) C_1-C_8 alkoxy, (6) C_1-C_{12} alkyl optionally substituted with 1-3 Cl, (7) C_3-C_{12} cycloalkyl, (8) C_5-C_{12} alkenyl containing one double bond, (9) C_1-C_8 acyloxy, (10) O-CH^2-phenyl, (11) phenyl optionally substituted with 1-3 -OH, -OCH_3, -OC_2H_5, -NO_2, -F, -Cl, -Br, -COOH and SO_3H, -$N(R^{1-1})(R^{1-2})$;

where R^{1-1} and R^{1-2} are the same or different and are –H, C_1-C_5 alkyl,

(12) furanyl, (13) tetrahydrofuranyl, (14) 2-thiophene, (15) pyrrolidinyl, (16) pyridinyl, (17) -OR^{1-3},

where R^{1-3} is C_1-C_4 alkyl,

(18) -NH_2, (19) -NHR^{1-4},

where R^{1-4} is C_1-C_3 alkyl or phenyl,

(20) $-NR^{1-4}R^{1-5}$,

where R^{1-5} is C_1-C_3 alkyl and R^{1-4} is as defined above, and where R^{1-4} and R^{1-5} can be taken together with the attached nitrogen atom to form a saturated mono-nitrogen C_5-C_7 heterocyclic ring including O,

(21) CH_2-OH, and (22) CH_2-OR^{1-6},

where R^{1-6} is C_1-C_4 alkyl, or CO-R^{1-7} is C_1-C_4 alkyl or -phenyl;

R^2 and R^4 are the same or different and are selected from the group consisting of (1) H, (2) -OH, (3) halogen, (4) CF_3, (5) OCH_3 provided that only one of R^2 or R^4 is –H, and (6) O-CO-R^{2-1},

where R^{2-1} is C_1-C_3 alkyl or –phenyl;

R^3 is selected from the group consisting of (1) H, (2) halogen, (3) -O-CH_3, (4) -O-C_2H_5, (5) piperdine, (6) 4-hydroxypyridine, (7) piperazine, unsubstituted or substituted with Q

where Q is a 5, 6-, 7- or 8-membered heterocyclic ring of the general formula -C*H=CH-CH=Z-Y^2=W* where the atoms or symbols representing an atom marked with an asterisk (*) are bonded to each other resulting in the formation of a ring where one of Z, Y^2 and W is –N= and the others are C=, unsubstituted or substituted with substituents selected from the group consisting of H, -C_1-C_4 alkyl, -NO_2, -NH_2, -NH-CO-[C_1-C_4 alkyl], -CN, -COOH, -O-[C_1-C_4 alkyl], halogen and N-oxides thereof; or Q is C_1-C_4 alkyl unsubstituted or substituted with substituents selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, tert-butyl, benzyl, phenyl, pyridyl, acetyl, difluoroacetyl, hydroxyacetyl, benzoyl, methoxy carbonyl, ethoxy carbonyl, 2-chloroethoxy carbonyl, 2-hydroxyethoxy carbonyl, 2-benzyloxyethyoxy carbonyl, 2-methoxyethoxy carbonyl, 2,2,2-trifluroethoxy carbonyl, cyanomethyl, 2-cyanoethyl, carbomethoxymethyl, 2-carbomethoxyethyl, 2-fluoroethoxy carbonyl, benzyloxy carbonyl, tertiary-butoxy carbonyl, methyl sulfonyl, phenyl sulfonyl, or paratoluenesulfonyl,

(8) phenyl, (9) pyridyl, (10) pyrazidyl, (11) pyridazinyl, (12) pyrimidinyl, (13) 1,2,3-triazinyl, (14) 1,2,4-triazinyl, (15) 1,2,5-triazinyl, (16) quinolinyl, (17) isoquinolinyl,

(18) quinoxalinyl, (19) quinazolinyl, (20) phthalazinyl, (21) cinnolinyl, (22) naphthylpyridinyl, (23) indolyl having nitrogen optionally substituted with R^{31-1}, (24) pyrrolopyridinyl having the saturated nitrogen substituted with R^{31-1}, (25) furanopyridinyl, (26) thienopyridinyl, (27) benzothiazolyl, (28) benzoxazolyl, (29) imidazolyl having the saturated nitrogen substituted with R^{31-1}, (30) pyrazolyl having the saturated nitrogen substituted with R^{31-1}, (31) thiazolyl, (32) isothiazolyl, (33) oxazolyl, (34) isoxazolyl, (35) pyrrolyl having nitrogen substituted with R^{31-1}, (36) furanyl, (37) thiophenyl wherein substituents 1-37 are optionally substituted with U and V, (38) 1,2,3-triazolyl, (39) 1,2,4-triazolyl having the saturated nitrogen substituted with R^{31-1}

where R^{31-1} is H, C_1-C_4 alkyl unsubstituted or substituted with one or more halogens, C_3-C_6 cycloalkyl, or $C(O)R^{31-2}$,

where R^{31-2} is -H, C_1-C_4 alkyl unsubstituted or substituted with one or more halogens, or phenyl unsubstituted or substituted with one or more halogens;

wherein 1,2,3-triazolyl and 1,2,4-triazolyl are unsubstituted or substituted with U;

each occurrence of V is independently selected from substituents selected from the group consisting of H, halogen, R^{3-1}, OR^{3-1};

where R^{3-1} is -H or C_1-C_4 alkyl or NO_2;

each occurrence of U is independently selected from the group consisting of (1) H, (2) C_1-C_8 alkyl unsubstituted or substituted with one or more substituents selected from the group consisting of halogens, -OH, =O other than at alpha position, $S(O)_nR^{3-2}$,

where R^{3-2} is C_1-C_4 alkyl or C_3-C_8 cycloalkyl and $NR^{3-3}R^{3-4}$,

where R^{3-3} and R^{3-4} are the same or different and are selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, $-(CH_2)_rCHOR^{3-5}$, and $(CH_2)_rNR^{3-6}R^{3-7}$, or where R^{3-3} and R^{3-4} taken together are selected from the group consisting of $(CH_2)O(CH_2)$, $(CH_2)_tCH(CO)R^{3-8}$, and $(CH_2)N(R^{3-8})(CH_2)_2$,

where R^{3-5} is H, or C_1-C_4 alkyl, or R^{3-6} and R^{3-7} are the same or different and are H, or C_1-C_4 alkyl or taken together are $(CH_2)_r$;

(3) C_2-C_5 alkenyl, (4) C_3-C_8 cycloalkyl, (5) OR^{3-3} where R^{3-3} is as defined above, (6) -CN, (7) S-$(O)_n$-R^{3-8}

where R^{3-8} is C_1-C_4 alkyl unsubstituted or substituted with one or more substituents selected from the group consisting of halogens, OH, CN, $NR^{3-3}R^{3-4}$ where R^{3-3} and R^{3-4} are as defined above, and CO_2R^{3-5} where R^{3-5} is as defined above, C_2-C_4 alkenyl, $NR^{3-9}R^{3-10}$,

where R^{3-9} is H, C_1-C_4 alkyl, or C_3-C_8 cycloalkyl and R^{3-10} is –H, C_1-C_4 alkyl, C_1-C_4 alkenyl, C_3-C_4 cycloalkyl, $-OR^{3-5}$, or $NR^{3-6}R^{3-7}$, where R^{3-5}, R^{3-6} and R^{3-7} are as defined above; N_3, $NHC(O)R^{3-11}$;

where R^{3-11} is C_1-C_4 alkyl optionally substituted with one or more halogens,

(8) $-S(O)_2-N=S(O)_iR^{3-14}R^{3-15}$,

where R^{3-14} and R^{3-15} are the same or different and are C_1-C_2 alkyl or taken together are $(CH_2)_q$-,

(9)-S-C(O)-R^{3-11} where R^{3-11} is as defined above; (10) tetrazoyl, (11) $NR^{3-3}R^{3-4}$ where R^{3-3} and R^{3-4} are as defined above, (12) $N(R^{3-3})COR^{3-11}$ where R^{3-3} and R^{3-11} are as defined above; (13) $-N(R^{3-3})-S-(O)_nR^{3-11}$ where R^{3-3} and R^{3-11} are as defined above, (14) $-CONR^{3-3}R^{3-4}$

where R^{3-3} and R^{3-4} are as defined above,

(15) $-C(O)R^{3-16}$

where R^{3-16} is –H, C_1-C_8 alkyl optionally substituted with $-OR^{3-5}$, $-OC(O)R^{3-5}$, $NR^{3-3}R^{3-4}$, $S(O)_nR^{3-17}$, C_3-C_8 cycloalkyl, or C_2-C_5 alkenyl optionally substituted with –CHO or $–CO_2R^{3-5}$, where R^{3-3}, R^{3-4} and R^{3-5} are as defined above and

where R^{3-17} is C_1-C_4 alkyl or C_3-C_8 cycloalkyl,

(16) $-C(=NR^{3-18})R^{3-16}$ where R^{3-16} is as defined above and

where R^{3-18} is $–NR^{3-3}R^{3-4}$, $-OR^{3-3}$ or $NHC(O)R^{3-3}$ where R^{3-3} and R^{3-4} are as defined above,

(17) $CR^{3-16}(OR^{3-19})OR^{3-20}$

where R^{3-16} is as defined above and R^{3-19} and R^{3-20} are the same or different and are C_1-C_4 alkyl or taken together are $–(CH_2)_j$-,

(18) $-C(NR^{3-3}R^{3-21})(R^{3-16})(R^{3-9})$, (19) $-C(OR^{3-5})(R^{3-16})(R^{3-4})$, (20) $-C(O-C(O)R^{3-5})(R^{3-16})(R^{3-4})$, (21) $-C(OR^{3-5})((CH_2)_t-NR^{3-3}(R^{3-4})(R^{3-4}))$, (22) $-C(NR^{3-3}R^{3-21})(R^{3-16})(R^{3-9})$,

where R^{3-3}, R^{3-4}, R^{3-9}, and R^{3-16} are as defined above and where R^{3-21} is R^{3-4} or $-NR^{3-4}R^{3-5}$ where R^{3-4} and R^{3-5} are as defined above;

with the proviso that at least one of the R^2, R^3 and R^4 is H,

X^1 is selected from the group consisting of NR^{15}, $CR^{16}R^{17}$, S, SO, SO_2 or O;

R^{15} is selected from the group consisting of (1) –H, (2) C_3-C_6 alkyl, (3) -$(CH_2)_p$-Aryl, (4) -$(CH_2)_p$-C(=O)-R^{15-1}, (5)-C(=O)-R^{15-1},(6) -C(=O)-$(CH_2)_p$-C(=O)R^{15-1}, (7) SO_2-R^{15-3}, (8) (C=O)-Het, (9) 2-pyridyl, (10) 2-pyrimidinyl, (11) 3-pyridazinyl or (12) 2-quinolyl;

where R^{15-1} is selected from the group consisting of -H, C_1-C_6 alkyl, Aryl, $(CH_2)_p$-Aryl, or –$(CH_2)_p$-OR^{15-2};

where R^{15-2} is selected from the group consisting of -H, C_1-C_6 alkyl, Aryl, $(CH_2)_p$-Aryl, or –C(=O)-C_1-C_6 alkyl;

where R^{15-3} is C_1-C_6 alkyl, or Aryl;

Aryl is phenyl, unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, -OH, $-NH_2$, SH, $-NO_2$ or –O-C(=O)-OCH_3;

Het is a 5-, 6-, 8-, 9-, or 10-membered heteroaromatic moiety having one or more atoms selected from the group consisting of N, O, and S;

R^{16} and R^{17} are each and independently selected from the group consisting of (1) –H, (2) C_1-C_6 alkyl, (3) C_1-C_6 alkoxy, (4) C_1-C_6 alkylthio, (5) -$(CH_2)_n$-OR^{16-1},(6) $NR^{16-2}R^{17-2}$, (7) -N=CH-$NR^{16-3}R^{17-3}$, (8) -C(=O)-$NR^{16-2}R^{17-2}$, (9) $(CH_2)_n$-C(=O)-R^{16-4}, and (10) $(CH_2)_n$-Q^1, -$(CH_2)_n$-W^1;

where R^{16-1} is –H, C_1-C_6 alkyl, -$(CH_2)_n$-OR^{16-5}, -$(CH_2)_n$-C(=O)-R^{16-4}, -C(=O)-$(CH_2)_n$-OR^{16-3}, or tosyl;

where R^{16-2} and R^{17-2} are each and independently selected from the group consisting of –H, C_1-C_6 alkyl, -$(CH_2)_n$-OR^{16-5}, -C(=O)-R^{16-4}, -C(=O)-$NR^{16-5}R^{17-5}$, -$(CH_2)_p$-Aryl, and –Het;

where R^{16-5} and R^{17-5} are each and independently selected from the group consisting of –H, C_1-C_6 alkyl or methoxymethyl;

where R^{16-3} and R^{17-3} are each and independently selected from the group consisting of –H, C_1-C_6 alkyl, -C(=O)-R^{16-4}, and $(CH_2)_p$-Aryl;

where R^{16-4} is selected from the group consisting of –H, -OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, -O-CH_2-O-C(=O)-R^{16-5} and –$(CH_2)_n$-C(=O)-OR^{16-5};

Q^1 is a saturated 5-membered heterocyclic moiety having 1-2 atoms selected from the group consisting of N, O, and S;

W^1 is a saturated 6-membered heterocyclic moiety having 1-2 atoms selected from the group consisting of N, O, and S;

or where R^{16} and R^{17} taken together are =O, =NR^{17-4}, =S, =$CR^{16-3}R^{17-3}$ or Q^1;

where R^{17-4} is selected from the group consisting of –OR^{16-1}, C_1-C_6 alkyl, C_1-C_6 alkoxy, and –$(CH_2)_p$-Aryl;

Y^1 is H or halogen;

Y_m: Y is CR^7 and m is 0, 1, or 2,

when m is 0, the Y moiety is not present, and therefore there is no central ring in formula I (i.e., the dotted line in formula I represents no bond);

when m is 1, Y forms a tricyclic-fused 5-membered ring with carbon 3 of the oxazolidinone ring, and R^7 is either one or two moieties,

when R^7 is two moieties comprising R^{7-1} and R^{7-2}, each is bound to the same carbon in the tricyclic-fused 5-membered ring, which in turn is bound to carbon 3 of the oxazolidinone ring (i.e., the dotted line in formula I is a single bond), and R^{7-1} and R^{7-2} are each independently H, C_1-C_3 alkyl, Cl, Br, OH, or I;

when R^7 is one moiety, either:

there is a double bond between the carbon atom to which R^7 is attached and carbon 3 of the oxazolidinone ring (i.e., the dotted line in formula I is a double bond), or

there is a single bond between the carbon atom to which R^7 is attached and carbon 3 of the oxazolidinone ring (i.e., the dotted line in formula I is a single bond), and R^7 is –C(=O)H;

and when m is 2, Y_m is CR^7CR^8, which forms a tricyclic-fused 6-membered ring with carbon 3 of the oxazolidinone ring, and R^7 and R^8 are each either one or two moieties,

when R^7 and R^8 are both one moiety, a double bond is formed between the carbon atoms that comprise Y to which they are attached, and R^7 and R^8 are both H,

when R^7 and R^8 are both two moieties, R^7 comprises R^{7-1} and R^{7-2}, where one of R^{7-1} and R^{7-2} is H and the other is H, OH, or $OC(=O)R^{7-3}$, where R^{7-3} is C_1-C_3 alkyl or phenyl, optionally substituted with 1 or 2 F, Cl, OH, or OCH_3, and R^8 comprises R^{8-1} and R^{8-2}, where one of R^{8-1} and R^{8-2} is H and the other is H, OH, or $OC(=O)R^{8-3}$, where R^{8-3} is C_1-C_3 alkyl or phenyl, optionally substituted with 1 or 2 F, Cl, OH, or OCH_3;

Z^1 is –O, -N, -S, $-SO_2$, SO, NR^{18}, $-SNR^{9-1}$, or $S(O)NR^{9-1}$,

where R^{18} is selected from the group consisting of –H, C_1-C_6 alkyl, $-C(=O)-R^{18-1}$, $-C(=O)-OR^{18-1}$ and $C(=O)-(CH_2)_p-C(=O)R^{18-1}$;

where R^{18-1} is H, C_1-C_6 alkyl, $-(CH_2)_p$-Aryl, or $-(CH_2)_p-OR^{18-2}$;

where R^{18-2} is –H, C_1-C_6 alkyl, or $(CH_2)_p$-Aryl;

where R^{9-1} is independently –H, C_1-C_4 alkyl (optionally substituted with –Cl, -F, -OH, C_1-C_4 alkoxy, NH_3, C_1-C_8 alkylamine or C_1-C_8 dialklylamine), –p-toluenesulfonyl, $C(R^9R^{10})$

where R^9 and R^{10} are each and independently -H, $-C_1$-C_8 alkyl, $-C_1$-C_8 alkoxy, $-C_1$-C_8 alkylthio, $-(CH_2)_m-OR^{51}$, $-O-(CH_2)_m-OR^{51}$, $NR^{42}R^{52}$, $-N=CH-NR^{44}R^{55}$, $-C(=O)-NR^{44}R^{55}$, $-C(=O)-NR^{42}R^{52}$ or $-(CH_2)_m-C(=A^1)-R^{41}$, or they may combine together to form =O, $=NR^{43}$, =S, $CR^{44}R^{54}$, or an optionally substituted, unsaturated or saturated 5- or 6-membered hetero ring having 1-3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom;

R^{41} is –H, $-(CH^2)_m$-OH, C_1-C_8 alkyl, C_1-C_8 alkoxy, $-O-CH_2-O-C(=O)-R^{11}$, or $-(CH_2)_m-C(=O)-OR^{11}$;

where R^{11} is –H, –H, C_1-C_8 alkyl, methoxymethyl,

R^{42} and R^{52} are each and independently –H, $-(CH_2)_m-OR^{11}$, C_1-C_8 alkyl, $-C(=O)-R^{41}$, $C(=O)-NR^{11}R^{12}$, $-(CH_2)_p$-phenyl, thiazol-2-yl, or they may combine together to form a pyrrolidino group, a piperidino group, a piperazino group, a morpholino group, or a thiomorphinolino group, each of may be substituted by C_1-C_4 alkyl or $-(CH_2)_m$-OH;

where R^{11} and R^{12} are each independently –H, C_1-C_8 alkyl, methoxymethyl,

R_{43} is –H, -OR^{51}, C_1-C_8 alkyl, C_1-C_8 alkoxy, -$(CH_2)_p$-phenyl, -$NR^{42}R^{52}$, -NH-C(=NH)-NH_2, [1,2,4]triazol-4-yl, or cyano;

R^{44} and R^{54} are each and independently –H, C_1-C_8-alkyl, -C(=O)-R^{41}, or –$(CH_2)_p$-phenyl;

R^{51} is –H, C_1-C_8 alkyl, C_1-C_8 alkyl substituted by one or more hydroxy, C_2-C_8 alkenyl, C_1-C_8 halogenoalkyl, -$(CH_2)_m$-OR^{11}, -$(CH_2)_m$-C(=O)-R_{41}, -C(=O)-$(CH_2)_m$-OR^{44} or tosyl;

R^9 optionally is $COOR^{9-2}$ where R^{9-2} is –C(O)-R^{9-3}, -PO_3 or –P(O)$(OH)_2$; where R^{9-3} is C_1-C_6 alkyl, -N$(R^{9-4})_2$, C_1-C_6 alkyl-N$(R^{9-4})_2$, -phenyl-N$(R^{9-4})_2$, -phenyl-NHC(O)CH_2NH_2, -C_2H_4-, morpholinyl, pyridinyl, C_1-C_6 alkyl-OH, C_1-C_6 alkyl-OCH_3, C_1-C_6 alkyl-C(O)CH_3, -O-C_1-C_6 alkyl-OCH_3, C_1-C_3 alkyl-piperazinyl (optionally substituted with C_1-C_3 alkyl), imidazolyl, C_1-C_6 alkyl-COOH, -$C(CH_2OH)_2CH_3$, where R^{9-4} is –H or C_1-C_6 alkyl; -$(CH_2)_p$-R^{9-5} where R^{9-5} is –H, -CH_3, CH_2CH_3, isopropyl, tert-butyl, phenyl, pyridyl, acetyl, difluoroacetyl, hydroxyacetyl, benzoyl, methoxy carbonyl, ethoxy carbonyl, 2,2,2-trifluoroethoxy carbonyl, cyanomethyl, 2-cyanoethyl, carbomethoxymethyl, 2-carbomethoxyethyl, 2-fluoroethoxy carbonyl, benzyloxy carbonyl, tertary-butoxy carbonyl, methyl sulfonyl, phenyl sulfonyl, or paratoluenesulfonyl;

R^9 optionally is a five membered heterocyclic ring (azoyl) of the general form C*H=N-D-B-A*- where the atoms or symbols representing an atom marked with an asterisk (*) are bonded to each other resulting in the formation of a ring, wherein A, B, and D are independently oxygen, nitrogen, sulfur or carbon, in all cases the piperazine nitrogen is attached to the carbon atom of the carbon-nitrogen double bond;

A^1 is oxygen atom or ethyleneketal;

i's are each and independently 0 or 1;

j's are each and independently 2 or 3;

k's are each and independently 1 or 2;

m's are each and independently 0, 1,or 2;

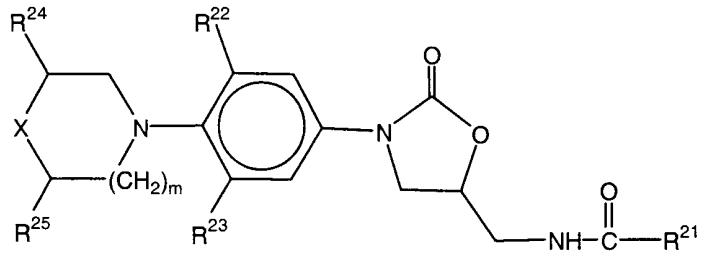
n's are each and independently 0, 1, or 2;

p's are each and independently 1, 2, 3 or 4;

q's are each and independently 3, 4, or 5;

t's are each and independently 1, 2, or 3.

In one aspect of the present invention, the oxazolidinone antibiotic is a compound of the formula III:



III

X is O, S, SO, SO_2SNR^{40} or $S(O)NR^{40}$

R^{21} is hydrogen, C_1-C_6 alkyl unsubstituted or substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy or $-O-CH_2$-phenyl; C_1-C_6 cycloalkyl, amino, C_1-C_8 alkyamino, C_1-C_8 dialkylamino or C_1-C_8 alkoxy;

R^{24} is H; CH_3, CN, CO_2H, CO_2R, or $(CH_2)_mR^{41}$ except when X is not O then R^{24} is H;

R^{22} and R^{23} are each and independently H, F, or Cl;

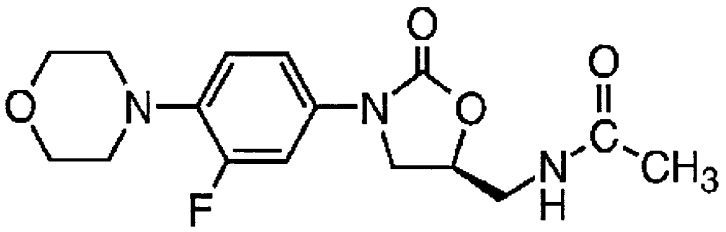
R^{25} is H except when X is O and R^{24} is CH_3 then R^{23} can be H or CH^3;

R^{40} is independently H, C_1-C_4 alkyl (unsubstituted or substituted with chloro, fluoro, hydroxy, C_1-C_8 alkoxy, amino, C_1-C_8 alkylamino, or C_1-C_8 dialkyamino) or p-toluenesulfonyl;

R^{41} is hydrogen, OH, OR^{21}, $OCOR^{21}$, NH_2, $NHCOR^{21}$ or $N(R^{40})_2$ and m is 0, 1 or 2.

The compounds of formula III are described in U.S Patents 5,688,792 and 5,880,118. These compounds are preferred, in part, because of their efficacy against multiply-resistant staphylococci and their low minimum inhibitory concentration values.

Oxazolidinone antibiotics and their synthesis are well known in the art. Examples of oxazolidinone antibiotics and specific synthesis schemes can be found in the following U.S. Patents: 5,929,248, 5,922,707, 5,880,118, 5,837,870, 5,801,246, 5,756,732, 5,736,545, 5,700,799, 5,652,238, 5,688,792, 5,668,286, 5,654,435, 5,654,428, 5,565,571, 5,547,950, 5,247,090, 5,231,188, 4,977,173, 4,948,801, 4,461,773, and 4,340,606, the entire contents of each patent being incorporated herein by reference. A particularly preferred oxazolidinone is a compound of formula IV:



IV

It has now been discovered that oxazolidinone antibiotics in general and the compounds of formulas III and IV in particular are amenable to topical administration on the eye. The oxazolidinone antibiotic can be supplied to the eye surface in a variety of ways, including as an aqueous ophthalmic solution or suspension, as an ophthalmic ointment, and as an ocular insert, but application is not limited thereto. Any technique and ocular dosage form that supplies an oxazolidinone antibiotic to the external eye surface is included within the notion of "topically applying." Although the external surface of the eye is typically the outer layer of the conjunctiva, it is possible that the sclera, cornea or other ocular tissue could be exposed such as by rotation of the eye or by surgical procedure and thus be an external surface.

The amount of oxazolidinone antibiotic topically supplied is effective to treat or prevent infection in a tissue of the eye. This means that the conditions of application result in a retarding or suppression of the infection. Typically at least about MIC_{50} for the targeted bacteria or parasite is delivered to the ocular tissue by the topical application of an effective amount. More concretely, the concentration within the ocular tissue is desired to be at least about 0.25 μg/g, preferably at least 1 μg/g, and more preferably about 10-50 μg/g. Generally, tissue concentrations that exceed about 50 μg/g, especially greater than 100 μg/g, are nearing or within a toxic response range. The amount of oxazolidinone antibiotic actually supplied to the external eye surface will almost always be much higher than the tissue concentration. This reflects the penetration hold up of the oxazolidinone antibiotic by the outer tissue layers of the eye, the loss of antibiotic due to natural clearing processes and that penetration is to some extent concentration driven. Thus, supplying greater amounts to the exterior will drive more antibiotic into the tissues.

The topical application of an oxazolidinone antibiotic can be used to treat or prevent a variety of conditions associated with ocular infection. For example, conditions of the lids including blepharitis, blepharconjunctivitis, meibomianitis, acute or chronic hordeolum, chalazion, dacryocystitis, dacryoadenities, and acne rosacea; conditions of the

conjunctiva including conjunctivitis, ophthalmia neonatorum, and trachoma; conditions of the cornea including corneal ulcers, superficial and interstitial keratitis, keratoconjunctivitis, foreign bodies, and post operative infections; and conditions of the anterior chamber and uvea including endophthalmitis, infectious uveitis, and post operative infections, are a few of the tissues and conditions that can be treated by topical application of an oxazolidinone antibiotic. The prevention of infection includes pre-operative treatment prior to surgery as well as other suspected infectious conditions or contact. Examples of prophylaxis situations include treatment prior to surgical procedures such as blepharoplasty, removal of chalazia, tarsorrhapy, procedures for the canualiculi and lacrimal drainage system and other operative procedures involving the lids and lacrimal apparatus; conjunctival surgery including removal of ptyregia, pingueculae and tumors, conjunctival transplantation, traumatic lesions such as cuts, burns and abrasions, and conjunctival flaps; corneal surgery including removal of foreign bodies, keratotomy, and corneal transplants; refractive surgery including photorefractive procedures; glaucoma surgery including filtering blebs; paracentesis of the anterior chamber; iridectomy; cataract surgery; retinal surgery; and procedures involving the extra-ocular muscles. The prevention of ophthalmia neonatorum is also included.

More generally, the oxazolidinone antibiotics can be used to treat or prevent ocular infections caused by a variety of bacteria or parasites, including but not limited to one or more of the following organisms: *Staphylococcus* including *Staphylococcus aureus* and *Staphylococcus epidermidis*; *Streptococcus* including *Streptococcus pneumoniae* and *Streptococcus pyogenes* as well as *Streptococci* of Groups C, F, and G and Viridans group of *Streptococci*; *Haemophilus influenza* including biotype III (*H. Aegyptius*); *Haemophilus ducreyi*; *Moraxella catarrhalis*; *Neisseria* including *Neisseria gonorrhoeae* and *Neisseria meningitidis*; *Chlamydia* including *Chlamydia trachomatis*, *Chlamydia psittaci*, and *Chlamydia pneumoniae*; *Mycobacterium* including *Mycobacterium tuberculosis* and *Mycobacterium* avium-intracellular complex as well as atypical mycobacterium including *M. marinum*, *M. fortuitm*, and *M. chelonae*; *Bordetella pertussis*; *Campylobacter jejuni*; *Legionella pneumophila*; *Bacteroides bivius*; *Clostridium perfringens*; *Peptostreptococcus* species; *Borrelia burgdorferi*; *Mycoplasma pneumoniae*; *Treponema pallidum*; *Ureaplasma urealyticum*; toxoplasma; malaria; and nosema.

The oxazolidinone antibiotic is applied to the exterior surface of the eye, usually in an ophthalmically acceptable composition which comprises an ophthalmically acceptable

carrier and the oxazolidinone antibiotic. The "ophthalmically acceptable carrier" is used in a broad sense and includes any material or composition that can contain and release the oxazolidinone antibiotic and that is compatible with the eye. Typically the ophthalmically acceptable carrier is water or an aqueous solution or suspension, but also includes oils such as those used to make ointments and polymer matrices such as used in ocular inserts. Generally, oxazolidinone antibiotics are soluble in water. Accordingly, an aqueous solution of an oxazolidinone antibiotic can be formed and used for topical application. A polymeric suspending agent may also be used to provide sustained release of the antibiotic. The polymeric suspending agent may be insoluble, thereby forming a polymeric suspension, or soluble, in which case no polymeric suspension is formed. Oxazolidinone can be present in suspension or solution, or both. One embodiment of the present invention is an aqueous composition comprising a soluble polymeric suspending agent in solution, with oxazolidinone in solution or suspension, or both. Ointments and solid dosage forms can also be used as delivery compositions as are well known in the art.

The concentration of oxazolidinone antibiotic present in the ophthalmic composition depends upon the dosage form, the release rate, the dosing regimen, and the location and type of infection. Generally speaking, the concentration is from about 0.01 to 5%, more typically 0.1 to 2%, for fluid compositions and 0.5 to 50% for solid dosage forms, however, the compositions are not limited thereto.

The fluid ophthalmic compositions of the present invention, including aqueous solutions, ointments and suspensions, have a viscosity that is suited for the selected route of administration. A viscosity in the range of from about 1,000 to 30,000 centipoise is useful for a drop. About 30,000 to about 100,000 centipoise is an advantageous viscosity range for ophthalmic administration in ribbon form. The viscosity can be controlled in many ways known to the worker skilled in the art.

The ophthalmic compositions may contain one or more of the following: surfactants, adjuvants including additional medicaments, buffers, antioxidants, tonicity adjusters, preservatives, thickeners or viscosity modifiers, and the like. Additives in the formulations may desirably include sodium chloride, EDTA (disodium edetate), and/or BAK (benzalkonium chloride), sorbic acid, methyl paraben, propyl paraben, chlorhexidine, glycerin, and sodium perborate. In a preferred embodiment, solutions can include sodium chloride, EDTA (disodium edetate), and/or BAK (benzalkonium chloride),

sorbic acid, chlorhexidine, glycerin, and sodium perborate. In another preferred embodiment, ointments can include methyl paraben, propyl paraben, and chlorbutanol.

A further aspect of the present invention involves the above-mentioned use of additional medicaments in combination with the oxazolidinone antibiotic. A composition comprising an oxazolidinone antibiotic, an additional medicament, and an ophthalmically acceptable carrier can advantageously simplify administration and allow for treating or preventing multiple conditions or symptoms simultaneously. The "additional medicaments," which can be present in any of the ophthalmic compositional forms described herein including fluid and solid forms, are pharmaceutically active compounds having efficacy in ocular application and which are compatible with an oxazolidinone antibiotic and with the eye. Typically, the additional medicaments include other antibiotics, antivirals, antifungals, anesthetics, anti-inflammatory agents including steroidal and non-steroidal anti-inflammatories, and anti-allergic agents. Examples of suitable medicaments include aminoglycosides such as amikacin, gentamycin, tobramycin, streptomycin, netilmycin, and kanamycin; macrolides like azithromycin and erythromycin; fluoroquinolones such as ciprofloxacin, norfloxacin, ofloxacin, trovafloxacin, lomefloxacin, levofloxacin, and enoxacin; sulfonamides; polymyxin; chloramphenicol; neomycin; paramomomycin; colistimethate; bacitracin; vancomycin; tetracyclines; rifampin and its derivatives ("rifampins"); cycloserine; beta-lactams; cephalosporins; amphotericins; fluconazole; flucytosine; natamycin; miconazole; ketoconazole; corticosteroids; diclofenac; flurbiprofen; ketorolac; suprofen; comolyn; lodoxamide; levocabastin; naphazoline; antazoline; and pheniramimane. These other medicaments are generally present in a pharmaceutically effective amount as is understood by workers of ordinary skill in the art. These amounts are generally within the range of from about 0.01 to 5%, more typically 0.1 to 2%, for fluid compositions and from 0.5 to 50% for solid dosage forms.

The aqueous ophthalmic compositions (solutions or suspensions) for use in the present invention use water which has no physiologically or ophthalmically harmful constituents. Typically purified or deionized water is used. The pH is adjusted by adding any physiologically and ophthalmically acceptable pH adjusting acids, bases or buffers to within the range of about 5.0 to 8.5. Examples of acids include acetic, boric, citric, lactic, phosphoric, hydrochloric, and the like, and examples of bases include sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate,

tromethamine, THAM (trishydroxymethylamino-methane), and the like. Salts and buffers include citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of the aforementioned acids and bases.

The osmotic pressure (π) of the aqueous ophthalmic composition is generally from about 10 milliosmolar (mOsM) to about 400 mOsM, more preferably from 260 to 340 mOsM. If necessary, the osmotic pressure can be adjusted by using appropriate amounts of physiologically and ophthalmically acceptable salts or excipients. Sodium chloride is preferred to approximate physiologic fluid, and amounts of sodium chloride ranging from about 0.01% to about 1% by weight, and preferably from about 0.05% to about 0.45% by weight, based on the total weight of the composition, are typically used. Equivalent amounts of one or more salts made up of cations such as potassium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfate, sodium bisulfate, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the above-stated range. Similarly, a sugar such as mannitol, dextrose, sorbitol, glucose and the like can also be used to adjust osmolality.

A preferred form of the present invention provides achieving a sufficiently high tissue concentration with a minimum of doses so that a simple dosing regimen can be used to treat or prevent bacterial or parasitic infections. To this end, a preferred technique involves forming or supplying a depot of oxazolidinone antibiotic in contact with the external surface of the eye. A depot refers to a source of oxazolidinone antibiotic that is not rapidly removed by tears or other eye clearance mechanisms. This allows for continued, sustained high concentrations of oxazolidinone antibiotic to be present in the fluid on the external surface of the eye by a single application. In general, it is believed that absorption and penetration are dependent on both the dissolved drug concentration and the contact duration of the external tissue with the drug-containing fluid. As the drug is removed by clearance of the ocular fluid and/or absorption into the eye tissue, more drug is provided, e.g. dissolved, into the replenished ocular fluid from the depot.

A depot can take a variety of forms so long as the oxazolidinone antibiotic can be provided in sufficient concentration levels therein and is releasable therefrom and that the depot is not readily removed from the eye. A depot generally remains for at least about 30 minutes after administration, preferably at least 2 hours and more preferably at least 4 hours. The term "remains" means that neither the depot composition nor the

oxazolidinone antibiotic is exhausted or cleared from the surface of the eye prior to the indicated time. In some embodiments, the depot can remain for up to eight hours or more. Typical ophthalmic depot forms include aqueous polymeric suspensions, ointments, and solid inserts.

Ointments are well known ophthalmic compositions and are essentially an oil-based delivery vehicle. Typical ointments use a petroleum and/or lanolin base to which is added the active ingredient, usually as 0.1 to 2%, and excipients. Common bases include mineral oil, petrolatum and combinations thereof, but oil bases are not limited thereto. An ointment is usually applied as a ribbon onto the lower eye lid. The disadvantage of ointments is that they are difficult to administer, are messy, and uncomfortable/inconvenient to the patient; i.e. temporarily blurred vision is common.

Inserts are another well known ophthalmic dosage form and are comprised of a matrix containing the active ingredient. The matrix is typically a polymer and the active ingredient is generally dispersed therein or bonded to the polymer matrix. The active ingredient is slowly released from the matrix through dissolution or hydrolysis of the covalent bond, etc. In some embodiments, the polymer is bioerodible (soluble) and the dissolution rate thereof can control the release rate of the active ingredient dispersed therein. In another form, the polymer matrix is a biodegradable polymer that breaks down such as by hydrolysis to thereby release the active ingredient bonded thereto or dispersed therein. The matrix and active ingredient can be surrounded with a polymeric coating such as in the sandwich structure of matrix/matrix+active/matrix, to further control release as is well known in the art. The kinds of polymers suitable for use as a matrix are well known in the art. The oxazolidinone antibiotic can be dispersed into the matrix material or dispersed amongst the monomer composition used to make the matrix material prior to polymerization. The amount of oxazolidinone antibiotic is generally from about 0.1 to 50%, more typically about 2 to 20%. The insert can be placed, depending on the location and the mechanism used to hold the insert in position, by either the patient or the doctor and is generally located under the upper eye lid. A variety of shapes and anchoring configurations, if any, are well known in the art. Preferably a biodegradable or bioerodible polymer matrix is used so that the spent insert does not have to be removed. As the biodegradable or bioerodible polymer is degraded, dissolved, or eroded, the trapped oxazolidinone antibiotic is released. Although inserts can provide long term release and

hence only a single application of the insert may be necessary, they are generally difficult to insert and are uncomfortable to the patient.

The preferred form is an aqueous polymeric suspension. Here, at least one of the oxazolidinone antibiotic or the polymeric suspending agent is suspended in an aqueous medium having the properties as described above. Typically the oxazolidinone antibiotic is in solution, although it is possible for the oxazolidinone antibiotic to be in suspension or both in solution and in suspension in significant amounts generally no less than 5% in either phase (weak to moderate water solubility and relatively high total concentrations). The polymeric suspending agent is preferably a suspension (i.e. water insoluble and/or water swellable), although water soluble suspending agents are also suitable for use with a suspension of the oxazolidinone antibiotic. The suspending agent serves to provide stability to the composition and to increase the residence time of the dosage form on the eye. It can also enhance the sustained release of the drug in terms of both longer release times and a more uniform release curve.

Examples of polymeric suspending agents include dextrans, polyethylene glycols, polyvinylpyrrolidone, polysaccharide gels, Gelrite®, cellulosic polymers like hydroxypropyl methylcellulose, and carboxy-containing polymers such as polymers or copolymers of acrylic acid, as well as other polymeric demulcents. A preferred polymeric suspending agent is a water swellable, water insoluble polymer, especially a crosslinked carboxy-containing polymer.

Crosslinked carboxy-containing polymers used in practicing this invention are, in general, well known in the art. In a preferred embodiment such polymers may be prepared from at least about 90% and preferably from about 95% to about 99.9% by weight, based on the total weight of monomers present, of one or more carboxy-containing monoethylenically unsaturated monomers (also occasionally referred to herein as carboxy-vinyl polymers). Acrylic acid is the preferred carboxy-containing monoethylenically unsaturated monomer, but other unsaturated, polymerizable carboxy-containing monomers, such as methacrylic acid, ethacrylic acid, β-methylacrylic acid (crotonic acid), cis-α-methylcrotonic acid (angelic acid), trans-α-methylcrotonic acid (tiglic acid), α-butylcrotonic acid, α-phenylacrylic acid, α-benzylacrylic acid, α-cyclohexylacrylic acid, β-phenylacrylic acid (cinnamic acid), coumaric acid (o-hydroxycinnamic acid), umbellic acid (p-hydroxycoumaric acid), and the like can be used in addition to or instead of acrylic acid.

Such polymers may be crosslinked by a polyfunctional crosslinking agent, preferably a difunctional crosslinking agent. The amount of crosslinking should be sufficient to form insoluble polymer particles, but not so great as to unduly interfere with sustained release of the oxazolidinone antibiotic. Typically the polymers are only lightly crosslinked. Preferably the crosslinking agent is contained in an amount of from about 0.01% to about 5%, preferably from about 0.1% to about 5.0%, and more preferably from about 0.2% to about 1%, based on the total weight of monomers present. Included among such crosslinking agents are non-polyalkenyl polyether difunctional crosslinking monomers such as divinyl glycol; 2,3-dihydroxyhexa-1,5-diene; 2,5-dimethyl-1,5-hexadiene; divinylbenzene; N,N-diallylacrylamide; N,N-diallymethacrylamide and the like. Also included are polyalkenyl polyether crosslinking agents containing two or more alkenyl ether groupings per molecule, preferably alkenyl ether groupings containing terminal $H_2C=C<$ groups, prepared by etherifying a polyhydric alcohol containing at least four carbon atoms and at least three hydroxyl groups with an alkenyl halide such as allyl bromide or the like, e.g., polyallyl sucrose, polyallyl pentaerythritol, or the like; see, e.g., Brown U.S. Pat. No. 2,798,053, the entire contents of which are incorporated herein by reference. Diolefinic non-hydrophilic macromeric crosslinking agents having molecular weights of from about 400 to about 8,000, such as insoluble di- and polyacrylates and methacrylates of diols and polyols, diisocyanate-hydroxyalkyl acrylate or methacrylate reaction products of isocyanate terminated prepolymers derived from polyester diols, polyether diols or polysiloxane diols with hydroxyalkylmethacrylates, and the like, can also be used as the crosslinking agents; see, e.g., Mueller et al. U.S. Pat. Nos. 4,192,827 and 4,136,250, the entire contents of each Patent being incorporated herein by reference.

The crosslinked carboxy-vinyl polymers may be made from a carboxy-vinyl monomer or monomers as the sole monoethylenically unsaturated monomer present, together with a crosslinking agent or agents. Preferably the polymers are ones in which up to about 40%, and preferably from about 0% to about 20% by weight, of the carboxy-containing monoethylenically unsaturated monomer or monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomer or monomers containing only physiologically and ophthalmically innocuous substituents, including acrylic and methacrylic acid esters such as methyl methacrylate, ethyl acrylate, butyl acrylate, 2-ethylhexylacrylate, octyl methacrylate, 2-hydroxyethyl-methacrylate, 3-hydroxypropylacrylate, and the like, vinyl acetate, N-vinylpyrrolidone, and the like; see

Mueller et al. U.S. Pat No. 4,548,990, the entire contents of which are incorporated herein by reference, for a more extensive listing of such additional monoethylenically unsaturated monomers.

Particularly preferred polymers are lightly crosslinked acrylic acid polymers wherein the crosslinking monomer is 2,3-dihydroxyhexa-1,5-diene or 2,3-dimethylhexa-1,5-diene. Preferred commercially available polymers include polycarbophil (Noveon AA-1) and Carbopol®. Most preferably, a carboxy-containing polymer system known by the tradename DuraSite®, containing polycarbophil, which is a sustained release topical ophthalmic delivery system that releases the drug at a controlled rate, is used in the aqueous polymeric suspension composition of the present invention.

The crosslinked carboxy-vinyl polymers used in practicing this invention are preferably prepared by suspension or emulsion polymerizing the monomers, using conventional free radical polymerization catalysts, to a dry particle size of not more than about 50 μm in equivalent spherical diameter; e.g., to provide dry polymer particles ranging in size from about 1 to about 30 μm, and preferably from about 3 to about 20 μm, in equivalent spherical diameter. Using polymer particles that were obtained by mechanically milling larger polymer particles to this size is preferably avoided. In general, such polymers will have a molecular weight which has been variously reported as being from about 250,000 to about 4,000,000, and from 3,000,000,000 to 4,000,000,000.

In the most preferred embodiment of the invention, the particles of crosslinked carboxy-vinyl polymer are monodisperse, meaning that they have a particle size distribution such that at least 80% of the particles fall within a 10 μm band of major particle size distribution. More preferably, at least 90% and most preferably at least 95%, of the particles fall within a 10 μm band of major particle size distribution. Also, a monodisperse particle size means that there is no more than 20%, preferably no more than 10%, and most preferably no more than 5% particles of a size below 1 μm. The use of a monodispersion of particles will give maximum viscosity and an increased eye residence time of the ophthalmic medicament delivery system for a given particle size. Monodisperse particles having a particle size of 30 μm and below are most preferred. Good particle packing is aided by a narrow particle size distribution.

The aqueous polymeric suspension normally contains 0.05 to 1.0%, preferably 0.1 to 0.5%, more preferably 0.1 to 0.25%, of the oxazolidinone antibiotic and 0.1 to 10%, preferably 0.5 to 6.5% of a polymeric suspending agent. In a further preferred

embodiment, which may comprise one or more solubility enhancers, the aqueous polymeric suspension normally contains 0.05 to 5.0%, preferably 0.1 to 2.0%, more preferably 0.2 to 1.50%, of the oxazolidinone antibiotic and 0.1 to 10%, preferably 0.5 to 6.5% of a polymeric suspending agent. In the case of the above described water insoluble, water-swellable crosslinked carboxy-vinyl polymer, a more preferred amount of the polymeric suspending agent is an amount ranging from 0.5 to 2.0%, preferably from 0.5% to about 1.2%, and in certain embodiments from 0.6 to 0.9%, based on the weight of the composition. Although referred to in the singular, it should be understood that one or more species of polymeric suspending agent such as the crosslinked carboxy-containing polymer can be used with the total amount falling within the stated ranges. In one preferred embodiment, the composition contains 0.5 to 1.0%, more preferably 0.6 to 0.8 % of a polycarbophil such as NOVEON AA-1. In another preferred embodiment, the oxazolidinone antibiotic is the compound of formula IV, and the suspension comprises from 0.1 to 5.0% of the compound of formula IV, more preferably 0.2 to 4% of the compound of formula IV, even more preferably 0.3 to 3.5% of the compound of formula IV, and most preferably from 1.0 to 2.0% of the compound of formula IV.

Solubility enhancers may be added to the aqueous compositions above in order to improve the solubility of the oxazolidinone antibiotic. Preferred solubility enhancers include polyethylene glycol, ethoxylated castor oil (trade name, Cremphor), and cyclodextrins such as hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α-, β-, and γ-cyclodextrin. A particularly preferred solubility enhancer is hydroxypropyl- β cyclodextrin (HPBC), which may be added to further improve the solubility characteristics of any of the aqueous compositions described above. In one embodiment, the composition comprises 0.1% to 20% hydroxypropyl-β-cyclodextrin, more preferably 1% to 15% hydroxypropyl-β-cyclodextrin, and even more preferably from 2.5% to 10% hydroxypropyl-β-cyclodextrin. The amount of solubility enhancer used will depend on the amount of oxazolidinone in the composition, with more solubility enhancer used for greater amounts of oxazolidinone.

In one embodiment, the amount of insoluble lightly crosslinked carboxy-vinyl polymer particles, the pH, and the osmotic pressure can be correlated with each other and with the degree of crosslinking to give a composition having a viscosity in the range of from about 500 to about 100,000 centipoise, and preferably from about 1,000 to about 30,000 or about 1,000 to about 10,000 centipoise, as measured at room temperature (about

25° C) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm. Alternatively, when the viscosity is within the range of 500 to 3000 centipoise, it may be determined by a Brookfield Model DV-11+, choosing a number cp-52 spindle at 6 rpm.

When water soluble polymers are used as the suspending agent, such as hydroxypropyl methylcellulose, the viscosity will typically be about 10 to about 400 centipoise, more typically about 10 to about 200 centipoises or about 10 to about 25 centipoise.

Aqueous polymeric suspensions of the present invention may be formulated so that they retain the same or substantially the same viscosity in the eye that they had prior to administration to the eye. Alternatively, they may be formulated so that there is increased gelation upon contact with tear fluid. For instance, when a formulation containing DuraSite® or other similar polyacrylic acid-type polymer is administered to the eye at a pH of less than about 6.7, the polymer will swell upon contact with tear fluid since it has a higher pH (around 7). This gelation or increase in gelation leads to entrapment of the oxazolidinone antibiotic, thereby increasing the difficulty for the antibiotic to diffuse out of the composition. All these events eventually lead to increased patient comfort and increased oxazolidinone antibiotic contact time with the eye tissues, thereby increasing the extent of drug absorption and duration of action of the formulation in the eye.

The viscous gels that result from fluid eye drops typically have residence times in the eye ranging from about 2 to about 12 hours, e.g., from about 3 to about 6 hours. The agents contained in these drug delivery systems will be released from the gels at rates that depend on such factors as the drug itself and its physical form, the extent of drug loading and the pH of the system, as well as on any drug delivery adjuvants, such as ion exchange resins compatible with the ocular surface, which may also be present.

The compositions used to topically deliver the oxazolidinone antibiotic of the present invention can be prepared from known or readily available materials through the application of known techniques by workers of ordinary skill in the art without undue experimentation. The oxazolidinone antibiotic can be combined with the other ingredients in the chosen dosage form by conventional methods known in the art.

The oxazolidinone antibiotic-containing composition is topically applied to an eye of a human or non-human animal, the latter including cows, sheep, horses, pigs, goats, rabbits, dogs, cats, and other mammals. The composition can be applied as a liquid drop,

ointment, a viscous solution or gel, a ribbon or as a solid. The composition can be topically applied, without limitation, to the front of the eye, under the upper eye lid, on the lower eye lid and in the cul-de-sac. The application can be as a treatment of an infection in the eye or as a preventive such as prior to surgery.

All of the percentages recited herein refer to weight percent, unless otherwise indicated. The following non-limiting examples serve to illustrate certain features of the present invention.

EXAMPLES 1, 3, 6, 8, and 9

Hydroxypropylmethyl cellulose, sodium chloride, edetate sodium (EDTA), and surfactant are dissolved in a beaker containing approximately 1/3 of the final weight of water and stirred for 10 minutes with an overhead stirred. The drug is added and stirred to disperse for 30 minutes. The solution is sterilized by autoclaving at 121°C. for 20 minutes. Alternately, the drug may be dry heat sterilized and added by aseptic powder addition or sterile filtration if water soluble. Mannitol, Poloxamer 407, BAK, and boric acid are dissolved separately in approximately ½ of the final weight of water and added by sterile filtration (0.22 um filter) and stirred for 10 minutes to form a mixture. The mixture is adjusted to desired pH with 10N sodium hydroxide while stirring, brought to a final weight with water by sterile filtration and aseptically filled into multi-dose containers.

EXAMPLES 2, 4, 5, 7, and 10

Noveon AA-1 is slowly dispersed into a beaker containing approximately 1/3 of the final weight of water and stirred for 1.5 hrs. with an overhead stirrer. Noveon AA-1 is an acrylic acid polymer available from B.F. Goodrich. Edetate sodium (EDTA), sodium chloride, and surfactant are then added to the polymer solution and stirred for 10 minutes after each addition. The polymer suspension is at a pH of about 3.0-3.5. The drug is added and stirred to disperse for 30 minutes. The mixture is sterilized by autoclaving at 121°C., for 20 minutes. Alternately, the drug may be dry heat sterilized and added by aseptic powder addition or by sterile filtration if the drug is water soluble. BAK, mannitol, and boric acid are dissolved separately in approximately ½ of the final weight of water, added to the polymer mixture by sterile filtration (0.22 um filter) and stirred for 10 minutes. The mixture is adjusted to the desired pH with 10N sodium hydroxide while stirring, brought to final weight with water and by sterile filtration and aseptically filled into multi-dose containers.

Component	1	2	3	4	5	6	7	8	9	10
Drug 1	0.1	0.5								
Drug 2			0.1	.05						
Drug 3					.5					
Drug 4						0.1				
Drug 5							0.5			
Drug 6								0.1		
Drug 7									0.1	0.5
NaCl	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Mannitol	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Boric Acid				0.75	0.75	0.75	0.75	0.75	0.75	0.75
EDTA	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
HPMC	2.0		2.0			2.0		2.0	2.0	
Noveon AA-1		0.8		0.8	0.8		0.8			0.8
BAK	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
NaOH	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Drug 1: N-((3-(-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (shown in formula IV).

Drug 2: (S)-N-((3-(3-fluoro-4-4-(1-oxothiomorpholin-4-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide.

Drug 3: (S)-N-((3-(3-fluoro-4-(3thiazolidinyl)phenyl)-2- oxo-5-oxazolidinyl)methyl)acetamide.

Drug 4: 3-(4-morpholinylpropionic acid, 2-(4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinyl)-2-oxoethyl ester.

Drug 5: 8-[5-(S)-[(Acetylamino)methyl]-3-oxo-3-oxazolidinyl]-1,2,4a, 5-tetrahydropyrazino[2, 1-c][1,4]benzoxazine-3(4-H)-carboxylic acid phenylmethyl ester.

Drug 6: (S)-1-(4-(5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl)-piperidine-4-carboxylic acid ethyl ester.

Drug 7:(S)-N-[(3-[3-Fluoro-4-[4-(2-oxazolyl)-1-piperaziayl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide(l-A).

EXAMPLES 11-32

Examples 11 through 32 are aqueous polymeric suspensions comprising the oxazolidinone compound of formula IV. Examples 11 through 32 are prepared in the following manner: Polycarbophil (Noveon AA-1) is slowly dispersed into a beaker containing approximately 1/3 of the final weight of water and stirred for 1.5 hrs with an overhead stirrer. EDTA, sodium chloride, and surfactant are then added to the polymer solution and stirred for 10 minutes after each addition. The polymer suspension is at a pH of about 3.0-3.5. The compound of formula IV is added and stirred to disperse for 30 minutes. The mixture is sterilized by autoclaving at 121°C., for 20 minutes. Alternately, the drug may be dry heat sterilized and added by aseptic powder addition or by sterile filtration if the drug is water soluble. The remaining components are dissolved separately in approximately ½ of the final weight of water, added to the polymer mixture by sterile filtration (0.22 um filter) and stirred for 10 minutes. The mixture is adjusted to the desired pH with 10N sodium hydroxide while stirring, brought to final weight with water and by sterile filtration and aseptically filled into multi-dose containers. The pH of each formulation is about 6, and the viscosity and osmolality is about 1500 cps and about 280 mOsm/kg, respectively.

The following table shows the compositions of examples of aqueous polymeric suspensions comprising the oxazolidinone compound of formula IV as well as controls lacking the compound of formula IV.

Example	12	13	14	15	16	17	18	19	20	21	22
Polycarbophil	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
EDTA	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sodium Chloride	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
BAK	0.01	0.01	-	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Chlorohexidine Gluconate	-	-	0.018	-	-	-	-	-	-	-	-
Glycerin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sorbitol	1.5	-	-	-	-	-	-	-	-	-	-
Mannitol	-	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
HPBC	-	2.5	-	-	-	-	-	-	2.5	2.5	2.5
Poloxamer-407	0.1	-	0.1	-	-	-	-	-	-	-	-
The compound of formula IV	0.25	0.50	0.25	0.20	0.20	0.30	0.10	-	0.50	0.25	-

Example	23	24	25	26	27	28	29	30	31	32	33
Polycarbophil	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
EDTA	0.1	0.1	0.1	0.1	0.025	0.1	0.1	0.025	0.1	0.1	0.1
Sodium Chloride	0.1	0.1	0.1	0.3	0.3	0.3	0.1	0.3	0.3	0.3	0.1
BAK	0.02	0.02	0.02	0.02	-	0.02	0.02	-	0.02	0.02	0.02
Chlorohexidine Gluconate	-	-	-	-	-	-	-	-	-	-	-
Glycerin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sorbitol	-	-	-	-	-	-	-	-	-	-	-
Mannitol	1.0	1.0	1.0	1.5	1.0	1.5	1.0	1.0	1.5	1.5	1.0
HPBC	5.0	5.0	5.0	2.5	5.0	-	5.0	5.0	-	2.5	5.0
Poloxamer-407	-	-	-	-	-	-	-	-	-	-	-
The compound of formula IV	1.0	0.5	-	0.50	0.50	0.2	1.0	-	-	-	-

The above discussion of this invention is directed primarily to preferred embodiments and practices thereof. It will be readily apparent to those skilled in the art that further changes and modifications in actual implementation of the concepts described herein can easily be made or may be learned by practice of the invention, without departing from the spirit and scope of the invention as defined by the following claims. What is claimed is:

CLAIMS

1. An aqueous polymeric suspension comprising water, 0.05% to 5.0% of an oxazolidinone antibiotic, and 0.1 to 10% of a polymeric suspending agent, wherein said polymeric suspending agent comprises a water-swellable water-insoluble crosslinked carboxy-vinyl polymer.

2. The suspension of claim 1, wherein said suspension comprises 0.1% to 2.0% of said oxazolidinone antibiotic and 0.5% to 6.5% of said polymeric suspending agent.

3. The suspension of claim 1, wherein said polymeric suspending agent further comprises at least 90% acrylic acid monomers and 0.1% to 5% crosslinking agent.

4. The suspension of claim 3, wherein said crosslinking agent comprises a difunctional crosslinking agent.

5. The suspension of claim 4, wherein said crosslinking agent is selected from the group consisting of divinyl glycol, 2,3-dihydroxyhexa-1,5-diene, 2,5-dimethyl-1,5-hexadiene, divinylbenzene, N,N-diallylacrylamide, N,N-diallylmethacrylamide, and mixtures thereof.

6. The suspension of claim 4, wherein said crosslinking agent is selected from the group consisting of 2,3-dihydroxyhexa-1,5-diene and 2,3-dimethylhexa-1,5-diene.

7. The suspension of claim 1, wherein said polymeric suspending agent further comprises a polycarbophil.

8. The suspension of claim 7, wherein said suspension comprises 0.5% to 1.0% of said polycarbophil.

9. The suspension of claim 1, further comprising an additional medicament.

10. The suspension of claim 9, wherein said additional medicament is selected from the group consisting of antibiotics, antivirals, antifungals, anesthetics, anti-inflammatory agents, and anti-allergic agents.

11. The suspension of claim 10, wherein said additional medicament is about 0.01% to about 5.0% of said suspension.

12. The suspension of claim 1, wherein said polymeric suspending agent has a monodisperse particle size distribution.

13. An aqueous polymeric suspension comprising water, 0.05% to 5.0% of an oxazolidinone antibiotic, and 0.1 to 10% of a polymeric suspending agent, wherein said polymeric suspending agent comprises a polycarbophil.

14. The suspension of claim 13, wherein said suspension comprises 0.1% to 2.0% of said oxazolidinone antibiotic and 0.5% to 6.5% of said polycarbophil.

15. The suspension of claim 14, wherein said suspension comprises 0.6% to 0.8% of said polycarbophil.

16. The suspension of claim 13, wherein said polymeric suspending agent has a monodisperse particle size distribution.

17. The suspension of claim 13, further comprising an additional medicament.

18. The suspension of claim 17, wherein said additional medicament is selected from the group consisting of antibiotics, antivirals, antifungals, anesthetics, anti-inflammatory agents, and anti-allergic agents.

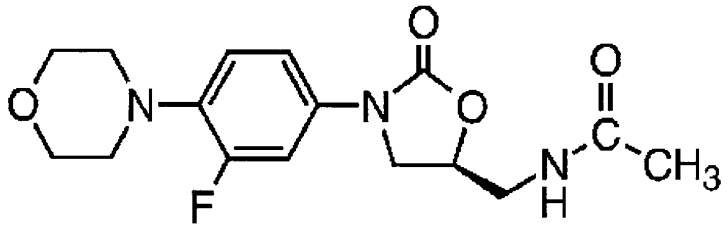
19. The suspension of claim 18, wherein said additional medicament is about 0.01% to about 5.0% of said suspension.

20. The suspension of claim 13, further comprising 0.1% to 5% difunctional crosslinking agent.

21. The suspension of claim 20, wherein said crosslinking agent is selected from the group consisting of divinyl glycol, 2,3-dihydroxyhexa-1,5-diene, 2,5-dimethyl-1,5-hexadiene, divinylbenzene, N,N-diallylacrylamide, N,N-diallylmethacrylamide, and mixtures thereof.

22. The suspension of claim 20, wherein said crosslinking agent is selected from the group consisting of 2,3-dihydroxyhexa-1,5-diene and 2,3-dimethylhexa-1,5-diene.

23. A composition comprising water, a polymeric suspending agent, and a compound of formula IV:



IV.

24. The composition of claim 23, wherein said composition comprises 0.1 to 5.0% of said compound of formula IV.

25. The composition of claim 23, wherein said composition comprises 0.2 to 4.0% of said compound of formula IV.

26. The composition of claim 23, further comprising a difunctional crosslinking agent.

27. The composition of claim 26, wherein said crosslinking agent is selected from the group consisting of divinyl glycol, 2,3-dihydroxyhexa-1,5-diene, 2,5-dimethyl-1,5-hexadiene, divinylbenzene, N,N-diallylacrylamide, N,N-diallylmethacrylamide, and mixtures thereof.

28. The composition of claim 27, wherein said crosslinking agent is selected from the group consisting of 2,3-dihydroxyhexa-1,5-diene and 2,3-dimethylhexa-1,5-diene.

29. The composition of claim 23, further comprising an additional medicament.

30. The composition of claim 29, wherein said additional medicament is selected from the group consisting of antibiotics, antivirals, antifungals, anesthetics, anti-inflammatory agents, and anti-allergic agents.

31. The composition of claim 30, wherein said additional medicament comprises about 0.01% to about 5.0% of said composition.

32. The composition of claim 23, wherein said polymeric suspending agent has a monodisperse particle size distribution.

33. The composition of claim 23, wherein said polymeric suspending agent comprises a polycarbophil.

34. The composition of claim 33, wherein said composition comprises 0.5% to 6.5% of said polycarbophil.

35. The composition of claim 34, wherein said composition comprises 0.6% to 0.8% of said polycarbophil.

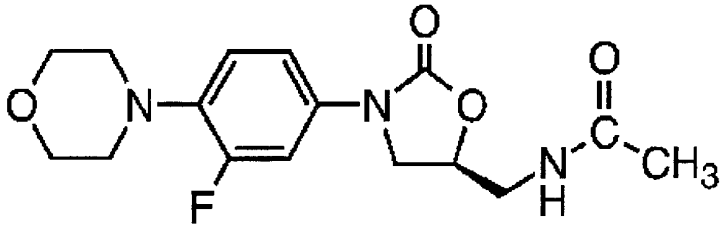
36. The composition of claim 23, wherein said polymeric suspending agent comprises a water-swellable, water-insoluble crosslinked carboxy-vinyl polymer.

37. The composition of claim 23, wherein said polymeric suspending agent comprises a cellulosic polymer.

38. The composition of claim 23, wherein said polymeric suspending agent comprises at least 90% acrylic acid monomers.

39. A composition comprising water, an oxazolidinone, a polymeric suspending agent, and a solubility enhancer.

40. The composition of claim 39, wherein said suspension comprises 0.1 to 5.0% of a compound of formula IV and wherein said solubility enhancer is a cyclodextrin:



IV.

41. The composition of claim 40, wherein said composition comprises 0.2 to 4.0% of said compound of formula IV and 0.1% to 20% of said cyclodextrin, wherein said cyclodextrin is hydroxypropyl-β-cyclodextrin.

42. The composition of claim 40, further comprising a difunctional crosslinking agent.

43. The composition of claim 42, wherein said crosslinking agent is selected from the group consisting of divinyl glycol, 2,3-dihydroxyhexa-1,5-diene, 2,5-dimethyl-1,5-hexadiene, divinylbenzene, N,N-diallylacrylamide, N,N-diallylmethacrylamide, and mixtures thereof.

44. The composition of claim 43, wherein said crosslinking agent is selected from the group consisting of 2,3-dihydroxyhexa-1,5-diene and 2,3-dimethylhexa-1,5-diene.

45. The composition of claim 40, further comprising an additional medicament.

46. The composition of claim 45, wherein said additional medicament is selected from the group consisting of antibiotics, antivirals, antifungals, anesthetics, anti-inflammatory agents, and anti-allergic agents.

47. The composition of claim 46, wherein said additional medicament is about 0.01% to about 5.0% of said composition.

48. The composition of claim 40, wherein said polymeric suspending agent has a monodisperse particle size distribution.

49. The composition of claim 40, wherein said polymeric suspending agent comprises a cellulosic polymer.

50. The composition of claim 40, wherein said polymeric suspending agent comprises at least 90% acrylic acid monomers.

51. The composition of claim 39, wherein said solubility enhancer is ethoxylated castor oil.

52. The composition of claim 40, wherein said cyclodextrin is an α-cyclodextrin.

53. The composition of claim 40, wherein said cyclodextrin is a β-cyclodextrin,

54. The composition of claim 40, wherein said cyclodextrin is a γ-cyclodextrin.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 00/24914

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/422 A61K31/424 A61K9/00 A61K47/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 352 781 A (DU PONT DE NEMOURS) 31 January 1990 (1990-01-31) claims 1,11 page 45, line 1 - line 5 ---	39
X,P	WO 00 18387 A (ALCON) 6 April 2000 (2000-04-06) claims 1,2,6,7 example 2 page 9, line 30 -page 11, line 2 ---	39,40, 45-47,49
A	WO 99 25344 A (PHARMACIA & UPJOHN) 27 May 1999 (1999-05-27) claims 1,2,4,6,9,10,12,14,16,17,22,26 example 2 page 4, line 2 page 4, line 16 --- -/--	1,9,13, 23,29, 39,49

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2001	13/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 00/24914

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 00 03710 A (PHARMACIA & UPJOHN) 27 January 2000 (2000-01-27) claims	1,13,23, 39

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/US 00/24914

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 352781 A	31-01-1990	US 4948801 A	14-08-1990
		AU 622465 B	09-04-1992
		AU 3911589 A	01-02-1990
		CA 1337526 A	07-11-1995
		DK 374389 A	30-01-1990
		FI 893618 A	30-01-1990
		HU 58062 A	28-01-1992
		JP 2124877 A	14-05-1990
		JP 2899319 B	02-06-1999
		NO 893076 A	30-01-1990
		NZ 230108 A	25-10-1991
		PT 91315 A	08-02-1990
		US 5130316 A	14-07-1992
		US 5043443 A	27-08-1991
		US 5254577 A	19-10-1993
		ZA 8905778 A	27-03-1991
WO 0018387 A	06-04-2000	AU 1310200 A	17-04-2000
WO 9925344 A	27-05-1999	AU 1582399 A	07-06-1999
		BR 9815615 A	24-10-2000
		EP 1032386 A	06-09-2000
		US 6040306 A	21-03-2000
WO 0003710 A	27-01-2000	AU 4953099 A	07-02-2000