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(54) **TETRACYCLINE COMPOSITIONS**

TETRACYCLIN-ZUSAMMENSETZUNGEN

COMPOSITIONS DE TÉTRACYCLINE

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to tetracycline compositions and methods for preparing and using the same. Some embodiments include a tetracycline with an excess of a divalent or trivalent cation.

BACKGROUND OF THE INVENTION

[0002] Tetracyclines are used as broad spectrum antibiotics to treat various bacterial infections, such as infections of the respiratory tract, sinuses, middle ear, urinary tract, and intestines, and can be used in the treatment of gonorrhoea, especially in patients allergic to β-lactams and macrolides. Tetracyclines interfere with the protein synthesis of Gram positive and Gram-negative bacteria by preventing the binding of aminoacyl-tRNA to the ribosome. The action of tetracyclines is bacteriostatic (preventing growth of bacteria) rather than killing (bactericidal).

[0003] Tetracyclines degrade rapidly to form epitetracycline, anhydrotetracycline, epianhydrotetracycline, and other degradation products. Once degraded, tetracyclines have small therapeutic value, since the degradation products have no therapeutically useful activity. Degradation begins as soon as the antiobiotic is in solution, and continues until reaching an equilibrium of antibiotic and epimer concentrations. The equilibrium point is temperature and pH dependent, with more epimer being formed at higher temperatures and lower pH. Oxidation and other side reactions cause further degradation. Thus, tetracyclines can have a limited existence in aqueous environments in their active form. Moreover, the degradation products of tetracyclines are toxic and can cause Fanconi syndrome, a potentially fatal disease affecting proximal tubular function in the nephrons of the kidneys.

[0004] There is a need to provide hospital staff with the flexibility and advantages that come with longer admixture and reconstitution times without the need for refrigeration so that for instance, a hospital pharmacist could prepare a solution the day before it is needed. Furthermore, often after a natural disaster such as hurricanes, earthquakes, or tsunamis, access to refrigeration equipment can be scarce and may be further impeded by the lack of electricity. Stable formulations of tetracyclines could be stored as a solution, negating the need for reconstitution, and allowing its use in inhalers or nebulizers for outpatient use.

[0005] In addition, some tetracyclines can cause tetracycline-induced hemolysis. This hemolysis can lead to venous phlebitis at the site of injection when administered intravenously, resulting in irritation and potentially limiting the volumes of infusion that can be tolerated. Thus, there is a need for formulations of such tetracyclines that reduce the incidence of hemolysis.

SUMMARY OF THE INVENTION

[0006] The present invention relates to tetracycline compositions and methods for preparing and using the same. Some embodiments include a tetracycline with an excess of a divalent or trivalent cation.

[0007] Some embodiments include pharmaceutical compositions. In some embodiments the pharmaceutical compositions comprise an aqueous solution of minocycline and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to minocycline is greater than 2:1 and wherein the solution does not comprise a pharmaceutically acceptable oil and is suitable for intravenous administration.

[0008] In some embodiments the pharmaceutical compositions comprise an aqueous solution of minocycline and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to minocycline is greater than 2:1 and wherein the solution has a pH greater than 4 and less than 5 and is suitable for intravenous administration.

[0009] In some embodiments the pharmaceutical compositions comprise an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and wherein the solution does not comprise a pharmaceutically acceptable oil, gluconate, or a pyridine-containing compound, has a pH greater than 2 and less than 7, and is suitable for intravenous administration.

[0010] In some embodiments, the solution does not comprise polyoxyethylene hydrogenated castor oil.

[0011] In some embodiments, the solution does not comprise an antioxidant.

[0012] In some embodiments, the solution does not comprise a pyridine-containing compound.

[0013] In some embodiments, the solution does not comprise nicotinamide.

[0014] In some embodiments, the solution does not comprise an alcohol.

[0015] In some embodiments, the solution does not comprise glycerol.

[0016] In some embodiments, the solution does not comprise polyethylene glycol.

[0017] In some embodiments, the solution does not comprise gluconate.

[0018] In some embodiments, the solution does not comprise a pyrrolidone compound.

[0019] In some embodiments, the solution does not comprise a water-miscible local anaesthetic.

[0020] In some embodiments, the water-miscible local anaesthetic is procaine.

[0021] In some embodiments, the solution does not comprise urea.

[0022] In some embodiments, the solution does not comprise lactose.

[0023] In some embodiments, the solution does not comprise a dehydrating agent. In some embodiments, the dehydrating agent is selected from the group consisting of ethyl acetate, acetic anhydride, absolute ethanol, ethyl acetate, acetic anhydride, and mixtures thereof.

[0024] In some embodiments, the solution has a pH of less than 7. In some embodiments, the solution has a pH of less than 6. In some embodiments, the solution has a pH of less than 5.

[0025] In some embodiments, the solution has a pH greater than 2 and less than 7. In some embodiments, the solution has a pH greater than 4 and less than 7. In some embodiments, the solution has a pH greater than 4 and less than 6. In some embodiments, the solution has a pH greater than 4 and less than 5.

[0026] In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 3:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 5:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 8:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 10:1.

[0027] In some embodiments, the osmolality of the solution is less than 500 mOsm/kg. In some embodiments, the osmolality of the solution is less than 400 mOsm/kg. In some embodiments, the osmolality of the solution is less than 350 mOsm/kg.

[0028] In some embodiments, the concentration of minocycline is at least 1 mg/ml. In some embodiments, the concentration of minocycline is at least 5 mg/ml. In some embodiments, the concentration of minocycline is at least 10 mg/ml.

[0029] In some embodiments, the solution comprises magnesium sulfate. In some embodiments, the solution comprises magnesium oxide. In some embodiments, the solution comprises magnesium acetate. In some embodiments, the solution comprises magnesium chloride.

[0030] In some embodiments, the solution comprises a buffer. In some embodiments, the solution comprises acetate.

[0031] In some embodiments, the solution comprises a base. In some embodiments, the base comprises NaOH.

[0032] In some embodiments, the cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In some embodiments, the cation is selected from magnesium, calcium, and zinc. In some embodiments, the cation is magnesium.

[0033] In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline. In some embodiments, the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the 7-dimethylamino-tetracycline is PTK796.

[0034] Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline, $MgCl_2$ and NaOH, wherein the Mg to minocycline molar ratio is 5:1, and the pH is greater than 4.5 and less than 5.5.

[0035] Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline, $MgSO_4$, and sodium acetate, wherein the Mg to minocycline molar ratio is 5:1, the pH is greater than 4.5 and less than 5.5, and the osmolality is greater than 275 mOsm/kg and less than 375 mOsm/kg.

[0036] Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline and $Mg(C_2H_3O_{2)2}$, wherein the Mg to minocycline molar ratio is 5:1, and the pH is greater than 4.5 and less than 5.5.

[0037] Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline, MgO4, and NaOH, wherein the Mg to minocycline molar ratio is 5:1, the pH is greater than 4.5 and less than 5.5, and the osmolality is greater than 150 mOsm/kg and less than 250 mOsm/kg.

[0038] Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, $MgSO_4$, and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 5.5 and less than 6.5.

[0039] Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, $MgSO_4$ and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 5.5 and less than 6.5.

[0040] Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, $MgCl_2$, and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 5.5 and less than 6.5.

[0041] Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, $MgCl_2$, and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 5.5 and less than 6.5.

[0042] Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, $MgSO_4$ and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 6.0 and less than 7.0.

[0043] Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, $MgSO_4$ and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 6.0 and less than 7.0.

[0044] Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, $CaCl_2$, and NaOH, wherein the Ca to tigecycline molar ratio is 5:1, and the pH is greater than 6.0 and less

than 7.0.

[0045] Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, $CaCl_2$, and NaOH, wherein the Ca to tigecycline molar ratio is 12:1, and the pH is greater than 6.0 and less than 7.0.

[0046] Some embodiments include water-soluble solid compositions comprising minocycline or a salt thereof and a salt that comprises a divalent or trivalent cation.

[0047] Some embodiments include water-soluble solid compositions comprising a 7-dimethylamino-tetracycline antibiotic or a salt thereof and a salt comprising a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and wherein the composition does not comprise gluconate or a pyridine-containing compound.

[0048] In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 1:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 2:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 3:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 5:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is at greater than 8:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 10:1.

[0049] Some embodiments include compositions in the form of a lyophile.

[0050] In some embodiments, the salt is magnesium sulfate.

[0051] In some embodiments, the salt is calcium chloride.

[0052] In some embodiments, the composition comprises sodium acetate.

[0053] In some embodiments, the composition comprises NaOH.

[0054] In some embodiments, the salt is selected from magnesium chloride, magnesium bromide, magnesium sulfate, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, gallium chloride, magnesium malate, magnesium citrate, magnesium acetate, calcium citrate, zinc acetate, and zinc citrate.

[0055] In some embodiments, the composition does not comprise an antioxidant.

[0056] In some embodiments, the composition does not comprise a pyridine-containing compound. In some embodiments, the composition does not comprise nicotinamide.

[0057] In some embodiments, the composition does not comprise gluconate.

[0058] In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline. In some embodiments, the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the 7-dimethylamino-tetracycline is PTK796.

[0059] Some embodiments include methods for preparing a pharmaceutical composition comprising dissolving the water-soluble solid composition of any one of the water-soluble solid compositions provided herein in water to form a solution

[0060] Some embodiments include methods for preparing a pharmaceutical composition comprising dissolving a 7-dimethylamino-tetracycline in a solution comprising a divalent or trivalent cation.

[0061] Some embodiments include methods for preparing a pharmaceutical composition comprising dissolving a 7-dimethylamino-tetracycline in a solution comprising a divalent or trivalent cation; adjusting the pH of the solution; and lyophilizing the composition.

[0062] In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline.

[0063] In some embodiments, the pH of the solution is adjusted to be less than 6. In some embodiments, the pH of the solution is adjusted to be less than 5.

[0064] In some embodiments, the pH of the solution is adjusted to be greater than 2 and less than 7. In some embodiments, the pH of the solution is adjusted to be greater than 4 and less than 7. In some embodiments, the pH of the solution is adjusted to be greater than 4 and less than 6. In some embodiments, the pH of the solution is adjusted to be greater than 4 and less than 5.

[0065] In some embodiments, adjusting the pH comprises adding an acid. In some embodiments, the acid is HCl.

[0066] In some embodiments, adjusting the pH comprises adding a base. In some embodiments, the base is NaOH.

[0067] In some embodiments, adjusting the pH comprises forming a buffer. In some embodiments, forming the buffer comprises adding sodium acetate.

[0068] In some embodiments, the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In some embodiments, the cation is selected from magnesium, calcium, and zinc. In some embodiments, the cation is magnesium.

[0069] Some embodiments include kits comprising a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises minocycline in an amount such that the molar ratio of the divalent or trivalent

cation to minocycline is greater than 2:1.

[0070] Some embodiments include kits comprising a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises a 7-dimethylamino-tetracycline antibiotic in an amount such that the molar ratio of the divalent or trivalent cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1.

[0071] In some embodiments, the diluent comprises an acid. In some embodiments, the acid is HCl.

[0072] In some embodiments, the diluent comprises a base. In some embodiments, the base is NaOH.

[0073] In some embodiments, the diluent comprises a buffer. In some embodiments, the diluent comprises sodium acetate.

[0074] In some embodiments, the pH of the diluent is greater than pH 6 and less than pH 8.

[0075] In some embodiments, the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In some embodiments, the cation is selected from magnesium, calcium, and zinc. In some embodiments, the cation is magnesium.

[0076] In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 3:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 5:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is at greater than 8:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 10:1.

[0077] In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline. In some embodiments, the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the 7-dimethylamino-tetracycline is PTK796.

[0078] Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition of any one of the pharmaceutical compositions provided herein to the subject via an intravenous route.

[0079] Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition made according to any one of the methods of preparing a pharmaceutical compositions provided herein to the subject via an intravenous route.

[0080] In some embodiments, the intravenous administration includes administering less than 200 ml of the composition.

[0081] In some embodiments, the intravenous administration includes administering the composition in less than 60 minutes.

[0082] Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition of any one of the pharmaceutical compositions provided herein to the subject via a topical route.

[0083] Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition made according to any one of the methods of preparing a pharmaceutical compositions provided herein to the subject via a topical route.

[0084] Some embodiments include compositions comprising tigecycline and a divalent or trivalent cation, wherein the molar ratio of said divalent or trivalent cation to said tigecycline is greater than 1:1.

[0085] In some embodiments, the tigecycline and divalent or trivalent cation are in aqueous solution.

[0086] In some embodiments, the molar ratio of said divalent or trivalent cation to said tigecycline is greater than 3:1.

BRIEF DESCRIPTION OF THE DRAWINGS

[0087]

FIG. 1 shows a graph of percent hemolysis of rabbit red blood cells incubated with various concentrations of minocycline in various solutions relative to hemolysis in water, in which the minocycline solutions formulated with divalent cations were adjusted to ph 5.85.

FIG. 2 shows a graph of percent hemolysis of rabbit red blood cells incubated with various concentrations of minocycline in various solutions relative to hemolysis in water.

FIG. 3 depicts a graph of rabbit RBC hemolysis caused by minocycline formulated in different ratios of $MgSO_4$.

FIG. 4 depicts a graph of rabbit RBC hemolysis caused by minocycline formulated in different ratios of $MgCl_2$.

FIG. 5 depicts a graph of rabbit RBC hemolysis caused by minocycline formulated in different ratios of $CaCl_2$.

FIG. 6 depicts a graph for minocycline uptake by HVEC at various concentrations of divalent cation.

FIG. 7 depicts a graph for minocycline uptake by HVEC at various concentrations of divalent cation.

DETAILED DESCRIPTION

[0088] The present invention relates to tetracycline compositions and methods for preparing and using the same. Some embodiments include a tetracycline with an excess of a metal cation. In some embodiments, the compositions have improved stability against both oxidative degradation and epimerization. Some such compositions are therefore more stable when dissolved, lyophilized, reconstituted, and/or diluted than other compositions. Some embodiments also provide compositions having a lower level of tetracycline-induced hemolysis and resulting phlebitis.

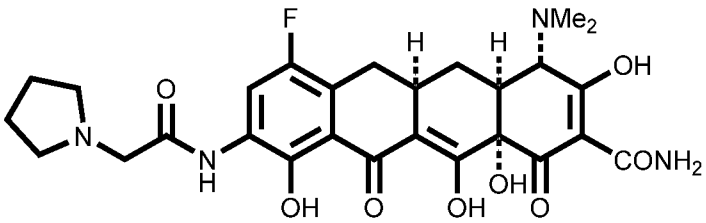
[0089] It was unexpectedly discovered that the incidence of tetracycline-induced hemolysis can be greatly decreased by formulating the tetracycline with divalent or trivalent cations. In some embodiments, high molar ratios of divalent or trivalent cations to tetracycline antibiotics significantly decreases hemolysis.

[0090] It was also unexpectedly discovered that the stability of aqueous solutions of tetracyclines can be greatly increased by the addition of divalent or trivalent cations. In some embodiments, the stability of aqueous solutions of tetracyclines increase with higher molar ratios of divalent or trivalent cations to tetracycline. Indeed, some such solutions were found to be stable for several weeks at 37 °C.

[0091] In certain compositions, the solubility of a tetracycline antibiotic is decreased in an aqueous solution comprising a multivalent cation. It has been unexpectedly discovered that increasing the molar ratio of multivalent cation to such tetracycline antibiotics can increase the solubility of the tetracycline. Accordingly, some embodiments described herein provide solutions of a tetracycline with improved solubility.

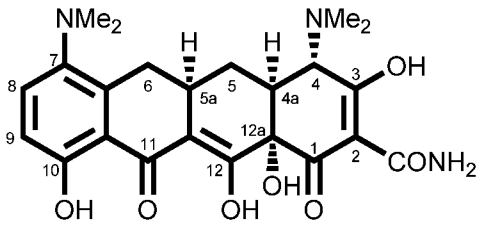
Compositions

[0092] Some embodiments include compositions comprising a tetracycline antibiotic or a salt thereof in combination with a divalent or trivalent cation. Tetracyclines include a family of structurally-related compounds that may have broad-spectrum antibiotic activities. Examples of tetracyclines include Tetracycline, Chlortetracycline, Oxytetracycline, Demeclocycline, Doxycycline, Lymecycline, Meclocycline, Methacycline, Minocycline, Rolitetracycline, Minocycline, Tigecycline, Chlorocycline, Glycylcyclines, Aminomethylcyclines, TP434, and PTK796, (also known as BAY 73-7388 and MK2764). The structure of TP434 is provided below:



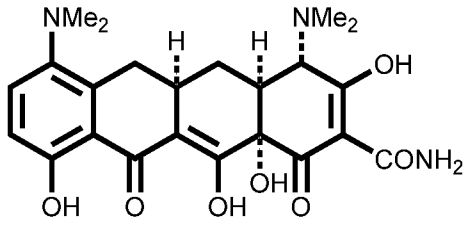
[0093] In one embodiment, the tetracycline antibiotic is selected from the group consisting of tetracycline, oxytetracycline, doxycycline, chlorocycline, minocycline, glycylcyclines and aminomethylcyclines. In one embodiment, the tetracycline is a glycylcycline. In one embodiment, the glycylcycline is tigecycline. In one embodiment, the tetracycline is an aminomethylcycline. In one embodiment, the aminomethylcycline is PTK796, also known as BAY 73-7388 and MK2764. In another embodiment, the tetracycline is selected from the group consisting of tetracycline, minocycline, tigecycline and PTK796. In one embodiment, the tetracycline antibiotic is tetracycline. In one embodiment, of the invention, the tetracycline is minocycline. In one embodiment, of the invention, the tetracycline is tigecycline. In yet another embodiment, of the invention, the tetracycline is PTK796. Some embodiments include a salt of a tetracycline antibiotic.

[0094] In some embodiments, the tetracycline antibiotic is a 7-dimethylamino-tetracycline. 7-dimethylamino-tetracyclines contain an additional dimethylamino substituent at the 7-position on the four-ring core. The 7-position is indicated on following numbered structure of minocycline:

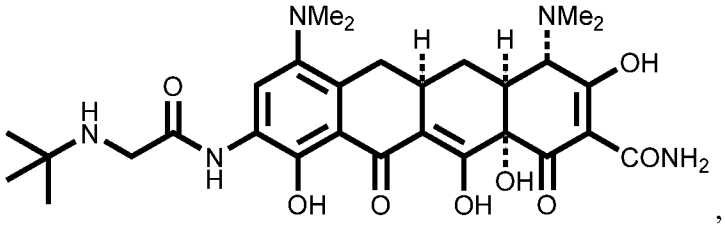


[0095] Examples of 7-dimethylamino-tetracyclines include minocycline, a glycylcycline (e.g., tigecycline) and PTK796. Example structures of such compounds include:

[0096] Minocycline:

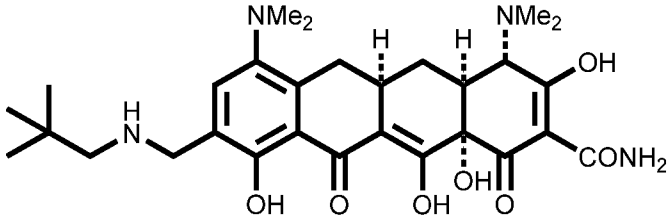


[0097] Tigecycline:



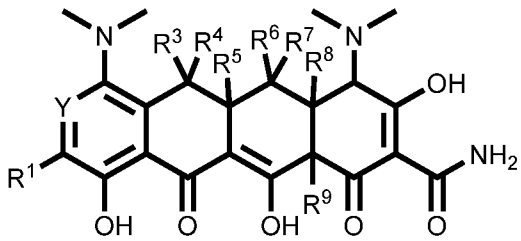
and

[0098] PTK796:



[0099] As used herein, "glycylcyclines" are 7-dimethylamino-tetracyclines having an N-alkylglycylamido side chain at position 9 of the four-ring core.

[0100] In some embodiments, the 7-dimethylamino-tetracycline antibiotic has the structure:



or tautomers thereof, wherein:

R^1 is selected from H, $-(CH_2)_nNHC(O)(CH_2)_nR^{10}$, and $-(CH_2)_nR^{10}$, where each n is independently an integer from 0 to 3, and

R^{10} is selected from $-NH-C_{1-8}$alkyl, $-NH-C_{1-8}$cycloalkyl, and a saturated 4-to-7-membered heterocycle containing one nitrogen atom, wherein if the connecting atom of R^{10} is carbon, the nitrogen atom is optionally substituted by C_1-C_4alkyl;

Y is CR^2 or N; and

R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are each independently selected from H, -OH, halogen, and C_{1-4} alkyl; or

optionally R^1 and R^2 together form a 6-membered aryl or heteroaryl ring, optionally substituted by one or two groups independently selected from H, R^1, -OH, halogen, and C_{1-4} alkyl.

[0101] In some embodiments, each of R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are hydrogen.

[0102] As used herein, "alkyl" refers to a straight- or branched-chain moiety containing only carbon and hydrogen. Alkyls may have any degree of saturation. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tertbutyl.

[0103] As used herein, "cycloalkyl" refers to a ring or ring system comprising only carbon in the ring backbone. Cycloalkyls may include one or more fused or bridged rings. Cycloalkyls may have any degree of saturation provided that at least one ring is not aromatic. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexenyl.

[0104] As used herein, "heterocycle" refers to a ring or ring system comprising at least one heteroatom in the ring backbone. Heterocycles may include one or more fused or bridged rings. Heterocycles may have any degree of saturation provided that at least one ring is not aromatic. Examples include pyrrolidine, piperidine, piperazine, and morpholino.

[0105] As used herein, "aryl" refers to an aromatic ring or ring system comprising only carbon in the ring backbone. Aryls may include one or more fused rings. Examples include phenyl and naphthyl.

[0106] As used herein, "heteroaryl" refers to an aromatic ring or ring system comprising at least one heteroatom in the ring backbone. Heteroaryls may include one or more fused rings. Examples include imidazole, oxazole, pyridine, and quinoline.

[0107] Some compositions include at least one multivalent cation. Multivalent cations include bivalent and trivalent cations, e.g., metal cations. The metal cations include common multivalent metal cations. In some embodiments, the metal cations include iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium.

[0108] Some compositions include a salt that comprises the cation. In one embodiment, the salts are inorganic metal salts and can include anhydrous, hydrated and solvated forms of the salts. In another embodiment, the salts are organic metal salts and include but are not limited to the anhydrous, hydrated and solvated forms of the salt. In one embodiment, the anion in the inorganic metal salts can include chloride, bromide, oxide, and sulfate salts. In one embodiment, the organic metal salts are those where the anion of the salt is selected from the GRAS (generally regarded as safe) list such as but not limited to acetate, citrate, gluconate, and malate salts. Suitable anions may also be found in see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania. In some embodiments, a composition can include more than one type of metal cation. In some such embodiments, the anions for each metal salt can be the same. In another embodiment, the anions for each metal salt are different. In another embodiment, the metal cation is included in the compositions provided herein as different salts of the same cation. In one embodiment the metal salts are all inorganic. In another embodiment, the metal salts are all organic. In yet another embodiment, the metal salts are a combination of organic and inorganic salts.

[0109] Examples of inorganic metal salts that may be included in the compositions provided herein include magnesium chloride (including the hexahydrate), magnesium bromide, magnesium sulfate (including the heptahydrate), magnesium oxide, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, and gallium chloride. Examples of inorganic metal salts that may be included in the compositions provided herein include magnesium malate, magnesium gluconate, magnesium citrate, magnesium acetate (including the trihydrate), calcium gluconate, calcium citrate, zinc gluconate, zinc acetate, and zinc citrate. The salts described herein include both their anhydrous and hydrated forms.

[0110] Some compositions provided herein include a tetracycline and divalent or trivalent cation, e.g., metal cation at particular molar ratios of divalent or trivalent cation to tetracycline. For example, some embodiments include compositions comprising a tetracycline and a divalent or trivalent cation, wherein the molar ratio of said divalent or trivalent cation to said tetracycline is greater than about 1:1. In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is greater than about 2:1, greater than about 3:1, greater than about 4:1, greater than about 5:1, greater than about 6:1, greater than about 7:1, greater than about 8:1, greater than about 9:1, greater than about 10:1, greater than about 11:1, greater than about 12:1, greater than about 13:1, greater than about 14:1, greater than about 15:1, greater than about 16:1, greater than about 17:1, greater than about 18:1, greater than about 19:1, greater than about 20:1, greater than about 21:1, greater than about 22:1, greater than about 23:1, greater than about 24:1, greater than about 25:1, greater than about 26:1, greater than about 27:1, greater than about 28:1, greater than about 29:1, and greater than about 30:1. In some embodiments, the molar ratio is greater than about 35:1, greater than about 40:1, greater than about 45:1, and greater than about 50:1,

[0111] In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is between about 1:1 to about 30:1, between about 5:1 to about 30:1, between about 10:1 to about 30:1, and between about 20:1 to about 30:1. In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is between about 1:1 to about 50:1, between about 5:1 to about 50:1, between about 10:1 to about 50:1, and between about 20:1 to about 50:1.

[0112] In some embodiments, the relative amounts of metal cation present in the compositions of the invention are those amounts which are in excess of the 1:1 metal cation: a tetracycline stoichiometry for each metal cation. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 100:1. In another embodiment

of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 50:1. In yet another embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 30:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 10:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 10:1 to 20:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 10:1 to 15:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 5:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 10:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 12:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 15:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 20:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 30:1.

[0113] Some compositions include carbohydrates in addition to a divalent or trivalent, cation. Suitable carbohydrates are those carbohydrates capable of reducing degradation of the tetracycline in at least one solid form prepared in at least one pH environment when compared to a solid form of a tetracycline prepared at the same pH environment lacking suitable carbohydrates. In one embodiment, the pH environment ranges from 3.0 to about 7.0, such as pHs ranging from about 4.0 to about 6.5, from about 5.0 to about 6.5, and from about 5.5 to about 6.5. In one embodiment, at least one solid form is chosen from powders and lyophilized cakes of a tetracycline. In another embodiment of the invention, carbohydrates are those carbohydrates capable of reducing degradation of the tetracycline in solution prepared in at least one pH environment when compared to a solution of a tetracycline prepared at the same pH environment lacking suitable carbohydrates. In one embodiment, the pH environment ranges from 3.0 to about 7.0, such as pHs ranging from about 4.0 to about 6.5, from about 5.0 to about 6.5, and from about 5.5 to about 6.5.

[0114] Suitable carbohydrates include mono and disaccharides e.g. an aldose monosaccharide or a disaccharide. Examples of suitable carbohydrates include but are not limited to the anhydrous, hydrated and solvated forms of compounds such as trehalose, lactose, mannose, sucrose and glucose. In one embodiment of the invention, the carbohydrate is a disaccharide. In another embodiment of the invention, the disaccharide is trehalose, lactose or sucrose. In yet another embodiment of the invention, the carbohydrate is lactose, including its different forms such as anhydrous lactose, lactose monohydrate or any other hydrated or solvated form of lactose. In one embodiment of the invention, the carbohydrate is trehalose, including its different forms such as anhydrous trehalose, trehalose dihydrate or any other hydrated or solvated form of trehalose.

[0115] In one embodiment of the invention, the suitable carbohydrate used is lactose monohydrate and the molar ratio of tigecycline to lactose monohydrate in the lyophilized powder or cake is between 1:0.2 to about 1:5. In another embodiment of the invention, the tigecycline to lactose monohydrate molar ratio is between 1:1.6 to about 1:3.3.

[0116] Some compositions include an antioxidant. Antioxidants can be used to prevent or reduce the oxidation of tetracyclines either in solution or in the solid state. Examples of antioxidants include ascorbic acid, citric acid, trehalose, butylated hydroxyl toluene (BHT), butylated hydroxyl anisole (BHA), sodium metabisulfite, d,1-α-tocopherol, and gentisic acid.

[0117] It will be appreciated that the compositions provided herein can include aerosols, liquids, and solids. Solids can include, for example, lyophilized compositions, such as powders, cakes, or the like. Such solids may be water soluble so that they may be used to prepare aqueous solutions. Liquids can include solutions or suspensions, which may be prepared from solid compositions. Liquids include solutions that may be prepared prior to manufacturing procedures such as lyophilization. In one embodiment, the solution may be stored for several hours prior to lyophilization in order to provide greater manufacturing flexibility. Liquids also include solutions that are prepared by reconstitution for use in administration to a patient. Some compositions include solutions made from the lyophilized powder or cake by, for example, reconstitution with saline or other pharmaceutically acceptable diluents. Pharmaceutically acceptable diluents are those listed by USP such as but not limited to water for injection, saline solution, lactated Ringer's solution for injection or dextrose solution. Some compositions include solutions resulting from diluting those reconstituted solutions with pharmaceutically acceptable diluents for use in intravenous bags.

[0118] In some embodiments, the pH of a liquid composition provided herein, such as an aqueous solution, is between about pH 2.0 to about pH 8.0, between about pH 2.5 to about pH 7.5. In some embodiments, the pH of the composition is between about pH 3.0 to about pH 7.0, between about pH 3.5 to about pH 6.5, between about pH 4.0 to about pH 6.5, between about pH 4.0 to about pH 6.0, between about pH 4.5 to about pH 6.0, between about pH 4.5 to about pH 5.5, between about pH 5.0 to about pH 5.5, between about pH 5.5 to about pH 6.5, between about pH 3.5 to about pH 4.5. In some embodiments, the pH of the solution is less than pH 7, less than pH 6, less than pH 5, less than pH 4, less than pH 3, and less than pH 2. In some embodiments the pH of the solution is greater than pH 2 and less than pH 7, greater than pH 4 and less than pH 7, greater than pH 4 and less than pH 6, and greater than pH 4 and less than pH 5.

[0119] In some embodiments, liquid compositions, such as an aqueous solution, can have an osmolality from about 300 mOsmol/kg to about 500 mOsmol/kg, from about 325 mOsmol/kg to about 450 mOsmol/kg, from about 350 mOsmol/kg to about 425 mOsmol/kg, or from about 350 mOsmol/kg to about 400 mOsmol/kg. In some embodiments, the osmolality of the formulation is greater than about 300 mOsmol/kg, about 325 mOsmol/kg, about 350 mOsmol/kg, about 375 mOsmol/kg, about 400 mOsmol/kg, about 425 mOsmol/kg, about 450 mOsmol/kg, about 475 mOsmol/kg, or about

500 mOsmol/kg. In some embodiments, liquid compositions can have an osmolality from about 200 mOsmol/kg to about 1250 mOsmol/kg. In another embodiment, the osmolality is between about 250 mOsmol /kg and about 1050 mOsmol/kg. In another embodiment, the osmolality is between about 250 mOsmol /kg and about 750 mOsmol/kg. In another embodiment, the osmolality is between about 350 mOsmol /kg and about 500 mOsmol/kg. In some embodiments, the osmolality of the solution is less than 500 mOsmol/kg, 450 mOsmol/kg, 400 mOsmol/kg, 350 mOsmol/kg, or 300 mOsmol/kg.

[0120] Some embodiments include an aqueous solution comprising a tetracycline having a concentration of at least 1 mg/ml, 5 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 35 mg/ml, 40 mg/ml, 45 mg/ml, or 50 mg/ml.

[0121] Some embodiments include an aqueous solution comprising a buffer, such as an acetate buffer (e.g., provided as sodium acetate), wherein the acetate has a concentration of at least 0.01 M, 0.02 M, 0.03 M, 0.04 M, 0.05 M, 0.1 M, 0.15 M, 0.20 M, 0.25 M, 0.30 M, 0.35 M, 0.40 M, 0.45 M, 0.50 M, 0.55 M, 0.60 M, 0.65 M, 0.70 M, 0.75 M, 0.80 M, 0.85 M, 0.90 M, or 0.95 M.

[0122] Some embodiments include an aqueous solution comprising a salt comprising divalent or trivalent cation, such as a magnesium salt (e.g., magnesium chloride or magnesium sulfate), having a concentration of at least 0.01 M, 0.02 M, 0.03 M, 0.04 M, 0.05 M, 0.1 M, 0.15 M, 0.20 M, 0.25 M, 0.30 M, 0.35 M, 0.40 M, 0.45 M, 0.50 M, 0.55 M, 0.60 M, 0.65 M, 0.70 M, 0.75 M, 0.80 M, 0.85 M, 0.90 M, or 0.95 M.

[0123] In one embodiment, liquid compositions, such as aqueous solutions, have a permeant ion concentration from about 30 mM to about 300 mM. In another embodiment, the permeant ion concentration is between 50 mM and 200 mM. In another embodiment, the permeant ion is selected from the list consisting of chloride and bromide. In another embodiment the permeant ion is chloride. In another embodiment, the permeant ion is bromide.

[0124] In some embodiments, aqueous solution compositions comprise a buffer. For example, in some embodiments, the solution comprises acetate. In some embodiments, aqueous solution compositions comprise a base such as NaOH. In some embodiments, aqueous solution compositions comprise an acid such as HCl.

[0125] It is contemplated that in some embodiments, reconstituted solutions may be stored in a reconstituted state at room temperature prior to further dilution for injection or topical administration. In some embodiments, storage times at room temperature after reconstitution are much longer than current compositions. In some embodiments, admixing can occur, for example, in an intravenous bag. To prepare an admixture, sufficient reconstituted solution is mixed in an intravenous bag containing a pharmaceutically acceptable diluent such as saline or dextrose solution such as 5DW.

[0126] The concentration of admixtures may easily be determined by those of ordinary skill in the art. The time available for admixture of reconstituted solutions from the compositions may be much longer than those of previously described formulations. Storage times of the admixtures at room temperature may also be much longer than those of the existing compositions. Once admixed, the tetracycline solution is ready for administration by or to the patient. The admixture may be administered alone or together with another pharmaceutical agent or composition.

[0127] In some embodiments, the composition does not comprise a pharmaceutically acceptable oil. In some embodiments, an oil can refer to a hydrocarbon compound that is liquid at room temperature and insoluble in water. Examples of pharmaceutically acceptable oils include polyoxyethylene hydrogenated castor oils such as PEG-40 hydrogenated castor oil and PEG-50 hydrogenated castor oil. More examples of pharmaceutically acceptable oils include olive oil, sesame oil, soybean oil, safflower oil, cottonseed oil, corn oil, sunflower oil, arachis oil, coconut oil, an omega-3 polyunsaturated oil, and an omega-3 marine triglyceride.

[0128] In some embodiments, the composition does not comprise a pyridine-containing compound. In one embodiment, the pyridine-containing compound is nicotinamide.

[0129] Although some embodiments include gluconate (e.g., as the gluconate salt of a divalent or trivalent metal cation), other embodiments include compositions that do not comprise gluconate.

[0130] In some embodiments, the composition does not comprise a nonaqueous tetracycline-solubilizing co-solvent. Such solubilizing co-solvents can include the oil, pyridine-containing compound, and gluconate described above.

[0131] Although some embodiments include an antioxidant, other embodiments include compositions that do not comprise an antioxidant (e.g., sodium or magnesium formaldehyde sulfoxylate; sodium sulfite, metabisulfite or bisulfite; sodium sulfide; alpha-monothioglycerol (also referred to as thioglycerol); and thiosorbitol).

[0132] Other various embodiments include compositions that do not include one or more of an alcohol (e.g., a polyhydric alcohol, such as, propylene glycol, ethylene glycol), glycerol, polyethylene glycol, a pyrrolidone-containing compound, a water-miscible local anaesthetic (e.g., procaine, tetracaine), urea, lactose, or a dehydrating agent (e.g., ethyl acetate, acetic anhydride, absolute ethanol, ethyl acetate, acetic anhydride, and mixtures thereof).

[0133] Some embodiments include compositions comprising a 7-dimethylamino-tetracycline and a cation. In some such embodiments the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the minocycline is minocycline HCl. In some embodiments the cation comprises Mg^{2+}. In some embodiments, the compositions include a salt selected from $MgCl_2$ (*e.g.,* $MgCl_2.6H_2O$), $MgSO_4$ (*e.g.* $MgSO_4.7H_2O$) and magnesium acetate (*e.g.,* $Mg(CH_3COO)_2.3H_2O$). In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1. In some embodiments, the molar ratio of divalent or trivalent cation to

minocycline is greater than 10:1, 20:1, 30:1, 40:1, or 50:1. Some embodiments include a buffer. In some such embodiments, the buffer includes NaOH, or sodium acetate (e.g., $NaCH_3COO.3H_2O$).

[0134] Some compositions comprise minocycline and $MgCl_2.6H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a base comprising NaOH. Some such embodiments are suitable for intravenous use.

[0135] Some compositions comprise minocycline and $MgSO_4.7H_{2O}$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising $NaCH_3COO.3H_2O$ with a pH in the range 4.5 - 5.5 and an osmolality in the range of about 275 - 375 mOsm/kg. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH and osmolality of a reconstituted solution can have a pH in the range 4.5 - 5.5 and an osmolality in the range of about 275 - 375 mOsm/kg. Some such embodiments are suitable for intravenous use.

[0136] Some embodiments comprise minocycline and $Mg(CH_3COO)_2.3H_2O$ with a Mg to minocycline molar ratio of about 5:1 with no buffer added. Some such embodiments are suitable for intravenous use.

[0137] Some embodiments include minocycline and $MgSO_4.7H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a base comprising NaOH with a pH in the range 5.5 - 6.5. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 5.5 - 6.5. Some such embodiments are suitable for intravenous use.

[0138] Some embodiments comprise tigecycline and $MgSO_4.7H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising NaOH with a pH in the range 5.5 - 6.5. Some embodiments comprise tigecycline and $MgSO_4.7H_2O$ with a Mg to minocycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 5.5 - 6.5. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 5.5 - 6.5. Some such embodiments are suitable for intravenous use.

[0139] Some embodiments comprise tigecycline and $MgCl_2.6H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising NaOH with a pH in the range 5.5 - 6.5. Some embodiments comprise tigecycline and $MgCl_2.6H_2O$ with a Mg to minocycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 5.5 - 6.5. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 5.5 - 6.5. Some such embodiments are suitable for intravenous use.

[0140] Some embodiments comprise tigecycline and $MgSO_4.7H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising NaOH with a pH in the range 6.0 - 7.0. Some embodiments comprise tigecycline and $MgSO_4.7H_2O$ with a Mg to minocycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 6.0 - 7.0. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 6.0 - 7.0. Some such embodiments are suitable for topical use. Some such compositions comprise tigecycline with greater than 90%, 95%, or 98% stability for at least 30 days. Some embodiments include compositions comprising an additional constituent such as benzalkonium chloride, a steroid such as hydrocortisone, dexamethasone, thonzonium bromide, tyloxapol, an antiseptic agent such as boric acid, a preservative such as benzalkonium chloride.

[0141] Some embodiments comprise tigecycline and $CaCl_2.6H_2O$ with a Ca: minocycline: molar ratio of about 5:1 in a base comprising NaOH with a pH in the range 6.0 - 7.0. Some embodiments comprise tigecycline and $CaCl_2.6H_2O$ with a Ca to tigecycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 6.0 - 7.0. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 6.0 - 7.0. Some such embodiments are suitable for topical use. Some such compositions comprise tigecycline with greater than 90%, 95%, 98% stability for at least 30 days. Some embodiments include compositions comprising an additional constituent such as benzalkonium chloride, a steroid such as hydrocortisone, dexamethasone, thonzonium bromide, tyloxapol, an antiseptic agent such as boric acid, a preservative such as benzalkonium chloride.

[0142] Some embodiments include pharmaceutical compositions comprising an aqueous solution of minocycline and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to minocycline is greater than 2:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than about 3:1, greater than about 5:1, greater than about 8:1, greater than about 10:1. In some embodiments, the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In particular embodiments, the divalent or trivalent cation is selected from magnesium, calcium, and zinc. In some embodiments, the solution comprises magnesium sulfate and/or magnesium oxide. In particular embodiments, the composition is suitable for intravenous administration.

[0143] More embodiments include a pharmaceutical composition comprising an aqueous solution of an 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than 3:1 and wherein the solution does not comprise an oil, gluconate, or a pyridine-containing compound, has a pH greater than 2 and less than 7, and is suitable for intravenous administration. In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and glycylcyclines (e.g. tigecy-

cline).

[0144] Some embodiments include a water-soluble solid composition, comprising minocycline or a salt thereof and a salt that comprises a divalent or trivalent cation. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than about 1:1, greater than about 2:1, greater than about 3:1, greater than about 5:1, greater than about 8:1, greater than about 10:1. In some embodiments, the salt is selected from magnesium chloride, magnesium bromide, magnesium sulfate, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, gallium chloride, magnesium malate, magnesium gluconate, magnesium citrate, calcium gluconate, calcium citrate, zinc gluconate, zinc acetate, and zinc citrate. In preferred embodiments, the salt is magnesium sulfate. In some embodiments, the composition comprises sodium acetate. In certain embodiments, the composition does not comprise an antioxidant, a pyridine-containing compound (e.g., nicotinamide), or gluconate.

[0145] More embodiments include water-soluble solid compositions comprising a 7-dimethylamino-tetracycline antibiotic and a salt comprising a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than 3:1 and wherein the composition does not comprise gluconate or a pyridine-containing compound. In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, glycylcyclines (e.g. tigecycline) and PTK796.

[0146] In some embodiments, the water-soluble compositions described above are in the form of a lyophile.

Methods of preparation

[0147] Some embodiments of the present invention include methods for preparing the compositions described herein. Some such methods include combining a tetracycline antibiotic and a divalent or trivalent cation. Some methods further comprise modifying the pH of the compositions. In some methods, modifying the pH comprises adjusting the pH with a pH modifying agent. Examples of pH modifying agents include hydrochloric acid, gentisic acid, lactic acid, citric acid, acetic acid, phosphoric acid, sodium hydroxide, sodium bicarbonate and sodium carbonate. In some embodiments, the pH-modifying agent includes any pharmaceutically acceptable acid, base or buffer capable of adjusting the pH of a tetracycline antibiotic/metal cation solution to between about 3.0 to about 7.0, about 4.0 to about 5.0, about 5.0 to 6.0, about 5.5 to 6.5, about 6.0 to 6.5 or about 4.2 to 4.8. In some embodiments, the acid, base or buffer is used to adjust the pH of a tetracycline antibiotic/metal cation solution to a pH less than 7, 6, 5, or 4. In some embodiments, the acid, base or buffer is used to adjust the pH of a tetracycline antibiotic/metal cation solution to a pH greater than 2 and less than 7, greater than 4 and less than 7, greater than 4 and less than 6, and greater than 4 and less than 5. Examples of such acids include but are not limited to hydrochloric acid, including 1.0 N HCl, gentisic acid, lactic acid, citric acid, acetic acid and phosphoric acid. Examples of suitable buffers include as components succinates and acetate. Examples of such bases include but are not limited to aqueous solutions of sodium hydroxide, including 1.0 N NaOH solution, sodium bicarbonate and sodium carbonate.

[0148] Compositions of the invention may be prepared via a number of acceptable methods. For example, the metal salts are dissolved in water and the tetracycline antibiotic is added to this solution. Alternatively, the antibiotic is dissolved first and the metal salt is added to the solution. The pH of the solution is then adjusted with an acid, a base or buffer. Other optional agents such as an antioxidant or carbohydrate are then dissolved in the solution. The final solution may be then be used directly in therapy or lyophilized to dryness to form a lyophilized powder or cake for later reconstitution.

[0149] In another example, a tetracycline antibiotic may be dry blended with the metal salts and other optional ingredients, and the residual mixture dissolved in water. After the pH of the solution is adjusted, the solution may then be used in therapy or lyophilized to dryness to form a powder or cake.

[0150] Lyophilization of solutions described herein may be accomplished by any pharmaceutically acceptable means. Once lyophilized, the compositions of the invention may be stored under an inert gas, such as nitrogen, to further slow the degradation process.

[0151] The tetracycline antibiotic used in the various preparation techniques may be any solid-state form of the tetracycline that is sufficiently soluble in water. Such solid-state forms include crystalline tetracycline polymorphs, amorphous forms and salts.

[0152] One embodiment for preparing a minocycline-containing pharmaceutical composition includes dissolving minocycline and a salt that comprises a divalent of trivalent cation in water to form a solution and adjusting the pH of the solution to be less than about 7, less than about 6, less than about 5, less than about 4, or less than about 3. In some embodiments, the pH of the solution is adjusted to be greater than about 2 and less than about 7, greater than about 4 and less than about 7, or greater than about 4 and less than about 6. In some embodiments, adjusting the pH comprises adding a base, e.g., NaOH. In some embodiments, adjusting the pH comprises forming a buffer. In some embodiments, forming the buffer comprises adding sodium acetate.

[0153] More embodiments for methods of preparing a minocycline-containing pharmaceutical composition includes dissolving minocycline in a solution comprising a divalent or trivalent cation; and adjusting the pH of the solution to be less than 7.

[0154] In some embodiments, a solution of a 7-dimethylamino-tetracycline can be prepared by adding a 7-dimethylamino-tetracycline, an aqueous solution of divalent or trivalent salt to provide a certain divalent or trivalent salt to 7-dimethylamino-tetracycline molar ratio. The pH of the solution can be adjusted to a certain pH with a buffer, acid, or a base. The osmolality of the solution can be adjusted to a certain osmolality. The solution can be lyophilized. The lyophilized solution can be reconstituted with a diluent such as water.

[0155] In some embodiments, a solution of a 7-dimethylamino-tetracycline can be prepared by adding a 7-dimethylamino-tetracycline to an acid, such as HCl. The solution can be lyophilized. The lyophilized solution can be reconstituted with a diluent comprising a divalent or trivalent salt to provide a certain divalent or trivalent salt to 7-dimethylamino-tetracycline molar ratio. The diluent can further comprise an acid, base, or buffer, such as sodium acetate, to provide a solution of a certain pH.

[0156] In some embodiments, minocycline can be in a buffer comprising $MgSO_4$ at pH 5. The solution can be lyophilized. The lyophilisate can be reconstituted in an aqueous diluent. In some embodiments, minocycline can be solubilized in an aqueous solution comprising HCl, MgSO4 and sodium acetate. The solution can be lyophilized. In some embodiments, minocycline can be solubilized in an aqueous solution comprising HCl. The solution can be lyophilized. The lyophilisate can be reconstituted in an aqueous solution. In some embodiments, the reconstituting solution can lack Mg.

Kits

[0157] Some embodiments of the present invention include kits comprising a composition described herein. Some kits include a single use container comprising a composition described herein. Single use containers include ampules, vials, and the like. The single-use container can comprise a lyophilized formulation of a composition described herein. Some kits include a diluent for reconstituting the lyophilized formulations of a composition or pharmaceutical composition described herein.

[0158] In some embodiments, the compositions of the invention may be prepared for single-dosage use. In this embodiment, the solutions of the invention are lyophilized in individual vials such as 20-mL vials. Upon lyophilization, the vials are stoppered with any acceptable stopper. The stoppered vials are then shipped for use. When needed, the vials can be reconstituted by adding sufficient diluents to achieve the desired concentration of tetracycline. The concentration of reconstituted solutions may be easily determined by those of ordinary skill in the art. Any pharmaceutically acceptable diluent may be used. Examples of such diluents include but are not limited to water, 0.9% saline, Lactated Ringer's injection solution and dextrose solutions including 5% dextrose (5DW).

[0159] In some embodiments, the diluent does not comprise a pharmaceutically acceptable oil (e.g., polyoxyethylene hydrogenated castor oils), a pyridine-containing compound (e.g., nicotinamide), gluconate, an antioxidant, an alcohol (e.g., a polyhydric alcohol, such as, propylene glycol, ethylene glycol), glycerol, polyethylene glycol, a pyrrolidone-containing compound, a water-miscible local anaesthetic (e.g., procaine, tetracaine), urea, lactose, or a dehydrating agent (e.g., ethyl acetate, acetic anhydride, absolute ethanol, ethyl acetate, acetic anhydride, and mixtures thereof). In some embodiments, the diluent does not comprise a tetracycline-solubilizing co solvent.

[0160] In some embodiments, the diluent contains the divalent or trivalent cation. For example, some embodiments include kits that comprise a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises minocycline in an amount such that the molar ratio of the divalent or trivalent cation to minocycline is greater than about 2:1. In some embodiments, the diluent comprises an acid, e.g., HCl. In some embodiments, the diluent comprises a buffer. In some embodiments, the buffer is sodium acetate.

[0161] More embodiments include kits comprising a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises a tetracycline antibiotic in an amount such that the molar ratio of the divalent or trivalent cation to tetracycline antibiotic is greater than 3:1.

[0162] More embodiments include single use vials comprising any composition wherein the vial comprises an amount of a tetracycline of at least 100 μg, 200 μg, 300 μg, 400 μg, 500 μg, 600 μg, 700 μg, 800 μg, 900 μg, 1000 μg. In some embodiments, the vial comprises an amount of a tetracycline of at least 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, and 130 mg. In some embodiments, the vial comprises an amount of a tetracycline of at least 100 mg, 200 mg, 300 mg, 400 mg, and 500 mg. In some embodiments, the vial comprises about 100 mg of a tetracycline. In some embodiments, the tetracycline is minocycline. In some embodiments, the tetracycline is tigecycline. In some such embodiments, a vial can comprise greater than 30 mg and less than 100 mg tigecycline.

Methods of treatment

[0163] Some embodiments include methods of treating or preventing a bacterial infection in a subject by administering

a composition described herein. "Treating," as used herein, refers to administering a pharmaceutical composition for therapeutic purposes to a patient suffering from a bacterial infection. "Preventing," as used herein, refers to treating a patient who is not yet infected, but who is susceptible to, or otherwise at risk of, a particular infection, whereby the treatment reduces the likelihood that the patient will develop an infection.

[0164] In some embodiments, the administration is via an intravenous route such as by administering an aqueous solution described herein intravenously.

[0165] Some such methods include administering an aqueous solution of minocycline and a divalent or trivalent cation to a subject via an intravenous route. Such solutions are described herein.

[0166] Some embodiments include administering an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation to a subject via an intravenous route, wherein the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than about 3:1 and wherein the solution does not comprise gluconate or a pyridine-containing compound and has a pH greater than 2 and less than 7.

[0167] In some embodiments of intravenous administration, the compositions described herein permit use of lower volumes and faster infusion times due to increased concentrations of tetracycline antibiotic and reduced injection site phlebitis as compared to currently available intravenous formulations. In some embodiments, the total volume administered is less than 50 ml, less than 60 ml, less than 70 ml, less than 80 ml, less than 90 ml, less than 100 ml, less than 110 ml, less than 120 ml, less than 130 ml, less than 140 ml, less than 150 ml, less than 200 ml, less than 300 ml, less than 400 ml, less than 500 ml, or less than 1000 ml. In some embodiments, about 100 ml is administered. In some embodiments, the entire volume to be administered is administered in less than 10 minutes, less than 20 minutes, less than 30 minutes, less than 40 minutes, less than 50 minutes, less than 60 minutes, less than 70 minutes, less than 80 minutes, less than 90 minutes, less than 2 hours, less than 3 hours, or less than 4 hours. In some embodiments, the entire volume is administered in 20 - 70 minutes. In some embodiments, the entire volume is administered in 30 - 60 minutes.

[0168] Some embodiments include administering a composition described herein by a topical route. Examples of topical routes include skin, eye, ear, rectal, vaginal, urethral. Methods of such administration are well known in the art and can include aqueous solution, spray, suppository, salve, or an ointment or the like. Accordingly, some embodiments include administering an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation to a subject via a topical route. In some such embodiments, the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than about 3:1. In some embodiments, the solution does not comprise gluconate or a pyridine-containing compound. In some embodiments, the solution has a pH greater than 2 and less than 7.

[0169] Other embodiments include administering a composition described herein by pulmonary inhalation. For example, compositions may be administered by inhalation of an aerosol of the composition. The aerosol may be formed using dry particles of the composition or by nebulization of a solution of suspension of the composition. Any suitable aerosolization device may be used, including dry-powder inhalers, metered-dose inhalers, and nebulizers.

[0170] The following examples illustrate various embodiments of the invention and are not intended to limit the invention in any way.

EXAMPLES

Example 1-Stability at 37 °C for solutions of Tigecycline or Tygacil® containing metal cations

[0171] General procedures: Some of following examples include experiments in which the stabilities of various aqueous solutions of a tetracycline were analyzed. Some solutions included a carbohydrate and/or various molar amounts of metal salts.

[0172] The pH of the solutions were adjusted with hydrochloric acid or sodium hydroxide solution. The solutions were incubated at room temperature (approximately 22 °C) or at 37 °C. Incubation of solutions at 37 °C was used as a model for long-term storage of solutions.

[0173] The stabilities of various aqueous solutions of a tetracycline were analyzed using HPLC. HPLC analyses were conducted on an Agilent 1200: Column: Eclipse Plus C18 4.6 x 150 mm, 5 μm. Detection: UV at 248 nm. Flow rate: 1.2 mL/min. Tigecycline retention time = 4.30 min. Gradient: Solvent A = 0.1% trifluoroacetic acid in acetonitrile. Solvent B = 0.1% trifluroacetic acid in water. TABLE 1 shows the HPLC gradient used.

TABLE 1

Time (min)	% Solvent A	% Solvent B
0.0	5	95
9.5	50	50

(continued)

Time (min)	% Solvent A	% Solvent B
10.0	5	95
15.0	5	95

[0174] A 10 mg/mL Tigecycline aqueous solution was prepared and 300 μL aliquots dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M $MgCl_2$ 0.1 M $CaCl_2$ or 0.1 M $ZnCl_2$ to achieve the desired molar ratio of Tigecycline : metal cation. The tubes were incubated in the dark at 37 °C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

[0175] A 10 mg/mL (17.08 mol/L) aqueous solution of Tygacil® (Lot D 90293, 53 mg), a commercial Tigecycline formulation containing lactose, was prepared, and 240 μL aliquots were dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M $MgCl_2$, 0.1 M $CaCl_2$ or 0.1 M $ZnCl_2$ to achieve the desired molar ratio of Tigecycline : metal cation. The tubes containing the solution were incubated in the dark at 37 °C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

[0176] The percentages of Tigecycline remaining at Day 0, 1, 2, 5, and 7 for solutions of Tigecycline at various molar ratios with $MgCl_2$, $CaCl_2$, or $ZnCl_2$ are shown in TABLE 2, TABLE 3, and TABLE 4, respectively. The percentages of Tigecycline remaining at Day 0, 1, 2, 5, and 7 for solutions of Tygacil® at various ratios with $MgCl_2$, $CaCl_2$, or $ZnCl_2$ are shown in TABLE 5, TABLE 6, and TABLE 7, respectively.

TABLE 2

$MgCl_2$: Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.42	98.93	97.68	92.31	85.95
5:1	99.45	98.85	97.30	88.64	81.41
2:1	99.50	98.57	96.85	84.95	73.95
1:1	99.64	98.64	96.70	82.54	67.87
0.5:1	99.60	98.45	96.52	79.39	62.20
0.2:1	99.56	98.44	95.91	72.81	53.83
0.1:1	99.50	98.29	95.66	67.28	48.68
0:1	99.53	98.23	95.18	58.42	40.90

TABLE 3

$CaCl_2$: Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.49	99.02	97.89	91.88	86.31
5:1	99.44	98.66	97.31	87.13	80.87
2:1	99.38	98.06	96.66	83.63	75.05
1:1	99.58	98.33	96.54	81.30	70.18
0.5:1	99.56	98.61	96.15	76.00	64.81
0.2:1	99.58	98.47	95.99	72.84	57.19
0.1:1	99.56	98.32	95.66	67.89	49.75
0:1	99.49	98.17	94.98	59.11	39.31

TABLE 4

$ZnCl_2$: Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.15	99.01	97.82	96.65	95.41
5:1	99.21	98.66	97.76	95.81	92.85
2:1	99.31	98.46	97.32	91.02	85.64
1:1	99.54	98.66	97.59	91.27	82.49
0.5:1	99.53	98.66	97.21	87.15	76.43
0.2:1	99.52	98.38	95.95	79.08	66.83
0.1:1	99.50	98.39	96.11	78.80	64.93
0:1	99.46	98.37	95.02	56.30	39.05

TABLE 5

$MgCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.61	99.38	98.97	96.51	93.52
5:1	99.47	99.46	98.83	95.38	90.55
2:1	99.49	99.32	98.72	93.20	84.03
1:1	99.63	99.38	98.55	89.21	74.30
0.5:1	99.59	99.28	98.36	86.97	68.84
0.2:1	99.54	99.26	98.43	86.41	64.91
0.1:1	99.48	99.19	98.19	72.43	44.71

TABLE 6

$CaCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.41	99.41	98.88	96.51	89.98
5:1	99.40	99.29	98.48	95.38	85.50
2:1	99.45	99.22	98.34	93.20	79.62
1:1	99.71	99.44	98.44	89.21	75.34
0.5:1	99.53	99.16	98.32	86.97	70.45
0.2:1	99.54	99.21	98.30	86.41	63.78
0:1	99.47	99.16	98.16	72.43	42.88

TABLE 7

$ZnCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.41	99.45	98.90	97.89	95.78
5:1	99.44	99.27	98.68	96.87	94.30
2:1	99.39	99.25	98.74	96.09	92.22
1:1	99.56	99.50	98.98	95.60	90.67
0.5:1	99.48	99.25	98.78	93.73	86.02
0.2:1	99.52	99.35	98.43	89.34	77.79

(continued)

$ZnCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
0:1	99.50	99.27	98.12	69.85	42.15

[0177] While Tigecycline decomposed in all tubes over 7 days, the rate of decomposition was significantly lower in solutions containing higher molar ratios of metal cation. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar; however, the rate of Tigecycline decomposition in the presence of zinc was significantly lower. The presence of lactose in the Tygacil® formulation further decreased the rate of decomposition.

Example 2-Stability at room temperature for solutions of Tigecycline or Tygacil® containing metal cations

[0178] A 10mg/mL Tigecycline aqueous solution was prepared and 240 μL aliquots dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M $MgCl_2$, 0.1 M $CaCl_2$ or 0.1 M $ZnCl_2$ to achieve the desired molar ratio of Tigecycline : metal cation. The tubes were incubated in the dark at 37 °C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

[0179] A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 240 μL aliquots were dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M $MgCl_2$, 0.1 M $CaCl_2$ or 0.1 M $ZnCl_2$ to achieve the desired molar ratio of Tigecycline : metal cation. The tubes were incubated in the dark at 37 °C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

[0180] The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, 21, 28, and 36 for solutions of Tigecycline at various molar ratios with $MgCl_2$, $CaCl_2$, or $ZnCl_2$ are shown in TABLE 8, TABLE 9, and TABLE 10, respectively. The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, 21, 28, and 36 for solutions of Tygacil® at various ratios with $MgCl_2$, $CaCl_2$, or $ZnCl_2$, are shown in TABLE 11, TABLE 12, and TABLE 13, respectively.

TABLE 8

$MgCl_2$: Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.58	99.32	99.46	99.03	98.62	95.52	91.90	85.33	76.89
5:1	99.45	99.32	99.41	98.74	98.16	94.04	87.10	76.71	62.60
2:1	99.51	99.27	99.43	98.46	96.97	89.87	76.29	58.07	40.67
1:1	99.66	99.45	99.36	98.35	96.49	85.88	66.59	46.07	31.90
0.5:1	99.64	99.40	99.35	97.76	96.16	81.98	59.70	39.79	28.16
0.2:1	99.56	99.37	99.28	97.93	95.45	75.81	50.38	34.00	24.19
0:1	99.46	99.24	99.15	97.01	94.08	61.98	38.99	24.55	16.33

TABLE 9

$CaCl_2$: Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.58	99.34	99.41	99.05	98.59	95.45	92.00	86.92	82.47
5:1	99.48	99.25	99.27	98.66	98.13	93.61	88.60	81.75	74.95
2:1	99.37	99.27	99.25	98.03	97.16	91.36	82.92	72.83	62.43
1:1	99.57	99.38	99.30	98.53	96.92	89.14	78.35	65.46	53.22
0.5:1	99.59	99.30	99.30	98.32	96.54	86.26	72.73	58.20	45.11
0.2:1	99.48	99.32	99.27	97.94	95.75	80.39	61.83	45.47	26.69
0:1	99.44	99.29	99.17	96.76	93.75	60.72	38.08	23.94	15.72

TABLE 10

$ZnCl_2$: Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.24	98.99	99.49	99.30	99.19	97.49	97.63	96.09	94.32
5:1	99.29	99.13	99.05	99.27	99.16	97.40	95.98	92.80	90.60
2:1	99.34	99.23	99.51	99.06	98.82	95.79	93.63	86.84	80.66
1:1	99.53	99.39	99.47	99.03	98.48	94.61	88.48	79.03	69.44
0.5:1	99.50	99.39	99.33	98.76	96.77	90.07	78.03	65.63	54.07
0.2:1	99.46	99.37	99.33	98.24	96.50	85.72	69.89	55.13	41.97
0:1	99.44	99.39	99.12	97.28	93.31	59.45	37.09	23.57	15.48

TABLE 11

$MgCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.44	99.53	99.34	99.25	99.07	97.30	95.37	92.20	86.32
5:1	99.44	99.61	99.60	99.45	99.32	97.66	95.34	90.98	83.58
2:1	99.48	99.63	99.56	99.43	99.19	96.67	91.94	81.95	66.57
1:1	99.55	99.62	99.61	99.09	99.11	96.50	89.71	74.36	55.95
0.5:1	99.49	99.64	99.60	99.33	98.70	95.10	84.39	64.70	45.04
0.2:1	99.49	99.63	99.57	99.28	98.89	94.03	79.53	57.09	37.94
0:1	99.44	99.57	99.57	99.25	98.78	89.19	65.09	42.56	28.38

TABLE 12

$CaCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.32	99.51	99.45	99.50	99.26	97.41	95.08	92.06	87.88
5:1	99.35	99.51	-	99.33	99.02	97.36	93.42	88.57	82.75
2:1	99.40	99.67	99.46	99.25	98.97	95.76	90.00	81.77	72.75
1:1	99.49	99.60	99.54	99.39	99.02	95.44	88.25	77.42	65.65
0.5:1	99.48	99.60	99.49	99.30	98.55	94.80	85.57	71.96	58.07
0.2:1	99.44	99.57	99.53	99.27	98.89	92.70	80.03	62.28	47.05
0:1	99.45	99.60	99.55	99.18	98.70	88.02	63.58	40.77	28.00

TABLE 13

$ZnCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	98.91	99.49	99.43	99.46	99.47	98.98	98.68	98.17	98.11
5:1	99.15	99.54	99.51	99.45	99.35	98.88	98.26	97.39	96.15
2:1	99.29	99.57	99.55	99.35	99.37	98.60	97.42	95.30	92.37
1:1	99.44	99.62	99.55	99.61	99.33	97.97	96.29	92.70	87.08
0.5:1	99.47	99.62	99.59	99.48	99.25	97.60	94.10	86.46	76.49
0.2:1	99.45	99.62	99.61	99.47	99.19	96.09	89.52	77.46	63.06

(continued)

$ZnCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
0:1	99.42	99.54	99.52	99.14	98.71	88.25	64.08	41.19	28.09

[0181] While Tigecycline decomposed in all tubes over 36 days, the rate of decomposition was significantly lower in solutions containing higher molar ratios of metal cation. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar; however, the rate of Tigecycline decomposition in the presence of zinc was significantly lower. The presence of lactose in the Tygacil® formulation further decreased the rate of decomposition.

Example 3-Stability at 37 °C for Tygacil solutions containing high concentrations of metal cations

[0182] A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 300 μL aliquots were dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 1 M $MgCl_2$, 1 M $CaCl_2$ or 1 M $ZnCl_2$ to achieve the desired molar ratio of Tigecycline : metal cation. The tubes were incubated in the dark at 37 °C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

[0183] The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, and 21 for solutions of Tygacil® at various ratios with $MgCl_2$, $CaCl_2$, or $ZnCl_2$ are shown in TABLE 14, TABLE 15, and TABLE 16, respectively.

TABLE 14

$MgCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
30:1	99.64	99.59	99.49	98.54	97.11	89.62	77.13
20:1	99.61	99.56	99.23	97.99	95.94	85.04	63.47
12:1	99.58	99.53	99.14	96.74	94.45	77.71	46.81
5:1	99.68	99.56	99.6	96.06	91.18	59.13	25.95
0:1	99.65	99.23	98.26	75.05	46.66	6.37	1.30

TABLE 15

$CaCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
30:1	99.58	99.55	99.29	97.79	95.9	86.94	69.71
20:1	99.62	99.51	99.18	97.00	93.81	80.6	55.28
12:1	99.60	99.41	98.94	94.94	91.13	69.3	40.59
5:1	99.65	99.42	98.66	92.83	85.72	53.1	24.74
0:1	99.60	99.34	98.25	74.61	45.63	6.26	1.53

TABLE 16

$ZnCl_2$: Tygacil® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
12:1	99.44	99.27	99.49	98.60	97.66	92.50	83.58
5:1	99.48	-	99.22	97.42	96.21	87.22	71.55
0:1	99.62	-	98.22	73.43	43.3	6.37	1.57

[0184] While Tigecycline decomposed in all tubes over 21 days, the rate of decomposition was significantly lower in solutions containing higher molar ratios of metal cation. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar, however, the rate of Tigecycline decomposition in the presence of zinc was significantly lower.

Example 4-Effect of pH on the stability of Tygacil® solutions containing metal cations at 37 °C

[0185] A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 1650 μL aliquots were dispensed into four 15 mL polypropylene tubes. The volume of each tube was adjusted to 5500 μL with various dilutions of 0.1 M $MgCl_2$, 0.1 M $CaCl_2$, or 0.1 M $ZnCl_2$, or water (control), to achieve the desired molar ratio of a 1:1 ratio of Tigecycline : metal cation. Sample solutions from each 15 ml tube were taken and adjusted to pH 4, 5, or 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Samples solutions were incubated in the dark at 37 °C. Samples were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline (expressed as a percentage of the starting concentration) in each sample was determined.

[0186] The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions of Tygacil® at 1:1 ratios with $MgCl_2$, $CaCl_2$, or $ZnCl_2$ at various pHs are shown in TABLE 17, TABLE 18, and TABLE 19, respectively. TABLE 20 shows percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions of Tygacil® only at various pHs

TABLE 17

pH for 1:1 $MgCl_2$: Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.51	98.89	98.89	95.72	90.92	54.54
pH 5	99.55	99.09	98.00	84.77	63.60	15.89
pH 6	99.53	98.36	95.79	44.81	23.71	5.19

TABLE 18

pH for 1:1 $CaCl_2$: Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.49	98.88	98.84	94.43	90.06	55.91
pH 5	99.66	99.02	97.8	81.96	69.23	28.89
pH 6	99.62	98.70	97.87	92.45	87.40	56.79

TABLE 19

pH for 1:1 $ZnCl_2$: Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.47	98.62	99.03	96.14	93.15	73.25
pH 5	99.6	99.21	98.96	93.02	83.48	39.93
pH 6	99.54	99.3	99.16	94.58	86.35	49.21

TABLE 20

pH for Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.48	99.07	98.93	94.28	87.05	44.75
pH 5	99.6	98.94	96.89	49.21	27.49	2.16
pH 6	99.47	95.27	59.56	10.74	2.4	5.22

[0187] While Tigecycline decomposed in all tubes over 14 days, the rate of decomposition was significantly lower in solutions with a pH lower than pH 6. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar at pH 4 and 5; however, the rate of Tigecycline decomposition in the presence of magnesium at pH 6 was significantly greater. The rate of Tigecycline decomposition at pH 4 and 5 in solutions containing zinc was lower than solutions containing magnesium or calcium. The rates of Tigecycline decomposition at pH 6, in solutions containing zinc or calcium were similar. The rate of Tigecycline decomposition at all pHs was much lower in the presence of metal cations, especially at higher pH.

Example 5-Effect of pH on the stability of Tygacil® solutions containing high concentrations of metal cations at 37°C

[0188] A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 1650 μL aliquots were dispensed into four 15 mL polypropylene tubes. The volume of each tube was adjusted to 5500 μL with various dilutions of 1 M $MgCl_2$, 1 M $CaCl_2$, or 1 M $ZnCl_2$, or water (control), to achieve the desired molar ratio of a 1:12 ratio of Tigecycline : metal cation. Sample solutions from each 15 ml tube were taken and adjusted to pH 4, 5, or 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Samples solutions were incubated in the dark at 37 °C. Samples were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

[0189] The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions of Tygacil® at 1:12 ratios with $MgCl_2$, $CaCl_2$, or $ZnCl_2$ at various pHs are shown in TABLE 21, TABLE 22, and TABLE 23, respectively.

TABLE 21

pH for 12:1 $MgCl_2$: Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.47	98.62	99.18	97.49	95.72	83.14
pH 5	99.61	98.87	99.12	96.53	93.72	69.08
pH 6	99.58	99.26	99.21	95.6	96.96	85.86

TABLE 22

pH for 12:1 $CaCl_2$: Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.48	97.24	98.89	96.01	92.85	73.05
pH 5	99.74	99.36	99.41	97.64	95.94	89
pH 6	99.61	99.44	99.48	98	97.09	92.18

TABLE 23

pH for 12:1 $ZnCl_2$: Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.49	99.29	99.36	98.73	98.35	95.19
pH 5	99.56	99.47	99.47	98.38	98.04	93.38
pH 6	99.65	99.38	99.49	98.78	98.79	97.67

[0190] While tigecycline decomposed in all tubes over 14 days, the rate of decomposition was slower in solutions at pH 6. The rates of Tigecycline decomposition in the presence of calcium were slower in solutions at greater pH. When formulated as Tygacil, the rates of tigecycline decomposition in the presence of zinc or magnesium were faster at pH 5.

Example 6-Effect of pH on the stability of minocycline solutions containing high concentrations of $MgCl_2$ at 37 °C

[0191] A 10 mg/mL Minocycline hydrochloride aqueous solution was prepared, and 2500 μL aliquots were dispensed into two 15 mL polypropylene tubes. The volume of each tube was adjusted to 5500 μL with either a dilution of 1 M $MgCl_2$ to achieve a molar ratio of a 1:10 ratio of Minocycline : metal cation, or water. Sample solutions from each 15 ml tube were taken and adjusted to pH 4, 5, or 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Sample solutions were incubated in the dark at 37 °C. Samples were taken at various time points and analyzed by HPLC. The fraction of minocycline remaining in each sample was determined.

[0192] The percentages of Minocycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions at various pHs of Minocycline at 1:10 ratio with $MgCl_2$, or Minocycline solutions alone are shown in TABLE 24, and TABLE 25, respectively.

TABLE 24

pH for 10:1 $MgCl_2$: Minocycline	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	98.63	96.97	96.46	94.76	93.43	84.32

(continued)

pH for 10:1 $MgCl_2$: Minocycline	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 5	98.69	97.05	96.19	93.01	89.31	75.42
pH 6	99.03	97.1	96.04	88.45	83.88	76.25

TABLE 25

pH for Minocycline alone	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	98.75	96.37	96.21	94.99	92.78	81.82
pH 5	98.41	96.72	95.29	85.01	75.14	35.43
pH 6	98.19	95.47	87.55	39.17	14.56	2.2

[0193] While Minocycline decomposed in all tubes over 14 days, the rate of decomposition was significantly lower in solutions containing magnesium, especially at higher pH.

Example 7-Stability of tigecycline solutions containing mixtures of $CaCl_2$ and $MgCl_2$ at pH 6 and 37 °C

[0194] A 10 mg/mL aqueous solution of Tigecycline was prepared, and 450 μL aliquots were dispensed into 15 mL polypropylene tubes. The volume of each tube was adjusted to 1500 μL with various dilutions of 1 M $MgCl_2$ and 1 M $CaCl_2$, or water (control), to achieve the desired molar ratios of Tigecycline : metal cation. Sample solutions from each 15 ml tube were taken and adjusted to pH 6 with 0.1 N or 1 N solutions of NaOH or HC1, taking care to minimize volume changes. Samples solutions were incubated in the dark at 37 °C. Samples were taken at various time points and analyzed by HPLC. The fraction of Tigecycline remaining in each sample was determined.

[0195] The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, and 21 for solutions of at various ratios of Tigecycline: $MgCl_2$: $CaCl_2$ at pH 6 are shown in TABLE 26.

TABLE 26

$MgCl_2$: $CaCl_2$: tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
5:5:1	98.25	98.77	98.23	96.91	92.13	83.64	65.21
5:10:1	98.37	98.23	98.59	97.76	96.10	89.74	79.83
10:5:1	98.17	98.21	98.46	96.59	93.90	80.00	59.39
10:10:1	98.32	98.24	98.50	97.38	95.62	87.14	72.88
5:0:1	98.18	97.93	97.53	90.58	76.71	40.42	12.54
10:0:1	98.16	98.00	98.23	94.91	89.12	62.54	35.75
15:0:1	98.25	98.13	98.21	96.23	92.32	72.15	48.75
20:0:1	98.2	98.08	98.28	96.46	93.72	78.66	57.66
0:5:1	98.11	98.15	98.28	97.19	95.68	89.2	77.2
0:10:1	98.12	98.2	98.55	97.1	96.53	91.74	84.69
0:15:1	98.15	98.21	98.59	97.5	96.93	92.71	86.37
0:20:1	98.28	98.63	98.57	97.4	97.35	93.09	87.45
0:0:1	97.91	88.97	60.59	16.36	7.33	4.14	0

[0196] While Tigecycline decomposed in all tubes over 21 days, the rate of decomposition was significantly lower in solutions containing greater relative amounts of calcium cations.

Example 8-Effects of $MgCl_2$ on minocyline-induced hemolysis in an *in vitro* model of venous phlebitis

[0197] *In vitro* hemolysis of rabbit red blood cells (RBCs) after exposure to minocycline formulated in $MgCl_2$ or $CaCl_2$ was compared to *in vitro* hemolysis of RBCs after exposure to minocycline in saline, or exposure to amphotericin B. Minocycline HCl (LKT laboratories) stock solutions were prepared with $MgCl_2$ in saline, saline, or lactated ringer, and the pH was adjusted with NaOH. Rabbit and sheep red blood cells (RBCs) were obtained from Innovative Research laboratory (Michigan, USA). Immediately before use, RBCs were washed three times in 0.9% saline and adjusted to a density of 5% in saline. 200 μl RBCs was added to 800 μl minocycline solution, and mixed by gentle inversion for 2-5 seconds. Samples were incubated at 37°C or 30 minutes or at 25 °C for 2-5 minutes. Incubated samples were centrifuged at 12000 x g for 4 minutes and the supernatants were removed and the hemoglobin absorbance was read at 540 nm. Samples were tested in triplicate. Amphotericin B (MP Biomedicals) and distilled H_2O, or Triton-x and distilled H_2O were used as positive controls; saline was used as a negative control. Percent hemolysis was calculated according to the following formula:

$$\text{Percent hemolysis} = \frac{\text{(absorbance of sample)-(absorbance of blank)}}{\text{Absorbance of Distilled } H_2O} \times 100$$

[0198] In a set of experiments, the pH of minocycline solutions formulated with divalent cations was adjusted to pH 5.85. For RBCs incubated in a minocycline saline solution, hemolysis was in the range of 44% - 84% (FIG. 1). For RBCs incubated in a minocycline with Mg^{2+} or Ca^{2+}, hemolysis was approximately 2%. Results summarizing the percent *in vitro* hemolysis of rabbit RBCs incubated with different formulations of minocycline or amphoteun B at 25 °C are summarized in Table 27.

TABLE 27

Solution	Hemolysis of RBCs in solution relative to water (%)
5 mg/ml minocycline, 10 equiv Mg, pH 5.85	2.8
2.5 mg/ml minocycline, 10 equiv Mg, pH 5.85	3.2
0.5 mg/ml minocycline, 10 equiv Mg, pH 5.85	2.3
5 mg/ml minocycline, 5 equiv Ca, pH 5.85	2.2
2.5 mg/ml minocycline, 5 equiv Ca, pH 5.85	2.94
0.5 mg/ml minocycline, 5 equiv Ca, pH 5.85	2.20
5 mg/ml minocycline, saline, pH 4.17	81.64
2.5 mg/ml minocycline, saline, pH 4.17	84.37
0.5 mg/ml minocycline, saline, pH 4.17	43.82
Amphoterin B	101.31

[0199] In another set of experiments, the pH of a minocycline solution formulated with divalent cations was not adjusted and was allowed to fall below the pH of minocycline in saline. For RBCs incubated in a minocycline saline solution, hemolysis was in the range of 44% - 84% (FIG. 2). For RBCs incubated in a minocycline with Mg^{2+} or Ca^{2+}, hemolysis was in the range of 0% - 5%. Results summarizing the percent *in vitro* hemolysis of rabbit RBCs incubated with different formulations of minocycline at low pH, or amphoteun B at 25 °C are summarized in Table 28.

TABLE 28

Solution	Hemolysis of RBCs in solution relative to water (%)
5 mg/ml minocycline, 10 equiv Mg, pH 3.5	0.88
2.5 mg/ml minocycline, 10 equiv Mg, pH 3.5	1.12
0.5 mg/ml minocycline, 10 equiv Mg, pH 3.5	2.20
5 mg/ml minocycline, 5 equiv Ca, pH 3.64	-

(continued)

Solution	Hemolysis of RBCs in solution relative to water (%)
2.5 mg/ml minocycline, 5 equiv Ca, pH 3.64	0.86
0.5 mg/ml minocycline, 5 equiv Ca, pH 3.64	4.92
5 mg/ml minocycline, saline, pH 4.17	81.64
2.5 mg/ml minocycline, saline, pH 4.17	84.37
0.5 mg/ml minocycline, saline, pH 4.17	43.82
Amphoterin B	101.31

[0200] Hemolysis of RBCs was reduced in an *in vitro* model of venous phlebitis with minocycline solutions formulated with divalent cations compared to minocycline solutions formulated without divalent cations.

[0201] In another set of experiments, hemolysis of rabbit RBCs was measured after exposure to 2.5 mg/ml minocycline formulated with different rations of divalent cations ($MgCl_2$, Mg SO_4, or $CaCl_2$). Hemolysis was compared to Minocycline HCl; Triton-x and H_2O were used as positive controls. Results are summarized in Table 29 and shown in FIG.s 4-6.

TABLE 29

2.5 mg/ml minocycline solution		Hemolysis of RBCs in solution relative to water (%)
Cation	Molar ratio cation: minocycline	
$MgSO_4$	1:2	22.52
	1:1	24.59
	2:1	40.87
	3:1	25.67
	5:1	2.86
	7:1	1.96
	10:1	0.19
$MgCl_2$	1:2	46.91
	1:1	63.77
	2:1	74.87
	3:1	64.62
	5:1	9.43
	7:1	1.57
	10:1	0.35
$CaCl_2$	1:2	75.22
	1:1	83.89
	2:1	50.84
	3:1	26.58
	5:1	1.16
	7:1	0.75
	10:1	0.40
Minocycline only		37.44
Triton-x		97.82

[0202] FIG. 3 and FIG. 4 show the degree of rabbit RBC hemolysis produced by minocycline formulated in different ratios of $MgSO_4$ or $MgCl_2$, respectively, compared to Minocycline only. The data indicates that a 5:1 molar ratio of magnesium to minocycline or greater inhibits the RBC hemolysis observed with minocycline alone. Minocycline (minocin) produced a relative RBC hemolysis of 37%. FIG. 5 shows the degree of rabbit RBC hemolysis produced by minocycline formulated in different ratios of $CaCl_2$. This data shows that a 5:1 molar ratio of calcium to minocycline inhibits the RBC hemolysis observed with minocycline HCl alone.

[0203] Overall, these data all suggest that high molar ratios (e.g., a 5:1 molar ratio or greater) of divalent cation (Mg^{+2} or Ca^{+2}) to minocycline results in significant inhibition of rabbit RBC hemolysis observed with minocycline HCl.

Example 9-Solubility of minocycline with divalent cations

[0204] Mixtures were prepared containing minocycline and divalent cations (Mg^{2+} or Ca^{2+}) at varying stoichiometry and pH. The solubility of minocycline was assessed according to the turbidity of the mixture at 0 hr, 24 hr, 48 hr, 72 hr, 96 hr, 120 hr, 144 hr, and 168 hr. A clear solution denoted complete solubility. Table 30 summarizes data for minocycline with Mg^{2+} at 0 hr and 24 hr. Table 31 summarizes data for minocycline with Ca^{2+} at 0 hr and 24 hr.

TABLE 30

Molar ratio cation (Mg^{2+}):		**0**		**1:2**		**1:1**		**2:1**		**3:1**		**5:1**		**7:1**		**10:1**	
Time (hr)		**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**
1 mg/ml	**pH 4**	○	○									○	○	○	○	○	○
Molar ratio cation (Mg^{2+}): minocycline		**0**		**1:2**		**1:1**		**2:1**		**3:1**		**5:1**		**7:1**		**10:1**	
Time (hr)		**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**
minocycline	**pH 5**	○	○									○	○	○	○	○	○
	pH 6	○	○									○	○	○	○	○	○
	pH 7	○	○									○	○	○	○	○	○
5 mg/ml minocycline	**pH 4**	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 6	○	○	●	●	●	●	●	●	●	●	○	●	○	●	○	○
10 **mg/ml minocycline**	**pH 4**	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	○	○	●	○	●	○	●	○	○	○	○	○	○
	pH 6	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●
20 mg/ml minocycline	**pH 4**	○	●									○	○	○	○	○	○
	pH 5	○	○									○	●	○	●	○	●
30 mg/ml minocycline	**pH 4**	○	●									○	○	○	○	○	○
	pH 5	○	●									○	●	○	●	○	●
● : **insoluble;** ○**: soluble**																	

TABLE 31

Molar ratio cation (Ca^{2+}): minocycline		**0**		**1:2**		**1:1**		**2:1**		**3:1**		**5:1**		**7:1**		**10:1**	
Time (hr)		**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**
1 mg/ml minocycline	**pH 4**	○	○									○	○	○	○	○	○
	pH 5	○	○									○	○	○	○	○	○
	pH 6	○	○									○	○	○	○	○	○
	pH 7	○	○									○	●	○	●	○	●

(continued)

Molar ratio cation (Ca^{2+}): minocycline		0		1:2		1:1		2:1		3:1		5:1		7:1		10:1	
Time (hr)		0	24	0	24	0	24	0	24	0	24	0	24	0	24	0	24
5 mg/ml minocycline	pH 4	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 6	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○
10 mg/ml minocycline	pH 4	○	○	○	○	○	○										
	pH 5	○	○	○	○	○	○										
	pH 6	○	○	○	○	○	○										
20 mg/ml minocycline	pH 4	○	●									○	○	○	○	○	○
	pH 5	○	○									○	○	○	○	○	○
30 mg/ml minocycline	pH 4	○	○									○	●	○	○	○	●
	pH 5	○	●									○	○	○	○	○	○
● : **insoluble**; ○: **soluble**																	

[0205] The data demonstrates that minocycline stays in solution upon intoruction of a cation at concentrations of 10 mg/ml and less if the pH is less than 5. At higher pH, introduction of a cation initially reduces solubility. For example, a 5 mg/ml minocycline solution at pH 6 becomes insoluble on addition of Mg^{2+}. Surprisingly, at a molar ratio of cation : minocycline of 5:1 or more, the minocycline of such solutions becomes soluble, suggesting that high ratios of cation increases the solubility of minocycline.

[0206] Table 32 summarizes data for minocycline with Mg^{2+} at 48 hr and 72 hr.

TABLE 32

Molar ratio cation (Mg^{2+}): minocycline		**0**		**1:2**		**1:1**		**2:1**		**3:1**		**5:1**		**7:1**		**10:1**	
Time (hr)		**48**	**72**	**48**	**72**	**48**	**72**	**48**	**72**	**48**	**72**	**48**	**72**	**48**	**72**	**48**	**72**
1 mg/ml minocycline	**pH 4**	○	○									○	○	○	○	○	○
	pH 5	○	○									○	○	○	○	○	○
	pH 6	○	○									○	○	○	○	○	○
	pH 7	○	○									○	○	○	○	○	○
5 mg/ml minocycline	**pH 4**	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Molar ratio cation (Mg^{2+}): minocycline		0		1:2		1:1		2:1		3:1		5:1		7:1		10:1	
Time (hr)		48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72
10 mg/ml minocycline	pH 6	○	○	●	●	●	●	●	●	●	●	●	●	●	●	○	●
	pH 4	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	●	●	○	●	●	●	●	●	●	●	○	●	○	●	○	○
	pH 6	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
20 mg/ml minocycline	pH 4	●	●									○	○	○	○	○	○
	pH 5	●	●									●	●	●	●	●	●
30 mg/ml minocycline	pH 4	●	●									○	○	○	○	○	○
	pH 5	●	●									●	●	●	●	●	●

● : insoluble; ○: soluble

Example 10-Long-term stability of tigecycline at various temperatures

[0207] Table 33, Table 34, and Table 35 show percentage remaining tigecycline for different formulations of tigecycline at pH 6, stored at 37°C, room temperature, and 4°C, respectively. Formulations of tigecycline comprising increasing concentrations of tigecycline and increasing concentrations of $CaCl_2$ showed increased stability.

TABLE 33

Salt	Formulation stored at 37 °C	Stability of tigecycline (%)					
		0 day	1 day	2 days	5 days	7 days	14 days
$MgCl_2$	12 eq 20 mg/mL	97.97	97.43	96.37	92.63	88.41	
	5 eq 20 mg/mL	98.09	97.38	96.42	88.64	81.62	
	2 eq 20	97.95	97.28	94.1	80.59	69.88	
	mg/mL						
	12eq3 mg/mL	98.17	98.05	97.08	93.78	88.16	
	5 eq 3 mg/mL	98.3	97.72	96.77	86.97	73.76	
	2 eq 3 mg/mL	98.21	97.22	93.75	62.21	45.31	
$CaCl_2$	12 eq 20 mg/mL	98.3	98	97.63	96.1	95.24	91.44
	5 eq 20 mg/mL	98.16	97.75	97.4	95.82	94.81	89.26
	2 eq 20 mg/mL	98.25	97.85	97.22	95.28	93.64	88.61
	12eq3 mg/mL	98.29	98.03	97.74	96.79	95.92	91.07
	5 eq 3 mg/mL	98.21	97.96	97.32	95.37	94.42	86.36
	2 eq 3 mg/mL	98.17	97.74	96.57	92.99	90.22	
$ZnCl_2$	1 eq 20 mg/mL	98.26	97.19	93.86	81.02	72.41	
	1 eq 3 mg/mL	98.29	97.88	96.73	86.5	74.32	

TABLE 34

Salt	Formulation stored at room temperature	Stability of tigecycline (%)					
		0 day	7 days	14 days	28 days	42 days	58 days
$MgCl_2$	12 eq 20 mg/mL	97.97	96.56	93.4	79.44		
	5 eq 20 mg/mL	98.09	94.2	82.17			
	2 eq 20 mg/mL	97.95	87.57	67.91			
	12 eq 3	98.17	97.22	94.91	80.14		
	mg/mL						
	5 eq 3 mg/mL	98.3	96.45	89.91			
	2 eq 3 mg/mL	98.21	92.66	66.91			
$CaCl_2$	12 eq 20 mg/mL	98.3	97.91	97.36	95.69	95.32	93.02
	5 eq 20 mg/mL	98.16	97.88	97.23	95.24	94.08	90.78
	2 eq 20 mg/mL	98.25	97.97	97.08	94.42	93.08	87.95
	12eq3 mg/mL	98.29	98.01	97.7	96.37	95.78	93.67
	5 eq 3 mg/mL	98.21	97.84	97.29	95.39	94.22	90.37
	2 eq 3 mg/mL	98.17	97.53	96.47	92.85	90.07	79.52

(continued)

Salt	Formulation stored at room temperature	Stability of tigecycline (%)					
		0 day	7 days	14 days	28 days	42 days	58 days
$ZnCl_2$	1 eq 20 mg/mL	98.26	82.44	65.73			
	1 eq 3 mg/mL	98.29	97.11	93.1			

TABLE 35

Salt	Formulation stored at 4°C	Stability of tigecycline (%)					
		0 day	14 day	28 days	35 days	58 days	162 days
$MgCl_2$	12 eq 20 mg/mL	97.97	97.68	96.16	95.36	89.95	
	5 eq 20 mg/mL	98.09	96.22	78.05	69.76		
	2 eq 20 mg/mL	97.95	91.23	54.38	43.33		
	12eq3 mg/mL	98.17	97.76	95.76	94.19	80.31	
	5 eq 3 mg/mL	98.3	97.48	91.75	86.21		
	2 eq 3 mg/mL	98.21	96.23	84.6	76.81		
$CaCl_2$	12 eq 20 mg/mL	98.3	98.28	97.78	97.61	97.87	96.4
	5 eq 20	98.16	97.97	97.65	97.79	97.78	95.22
	mg/mL						
	2 eq 20 mg/mL	98.25	98.08	97.69	97.8	97.75	94.9
	12eq3 mg/mL	98.29	98.37	98.16	97.79	98.15	97.27
	5 eq 3 mg/mL	98.21	98.17	97.97	97.76	97.99	96.75
	2 eq 3 mg/mL	98.17	98.14	97.45	97.53	97.56	93.35
$ZnCl_2$	1 eq 20 mg/mL	98.26	77.12	53.06	45.63		
	1 eq 3 mg/mL	98.29	97.73	96.38	95.02	88.53	

Example 11-Solubility of tetracycline formulations

[0208] The solubility of four non-dimethlyamino tetracyclines, with and without Mg^{2+}, was examined. The results are summarized in Table 36.

TABLE 36

Molar ratio cation (Mg^{2+}): antibiotic		0	0.5: 1	1:1	2:1	3:1	5:1	7:1	10: 1
10 mg/ml tetracycline	pH 4	●	●	●	●	●	●	●	●
	pH 5	0	●	●	●	●	●	●	●
	pH 6	●	●	●	●	●	●	●	●
10 mg/ml chlortetracycline	pH 4	●					○	○	○
	pH 5	●					●	●	●
	pH 6	●					●	●	●
10 mg/ml doxycycline	pH 4	○					●	●	●
	pH 5	○					●	●	●
	pH 6						○#	○#	○#

(continued)

Molar ratio cation (Mg^{2+}): antibiotic		0	0.5: 1	1:1	2:1	3:1	5:1	7:1	10: 1
10 mg/ml oxytetracycline	pH 4	●					●	●	●
	pH 5	●					●	○	○
	pH 5	●					●	○	○
● : insoluble; ○: soluble; #: fell out of solution after 24 hrs at room temperature									

[0209] A comparison with the results for minocycline described in Example 9 indicates that non-dimethylamino-tetracylines, such as tetracycline, chlortetracycline, doxycycline, and oxytetracycline have solubility characteristics that differ from dimethylamino-tetracylines. For example, as summarized in Table 36, tetracycline remains insoluble at various pH and amounts of a divalent cation such as Mg^{2+}. Chlortetracycline becomes soluble with increasing concentrations of a divalent cation, but remains insoluble in the absence of any divalent cation, such as Mg^{2+}. Doxycycline is soluble in the absence of divalent cations, such as Mg^{2+}, but is insoluble in the presence of divalent cations at low pH. Similarly, oxytetracycline remains insoluble in the presence of divalent cations, such as Mg^{2+}, at low pH.

Example 12 - Study of the effect of Mg^{2+} on the uptake of minocycline in human umbilical vein endothelial cells (HUVEC)

[0210] Cells and reagents: Human umbilical vein endothelial cells (HUVEC) were purchased from Lonza and maintained according to manufacturer's recommendations in EGM-2 media. A 10 mg/mL solution of minocycline was prepared in 13.6 mg/mL Na-acetate without addition of Mg. This stock solution was further diluted in saline to 1 mg/mL with addition of Mg in the form of 1 M $MgSO_4$ to generate the following molar ratios of Mg to minocycline: 0, 1, 2.5, 5, 10, 25.

[0211] Uptake experimental conditions: HUVECs were seeded at 4.5 X 10^5 cells/well density in 6-well plates in EGM-2 media. Two days after seeding, cells were washed once with 2 mL of saline, and then 2 mL of 1 mg/mL drug solution in saline prepared as described above was placed in each well in triplicate. Plates were incubated in a CO_2 incubator at 37°C for 30 min. Drug solutions were aspirated and cells were washed once with 2 mL of saline. 0.5 mL of saline was placed in each well and the cell monolayer was scraped using a plastic cell scraper. Cell suspensions were transferred to 1.5 mL plastic tubes and sonicated for 30 sec at maximal power. Cell lysates were spun down for 10 min on a table top microcentrifuge at maximum speed and supernatants were collected. Several wells of HUVEC cells were treated with saline only and processed the same way as drug-treated cells to generate mock cell lysate which was used below for calibration curve preparation.

[0212] Sample preparation for LCMS analysis: To prepare a calibration curve, 1 mg/mL minocycline solution in water was diluted in mock cell lysate to produce 100 μl of standards with the following concentrations: 10, 5, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.02, 0.01 μg/ml.

[0213] 50 μl of supernatants from drug-treated samples or standards were mixed with 200 μl of 1% trifluoroacetic acid in acetonitrile containing 1 μg/mL of gatifloxacin, vortexed and centrifuged at 3000 g for 30 min at RT. 150 μl of supernatants was removed and mixed with 450 μl of water. After vortexing, the mixture was centrifuged at 3000 g for 5 min at RT. Supernatants were collected and subjected to LCMS analysis to determine minocycline concentration.

[0214] Data processing: Uptake data were presented as percentage relative to the sample with no Mg present, which was considered as 100%.

[0215] Uptake of minocycline at 1 mg/mL in saline with various Mg/minocycline ratios was tested in HUVEC with an incubation time was 30 min. The results are summarized in FIG. 6 and FIG. 7. FIG.s 6 and 7 demonstrate that a decrease in intracellular uptake of minocycline is observed as the concentration of a divalent cation, such as Mg^{2+} increases. While not being bound by any particular theory, this result suggests that the mechanism for the reduction in hemolysis observed in the minocycline/cation formulations described herein may be attributed to reduced RBC updake.

Example 13 - Preparing certain formulations of dimethylamino-tetracylines

Formulation 1

[0216] A formulation comprising minocycline with $MgCl_2$ and NaOH suitable for intravenous administration is prepared. 100 mg minocycline is added to a 10 ml aqueous solution of $MgCl_2$6HO to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/ml minocycline solution. The pH of the mixture is adjusted by adding NaOH to a pH in the range of pH 4.5 - pH 5.5. A single attempt of lyophilization resulted in a non-flocculent solid.

Formulation 2

[0217] A formulation comprising minocycline with MgO_4 and sodium acetate suitable for intravenous administration is prepared. 100 mg minocycline is added to an aqueous solution of $MgSO_4 \cdot 7H_2O$ to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/ml minocycline solution. The pH of the solution is adjusted by adding sodium acetate to a pH in the range of pH 4.5 - pH 5.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 4.5 - pH 5.5 and an osmolality in the range of 275 mOsm/kg - 375 mOsm/kg.

Formulation 3

[0218] A formulation comprising minocycline with $Mg(C_2H_3O_2)_2$ suitable for intravenous administration is prepared. 100 mg minocycline is added to an aqueous solution of $Mg(C_2H_3O_2)_2.3H_2O$ to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/ml minocycline solution. The solution is then lyophilized to dryness.

Formulation 4

[0219] A formulation comprising minocycline with $MgSO_4$ and NaOH suitable for intravenous administration is prepared. 100 mg minocycline is added to an aqueous solution of $MgSO_4$.7H to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/ml minocycline solution. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 4.5 - pH 5.5. The solution is lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 4.5 - pH 5.5 and an osmolality in the range of 150 mOsm/kg - 250 mOsm/kg.

Formulation 5

[0220] A formulation comprising tigecycline with MgO4 and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of $MgSO_4.7H_2O$ to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5 - pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5 - pH 6.5.

Formulation 6

[0221] A formulation comprising tigecycline with $MgSO_4$ and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of $MgSO_4.7H_2O$ to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5 - pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5 - pH 6.5.

Formulation 7

[0222] A formulation comprising tigecycline with $MgCl_2$ and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of $MgCl_2.6H_2O$ to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5 - pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5 - pH 6.5.

Formulation 8

[0223] A formulation comprising tigecycline with $MgCl_2$ and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of $MgCl_2.6H_2O$ to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5 - pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5 - pH 6.5.

Formulation 9

[0224] A formulation comprising tigecycline with $MgSO_4$ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of $MgSO_4.7H_2O$ to provide a cation to tigecycline molar ratio of 5:1.

The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0 - pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0 - pH 7.0.

Formulation 10

[0225] A formulation comprising tigecycline with $MgSO_4$ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of $MgSO_4.7H_2O$ to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0 - pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0 - pH 7.0.

Formulation 11

[0226] A formulation comprising tigecycline with $CaCl_2$ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of $CaCl_2.6H_2O$ to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0 - pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0 - pH 7.0.

Formulation 12

[0227] A formulation comprising tigecycline with $CaCl_2$ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of $CaCl_2.6H_2O$ to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0 - pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0 - pH 7.0.

Example 14 -Minocycline kits

Kit 1

[0228] A kit is prepared comprising two vials. The first vial is prepared by dissolving 108 mg minocycline HCl in an acidic solution. The solution is lyophilized to dryness. The second vial contains 10 ml diluent that includes 26.9 mg/ml $MgSO_4.7H_2O$ and 13.6 mg/mL $Na(C_2H_3O_2)_2.3H_2O$. The lyophile is then reconstituted with the diluent prior to use.

Kit 2

[0229] A kit is prepared comprising two vials. The first vial is prepared by dissolving 108 mg minocycline HCl in an acidic solution. The solution is lyophilized to dryness. The second vial contains 10 ml diluent that includes 26.9 mg/ml $MgSO_4.7H_2O$ and enough NaOH to adjust the pH to approximately 5. The lyophile is then reconstituted with the diluent prior to use.

Claims

1. A pharmaceutical composition, comprising

   (A) an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a magnesium cation, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than 2:1 and wherein the solution does not comprise a pharmaceutically acceptable oil, has a pH greater than 4 and less than 7, has an osmolality less than 500 mOsmol/kg, and is suitable for intravenous administration, preferably the 7-dimethylamino-tetracycline antibiotic is minocycline, or

   (B) comprising an aqueous solution of minocycline and a magnesium cation, wherein the concentration of minocycline is at least 1 mg/ml, wherein the molar ratio of magnesium cation to minocycline is greater than 2:1 and wherein the solution has a pH greater than 4 and less than 5 and is suitable for intravenous administration.

2. The pharmaceutical composition of claim 1, wherein the solution does not comprise a component selected from the group consisting of polyoxyethylene hydrogenated castor oil, an antioxidant, a pyridine-containing compound, nicotinamide, an alcohol, glycerol, polyethylene glycol, gluconate, a pyrrolidone compound, a water-miscible local anaesthetic, procaine, urea, lactose, and a dehydrating agent selected from the group consisting of ethyl acetate, acetic anhydride, absolute ethanol, ethyl acetate, acetic anhydride, and mixtures thereof.

3. The pharmaceutical composition of claim 1 alternative (A), wherein the solution has a pH of less than 7, preferably less than 6, more preferably less than 5, or wherein the solution has a pH greater than 4 and less than 6, preferably greater than 4 and less than 5.

4. The pharmaceutical composition of claim 1, wherein the molar ratio of divalent or trivalent cation to minocycline is greater than 3:1, preferably greater than 5:1, more preferably greater than 8:1, much more preferably greater than 10:1,
or wherein the osmolality of the solution is less than 400 mOsm/kg, preferably less than 350 mOsm/kg,
or wherein the solution comprises a salt selected from the group consisting of magnesium sulfate, magnesium oxide, magnesium acetate and magnesium chloride,
or wherein the solution comprises a buffer,
or wherein the solution comprises a base.

5. The pharmaceutical composition of claim 1, wherein the concentration of minocycline is at least 5 mg/ml, more preferably at least 10 mg/ml.

6. The pharmaceutical composition of claim 4, wherein the solution comprises acetate, or wherein the base comprises NaOH.

7. The pharmaceutical composition of claim 1 alternative (A), wherein the 7-dimethylamino-tetracycline is selected from PTK796, and a glycylcycline, preferably wherein the glycylcycline is tigecycline.

8. The pharmaceutical composition of claim 1 alternative (A) comprising:

10 mg/ml minocycline, $MgCl_2$, and NaOH, wherein the Mg to minocycline molar ratio is 5:1, and the pH is greater than 4.5 and less than 5.5, or 10 mg/ml minocycline, $MgSO_4$, and sodium acetate, wherein the Mg to minocycline molar ratio is 5:1, the pH is greater than 4.5 and less than 5.5, and the osmolality is greater than 275 mOsm/kg and less than 375 mOsm/kg, or
10 mg/ml minocycline and $Mg(C_2H_3O_2)_2$, wherein the Mg to minocycline molar ratio is 5:1, and the pH is greater than 4.5 and less than 5.5, or
10 mg/ml minocycline, $MgSO_4$, and NaOH, wherein the Mg to minocycline molar ratio is 5:1, the pH is greater than 4.5 and less than 5.5, and the osmolality is greater than 150 mOsm/kg and less than 250 mOsm/kg.

9. The pharmaceutical composition of claim 1 alternative (A) comprising 5 mg/ml tigecycline, $MgCl_2$ or $MgSO_4$, and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 5.5 and less than 6.5, or wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 5.5 and less than 6.5.

10. The pharmaceutical composition of claim 1 alternative (A) suitable for topical administration comprising 5 mg/ml tigecycline, $MgSO_4$, and NaOH, wherein the Mg to tigecycline molar ratio is 5:1 or 12:1, and the pH is greater than 6.0 and less than 7.0.

11. A water-soluble solid composition, comprising a 7-dimethylamino-tetracycline antibiotic or a salt thereof and a salt comprising a divalent or trivalent cation wherein the molar ratio of divalent or trivalent cation to 7-dimethylamino-tetracycline is greater than 3:1 and wherein upon dissolution of the solid composition in water a solution having a pH greater than 4 and less than 7 is formed, preferably the 7-dimethylamino-tetracycline antibiotic or a salt thereof is minocycline or a salt thereof.

12. The composition of claim 11, wherein the molar ratio of divalent or trivalent cation to the 7-dimethylamino-tetracycline antibiotic is greater than 5:1, preferably greater than 8:1, preferably greater than 10:1, or wherein the composition is in the form of a lyophile, or wherein the composition comprises sodium acetate, or wherein the composition comprises NaOH, or wherein the salt is selected from magnesium chloride, magnesium bromide, magnesium sulfate, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, gallium chloride, magnesium malate, magnesium citrate, magnesium acetate, calcium citrate, zinc acetate, and zinc citrate, or wherein the composition does not comprise a component selected from the group consisting of an antioxidant, a pyridine-containing compound, nicotinamide, gluconate, or wherein the 7-dimethylamino-tetracycline is selected from PTK796, and a glycylcycline.

13. A method for preparing a pharmaceutical composition comprising:

dissolving the water-soluble solid composition of any one of claims 11 to 12 in water to form a solution.

14. A method for preparing a pharmaceutical composition comprising:

dissolving a 7-dimethylamino-tetracycline in a solution comprising a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to 7-dimethylamino-tetracycline in the solution is greater than 3:1 adjusting the pH of the solution to be greater than 4 and less than 7; and
lyophilizing the composition,
preferably the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline.

15. The method of claim 14, wherein the pH of the solution is adjusted to be less than 6, preferably less than 5, or wherein the pH of the solution is adjusted to be greater than 4 and less than 6, preferably greater than 4 and less than 5, or
wherein adjusting the pH comprises adding an acid or adding a base or forming a buffer, preferably the acid is HCl or the base is NaOH, or the buffer comprises adding sodium acetate, or
wherein the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium.

16. A kit, comprising:

a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and
a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises (C) minocycline in an amount such that the molar ratio of the divalent or trivalent cation to minocycline is greater than 2:1, or
wherein the solid composition comprises (D) a 7-dimethylamino-tetracycline antibiotic in an amount such that the molar ratio of the divalent or trivalent cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1, and wherein dissolving the solid composition in the diluent produces a solution having a pH greater than 4 and less than 7.

17. The kit of claim 16, wherein the diluent comprises an acid, or a base, or a buffer; preferably the acid is HCl or the base is NaOH or the diluent comprises sodium acetate, or wherein the pH of the diluent is greater than pH 6 and less than pH 8, or
wherein the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium, or
wherein the molar ratio of divalent or trivalent cation to minocycline is greater than 3:1, or wherein the 7-dimethylamino-tetracycline of alternative (D) is selected from minocycline, PTK796, and a glycylcycline.

18. The kit of claim 16, wherein the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 5:1, preferably greater than 8:1, more preferably greater than 10:1.

19. The kit of claim 18, the composition of claim 12 and the method of claim 15, wherein the glycylcycline is tigecycline.

20. The pharmaceutical composition of any one of claims 1 to 10 for use in treating or preventing a bacterial infection in a subject, wherein the pharmaceutical composition is administered via an intravenous route or via a topical route.

21. A pharmaceutical composition made according to the method of any one of claims 13 to 15 for use in treating or preventing a bacterial infection in a subject, wherein the pharmaceutical composition is administered via an intravenous route or via a topical route.

22. The pharmaceutical composition of any one of claims 20 to 21, wherein an intravenous dose comprises less than 200 ml of the composition or
wherein the composition is administered in less than 60 minutes via an intravenous route.

23. A composition comprising an aqueous solution of tigecycline and a divalent or trivalent cation, wherein the molar ratio of said divalent or trivalent cation to said tigecycline is greater than 2:1 and wherein the solution has a pH greater than 4 and less than 7, preferably wherein the molar ratio of said divalent or trivalent cation to said tigecycline is greater than 3:1.

Patentansprüche

1. Eine pharmazeutische Zusammensetzung, umfassend:

   (A) eine wässrige Lösung eines 7-Dimethylamino-tetracyclin-Antibiotikums und eines Magnesiumkations, wobei das molare Verhältnis des Magnesiumkations zu dem 7-Dimethylamino-tetracyclin-Antibiotikum größer als 2:1 ist und wobei die Lösung kein pharmazeutisch annehmbares Öl umfasst, einen pH von größer als 4 und kleiner als 7 aufweist, eine Osmolalität von kleiner als 500 mOsmol/kg aufweist und für eine intravenöse Verabreichung geeignet ist, wobei das 7-Dimethylamino-tetracyclin-Antibiotikum bevorzugt Minocyclin ist oder
   (B) eine wässrige Lösung von Minocyclin und einem Magnesiumkation, wobei die Konzentration von Minocyclin wenigstens 1 mg/ml ist, wobei das molare Verhältnis des Magnesiumkations zu dem Minocyclin größer als 2:1 ist und wobei die Lösung einen pH von größer als 4 und kleiner als 5 aufweist und die Lösung für eine intravenöse Verabreichung geeignet ist.

2. Die pharmazeutische Zusammensetzung gemäß Anspruch 1, wobei die Lösung keine Komponente enthält, die aus der Gruppe bestehend aus Polyoxyethylen-hydriertem Castor-Öl, einem Antioxidans, einer pyridinhaltigen Verbindung, Nikotinamid, einem Alkohol, Glycerin, Polyethylenglykol, Gluconat, einer Pyrrolidonverbindung, einem mit Wasser mischbaren Lokalanästhetikum, Procain, Harnstoff, Laktose und einem dehydrierenden Mittel, ausgewählt aus der Gruppe bestehend aus Ethylacetat, Essigsäureanhydrid, absolutem Alkohol, Ethylacetat, Essigsäureanhydrid und Mischungen daraus ausgewählt ist.

3. Die pharmazeutische Zusammensetzung gemäß Anspruch 1, Alternative (A), wobei die Lösung einen pH von kleiner als 7, bevorzugt kleiner als 6, weiter bevorzugt kleiner als 5 aufweist, oder wobei die Lösung einen pH von größer als 4 und kleiner als 6, bevorzugt größer als 4 und kleiner als 5 aufweist.

4. Die pharmazeutische Zusammensetzung gemäß Anspruch 1, wobei das molare Verhältnis des zweibindigen oder dreibindigen Kations zu Minocyclin größer als 3:1, bevorzugt größer als 5:1, weiter bevorzugt größer als 8:1 und noch weiter bevorzugt größer als 10:1 ist oder wobei die Osmolalität der Lösung kleiner als 400 mOsm/kg, bevorzugt kleiner als 350 mOsm/kg ist,
   oder wobei die Lösung ein Salz enthält, ausgewählt aus der Gruppe bestehend aus Magnesiumsulfat, Magnesiumoxid, Magnesiumacetat und Magnesiumchlorid,
   oder wobei die Lösung einen Puffer enthält,
   oder wobei die Lösung eine Base enthält.

5. Die pharmazeutische Zusammensetzung gemäß Anspruch 1, wobei die Konzentration von Minocyclin wenigstens 5 mg/l, weiter bevorzugt wenigstens 10 mg/l ist.

6. Die pharmazeutische Zusammensetzung gemäß Anspruch 4, wobei die Lösung Acetat umfasst oder wobei die Base NaOH umfasst.

7. Die pharmazeutische Zusammensetzung gemäß Anspruch 1, Alternative (A), wobei das 7-Dimethylamino-tetracyclin ausgewählt ist aus PTK796 und einem Glycylcyclin, wobei das Glycylcyclin bevorzugt Tigecyclin ist.

8. Die pharmazeutische Zusammensetzung gemäß Anspruch 1, Alternative (A), enthaltend:

   10 mg/ml Minocyclin, $MgCl_2$ und NaOH, wobei das molare Verhältnis von Mg zu Minocyclin 5:1 ist und der pH größer als 4,5 und kleiner als 5,5 ist, oder
   10 mg/ml Minocyclin, $MgSO_4$ und Natriumacetat, wobei das molare Verhältnis von Mg zu Minocyclin 5:1 ist, der pH größer als 4,5 und kleiner als 5,5 ist und die Osmolalität größer als 275 mOsm/kg und kleiner als 375 mOsm/kg ist, oder
   10 mg/ml Minocyclin und $Mg(C_2H_3O_2)_2$, wobei das molare Verhältnis von Mg zu Minocyclin 5:1 ist und der pH größer als 4,5 und kleiner als 5,5 ist, oder
   10 mg/ml Minocyclin, $MgSO_2$ und NaOH, wobei das molare Verhältnis von Mg zu Minocyclin 5:1 ist, der pH größer als 4,5 und kleiner als 5,5 ist und die Osmolalität größer als 150 mOsm/kg und kleiner als 250 mOsm/kg ist.

9. Die pharmazeutische Zusammensetzung gemäß Anspruch 1, Alternative (A), enthaltend 5 mg/ml Tigecyclin, $MgCl_2$ oder $MgSO_4$ und NaOH, wobei das molare Verhältnis von Mg zu Tigecyclin 5:1 ist und der pH größer als 5,5 und kleiner als 6,5 ist, oder wobei das molare Verhältnis von Mg zu Tigecyclin 12:1 ist und der pH größer als 5,5 und

kleiner als 6,5 ist.

10. Die pharmazeutische Zusammensetzung gemäß Anspruch 1, Alternative (A), geeignet für eine tropische Verabreichung, enthaltend 5 mg/ml Tigecyclin, $MgSO_4$ und NaOH, wobei das molare Verhältnis von Mg zu Tigecyclin 5:1 oder 12:1 und der pH größer als 6,0 und kleiner als 7,0 ist.

11. Eine wasserlösliche feste Zusammensetzung, enthaltend ein 7-Dimethylamino-tetracyclin-Antibiotikum oder ein Salz davon und ein Salz, das ein zweibindiges oder dreibindiges Kation enthält, wobei das molare Verhältnis des zweibindigen oder dreibindigen Kations zu dem 7-Dimethylamino-tetracyclin größer als 3:1 ist und wobei durch das Lösen der festen Zusammensetzung in Wasser eine Lösung mit einem pH von größer als 4 und kleiner als 7 gebildet wird, wobei bevorzugt das 7-Dimethylaminotetracyclin-Antibiotikum oder ein Salz davon Minocyclin oder ein Salz davon darstellt.

12. Die Zusammensetzung gemäß Anspruch 11, wobei das molare Verhältnis des zweibindigen oder dreibindigen Kations zu dem 7-Dimethylaminotetracyclin-Antibiotikum größer als 5:1, bevorzugt größer als 8:1, weiter bevorzugt größer als 10:1 ist, oder wobei die Zusammensetzung in Form eines Lyophils vorliegt, oder wobei die Zusammensetzung Natriumacetat enthält, oder wobei die Zusammensetzung NaOH enthält, oder wobei das Salz ausgewählt ist aus Magnesiumchlorid, Magnesiumbromid, Magnesiumsulfat, Kalziumchlorid, Kalziumbromid, Kalziumsulfat, Zinkchlorid, Galliumchlorid, Magnesiummalat, Magensiumcitrat, Magnesiumacetat, Kalziumcitrat, Zinkacetat und Zinkcitrat, oder wobei die Zusammensetzung keine Komponente enthält, die aus der Gruppe bestehend aus einem Antioxidant, einer pyridinhaltigen Verbindung, Nikotinamid, Gluconat ausgewählt ist, oder wobei das 7-Dimethylaminotetracyclin ausgewählt ist aus PTK796 und einem Glycylcyclin.

13. Ein Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend:

Lösen der wasserlöslichen festen Zusammensetzung gemäß einem der Ansprüche 11 bis 12 in Wasser, um eine Lösung zu bilden.

14. Ein Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend:

Lösen eines 7-Dimethylamino-tetracyclins in einer Lösung, enthaltend ein zweibindiges oder dreibindiges Kation, wobei das molare Verhältnis des zweibindigen oder dreibindigen Kations zu dem 7-Dimethylaminotetracyclin in der Lösung größer als 3:1 ist, Einstellen des pH-Werts der Lösung, sodass dieser größer als 4 und kleiner als 7 ist, und Lyophilisieren der Zusammensetzung,
wobei das 7-Dimethylamino-tetracyclin bevorzugt ausgewählt ist aus Minocyclin, PTK796 und einem Glycylcyclin.

15. Das Verfahren gemäß Anspruch 14, wobei der pH der Lösung so eingestellt ist, dass er kleiner als 6, bevorzugt kleiner als 5 ist, oder wobei der pH der Lösung so eingestellt ist, dass er größer als 4 und kleiner als 6, bevorzugt größer als 4 und kleiner 5 ist, oder
wobei das Einstellen des pH-Werts die Zugabe einer Säure oder die Zugabe einer Base oder das Bilden eines Puffers umfasst, wobei es bevorzugt ist, dass die Säure HCl oder die Base NaOH ist, oder der Puffer das Zugeben von Natriumacetat umfasst, oder
wobei das zweibindige oder dreibindige Kation ausgewählt ist aus Eisen, Kupfer, Zink, Mangan, Nickel, Kobalt, Aluminium, Kalzium, Magnesium und Gallium.

16. Ein Kit, enthaltend:

einen ersten Behälter, der ein Verdünnungsmittel, das eine wässrige Lösung eines zweibindigen oder dreibindigen Kations umfasst, enthält und einen zweiten Behälter, der eine feste Zusammensetzung, die in dem Verdünnungsmittel löslich ist, enthält, wobei die feste Zusammensetzung (C) Minocyclin in einer Menge enthält, sodass das molare Verhältnis des divalenten oder trivalenten Kations zu Minocyclin größer als 2:1 ist, oder wobei die feste Zusammensetzung (D) ein 7-Dimethylamino-tetracyclin-Antibiotikum in einer Menge enthält, sodass das molare Verhältnis des divalenten oder trivalenten Kations zu dem 7-Dimethylamino-tetracyclin-Antibiotikum größer als 3:1 ist
und wobei das Lösen der festen Verbindung in dem Verbindungsmittel eine Lösung bewirkt, die einen pH von größer als 4 und kleiner als 7 aufweist.

17. Der Kit gemäß Anspruch 16, wobei das Verdünnungsmittel eine Säure oder eine Base oder einen Puffer umfasst, wobei es bevorzugt ist, dass die Säure HCl oder die Base NaOH ist oder das Verdünnungsmittel Natriumacetat enthält, oder
wobei der pH des Verdünnungsmittels größer als pH 6 und kleiner als pH 8 ist, oder
wobei das zweibindige oder dreibindige Kation ausgewählt ist aus Eisen, Kupfer, Zink, Mangan, Nickel, Kobalt, Aluminium, Kalzium, Magnesium und Gallium, oder
wobei das molare Verhältnis des zweibindigen oder dreibindigen Kations zu Minocyclin größer als 3:1 ist, oder
wobei das 7-Dimethylamino-tetracyclin der Alternative (D) ausgewählt ist aus Minocyclin, PTK796 und einem Glycylcyclin.

18. Der Kit gemäß Anspruch 16, wobei das molare Verhältnis des zweibindigen oder dreibindigen Kations zu dem Minocyclin oder dem 7-Dimethylaminotetracyclin-Antibiotikum größer als 5:1, bevorzugt größer als 8:1, weiter bevorzugt größer als 10:1 ist.

19. Der Kit gemäß Anspruch 18, die Zusammensetzung gemäß Anspruch 12 und das Verfahren gemäß Anspruch 15, wobei das Glycylcyclin Tigecyclin ist.

20. Die pharmazeutische Zusammensetzung gemäß einem der Ansprüche 1 bis 10 zur Verwendung bei der Behandlung oder der Vorbeugung einer bakteriellen Infektion bei einem Patienten, wobei die pharmazeutische Zusammensetzung über eine intravenöse Route oder über eine topische Route verabreicht wird.

21. Eine pharmazeutische Zusammensetzung, hergestellt nach dem Verfahren gemäß einem der Ansprüche 13 bis 15 für die Verwendung bei der Behandlung oder der Vorbeugung einer bakteriellen Infektion bei einem Patienten, wobei die pharmazeutische Zusammensetzung über eine intravenöse Route oder über eine topische Route verabreicht wird.

22. Die pharmazeutische Zusammensetzung gemäß einem der Ansprüche 20 oder 21, wobei eine intravenöse Dosis weniger als 200 ml der Zusammensetzung umfasst, oder
wobei die Zusammensetzung in weniger als 60 Minuten über eine intravenöse Route verabreicht wird.

23. Eine Zusammensetzung, enthaltend eine wässrige Lösung von Tigecyclin und ein zweibindiges oder dreibindiges Kation, wobei das molare Verhältnis des zweibindigen oder dreibindigen Kations zu dem Tigecyclin größer als 2:1 ist und wobei die Lösung einen pH von größer als 4 und kleiner als 7 aufweist, wobei bevorzugt das molare Verhältnis des zweibindigen oder dreibindigen Kations zu dem Tigecyclin größer als 3:1 ist.

Revendications

1. Composition pharmaceutique comprenant :

   A) une solution aqueuse d'un antibiotique de type 7-(diméthyl-amino)-tétracycline et de cation de magnésium, dans laquelle le rapport molaire du cation de magnésium à l'antibiotique de type 7-(diméthyl-amino)-tétracycline est supérieur à 2/1 et laquelle solution ne contient pas d'huile pharmacologiquement admissible, présente un pH supérieur à 4 et inférieur à 7, ainsi qu'une osmolalité inférieure à 500 mOsmol/kg, et convient pour administration par voie intraveineuse, et dans laquelle, de préférence, l'antibiotique de type 7-(diméthyl-amino)-tétracycline est de la minocycline ;
   B) ou une solution aqueuse de minocycline et de cation de magnésium, dans laquelle la concentration de minocycline vaut au moins 1 mg/mL et le rapport molaire du cation de magnésium à la minocycline est supérieur à 2/1, et laquelle solution présente un pH supérieur à 4 et inférieur à 5 et convient pour administration par voie intraveineuse.

2. Composition pharmaceutique conforme à la revendication 1, dans laquelle la solution ne contient pas de composant choisi dans l'ensemble formé par de l'huile de ricin hydrogénée et polyéthoxylée, un antioxydant, un composé comportant un fragment de type pyridine, du nicotinamide, un alcool, du glycérol, un polyéthylène-glycol, un gluconate, un composé de type pyrrolidone, un anesthésique local miscible à l'eau, de la procaïne, de l'urée, du lactose, et un agent déshydratant choisi dans l'ensemble constitué par les acétate d'éthyle, anhydride acétique, éthanol absolu, acétate d'éthyle, anhydride acétique et leurs mélanges.

3. Composition pharmaceutique conforme à la revendication 1, variante (A), dans laquelle la solution présente un pH inférieur à 7, de préférence inférieur à 6 et mieux encore inférieur à 5, ou dans laquelle la solution présente un pH supérieur à 4 et inférieur à 6, de préférence supérieur à 4 et inférieur à 5.

4. Composition pharmaceutique conforme à la revendication 1, dans laquelle

- le rapport molaire du cation divalent ou trivalent à la minocycline est supérieur à 3/1, de préférence supérieur à 5/1, mieux encore supérieur à 8/1, et surtout, supérieur à 10/1,
- ou l'osmolalité de la solution vaut moins de 400 mOsmol/kg, et de préférence moins de 350 mOsmol/kg,
- ou la solution contient un sel choisi dans l'ensemble formé par les sulfate de magnésium, oxyde de magnésium, acétate de magnésium et chlorure de magnésium,
- ou la solution comprend un tampon,
- ou la solution comprend une base.

5. Composition pharmaceutique conforme à la revendication 1, dans laquelle la concentration de minocycline vaut au moins 5 mg/mL, et de préférence, au moins 10 mg/mL.

6. Composition pharmaceutique conforme à la revendication 4, dans laquelle la solution comprend de l'ion acétate, ou la base comprend de l'hydroxyde de sodium.

7. Composition pharmaceutique conforme à la revendication 1, variante (A), dans laquelle la 7-(diméthyl-amino)-tétracycline est choisie parmi le composé PTK796 et une glycyl-cycline, cette glycylcycline étant de préférence la tigécycline.

8. Composition pharmaceutique conforme à la revendication 1, variante (A), comprenant :

- 10 mg/mL de minocycline, du chlorure de magnésium et de l'hydroxyde de sodium, le rapport molaire du magnésium à la minocycline valant 5/1 et le pH valant plus de 4,5 et moins de 5,5 ;
- ou 10 mg/mL de minocycline, du sulfate de magnésium et de l'acétate de sodium, le rapport molaire du magnésium à la minocycline valant 5/1, le pH valant plus de 4,5 et moins de 5,5 et l'osmolalité valant plus de 275 mOsmol/kg et moins de 375 mOsmol/kg ;
- ou 10 mg/mL de minocycline et de l'acétate de magnésium $Mg(C_2H_3O_2)_2$, le rapport molaire du magnésium à la minocycline valant 5/1 et le pH valant plus de 4,5 et moins de 5,5 ;
- ou 10 mg/mL de minocycline, du sulfate de magnésium et de l'hydroxyde de sodium, le rapport molaire du magnésium à la minocycline valant 5/1, le pH valant plus de 4,5 et moins de 5,5 et l'osmolalité valant plus de 150 mOsmol/kg et moins de 250 mOsmol/kg.

9. Composition pharmaceutique conforme à la revendication 1, variante (A), qui comprend 5 mg/mL de tigécycline, du chlorure ou du sulfate de magnésium, et de l'hydroxyde de sodium, et dans laquelle le rapport molaire du magnésium à la tigécycline vaut 5/1 et le pH vaut plus de 5,5 et moins de 6,5 ou bien le rapport molaire du magnésium à la tigécycline vaut 12/1 et le pH vaut plus de 5,5 et moins de 6,5,

10. Composition pharmaceutique conforme à la revendication 1, variante (A), appropriée pour administration par voie topique, qui comprend 5 mg/mL de tigécycline, du sulfate de magnésium et de l'hydroxyde de sodium, et dans laquelle le rapport molaire du magnésium à la tigécycline vaut 5/1 ou 12/1 et le pH vaut plus de 6,0 et moins de 7,0.

11. Composition solide soluble dans l'eau, comprenant un antibiotique de type 7-(diméthyl-amino)-tétracycline, ou un sel d'un tel antibiotique, et un sel comprenant un cation divalent ou trivalent, dans laquelle le rapport molaire du cation divalent ou trivalent à la 7-(diméthyl-amino)-tétracycline est supérieur à 3/1, laquelle composition solide donne, après dissolution dans de l'eau, une solution dont le pH vaut plus de 4 et moins de 7, et dans laquelle, de préférence, l'antibiotique de type 7-(diméthyl-amino)-tétracycline, ou le sel d'un tel antibiotique, est de la minocycline ou de l'un de ses sels.

12. Composition conforme à la revendication 11,

- dans laquelle le rapport molaire du cation divalent ou trivalent à la 7-(diméthyl-amino)-tétracycline est supérieur à 5/1, de préférence supérieur à 8/1 et mieux encore supérieur à 10/1,
- ou laquelle composition se présente sous forme de lyophilisat,

- ou laquelle composition comprend de l'acétate de sodium,
- ou laquelle composition comprend de l'hydroxyde de sodium,
- ou dans laquelle le sel est choisi parmi les chlorure de magnésium, bromure de magnésium, sulfate de magnésium, chlorure de calcium, bromure de calcium, sulfate de calcium, chlorure de zinc, chlorure de gallium, malate de magnésium, citrate de magnésium, acétate de magnésium, citrate de calcium, acétate de zinc et citrate de zinc,
- ou laquelle composition ne contient pas de composant choisi dans l'ensemble formé par un antioxydant, un composé comportant un fragment de type pyridine, du nicotinamide, et un gluconate,
- ou dans laquelle la 7-(diméthyl-amino)-tétracycline est choisie parmi le composé PTK796 et une glycyl-cycline.

13. Procédé de préparation d'une composition pharmaceutique, comportant le fait de dissoudre dans de l'eau une composition solide soluble dans l'eau, conforme à l'une des revendications 11 et 12, de manière à en faire une solution.

14. Procédé de préparation d'une composition pharmaceutique, comportant les étapes suivantes :

- dissoudre une 7-(diméthyl-amino)-tétracycline dans une solution comprenant un cation divalent ou trivalent, le rapport molaire du cation divalent ou trivalent à la 7-(diméthyl-amino)-tétracycline au sein de la solution étant supérieur à 3/1,
- ajuster le pH de la solution de telle sorte qu'il vaille plus de 4 et moins de 7,
- et lyophiliser la composition,

étant entendu que, de préférence, la 7-(diméthyl-amino)-tétracycline est choisie parmi la minocycline, le composé PTK796 et une glycylcycline.

15. Procédé conforme à la revendication 14, dans lequel

- on ajuste le pH de la solution de telle sorte qu'il vaille moins de 6, de préférence moins de 5, ou l'on ajuste le pH de la solution de telle sorte qu'il vaille plus de 4 et moins de 6, et de préférence, plus de 4 et moins de 5,
- ou l'ajustement du pH comporte l'addition d'un acide, l'addition d'une base ou la formation d'un tampon, et de préférence, l'acide est de l'acide chlorhydrique, ou la base est de l'hydroxyde de sodium, ou la formation d'un tampon comporte l'addition d'acétate de sodium,
- ou le cation divalent ou trivalent est choisi parmi les ions de fer, de cuivre, de zinc, de manganèse, de nickel, de cobalt, d'aluminium, de calcium, de magnésium, et de gallium.

16. Trousse comprenant

- un premier récipient comprenant un diluant qui comprend une solution aqueuse d'un cation divalent ou trivalent,
- et un deuxième récipient comprenant une composition solide soluble dans le diluant,

laquelle composition solide comprend (C) de la minocycline en une quantité telle que le rapport molaire du cation divalent ou trivalent à la minocycline vaut plus de 2/1,
ou laquelle composition solide comprend (D) un antibiotique de type 7-(diméthyl-amino)-tétracycline, en une quantité telle que le rapport molaire du cation divalent ou trivalent à l'antibiotique de type 7-(diméthyl-amino)-tétracycline vaut plus de 3/1,

- étant entendu que la dissolution de la composition solide dans le diluant donne une solution dont le pH vaut plus de 4 et moins de 7.

17. Trousse conforme à la revendication 16, dans laquelle

- le diluant comprend un acide, une base ou un tampon, et de préférence, l'acide est de l'acide chlorhydrique, ou la base est de l'hydroxyde de sodium, ou le tampon comprend de l'acétate de sodium,
- ou le pH du diluant est supérieur à 6 et inférieur à 8,
- ou le cation divalent ou trivalent est choisi parmi les ions de fer, de cuivre, de zinc, de manganèse, de nickel, de cobalt, d'aluminium, de calcium, de magnésium, et de gallium,
- ou le rapport molaire du cation divalent ou trivalent à la minocycline vaut plus de 3/1,
- ou la 7-(diméthyl-amino)-tétracycline de la variante (D) est choisie parmi la minocycline, le composé PTK796 et une glycyl-cycline.

18. Trousse conforme à la revendication 16, dans laquelle le rapport molaire du cation divalent ou trivalent à la minocycline ou à l'antibiotique de type 7-(diméthyl-amino)-tétracycline est supérieur à 5/1, de préférence supérieur à 8/1 et mieux encore supérieur à 10/1.

19. Trousse conforme à la revendication 18, composition conforme à la revendication 12, et procédé conforme à la revendication 15, dans laquelle ou lequel la glycyl-cylcine est de la tigécycline.

20. Composition pharmaceutique conforme à l'une des revendications 1 à 10 pour utilisation dans le traitement ou la prévention d'une infection bactérienne chez un sujet, laquelle composition pharmaceutique est administrée par voie intraveineuse ou par voie topique.

21. Composition pharmaceutique, préparée selon un procédé conforme à l'une des revendications 13 à 15, pour utilisation dans le traitement ou la prévention d'une infection bactérienne chez un sujet, laquelle composition pharmaceutique est administrée par voie intraveineuse ou par voie topique.

22. Composition pharmaceutique conforme à l'une des revendications 20 et 21, de laquelle composition une dose pour intraveineuse comprend moins de 200 mL, ou laquelle composition est administrée en moins de 60 minutes par voie intraveineuse.

23. Composition comprenant une solution aqueuse de tigécycline et d'un cation divalent ou trivalent, dans laquelle le rapport molaire dudit cation divalent ou trivalent à ladite tigécycline est supérieur à 2/1, et laquelle solution présente un pH supérieur à 4 et inférieur à 7, et dans laquelle, de préférence, le rapport molaire dudit cation divalent ou trivalent à ladite tigécycline est supérieur à 3/1.

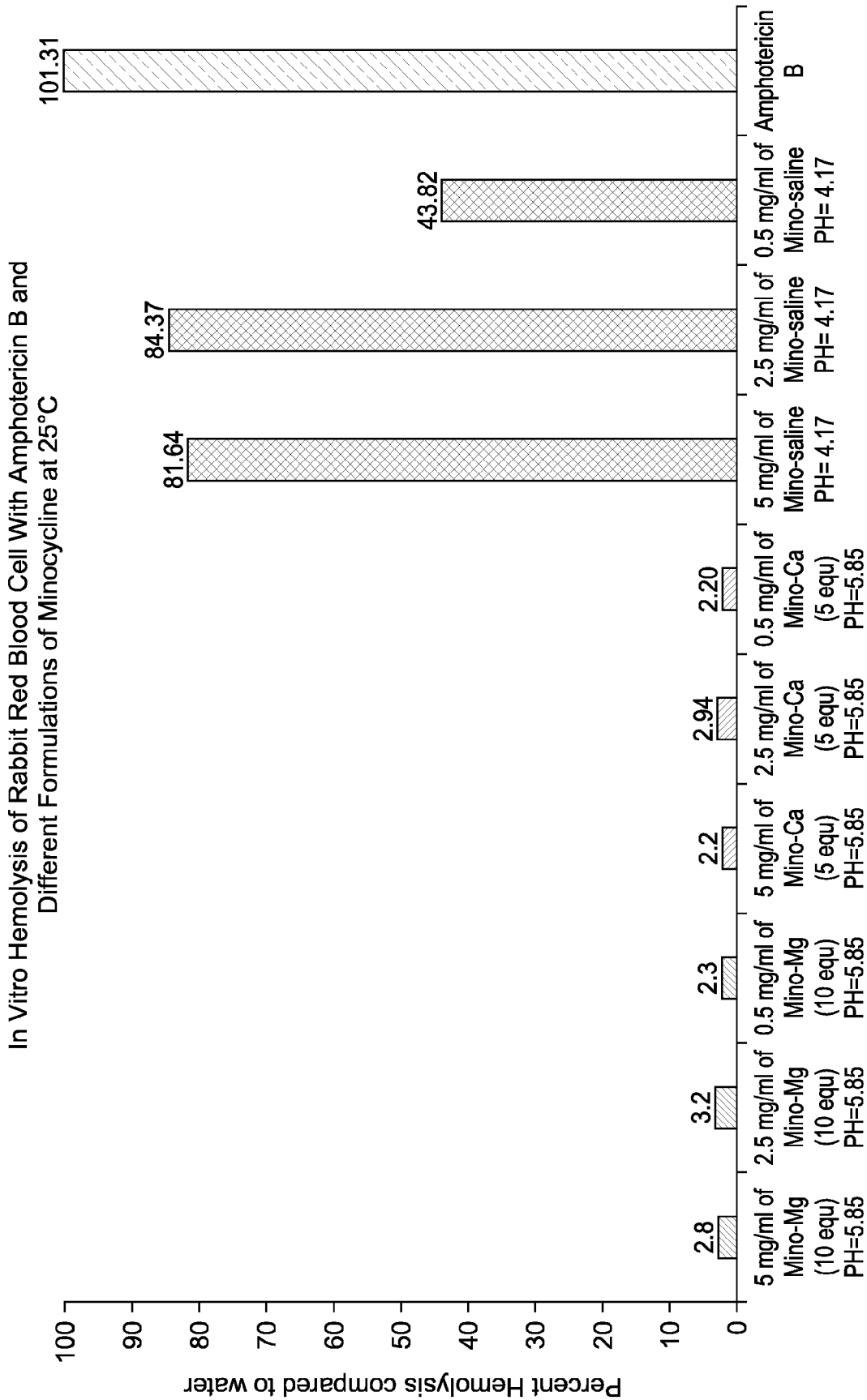

In Vitro Hemolysis of Rabbit Red Blood Cell With Amphotericin B and Different Formulations of Minocycline at 25°C
Percent Hemolysis compared to water
0
10
20
30
40
50
60
70
80
90
100
2.8
3.2
2.3
2.2
2.94
2.20
81.64
84.37
43.82
101.31
5 mg/ml of Mino-Mg (10 equ) PH=5.85
2.5 mg/ml of Mino-Mg (10 equ) PH=5.85
0.5 mg/ml of Mino-Mg (10 equ) PH=5.85
5 mg/ml of Mino-Ca (5 equ) PH=5.85
2.5 mg/ml of Mino-Ca (5 equ) PH=5.85
0.5 mg/ml of Mino-Ca (5 equ) PH=5.85
5 mg/ml of Mino-saline PH= 4.17
2.5 mg/ml of Mino-saline PH= 4.17
0.5 mg/ml of Mino-saline PH= 4.17
Amphotericin B

FIG. 1

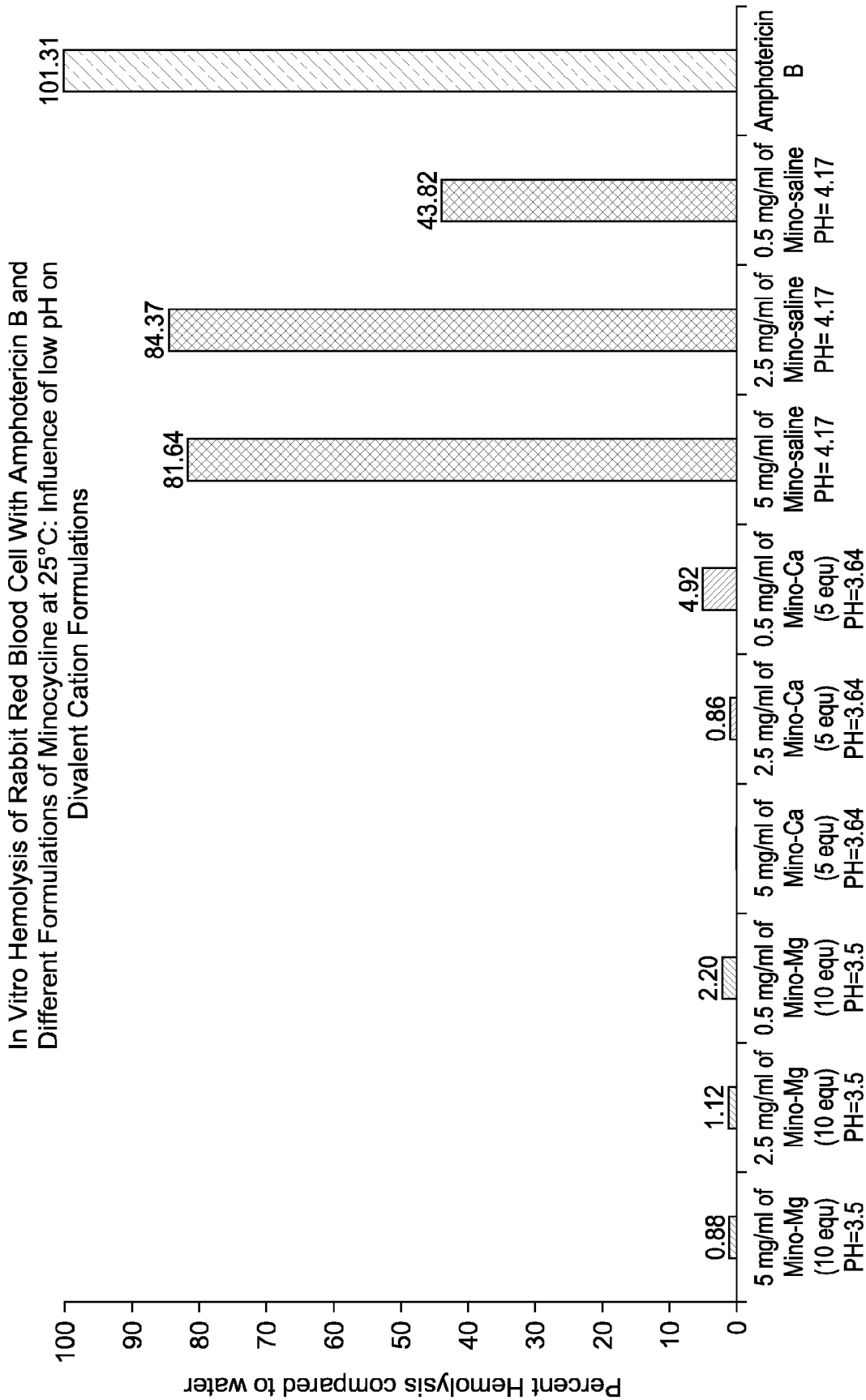

In Vitro Hemolysis of Rabbit Red Blood Cell With Amphotericin B and Different Formulations of Minocycline at 25°C: Influence of low pH on Divalent Cation Formulations
Percent Hemolysis compared to water
0
10
20
30
40
50
60
70
80
90
100
0.88
1.12
2.20
0.86
4.92
81.64
84.37
43.82
101.31
5 mg/ml of Mino-Mg (10 equ) PH=3.5
2.5 mg/ml of Mino-Mg (10 equ) PH=3.5
0.5 mg/ml of Mino-Mg (10 equ) PH=3.5
5 mg/ml of Mino-Ca (5 equ) PH=3.64
2.5 mg/ml of Mino-Ca (5 equ) PH=3.64
0.5 mg/ml of Mino-Ca (5 equ) PH=3.64
5 mg/ml of Mino-saline PH= 4.17
2.5 mg/ml of Mino-saline PH= 4.17
0.5 mg/ml of Mino-saline PH= 4.17
Amphotericin B

FIG. 2

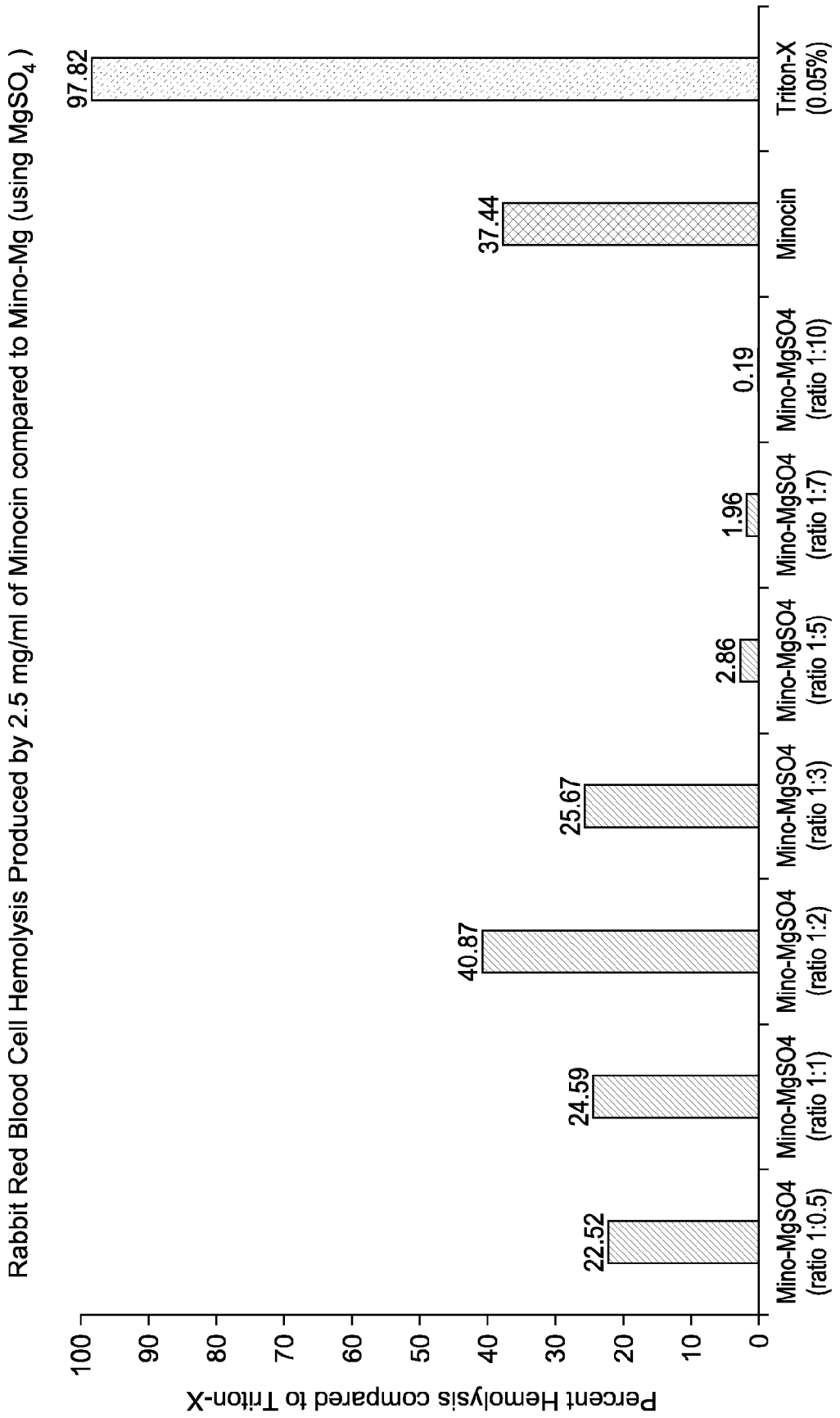

Rabbit Red Blood Cell Hemolysis Produced by 2.5 mg/ml of Minocin compared to Mino-Mg (using MgSO4)
Percent Hemolysis compared to Triton-X
0
10
20
30
40
50
60
70
80
90
100
22.52
24.59
40.87
25.67
2.86
1.96
0.19
37.44
97.82
Mino-MgSO4 (ratio 1:0.5)
Mino-MgSO4 (ratio 1:1)
Mino-MgSO4 (ratio 1:2)
Mino-MgSO4 (ratio 1:3)
Mino-MgSO4 (ratio 1:5)
Mino-MgSO4 (ratio 1:7)
Mino-MgSO4 (ratio 1:10)
Minocin
Triton-X (0.05%)

FIG. 3

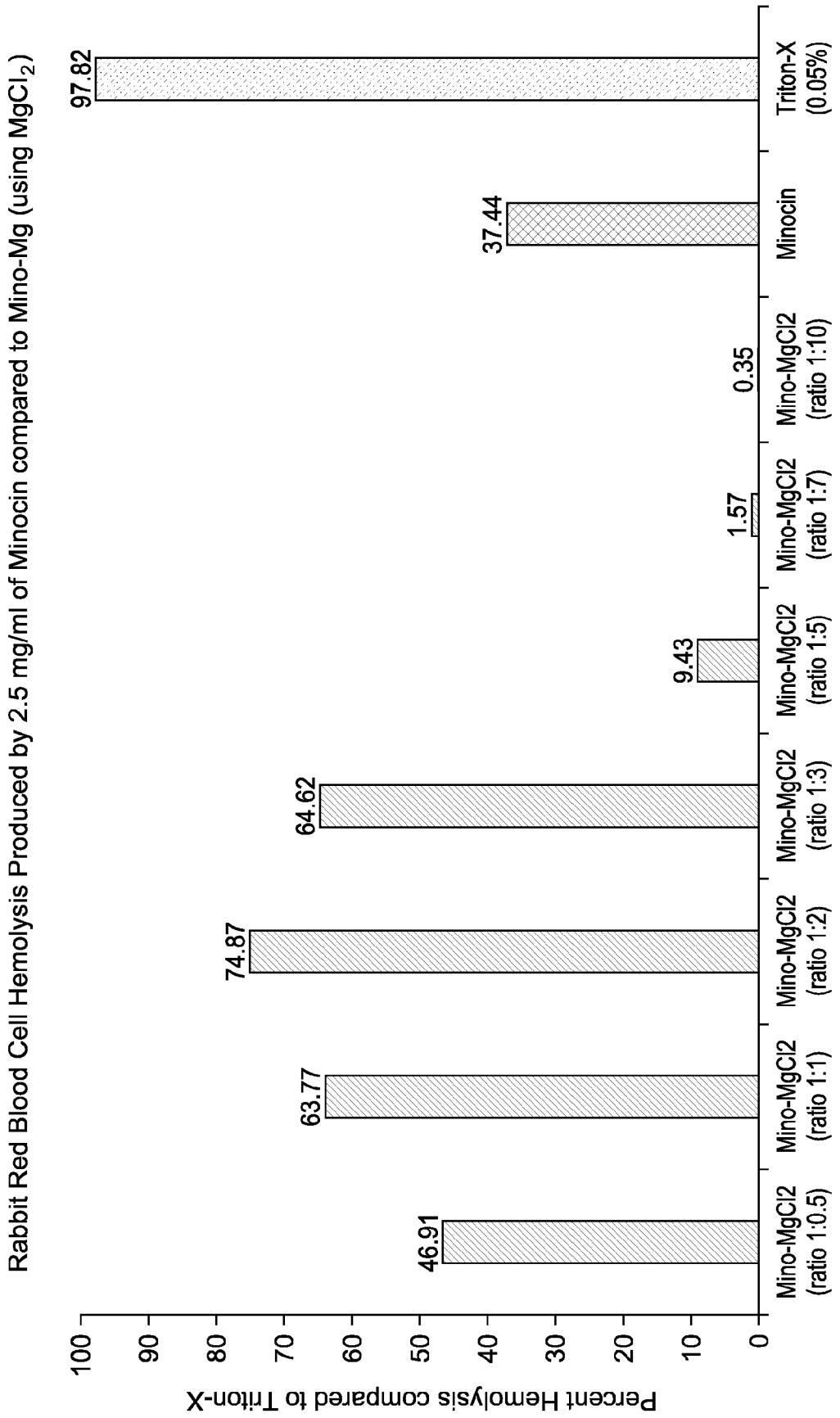

Rabbit Red Blood Cell Hemolysis Produced by 2.5 mg/ml of Minocin compared to Mino-Mg (using $MgCl_2$)
Percent Hemolysis compared to Triton-X
0
10
20
30
40
50
60
70
80
90
100
46.91
63.77
74.87
64.62
9.43
1.57
0.35
37.44
97.82
Mino-MgCl2 (ratio 1:0.5)
Mino-MgCl2 (ratio 1:1)
Mino-MgCl2 (ratio 1:2)
Mino-MgCl2 (ratio 1:3)
Mino-MgCl2 (ratio 1:5)
Mino-MgCl2 (ratio 1:7)
Mino-MgCl2 (ratio 1:10)
Minocin
Triton-X (0.05%)

FIG. 4

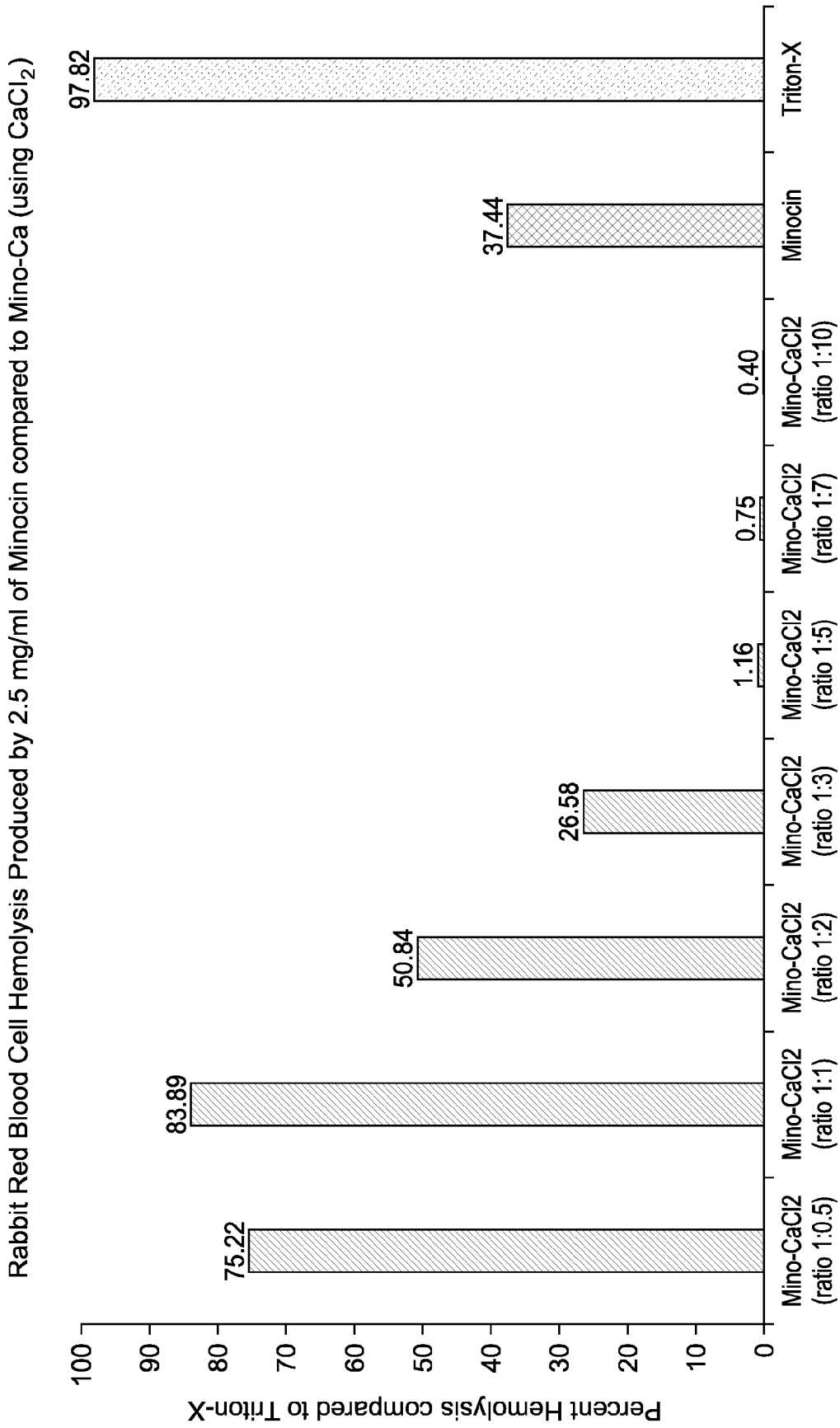

Rabbit Red Blood Cell Hemolysis Produced by 2.5 mg/ml of Minocin compared to Mino-Ca (using $CaCl_2$)
Percent Hemolysis compared to Triton-X
0
10
20
30
40
50
60
70
80
90
100
75.22
83.89
50.84
26.58
1.16
0.75
0.40
37.44
97.82
Mino-CaCl2 (ratio 1:0.5)
Mino-CaCl2 (ratio 1:1)
Mino-CaCl2 (ratio 1:2)
Mino-CaCl2 (ratio 1:3)
Mino-CaCl2 (ratio 1:5)
Mino-CaCl2 (ratio 1:7)
Mino-CaCl2 (ratio 1:10)
Minocin
Triton-X

FIG. 5

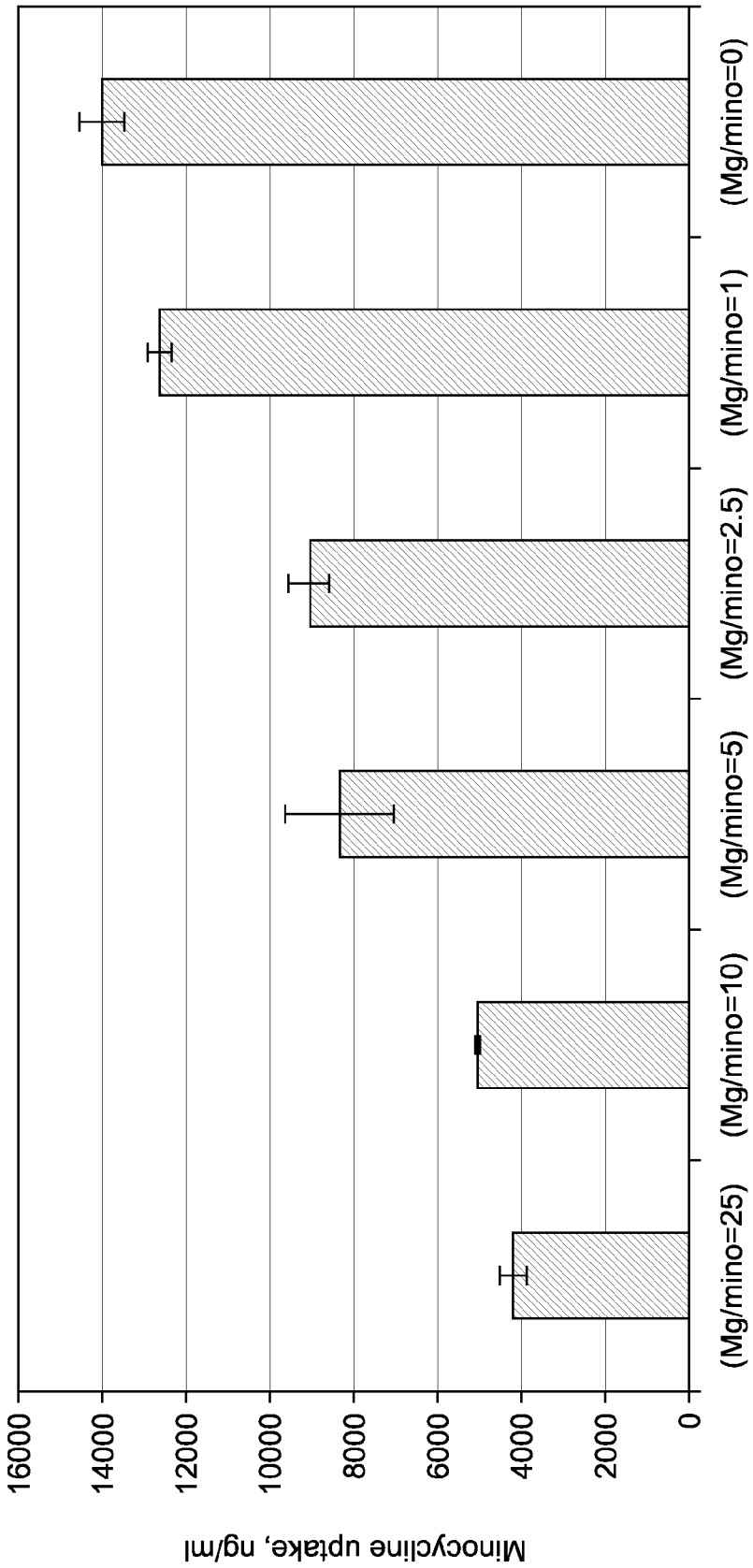

Minocycline uptake, ng/ml
16000
14000
12000
10000
8000
6000
4000
2000
0
(Mg/mino=25)
(Mg/mino=10)
(Mg/mino=5)
(Mg/mino=2.5)
(Mg/mino=1)
(Mg/mino=0)

FIG. 6

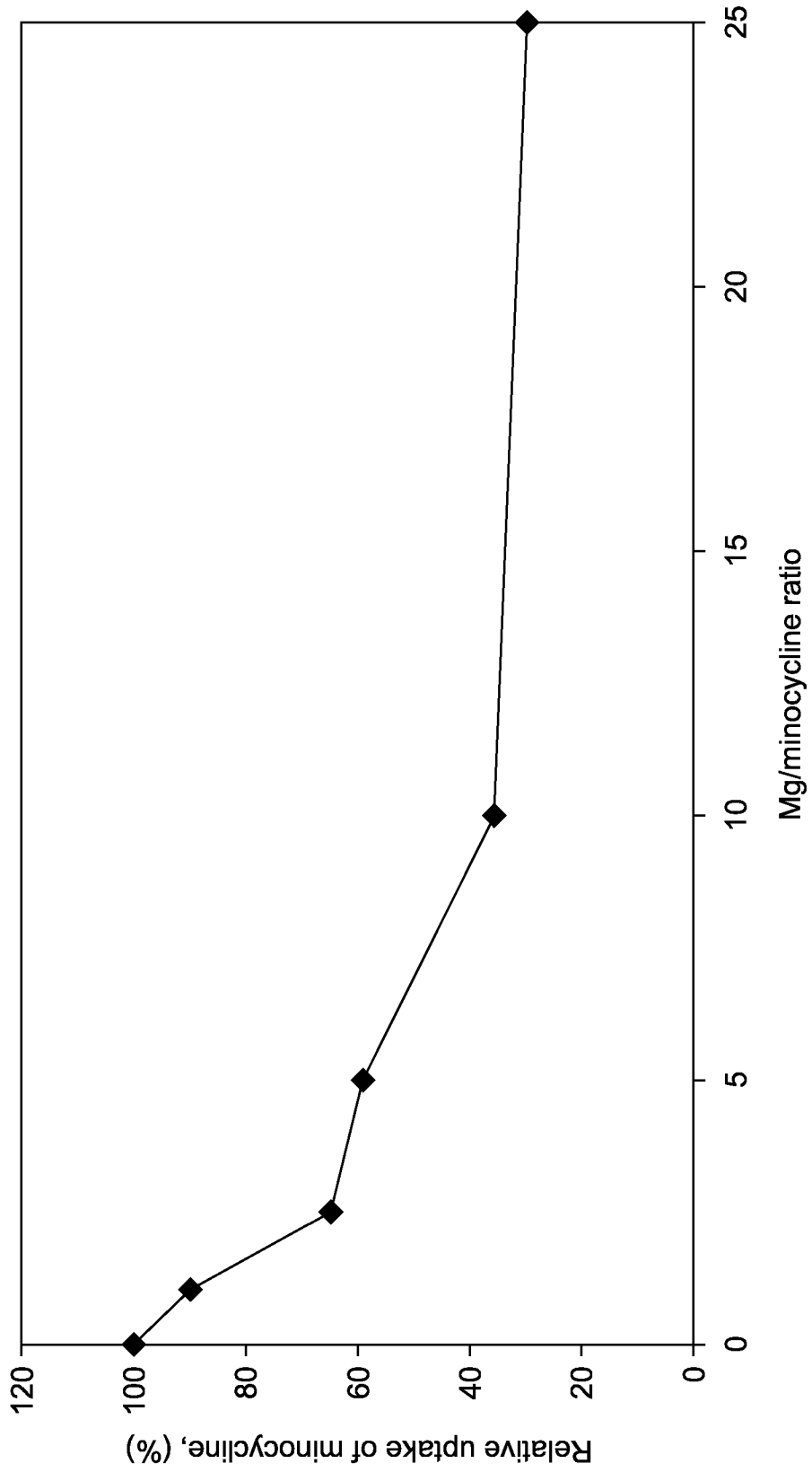

Relative uptake of minocycline, (%)
120
100
80
60
40
20
0
0
5
10
15
20
25
Mg/minocycline ratio

FIG. 7

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

- Remington's Pharmaceutical Sciences. Mack Publishing Company **[0108]**

TETRACIKLIN-KÉSZÍTMÉNYEK

Szabadalmi igénypontok

1. Gyógyászati készítmény, amely tartalmazza

(A) 7-dimetilamino-tetraciklin antibiotikum és magnézium kation vizes oldatát, ahol a magnézium kation mólaránya 7-dimetilamino-tetraciklin antibiotikumhoz képest nagyobb, mint 2:1, és ahol az oldat nem tartalmaz gyógyászatilag elfogadható olajat, pH-ja magasabb, mint 4 és alacsonyabb, mint 7, ozmolalitása alacsonyabb, mint 500 mOsmol/kg és alkalmas intravénás beadásra, ahol előnyösen a 7-dimetilamino-tetraciklin antibiotikum minociklin vagy

(B) minociklin és magnézium kation vizes oldatát, ahol a minociklin koncentrációja legalább 1 mg/ml, ahol a magnézium kation mólaránya a minociklinhez képest nagyobb, mint 2:1, és ahol az oldat pH-ja magasabb, mint 4 és alacsonyabb, mint 5, és alkalmas intravénás beadásra.

2. Az 1. igénypont szerinti gyógyászati készítmény, ahol az oldat nem tartalmaz a következők alkotta csoportból választott összetevőt: polioxietilén hidrogénezett ricinusolaj, antioxidáns, pirinintartalmú vegyület, nikotinamid, alkohol, glicerin, polietilén-glikol, glükonát, pirrolidonvegyület, vízzel elegyedő, lokális anesztetikum, prokain, karbamid, laktóz és a következők alkotta csoportból választott dehidratálószer: etil-acetát, ecetsav-anhidrid, abszolút etanol, etil-acetát, ecetsav-anhidrid és ezek keverékei.

3. Az 1. igénypont (A) változat szerinti gyógyászati készítmény, ahol az oldat pH-ja alacsonyabb, mint 7, előnyösen alacsonyabb, mint 6, még előnyösebben alacsonyabb, mint 5 vagy ahol az oldat pH-ja magasabb, mint 4 és alacsonyabb, mint 6, előnyösen magasabb, mint 4 és alacsonyabb, mint 5.

4. Az 1. igénypont szerinti gyógyászati készítmény, ahol a kétértékű vagy háromértékű kationok mólaránya a minociklinhez képest nagyobb, mint 3:1, előnyösen nagyobb, mint 5:1, még előnyösebben nagyobb, mint 8:1, még sokkal előnyösebben nagyobb, mint 10:1,

vagy ahol az oldat ozmolalitása alacsonyabb, mint 400 mOsmol/kg, előnyösen alacsonyabb, mint 350 mOsmol/kg,

vagy ahol az oldat tartalmaz sót, amely a következők alkotta csoportból választott: magnézium-szulfát, magnézium-oxid, magnézium-acetát és magnézium-klorid,

vagy ahol az oldat puffert tartalmaz,

vagy ahol az oldat bázist tartalmaz.

5. Az 1. igénypont szerinti gyógyászati készítmény, ahol a minociklin koncentrációja legalább 5 mg/ml, előnyösebben legalább 10 mg/ml.

6. A 4. igénypont szerinti gyógyászati készítmény, amelyben az oldat acetátot tartalmaz vagy amelyben a bázis NaOH-t tartalmaz.

7. Az 1. igénypont (A) változat szerinti gyógyászati készítmény, amelyben a 7-dimetilamino-tetraciklin a következők közül választott: PTK796 és glicilciklin, ahol előnyösen a glicilciklin tigeciklin.

8. Az 1. igénypont (A) változat szerinti gyógyászati készítmény, amely tartalmaz:

10 mg/ml minociklint, $MgCl_2$-t és NaOH-t, ahol a Mg mólaránya a minociklinhez képest 5:1, és a pH magasabb, mint 4,5 és alacsonyabb, mint 5,5, vagy 10 mg/ml minociklint, $MgSO_4$-t és nátrium-acetátot, ahol a Mg mólaránya a minociklinhez képest 5:1, és a pH magasabb, mint 4,5 és alacsonyabb, mint 5,5, és az

ozmolalitás magasabb, mint 275 mOsm/kg és alacsonyabb, mint 375 mOsm/kg, vagy

10 mg/ml minociklint, $Mg(C_2H_3O_2)_2$-t, ahol a Mg mólaránya a minociklinhez képest 5:1, és a pH magasabb, mint 4,5 és alacsonyabb, mint 5,5, vagy 10 mg/ml minociklint, $MgSO_4$-t és NaOH-t, ahol a Mg mólaránya a minociklinhez képest 5:1, és a pH magasabb, mint 4,5 és alacsonyabb, mint 5,5, és az ozmolalitás magasabb, mint 150 mOsm/kg és alacsonyabb, mint 250 mOsm/kg,

9. Az 1. igénypont (A) változat szerinti gyógyászati készítmény, amely 5 mg/ml tigeciklint, $MgCl_2$-t vagy $MgSO_4$-t és NaOH-t tartalmaz, ahol a Mg mólaránya a tigeciklinhez képest 5:1, és a pH magasabb, mint 5,5 és alacsonyabb, mint 6,5, vagy ahol a Mg mólaránya a tigeciklinhez képest 12:1, és a pH magasabb, mint 5,5 és alacsonyabb, mint 6,5.

10. Az 1. igénypont (A) változat szerinti gyógyászati készítmény, amely alkalmas topikális beadásra, és amely 5 mg/ml tigeciklint, $MgSO_4$-t és NaOH-t tartalmaz, ahol a Mg mólaránya a tigeciklinhez képest 5:1 vagy 12:1, és a pH magasabb, mint 6,0 és alacsonyabb, mint 7,0.

11. Vízoldható szilárd készítmény, amely tartalmaz 7-dimetilamino-tetraciklin antibiotikumot vagy tartalmazza annak sóját, továbbá a kétértékű vagy háromértékű kationt tartalmazó sót, ahol a kétértékű vagy háromértékű kationok mólaránya a 7-dimetilamino-tetraciklin antibiotikumhoz képest nagyobb, mint 3:1, és ahol a szilárd készítmény vízben történő feloldása során 4-nél magasabb és 7-nél alacsonyabb pH-értékű oldat keletkezik, előnyösen ahol a 7-dimetilamino-tetraciklin antibiotikum vagy sója minociklin vagy sója.

12. A 11. igénypont szerinti készítmény, ahol a kétértékű vagy háromértékű kationok mólaránya a 7--dimetilamino-tetraciklin antibiotikumhoz képest nagyobb, mint 5:1, előnyösen nagyobb, mint 8:1, előnyösen nagyobb, mint 10:1, vagy ahol a készítmény liofil formában van jelen, vagy ahol a készítmény nátrium acetátot tartalmaz, vagy ahol a készítmény NaOH-t tartalmaz, vagy ahol a só a következők közül választott: magnézium-klorid, magnézium-bromid, magnézium-szulfát, kalcium-klorid, kalcium-bromid, kalcium-szulfát, cink-klorid, gallium-klorid, magnézium-malát, magnézium-citrát, kalcium-citrát, cink-acetát és cink-citrát, vagy ahol a készítmény nem tartalmaz a következők alkotta csoportból választott összetevőt: antioxidáns, pridin-tartalmú vegyület, nikotinamid, glükonát vagy ahol a 7-dimetilamino-tetraciklin antibiotikum PTK796 és glicilciklin közül választott.

13. Eljárás gyógyászati készítmény elállítására, amely tartalmazza a 11-12. igénypontok bármelyike szerinti vízoldható szilárd készítmény feloldását vízben oldatot létrehozva.

14. Eljárás gyógyászati készítmény előállítására, amely tartalmazza a következőket:
7-dimetilamino-tetraciklin feloldását oldatban, amely tartalmaz kétértékű vagy háromértékű kationt, ahol a kétértékű vagy háromértékű kationok mólaránya a 7-dimetilamino-tetraciklinhez képest nagyobb, mint 3:1,
az oldat pH-jának beállítását 4-nél magasabb és 7-nél alacsonyabb értékre; és
a készítmény liofilizálását.

15. A 14. igénypont szerinti eljárás, ahol az oldat pH-ját 6-nál alacsonyabb, előnyösen 5-nél alacsonyabb értékre állítjuk be, vagy ahol az oldat pH-ját 4-nél magasabb és 6-nál alacsonyabb, előnyösen 4-nél magasabb és 5-nél alacsonyabb értékre állítjuk be, vagy
ahol a pH beállítása tartalmazza sav hozzáadását vagy bázis hozzáadását vagy puffer kialakítását, előnyösen a sav HCl vagy a bázis NaOH, vagy a puffer tartalmazza nátrium-acetát hozzáadását, vagy
ahol a kétértékű vagy háromértékű kation a következők közül választott: vas, réz, cink, mangán, nikkel, kobalt, alumínium, kalcium, magnézium és gallium.

16. Készlet, amely tartalmaz:

első konténert, amely kétértékű vagy háromértékű kation vizes oldatát tartalmazó hígítószert tartalmaz; és

második konténer, amely tartalmaz egy, a hígítószerben oldható szilárd készítményt, ahol a szilárd készítmény tartalmaz (C) minociklint olyan mennyiségben, hogy a kétértékű vagy háromértékű kation mólaránya a minociklinhez képest nagyobb, mint 2:1, vagy

ahol a szilárd készítmény tartalmaz (D) 7-dimetilamino-tetraciklin antibiotikumot olyan mennységben, hogy a kétértékű vagy háromértékű kation mólaránya a 7-dimetilamino-tetraciklin antibiotikumhoz képest nagyobb, mint 3:1,

és ahol a szilárd készítmény feloldása a hígítószerben 4-nél magasabb és 7-nél alacsonyabb pH-jú oldatot eredményez.

17. A 16. igénypont szerinti készlet, ahol a hígítószer tartalmaz savat vagy bázist vagy puffert; és előnyösen a sav HCl vagy a bázis NaOH vagy a hígítószer tartalmaz nátrium-acetátot vagy ahol a hígítószer pH-ja magasabb, mint 6 és alacsonyabb, mint 8, vagy

ahol a kétértékű vagy háromértékű kation a következők közül választott: vas, réz, cink, mangán, nikkel, kobalt, alumínium, kalcium, magnézium és gallium, vagy

ahol a kétértékű vagy háromértékű kation mólaránya a minociklinhez képest nagyobb, mint 3:1 vagy ahol a (D) változat szerinti 7-dimetilamino-tetraciklin a következők alkotta csoportból választott: minociklin, PTK796 és glicilciklin.

18. A 16. igénypont szerinti készlet, ahol a kétértékű vagy háromértékű kationok mólaránya a minociklinhez képest nagyobb, mint 5:1, előnyösen nagyobb, mint 8:1, még előnyösebben nagyobb, mint 10:1.

19. A 18. igénypont szerinti készlet, a 12. igénypont szerinti készítmény vagy a 15. igénypont szerinti eljárás, ahol a glicilciklin tigeciklin.

20. Az 1-10. igénypontok bármelyike szerinti, gyógyászati készítmény személyben bakteriális fertőzés kezelésében vagy megelőzésében történő alkalmazásra, ahol a gyógyászati készítmény intravénás úton vagy topikális úton beadott.

21. A 13-15. igénypontok bármelyike szerinti eljárással elkészített gyógyászati készítmény személyben bakteriális fertőzés kezelésében vagy megelőzésében történő alkalmazásra, ahol a gyógyászati készítmény intravénás úton vagy topikális úton beadott.

22. A 20-21. igénypontok bármelyike szerinti gyógyászati készítmény, ahol intravénás dózis kevesebb mint 200 ml készítményt tartalmaz vagy

ahol a készítmény intravénás úton kevesebb, mint 60 perc alatt beadott.

23. Tigeciklin vizes oldatát és kétértékű vagy háromértékű kationt tartalmazó készítmény, ahol a kétértékű vagy háromértékű kation mólaránya a tigeciklinhez képest nagyobb, mint 2:1, és ahol az oldat pH-ja magasabb, mint 4 és alacsonyabb, mint 7, előnyösen ahol a kétértékű vagy háromértékű kation mólaránya a tigeciklinhez képest nagyobb, mint 3:1.