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(54) Title: EXTENDED RELEASE MINOCYCLINE COMPOSITIONS AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The present invention relates to extended or controlled release pharmaceutical compositions of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline) or non-toxic acid addition salts thereof. More particularly, it relates to a once-a-day delivery system for minocycline that maintains its therapeutic plasma concentrations in a patient for twenty-four hours. The extended release pharmaceutical composition includes a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration. Each hydrophilic matrix forming polymer differs at least in viscosity.

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EXTENDED RELEASE MINOCYCLINE COMPOSITIONS AND PROCESSES FOR THEIR PREPARATION

Technical Field of the Invention

The present invention relates to extended release pharmaceutical compositions of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline) or non-toxic acid addition salts thereof. More particularly, it relates to once-a-day delivery systems for minocycline that maintain the therapeutic plasma concentrations in a patient for twenty-four hours.

Background of the Invention

Minocycline and its non-toxic acid addition salts are widely used in therapy primarily for their antimicrobial effects. The preparation of minocycline is disclosed in U.S. Patent Nos. 3,148,212 and 3,226,436.

Minocycline hydrochloride, a pharmaceutically acceptable salt of the drug, has been available in the United States in the form of immediate release oral capsules containing 100 mg of the drug. It is typically administered in doses of about 200 mg initially followed by 100 mg every twelve hours; or 200 mg initially followed by 50 mg every six hours in humans. Oral dosage units typically include from about 50 mg to about 100 mg of minocycline hydrochloride.

Minocycline is absorbed at different rates in different portions of the gastrointestinal tract. Traditional pharmaceutical forms and delayed release forms containing minocycline require frequent ingestion of multiple doses per day, resulting in wide variations in serum concentration throughout the course of treatment, and ultimately in poor patient compliance. There have been many attempts to prepare controlled release formulations of minocycline, with varying degrees of success.

U.S. Patent No. 5,283,065 discloses a controlled release pharmaceutical composition in oral tablet dosage form comprising two types of granules, active granules and compressible granules. The active granules include the active ingredient blended with a diluent and the compressible granules include a mono- or disaccharide in a diffusible matrix. The compressible granules distort and fill voids to provide a cushion to prevent the active granules from breaking during the tableting process. This protects against any loss of controlled release properties.

U.S. Patent No. 5,413,777 discloses a pulsatile once-a-day delivery system which maintains therapeutic blood level concentrations of minocycline in a patient for twenty-four hours by once-a-day administration. The dosage form comprises an initial loading or first pulse of minocycline powder or minocycline containing coated or uncoated quick release granules. It

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also includes a second loading or second pulse of minocycline containing pH sensitive polymer coated spherical granules, administered either simultaneously or separately up to about 120 minutes apart.

The approaches used by the prior art are either based on the use of enteric polymers or on preparing different types of granules. These approaches make the process complicated, expensive, and time-consuming. The present invention relates to an extended release composition of minocycline that addresses the problems associated with the prior art.

Summary of the Invention

In one general aspect there is provided an extended release pharmaceutical composition that includes a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration. Each hydrophilic matrix forming polymer differs at least in viscosity.

Embodiments of the extended release pharmaceutical composition may include one or more of the following features. For example, the hydrophilic matrix forming polymers may be cellulose derivatives. The cellulose derivatives may be a mixture of at least two different viscosity grades. The cellulose derivatives may be one or more of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose or combinations thereof. The cellulose derivative may be hydroxypropyl methylcellulose and/or hydroxypropyl cellulose. The cellulose derivative may be a mixture of low viscosity and medium viscosity grades of hydroxypropyl methylcellulose. The cellulose derivative may be a mixture of low viscosity and medium viscosity grades of hydroxypropyl cellulose.

The concentration of the hydrophilic matrix forming polymers may range from about 5.0 to about 25 weight percent of the total composition.

The minocycline non-toxic acid addition salt may be a hydrochloride.

The composition may further include one or more pharmaceutically acceptable excipients. The pharmaceutical excipients may be one or more diluents, binders, lubricants, glidants, disintegrants, colorants and flavoring agents.

The pharmaceutical composition may be in the form of pellets, beads, granules, tablets or pill and, in particular, in the form of a tablet. The tablet may be prepared by direct compression, wet granulation or compaction. The tablet may further include a coating. The coating may be

non-functional or functional. The functional coating may be an enteric coating. The enteric coating may be acrylic polymers or cellulose ethers. The cellulose ether may be one or more of hydroxypropyl cellulose, hydroxypropyl methylcellulose or mixtures thereof.

The pharmaceutical composition may have an area-under-the-curve (AUC) comparable to the area-under-the-curve (AUC) of the commercially available twice-daily immediate release dosage form.

In another general aspect there is provided an extended release pharmaceutical composition that includes a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration. The extended release pharmaceutical composition when administered once daily has an Area Under the Curve within 80% and 125% of the commercially available minocycline hydrochloride administered twice daily.

Embodiments of the composition may include any one or more of the features described above or the following. For example, the hydrophilic matrix forming polymers may be two or more cellulose derivatives. The cellulose derivatives may be a mixture of at least two different viscosity grades.

In another general aspect there is provided a process for preparing an extended release pharmaceutical composition that includes a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration. Each polymer differs at least in viscosity. The process includes: dry blending minocycline with two or more hydrophilic polymers to form a blend, granulating the blend, drying and sizing the granules, and compressing the dried and sized granules.

Embodiments of the process may include any one or more of the features described above or the following. For example, the process may further include dry blending the minocycline and hydrophilic polymers with additional pharmaceutical excipients.

The hydrophilic polymers may be cellulose derivatives. The cellulose derivatives may be a mixture of two different viscosity grades. The cellulose derivatives may be one or more of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose or combinations thereof. The cellulose derivative may be hydroxypropyl methylcellulose and/or hydroxypropyl cellulose.

The cellulose derivative may be a mixture of low viscosity and medium viscosity grades of hydroxypropyl methylcellulose. The cellulose derivative may be a mixture of low viscosity and medium viscosity grades of hydroxypropyl cellulose. The concentration of the hydrophilic polymers may range from about 5.0 to about 25 weight percent of the total composition.

The minocycline non-toxic acid addition salt may be hydrochloride.

The composition may be in the form of pellets, beads, granules, tablets or pills. If a tablet, the tablet may be prepared by direct compression, wet granulation or compaction. The process may further include coating the tablet. The coating may be a non-functional or a functional coating. The functional coating may be an enteric coating. The enteric coating may be acrylic polymers or cellulose ethers.

In another general aspect there is provided a method of treating a bacterial infection in a mammal. The method includes administering an extended release pharmaceutical composition that includes a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration. Each polymer differs at least in viscosity.

Embodiments of the method of treating may include any one or more of the features described above.

In another general aspect there is provided a method of treating a bacterial infection in a mammal. The method includes administering an extended release pharmaceutical composition comprising a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration. The extended release pharmaceutical composition administered once daily has an Area Under the Curve within 80% and 125% of the commercially available minocycline hydrochloride administered twice daily.

Embodiments of the method of treating may include any one or more of the features described above or the following. For example, the hydrophilic matrix forming polymers may include two or more cellulose derivatives. The cellulose derivatives may be a mixture of at least two different viscosity grades.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

In seeking to develop extended release minocycline dosage forms, the inventors have developed a number of dosage forms and processes for their preparation. For example, the inventors have developed an extended release pharmaceutical composition that includes 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline) or non-toxic acid addition salts thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration. Within these dosage forms the hydrophilic matrix forming polymers differ at least in viscosity.

The term hydrophilic matrix, as used herein, refers to a generally uniform mixture of the minocycline, hydrophilic polymers and, optionally, other pharmaceutically acceptable excipients.

Suitable hydrophilic polymers may include one or more cellulose derivatives such as hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose or combinations thereof.

An improved release profile can also be obtained by mixing polymers with different swelling properties, such as hydroxypropyl methylcellulose and sodium carboxymethylcellulose, or by using the different viscosity grades of the same polymer. For example, the improved release profile can be provided by a mixture of low and medium viscosity grades of hydroxypropyl methylcellulose or hydroxypropyl cellulose.

The hydrophilic polymers may be further characterized according to their viscosities in a 2% w/w aqueous solution. They can be defined as low viscosity (less than about 1,000 cPs), medium viscosity (about 1,000 cPs to about 10,000 cPs), and high viscosity (greater than about 10,000 cPs) polymers.

Suitable hydroxypropyl methylcellulose polymers of a low viscosity grade include one or more of those available under the brand names Methocel E5, Methocel E-15 LV, Methocel E50 LV, Methocel K100 LV and Methocel F50 LV whose 2% by weight aqueous solutions have viscosities of 5 cPs, 15 cPs, 50 cPs, 100 cPs and 50 cPs, respectively. Suitable hydroxypropyl methylcellulose polymers having medium viscosity may include one or more of those available under the brand names Methocel E4M and Methocel K4M both of whose 2% by weight aqueous solutions have a viscosity of 4000 cPs. Suitable hydroxypropyl methylcellulose polymers having high viscosity may include one or more of those available under the brand names Methocel K15M and Methocel K100M whose 2% by weight aqueous solutions have viscosities of 15,000 cPs and 100,000 cPs, respectively.

The polymer concentration depends on the type of polymer used. For example, hydroxypropyl methylcellulose polymers may generally be present in the pharmaceutical composition in an amount from about 5.0% to about 25.0% by weight.

Suitable hydroxypropyl cellulose polymers may include one or more polymers available under the brand names Klucel™ and HPC™, available from Aqualon and Nippon Soda Co. Examples of low viscosity hydrophilic polymers are the hydroxypropyl cellulose polymers available under the brand names Klucel EF, Klucel LF, Klucel JF and Klucel GF whose 2% by weight aqueous solutions have viscosities less than 1,000 cPs. An example of a medium viscosity hydrophilic polymer is the hydroxypropyl cellulose polymer, available under the brand name Klucel ME, whose 2% by weight aqueous solution has a viscosity in the range from 4,000-6,500 cPs. Examples of low viscosity hydrophilic polymers are the hydroxypropyl cellulose polymers available under the brand names HPC-SL, HPC-L, and HPC-M whose 2% by weight aqueous solutions have viscosities of 3-6 cPs, 6-10 cPs, and 150-400 cPs, respectively. HPC-H, another HPC polymer, has a viscosity of 1,000-4,000 cPs and is an example of a medium viscosity hydrophilic polymer. The hydroxypropyl cellulose polymers may be present in an amount from about 5.0% to about 25.0% by weight.

In addition to the active ingredient and hydrophilic polymers, the hydrophilic matrix may additionally contain other pharmaceutically acceptable excipients, which act in one or more capacities as diluents, binders, lubricants, glidants, disintegrants, colorants or flavoring agents.

Suitable diluents include one or more of any conventional diluent such as lactose, microcrystalline cellulose, starch, calcium hydrogen phosphate, sucrose and mannitol.

Suitable binders include one or more of starch, sugars, gums, low molecular weight hydroxypropyl methylcellulose and hydroxypropyl cellulose.

Suitable lubricants include one or more of talc, magnesium stearate, calcium stearate, polyethylene glycol, hydrogenated vegetable oils, stearic acid, sodium stearyl fumarate and sodium benzoate.

Suitable glidants include one or more of colloidal silicon dioxide (aerosil) or talc.

Suitable coloring or flavoring agents include those approved for use by the United States Food and Drug Administration (FDA) and are well known to those skilled in the art.

The pharmaceutical compositions may be administered orally in the form of pellets, beads, granules, tablets or pills. The tablets can be prepared by techniques known in the art including one or more of direct compression, wet granulation, fluid bed granulation or

compaction. Tablets and pills can additionally be prepared with non-functional coatings. The coating generally includes film-forming polymers such as one or more of cellulose ethers, acrylic polymer or a mixture of polymers. The cellulose ethers may include, for example, one or more of hydroxypropyl cellulose, hydroxypropyl methylcellulose and the like.

As noted above, the pharmaceutical composition of this invention will maintain therapeutic levels of minocycline over a 24-hour dosing period, thus providing once daily dosing. In order to obtain this benefit, it is necessary for the once-a-day minocycline dosage form to achieve certain pharmacokinetic parameters, when compared to a twice-a-day minocycline dosage form.

Peak plasma concentration (Cmax) for the once-a-day minocycline (OD) dosage form in the present invention is comparable to the Cmax for a twice-a-day (*bid*) dosage form of commercially available Minocin® currently marketed by Lederle Laboratories, when each is evaluated in fasting subjects.

In addition to equivalent peak levels, it is also important that the total amount of the minocycline absorbed from the OD dosage form should not differ significantly, when compared to a *bid* dosage form over a 24-hour dosing interval. Methods for quantifying drug absorption are well known to those skilled in the art.

Area under the plasma concentration-time curve (AUC) for the OD dosage form of the present invention is comparable to the AUC of the *bid* dosage form of Minocin®, when each is evaluated in fasting subjects over a 24-hour period.

An AUC of at least 80% is achieved with the formulations of this invention, when compared to a bid dosage form over a 24-hour interval. Values below 80% tend to negatively impact trough levels leading to sub-therapeutic concentrations of minocycline and loss of antimicrobial activity. AUC in excess of 125% should also be avoided. Thus with respect to the extent of absorption, the pharmaceutical composition of the present invention is comparable to the commercially available *bid* dosage form.

The following examples illustrate extended release minocycline compositions and processes of making the compositions as disclosed in the various embodiments discussed throughout the specification. The examples are merely provided to illustrate the composition and processes for their preparation and are not intended to be limiting. The obvious variations of these compositions are contemplated to be within the scope of the present invention and the appended claims.

Example 1

This example illustrates the preparation of extended or controlled release tablets of minocycline having compositions as given in Table 1.

Hydroxypropyl methylcellulose medium viscosity grade and hydroxypropyl methylcellulose low viscosity grade were loaded into a mixer and dry blended with minocycline hydrochloride. Microcrystalline cellulose and lactose were added and the mixture was further blended for 10 minutes. The blend was granulated using a mixture of isopropyl alcohol and water until proper granulation was obtained. The granules were dried, ground and sifted to the appropriate size.

Talc, magnesium stearate and colloidal silicon dioxide were screened and blended with dried granules. The final blend was then loaded into a hopper and compressed into tablets.

Four different formulations I, II, III and IV were prepared according to the general method described above. The compositions for different tablet formulations are given in Table 1.

Table 1: Compositions for different tablet formulations.

Ingredients	mg/tablet			
	I	II	III	IV
Minocycline hydrochloride	200	200	200	200
Hydroxypropyl methylcellulose- medium viscosity	18	25	75	47
Hydroxypropyl methylcellulose- low viscosity	25	25	25	25
Microcrystalline cellulose	123.5	120	95	109
Lactose	123.5	120	95	109
Talc	3	3	3	3
Magnesium stearate	5	5	5	5
Colloidal silicon dioxide	2	2	2	2

Pharmacokinetic evaluation of once-a-day extended release pharmaceutical composition of minocycline hydrochloride:

A bioavailability study to determine the concentration time plasma profile was performed on healthy subjects. The study was conducted by a Phase I, single dose, open, randomized, three period, balanced cross-over design as described below.

Twelve (12) healthy adult subjects were enrolled and all of them completed all phases of the study. The mean age of subjects of the study was 28 years (range: 21 to 35 years). No drugs including over-the-counter drugs were allowed 72 hours before or throughout the study period.

Minocycline hydrochloride 200mg once daily extended release tablets (A & B) corresponding to Formulations I and II of Table 1; and 2 x 100mg of minocycline capsules (Minocin®) currently marketed by Lederle Laboratories corresponded to the Reference Formulation (C) were used.

The study was divided into three periods with a one-week wash-out interval separating each period. Subjects were randomized into three equal groups, which were then randomly assigned to either dosage regimen A, B or C. Dosing regimen sequence followed a three by three Latin Square design where three regimen sequences were employed. The dosing regimens A, B and C were as follows:

Regimen A: (1 x 200mg) '**A**' tablets were administered as a single oral dose with 240 ml of water following a 12-hour overnight fast.

Regimen B: (1 x 200mg) '**B**' tablets were administered as a single oral dose with 240 ml of water following a 12 hour overnight fast.

Regimen C: (2 x 100mg) '**C**' Minocin® capsules were administered, one at 0 hours with 240 ml of water following a 12 hour overnight fast and the other after 12 hours with 240 ml of water, following 2 hour fast.

The blood samples (6 ml) were collected prior to dosing (0 hour) and at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0 and 24.0 hours after each dose. Plasma samples were assayed for minocycline hydrochloride using a validated high performance liquid chromatographic procedure.

The OD formulations (A and B) gave plasma concentration time profile desirable for once-a-day dosage form, in that the peak plasma concentration (Cmax) was comparable to that for the immediate release drug. The total bioavailability of minocycline measured as area under the curve (AUC_{0-t}) was also comparable to that of immediate release capsules given twice daily indicating that all of the drug was released from the formulation and absorbed during its transit through the gastrointestinal tract.

Values for minocycline hydrochloride pharmacokinetic parameters, including observed Cmax, Tmax, and AUC_{0-t}, were calculated using standard non-compartmental methods.

Table 2: Summary of the pharmacokinetic results obtained after single dosing in the above study

Parameters	Regimen A	Regimen B	Regimen C
Cmax (ng/ml)	1415.159±300.949	1256.768±283.731	1083.895±188.508
Tmax (hr)	3.0±0.850	3.333±0.750	2.36±0.75
AUC (0-t) (ng.hr /ml)	17309.690±3476.907	16245.706±4465.635	13923.700±1160.423

As evident above, the therapeutic efficacy of the once-a-day formulation was comparable to the marketed immediate release dosage form of minocycline (Minocin® capsules) given in twice-a-day regimen.

Food Effect Study:

Bioavailability of minocycline 200 mg OD formulations prepared according to Example II was compared under fasting conditions, as well as after a high fat meal in healthy adult male subjects.

The study was conducted as a single dose, two treatment, two period, food effect study in 12 healthy adult male subjects. In each of the two study periods, 6 subjects received a single oral dose of test formulation (formulation II of Table 1) on an empty stomach in the morning and other 6 subjects received the same formulation in the morning, 20 minutes after having the US FDA defined high fat breakfast. The OD formulations were administered with 240 ml of water.

Wash out period of five days separated the doses. The blood samples (5 ml) were collected 1 hour before dosing and at 0.5, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 14, 16, 20 and 24 hours after dosing. Plasma samples were assayed for minocycline hydrochloride using a validated high performance liquid chromatographic procedure. The results of the study are shown in Table 3.

Table 3: Summary of the pharmacokinetic parameters obtained under fed and fasted conditions

Parameters	Fasted subjects	Fed subjects
Cmax (ng/ml)	1572.616 ± 297.597	1735.471 ± 363.626
Tmax (hr)	3.625 ± 0.528	3.708 ± 0.656
AUC_{0-t} (ng.hr/ml)	19068.629 ± 2804.013	17601.091±4823.965

The results show that the therapeutic efficacy of the OD formulations under fed conditions was comparable to the therapeutic efficacy under fasted conditions.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations in the preferred methods of the present invention may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

We Claim:

1. An extended release pharmaceutical composition comprising a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration, wherein each hydrophilic matrix forming polymer differs at least in viscosity.

2. The pharmaceutical composition according to claim 1, wherein the hydrophilic matrix forming polymers comprise cellulose derivatives.

3. The pharmaceutical composition according to claim 2, wherein the cellulose derivatives comprise a mixture of at least two different viscosity grades.

4. The pharmaceutical composition according to claim 2, wherein the cellulose derivatives comprise one or more of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose or combinations thereof.

5. The pharmaceutical composition according to claim 4, wherein the cellulose derivative comprises hydroxypropyl methylcellulose.

6. The pharmaceutical composition according to claim 4, wherein the cellulose derivative comprises hydroxypropyl cellulose.

7. The pharmaceutical composition according to claim 2, wherein the cellulose derivative comprises a mixture of low viscosity and medium viscosity grades of hydroxypropyl methylcellulose.

8. The pharmaceutical composition according to claim 2, wherein the cellulose derivative is a mixture of low viscosity and medium viscosity grades of hydroxypropyl cellulose.

9. The pharmaceutical composition according to claim 1, wherein the concentration of the hydrophilic matrix forming polymers ranges from about 5.0 to about 25 weight percent of the total composition.

10. The pharmaceutical composition according to claim 1, wherein the minocycline non-toxic acid addition salt is hydrochloride.

11. The pharmaceutical composition according to claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients.

12. The pharmaceutical composition according to claim 11, wherein the excipients comprise one or more diluents, binders, lubricants, glidants, disintegrants, colorants and flavoring agents.

13. The pharmaceutical composition according to claim 1, wherein the composition is in the form of pellets, beads, granules, tablets or pills.

14. The pharmaceutical composition according to claim 13, wherein the composition is in the form of a tablet.

15. The pharmaceutical composition according to claim 14, wherein the tablet is prepared by direct compression, wet granulation or compaction.

16. The pharmaceutical composition according to claim 14, wherein the tablet further comprises a coating.

17. The pharmaceutical composition according to claim 16, wherein the coating is non-functional or functional.

18. The pharmaceutical composition according to claim 17, wherein the functional coating comprises an enteric coating.

19. The pharmaceutical composition according to claim 18, wherein the enteric coating comprises acrylic polymers or cellulose ethers.

20. The pharmaceutical composition according to claim 19, wherein the cellulose ether comprises one or more of hydroxypropyl cellulose, hydroxypropyl methylcellulose or mixtures thereof.

21. The pharmaceutical composition according to claim 1, wherein the composition has area-under-the-curve (AUC) comparable to the area-under-the-curve (AUC) of twice-daily immediate release dosage form.

22. An extended release pharmaceutical composition comprising a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration, wherein the extended release pharmaceutical composition administered once daily has an Area Under the Curve within 80% and 125% of the commercially available minocycline hydrochloride administered twice daily.

23. The extended release pharmaceutical composition according to claim 22, wherein the hydrophilic matrix forming polymers comprise two or more cellulose derivatives,

wherein the cellulose derivatives comprise a mixture of at least two different viscosity grades.

24. A process for preparing an extended release pharmaceutical composition comprising a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration, wherein each polymer differs at least in viscosity, the process comprising:

dry blending minocycline with two or more hydrophilic polymers to form a blend;

granulating the blend;

drying and sizing the granules; and

compressing the dried and sized granules.

25. The process according to claim 24, further comprising dry blending the minocycline and hydrophilic polymers with additional pharmaceutical excipients.

26. The process according to claim 24, wherein the hydrophilic polymers comprise cellulose derivatives.

27. The process according to claim 25, wherein the cellulose derivatives comprise a mixture of two different viscosity grades.

28. The process according to claim 25, wherein the cellulose derivatives comprise one or more of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose or combinations thereof.

29. The process according to claim 26, wherein the cellulose derivative comprises hydroxypropyl methylcellulose.

30. The process according to claim 26, wherein the cellulose derivative comprises hydroxypropyl cellulose.

31. The process according to claim 26, wherein the cellulose derivative comprises a mixture of low viscosity and medium viscosity grades of hydroxypropyl methylcellulose.

32. The process according to claim 26, wherein the cellulose derivative comprises a mixture of low viscosity and medium viscosity grades of hydroxypropyl cellulose.

33. The process according to claim 24, wherein the concentration of the hydrophilic polymers ranges from about 5.0 to about 25 weight percent of the total composition.

34. The process according to claim 24, wherein the minocycline non-toxic acid addition salt is hydrochloride.

35. The process according to claim 24, wherein the composition is in the form of pellets, beads, granules, tablets or pills.

36. The process according to claim 35, wherein the tablet is prepared by direct compression, wet granulation or compaction.

37. The process according to claim 36, further comprising coating the tablet.

38. The process according to claim 37, wherein the coating comprises a non-functional, or functional coating.

39. The process according to claim 38, wherein the functional coating comprises an enteric coating.

40. The process according to claim 39, wherein the enteric coating comprises acrylic polymers or cellulose ethers.

41. A method of treating a bacterial infection in a mammal, the method comprising administering an extended release pharmaceutical composition comprising a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration, wherein each polymer differs at least in viscosity.

42. A method of treating a bacterial infection in a mammal, the method comprising administering an extended release pharmaceutical composition comprising a mixture of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline), or a non-toxic acid addition salt thereof, and two or more hydrophilic matrix forming polymers configured to form a matrix upon administration, wherein the extended release pharmaceutical composition administered once daily has an Area Under the Curve within 80% and 125% of the commercially available minocycline hydrochloride administered twice daily.

43. The extended release pharmaceutical composition according to claim 42, wherein the hydrophilic matrix forming polymers comprise two or more cellulose derivatives, wherein the cellulose derivatives comprise a mixture of at least two different viscosity grades.