

Description

The invention relates to pharmaceutical delivery systems for the prolonged controlled release of 7-dimethylamino-6-deoxy-6-demethyltetracycline (minocycline) or non-toxic acid addition salts thereof. It provides a once-a-day delivery system which maintains therapeutic blood level concentrations of the medicament in a patient for twenty-four hours by the once-a-day administration of custom designed formulations comprising an initial loading or first pulse of minocycline powder or minocycline containing coated or uncoated quick release granules and a secondary loading or second pulse of minocycline containing pH sensitive polymer coated spherical granules either administered simultaneously or separately up to 120 minutes apart. Multi-coated spheronized pharmaceutical compositions comprising initial and secondary minocycline loadings as well as oral dosage unit forms of all of the above are provided as well.

These pharmaceutical delivery systems, compositions and oral dosage unit forms will provide therapeutic plasma level concentrations of minocycline in the therapeutic range for effective antibacterial activity for up to twenty-four hours.

The tetracycline compound, 7-dimethylamino-6-deoxy-6-demethyltetracycline, and its non-toxic acid addition salts are widely used in therapy primarily for their antimicrobial effects. Commonly assigned Boothe et al, U.S. Patent No. 3,148,212, and Pesti et al, U.S. Patent No. 3,226,436, describe the preparation of minocycline. Although the compounds have achieved widespread use in oral dosage forms, they have several drawbacks.

The minimum therapeutically effective blood serum or plasma concentration level of minocycline in a human subject varies according to the organism causing the infection. The concentration is determined in vivo by clinical evaluation and in vitro by microbiological assays. Currently, the minimum therapeutically effective concentration is believed to be in the range of from 0.1 to 1.0 μg of minocycline/ml of serum.

Organisms currently known to be susceptible to minocycline therapy include a wide range of gram-negative and gram-positive bacteria including, but not limited to agents of rickettsiae (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, tick fevers); *Mycoplasma pneumoniae* (PPL0, Eaton agent); agents of psittacosis and ornithosis; agents of lymphogranuloma venereum and granuloma inguinale; the spirochetal agent of relapsing fever (*Borrelia recurrentis*); the agent of Lyme disease (*Borrelia burgdorferi*), the agents of acne (*Propionibacterium Corynebacterium acnes*); the microorganisms *Haemophilus ducreyi* (chancroid), *Yersinia pestis*

and *Francisella tularensis*, formerly *Pasteurella pestis* and *Pasteurella tularensis*, *Bartonella bacilliformis*, *Bacteroides* species, *Vibrio comma* and *Vibrio fetus*, *Brucella* species, *Escherichia coli*, *Enterobacter aerogenes* (formerly *Aerobacter aerogenes*), *Shigella* species, *Mima* species, *Herellea* species, *Haemophilus influenzae* (respiratory infections), *Klebsiella* species (respiratory and urinary infections), many *Streptococcus* species including strains of *Streptococcus pyogenes* and *Streptococcus faecalis*, *Streptococcus pneumoniae*, *Staphylococcus aureus* (skin and soft tissue infections), *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Treponema pallidum* and *Treponema pertenue* (syphilis and yaws), *Listeria monocytogenes*, *Clostridium* species, *Bacillus anthracis*, *Fusobacterium fusiforme* (Vincent's infection), *Actinomyces* species; and in the treatment of acute intestinal amebiasis and inclusion conjunctivitis. Physician's Desk Reference, 1987, Medical Economics Company, Oradell, NJ (PDR 43rd Ed.).

Recent discovery shows that minocycline is absorbed at different rates in different portions of the gastrointestinal tract. Intubation studies in human patients have demonstrated that bioavailability of minocycline in the gastrointestinal tract, based upon 100 percent absorption in the stomach, is 106 percent in the duodenum, 80 percent in the jejunum and 58 percent in the ileum, indicating that minocycline demonstrates reduced absorption in the lower gastrointestinal tract.

The human stomach empties in about one hour in a fasting subject and in about one to about four hours with food. The half life of minocycline when taken without food is approximately 10 hours. When taken with food, the half life is extended to approximately 14 to 16 hours.

It has not been possible to achieve a once-a-day therapeutic blood level of minocycline using only delayed release granules of minocycline with or without food ingestion. Traditional pharmaceutical forms and traditional 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 in poor patient compliance. This indicates a need for a custom designed once-a-day delivery system for minocycline to provide optimal therapeutic effect and patient compliance.

Shepard, U.S. Patent No. 3,080,294, discloses a sustained release pharmaceutical tablet comprising an inner core coated with multiple layers of an active medicament mixture, each layer releasing a portion of active medicament as it is successively dissolved. Such layers are not pH adapted, however.

Amann, U.S. Patent No. 3,865,935, discloses erythromycin tablets which are stable outside the

stomach but which produce immediate action upon disintegration in the stomach. These tablets require sodium citrate or sodium citrate dihydrate and do not yield a controlled release of prolonged duration.

McAinsh et al, U.S. Patent No. 4,138,475, disclose that propranolol or a pharmaceutically acceptable salt thereof can be formulated into a sustained release pharmaceutical composition by mixing with a non-water-swellaable microcrystalline cellulose and forming into spheroids. These spheres are coated with a heavy film of hydroxypropyl methylcellulose and/or a plasticizer to eliminate any release of the drug in the stomach. The film coated spheroids are then filled into gelatin capsules. Apart from the fact that propranolol is used as a beta-blocker to treat heart problems and not for oral antimicrobial use, there is no hint or suggestion in McAinsh et al that the pharmaceutical compositions should be used with tetracycline compounds.

Dempski, et al, U.S. Patent No. 4,173,626, disclose capsules comprising uncoated indomethacin (U.S. Patent No. 3,161,654) pellets for immediate release, coated indomethacin pellets for prolonged release, and non-medicated pellets as volume fill. Indomethacin is a prostaglandin synthetase inhibitor and is not an antibacterial agent. Furthermore, the coatings are not pH adapted.

Hess, et al, U.S. Patent No. 4,353,887, disclose a divisible tablet comprising medicament containing granules wherein the surface area of the tablet is not materially increased by division.

In Bechgaard, U.S. Patent No. 4,806,909, the placement of a sparingly soluble active substance, such as tetracycline, in an oral controlled release dosage form is disclosed. The sparingly soluble active substance must be used with a dispersion-enhancing substance, such as an anionic detergent, to promote solubility in intestinal fluids. The composition is formed into small spheres and enteric coated to eliminate any release of drug in the stomach. The coated spheres are tableted or loaded into capsules. There is no teaching that such a dosage form can be used to provide a once-a-day delivery system of therapeutically effective amounts of 7-dimethylamino-6-deoxy-6-demethyl-tetracycline or its non-toxic acid addition salts, and particularly a delivery system which is not dependent upon the ingestion of food. Moreover, the requirement of a dispersion-enhancing substance, especially an anionic detergent, is a negative factor.

In Ventouras, U.S. Patent No. 4,784,858, a controlled release tablet comprising (1) coated cores, not necessarily spheronized, comprising a core of a water-soluble pharmaceutically active substance dispersed in a water-insoluble polymeric excipient and a swellaable water-insoluble polymeric sub-

stance; and (2) a coating of an elastic, water insoluble and semi-permeable diffusion film of a polymer is disclosed. Here, the core is made to expand with water, causing the surface of the coating to extend, making it permeable, and thereby releasing the medicament in the core.

U.K. Patent Publication No. GB 2,041,222 discloses the tableting of microcapsules of indoprofen. Other active medicaments may be included in the tablet. The microcapsules are not formed by spheronization, and these tablets are only suitable for high dosage delivery.

The incorporation of water insoluble medicament containing spheroids comprised of microcrystalline cellulose and at least one cellulose derivative into capsules, sachets, and cachets is disclosed in U.K. Patent Publication No. GB 2,202,143. Sustained release is accomplished by the necessary inclusion of the cellulose derivative.

Parke-Davis has recently offered for use by the medical profession, capsules under the trademark DORYX® containing specially coated pellets of doxycycline hyclate for oral administration. See, PDR 43rd Ed. (Pages 1487 - 1489). In contrast to minocycline hydrochloride and its isomers and analogs, doxycycline hyclate does not contain an alkyl amino group at either the 7- or the 9-position. The Parke-Davis pellets are said to comprise lactose, microcrystalline cellulose and povidone (polyvinylpyrrolidone) in addition to the doxycycline compound. The disclosure in PDR 43rd Ed. is unclear as to the advantages for using such film coated pellets, but it is believed that the film is used to minimize release in the stomach and any resulting gastric distress and not to provide a once-a-day dosage form.

Valorose et al, U.S. Patent No. 4,837,030, disclose hard gelatin or soft gelatin capsules filled with minocycline comprising spherical granules.

In US-A-4 250 166 long acting preparation of Cefalexin are disclosed having a coating layer, the solubility of which is pH-dependent and dissolves in the upper intestine.

It has now been discovered that a specific minocycline composition can be formulated to provide at least minimum therapeutic serum levels of the minocycline in a human subject for 24 hours through once-a-day two pulse administration systems, comprising an initial loading component providing the first pulse which is absorbed up to 100 percent in the stomach and a secondary loading component providing the second pulse which is absorbed up to 100 percent in the duodenum and the upper part of the small intestine.

These formulations can also be processed into liquid, capsule, or tablet oral dosage unit forms.

FIG. 1 is a graphic illustration of a method for the production of uncoated quick release granules

and precursors of pH sensitive polymer coated spherical granules according to the present invention.

FIG. 2 is a graphic illustration of a method for the production of coated quick release granules and pH sensitive polymer coated spherical granules according to the present invention.

FIG. 3 is a graphic illustration of a method for the preparation of multi-coated once-a-day minocycline delivery system compositions according to the present invention.

FIG. 4 is a graphic illustration of a multi-coated once-a-day minocycline delivery system having a minocycline core according to the present invention.

FIG. 5 is a graphic illustration of a multi-coated once-a-day minocycline delivery system having minocycline on a non-pareil seed core or sugar and/or starch crystal core according to the present invention.

FIG. 6 is a graphic illustration of the release rate of minocycline from pH sensitive polymer coated spherical granules adapted to release the minocycline in a medium having a pH of 5.0 according to the present invention.

FIG. 7 is a graphic illustration of the release rate of minocycline hydrochloride from pH sensitive polymer coated spherical granules adapted to release the minocycline hydrochloride in a medium having a pH greater than 5.5 according to the present invention.

FIG. 8 is a graphic illustration of the release rate of minocycline from pH sensitive polymer coated spherical granules adapted to release the minocycline in a medium having a pH of 4.0 to 7.5 according to the present invention.

FIG. 9 is a graphic illustration of the release rate of minocycline from pH sensitive polymer coated spherical granules adapted to release the minocycline in a medium having a pH of 4.0 to 7.5 according to the present invention.

FIG. 10 is a graphic illustration of blood serum concentration levels of once-a-day administration of minocycline to human subjects in oral dosage unit forms according to the present invention and twice-a-day administration of minocycline in oral dosage unit form presently available from Lederle Laboratories.

FIG. 11 is a graphic illustration of the release rate of minocycline from capsules containing a mixture of quick release granules adapted to release minocycline immediately in the stomach and pH sensitive polymer coated spherical granules adapted to release minocycline in a medium having a pH of 5.0 in accordance with the present invention.

FIG. 12 is a graphic illustration of blood serum concentration levels on the third consecutive day of

once-a-day minocycline administration to human subjects in oral dosage unit forms according to the present invention and on the third consecutive day of minocycline administration comprising an initial loading single administration of two oral dosage unit forms presently available from Lederle Laboratories followed by a single oral dosage form presently available from Lederle Laboratories every 12 hours (twice-a-day).

FIG. 13 is a graphic illustration of blood serum concentration levels on the first day of once-a-day minocycline administration to human subject in oral dosage unit form according to the present invention and single administration of two oral dosage unit form presently available from Lederle Laboratories.

FIG. 14 is a graphic illustration of the release rate of minocycline from capsules containing a mixture of quick release granules adapted to release minocycline in the stomach and pH sensitive polymer coated spherical granules adapted to release minocycline in a medium having a pH of greater than 5.5 in accordance with the present invention.

FIG. 15 is a graphic illustration of blood serum concentration levels of minocycline administered to fasting and to non-fasting human subjects in oral dosage unit form capsules containing a mixture of quick release granules adapted to release minocycline in the stomach and pH sensitive polymer coated spherical granules adapted to release minocycline in a medium having a pH of greater than 5.5 in accordance with the present invention.

According to the present invention there are provided pharmaceutical delivery systems as defined in claim 1 adapted to provide a therapeutically effective blood concentration level of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof for a sustained period of time of up to twenty-four hours in a single dose comprising (I) a multiple delivery vehicle system comprising (A) an initial loading therapeutically effective number of quick release granules which comprise (a) (i) an effective amount of at least one pharmaceutically acceptable excipient; and (ii) an effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof, on or in the quick release granules; and optionally (b) a substantially uniform polymer coating, on the quick release granules and which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9; the quick release granules being adapted to release substantially completely the minocycline in a medium having a pH of less than 3.9; (A-1) an initial loading therapeutically effective amount of a finely divided powder comprising (a) an effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic addition salt

thereof; and optionally (b) an independent effective amount of at least one pharmaceutically acceptable excipient which may be the same as or different than (I)(A)(a)(i); or (A-2) an initial loading therapeutically effective combination of (A) and (A-1); and (B) a secondary loading therapeutically effective number of pH sensitive polymer coated spherical granules which comprise (a) (i) an independent effective amount of at least one pharmaceutically acceptable excipient which may be the same as or different than (I)(A)(a)(i) or (I)(A-1)-(b); and (ii) an independent effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyl-tetracycline or a non-toxic acid addition salt thereof, on or in the coated spherical granules; and (b) a substantially uniform pH sensitive polymer coating, the polymer of which may be the same as or different than (I)(A)(b), on the coated spherical granules and which is substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5; the coated spherical granules thereby being adapted to release substantially completely the minocycline in a medium having a pH in the range of from 4.0 to 7.5; or (II) one or more multi-coated spheronized pharmaceutical single delivery vehicle compositions comprising (A) a core comprised of (a) a full or a partial secondary loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyl-tetracycline or a non-toxic acid addition salt thereof; or (b) at least one granule comprised of (i) an effective amount of at least one pharmaceutically acceptable excipient; and (ii) a full or a partial secondary loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyl-tetracycline or a non-toxic acid addition salt thereof, on or in said granule; having applied thereon (B) a substantially uniform pH sensitive polymer coating which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5; the core thereby being adapted to release substantially completely the minocycline in a medium having a pH in the range of from 4.0 to 7.5; having applied thereon (C) a quick release coating comprising a full or a partial initial loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyl-tetracycline or a non-toxic acid addition salt thereof; and optionally having applied thereon (D)(a) a substantially uniform polymer coating, the polymer of which may be the same as or different than (B), and which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9; (b) a polymer overcoat, the polymer of which may be the same as or different than (B) or (D)(a); or (c) a combination of (a) and thereon (b).

The invention further contemplates oral dosage units in the form of pharmaceutically acceptable

liquid carriers containing the above compositions or systems, hard or soft shell capsules at least partially filled with the above compositions or systems, and tablets formed from the above compositions or systems.

A therapeutic level of the minocycline in the blood stream of a warm-blooded mammal for 24 hours can be maintained by the ingestion of the pharmaceutical delivery systems or oral dosage units above. The initial loading component can be administered up to 120 and preferably up to 60 minutes before the secondary loading component or the two components can be administered simultaneously.

A preferred embodiment of the present invention contemplates a pharmaceutical delivery system comprising a mixture of (A) an initial loading therapeutically effective number of quick release granules which comprise (a) (i) an effective amount of at least one pharmaceutically acceptable excipient; and (ii) an effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyl-tetracycline or a non-toxic acid addition salt thereof, on or in the quick release granules; and optionally (b) a substantially uniform polymer coating which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9; the quick release granules being adapted to release substantially completely the minocycline in a medium having a pH of less than 3.9; and (B) a secondary loading therapeutically effective number of pH sensitive polymer coated spherical granules which comprise (a) (i) an independent effective amount of at least one pharmaceutically acceptable excipient which may be the same as or different than (A)(a)(i); and (ii) an independent effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyl-tetracycline or a non-toxic acid addition salt thereof, on or in the coated spherical granules; and (b) a substantially uniform pH sensitive polymer coating, the polymer of which may be the same or different than (A)(b), on the coated spherical granules and which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5; the coated spherical granules thereby being adapted to release substantially completely the minocycline in a medium having a pH in the range of from 4.0 to 7.5.

For maintaining therapeutic levels of 7-dimethylamino-6-deoxy-6-demethyl-tetracycline or a non-toxic acid addition salt thereof in the blood stream of a warm-blooded mammal for 24 hours ingestion of an initial loading therapeutically effective number of the quick release granules either simultaneously with, or followed sequentially within up to 120 minutes and preferably up to 60 minutes, by the ingestion of a secondary loading therapeutically effective number of the pH sensitive

polymer coated spherical granules in the delivery systems or oral dosage unit forms can be contemplated.

A method for the preparation of a pharmaceutical delivery system is provided comprising the steps of:

(A) forming an initial loading component by (a) blending (i) an effective amount of at least one pharmaceutically acceptable excipient; and (ii) an effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof; (b) granulating; (c) extruding; (d) spheronizing the resultant extrudate to form quick release granules which are adapted to release substantially completely the minocycline in a medium having a pH of less than 3.9; (e) drying; and optionally (f) coating the quick release granules with a substantially uniform polymer coating which is rapidly and substantially completely erodible in a medium of a pH of less than 3.9; or

(A-1) forming an initial loading component by (a) dividing 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof into a fine powder; and optionally (b) mixing the powder with an effective amount of a pharmaceutically acceptable excipient; and

(B) forming a secondary loading component by (a) blending (i) an independent effective amount of at least one pharmaceutically acceptable excipient which may be the same as or different than (A)(a)(i) or (A-1)(b); and (ii) an independent effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof; (b) granulating; (c) extruding; (d) spheronizing the resultant extrudate to form precursors of coated spherical granules; (e) drying; and (f) coating the precursors with a substantially uniform polymer coating, the polymer of which may be the same as or different than that in optional step (A)(f) and which is substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5.

Additionally, a method for the preparation of pharmaceutical compositions in oral dosage unit forms comprising a liquid comprising the additional step of mixing either the initial or the secondary loading component or both, either together or independently, with a pharmaceutically acceptable liquid carrier, comprising a capsule comprising the additional step of at least partially filling a hard or a soft shell capsule with either the initial or the secondary loading component or both, either together or independently, and optionally then sealing the capsules, and comprising a tablet comprising the additional optional step of adding a lubricant and the step of forming a tablet from either the initial or

the secondary loading component or both, either together or independently, are provided.

A method is also provided for the preparation of multi-coated composition pharmaceutical delivery systems comprising the steps of forming a core from one or more spherical granules prepared by (a) blending (i) an effective amount of at least one pharmaceutically acceptable excipient; and (ii) a full or a partial secondary loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof; (b) granulating; (c) extruding; (d) spheronizing the resultant extrudate to form one or more spherical granules; and (e) drying the spherical granules; (A-1) forming a core from a full or a partial secondary loading effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof; or (A-2) forming a core by coating a non-pareil seed or a sugar crystal with a full or a partial secondary loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof; (B) coating the core with a substantially uniform polymer coating which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5; the core thereby being adapted to release substantially completely the minocycline in a medium having a pH in the range of from 4.0 to 7.5; to form a single coated core; (C) coating the single coated core with a quick release coating comprising a full or a partial initial loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof to form a multi-coated composition; and optionally (D) coating the multi-coated composition with (a) a substantially uniform polymer coating, the polymer of which may be the same as or different than (B) and which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9; (b) a polymer overcoat, the polymer of which may be the same as (B) or (D)(a); or (c), a combination of (a) and thereon (b).

The pharmaceutical delivery systems and the liquid, capsule and tablet oral dosage unit forms described above provide once-a-day prolonged effect controlled release forms of minocycline which maintain therapeutic blood levels for periods of up to twenty-four hours resulting in desirable and effective antibacterial therapy and less frequent administration to a subject. They also avoid high local concentrations in a system which may cause side effects such as gastroirritability.

The discovered novel pharmaceutical delivery systems comprise mixed blends or separate administration units of an initial loading of a therapeutically effective number of coated and/or

uncoated quick release granules and a secondary loading of a therapeutically effective number of pH sensitive polymer coated spherical granules, mixed blends or separate administration units of an initial loading of a therapeutically effective amount of finely divided minocycline powder and a secondary loading of a therapeutically effective number of pH sensitive polymer coated spherical granules, or multi-coated compositions. These systems and compositions can be formed into liquid, capsule, tablet or the like oral dosage unit forms as well. Many benefits can be realized from these novel delivery systems and oral dosage unit forms over conventional controlled release formulations. They result in a superiorly controlled and prolonged delivery of minocycline to a subject which in turn results in the ability of once-a-day dosages of 7-dimethylamino-6-deoxy-6-demethyltetracycline or non-toxic acid addition salts thereof in the compositions and oral dosage unit forms to sustain a desired blood level concentration in a subject for a relatively long period of time of up to twenty-four hours. Therefore, less frequent administration of the minocycline compound to a subject, possibly fewer and lessened side effects, including reduced gastroirritability, and better subject compliance with a medicament regimen are possible.

Oral dosage unit forms are those which are orally administered and contain medicaments which are absorbed into the blood stream from the alimentary tract.

An initial loading of a therapeutically effective amount of minocycline powder or number of quick release granules is that amount or number which provides an immediate or rapid and substantially complete release in a medium having a pH of less than 3.9 and, preferably in a range of from 1.0 to 2.5, such as in the human stomach and thereby delivers and maintains a recommended dosage or concentration level of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof to the blood stream or plasma of a subject within a recommended period of time and maintains that level or a further recommended level for a further recommended period of time. This provides a first pulse of minocycline, preferably in the stomach, which quickly attains therapeutic plasma drug levels, i.e. at least that amount determined by in vivo clinical evaluation or in vitro microbiological assay to treat successfully infections caused by the invading organism or organisms.

A secondary loading therapeutically effective amount of minocycline powder or number of pH sensitive polymer coated spherical granules is that amount or number which provides a controlled release in a medium having a pH in the range of from 4.0 to 7.5 and preferably from 4.0 to 6, as in the human upper intestinal tract and particularly in

the duodenum, and thereby delivers and maintains a further recommended dosage or concentration level of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof to the blood stream or plasma of a subject within an independent recommended period of time and maintains that level or a different recommended level for an independent additional recommended period of time. This second pulse provides a delayed release and a controlled release of minocycline, preferably in the duodenum, which extends therapeutic plasma drug levels initially achieved by the first pulse, i.e. at least that amount determined effective for the particular organism causing the infection as described above, for a total prolonged period of time, i.e. up to 24 hours.

The initial loading of the minocycline can be achieved by the administration of quick release granules containing the minocycline, by a finely divided powder of minocycline, by other compositions containing the minocycline compound, or by the quick release coating of one or more multi-coated compositions. The secondary loading can either be administered simultaneously, as in mixed blends of initial loading and secondary loading components or in one or more multi-coated compositions or in the oral dosage unit forms derived therefrom, or sequentially, after the initial loading generally within up to 120 minutes and preferably within up to 60 minutes, in separate administration units of initial and secondary loading components. The total period of time this therapeutic plasma drug level is maintained, i.e. from the combined effect of the two different types of granules, from the multi-coated compositions or from any other initial loading components administered simultaneously or prior to the pH sensitive polymer coated spherical granules of the pharmaceutical delivery systems or the oral dosage unit forms of the present invention, is preferably 24 hours. Therefore, only one dosage unit will provide effective antimicrobial therapy for an entire day, the total therapeutic amount, i.e. the initial loading therapeutically effective amount or number plus the secondary loading therapeutically effective number, being that amount and/or number which will achieve and will maintain at least a therapeutically effective concentration of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof/ml of serum or plasma in the blood serum or plasma of a human subject for 24 hours.

The salts of minocycline useful in the present invention are the non-toxic acid addition salts, e.g. sulfonic, trichloroacetic, hydrochloric acid salts.

The last named compound is also known as minocycline hydrochloride. Typically, minocycline hydrochloride has been administered orally in a

daily dosage-of 100 to 400 mg in at least two and often more divided doses a day in a normal adult human being. It is commercially available in many forms under the tradename Minocin® from Lederle Laboratories - Wayne, New Jersey (PDR 43rd Ed.).

It should additionally be noted that minocycline hydrochloride readily undergoes epimerization and oxidative degradation to epiminocycline, a pharmacologically inactive and undesirable tetracycline compound. The amount of the epimer should be minimal but may range as high as from 1.5 percent to 10 percent without affecting the intended once daily dose of the present invention.

Preferably, the pharmaceutical delivery systems and oral dosage unit forms of the present invention will contain from 25 mg to 400 mg of 7-dimethylamino-6-deoxy-6-demethyltetracycline or non-toxic acid addition salt thereof and most preferably from 80 mg to 280 mg. Preferably, the ratio of initial loading component, i.e. minocycline powder, quick release granules, quick release coating or the like, to the secondary loading component, i.e. pH sensitive polymer coated spherical granules or single coated core, ranges from 20:80 to 80:20 by weight of initial loading component and secondary loading component combined and most preferably from 30:70 to 70:30. Preferably, the initial loading component, the secondary loading component, or both independently contain from 20 to 200 mg of minocycline.

The rapid and substantially complete release of the initial loading component is such that the initial loading component releases greater than 70 percent and preferably greater than 80 percent of the minocycline in less than 90 minutes and preferably less than 60 minutes in a medium of aqueous buffer, e.g. hydrochloric acid and/or acetate buffer, having a pH of less than 3.9. Therefore, any polymer coating of the initial loading component must be specifically rapidly and substantially erodible or dissolvable to permit the initial loading component to meet these conditions.

The rapid and substantially complete release of the secondary loading component or single coated core is such that the secondary loading component or single coated core releases greater than 50 percent and preferably greater than 70 percent of the minocycline in less than 90 minutes in a medium of aqueous buffer, e.g. acetate and/or phosphate buffer, having a pH in the range of from 4.0 to 7.5. Therefore, the pH sensitive polymer coating must be specifically rapidly and substantially completely erodible or dissolvable to permit the secondary loading component or single coated core to meet these conditions.

Further preferred embodiments of the present invention provide additionally that either from 5 to 20 percent of the minocycline in the secondary

loading component or single coated core is released in about 2 hours when suspended in a medium of simulated gastric fluid having a pH of about 1.2 at about 37°C or from 20 to 50 percent of the minocycline in the secondary loading component or single coated core is released in about 2 hours when suspended in a medium of simulated gastric fluid having a pH of about 1.2 at about 37°C.

The drug is released when it may be determined by a standard assay.

Many pharmaceutical excipients will be suitable for use in this invention. Judicious selection will be easy with the requirements and the test procedures mentioned herein kept in mind. An excipient with a known degree of solubility and swellability in the respective juices of the stomach and the upper small intestine, particularly the duodenum, should be used. Such excipients in either the quick release granules, the pH sensitive polymer coated spherical granules, the core or a combination of any of the foregoing include lactose, other mono- or di-saccharides, microcrystalline cellulose, starch, sodium carboxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, crosscarmellose sodium, pregelatinized starch, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, hydroxypropyl methylcellulose, cellulose acetate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, microcrystalline cellulose in combination with lactose, microcrystalline cellulose in combination with sodium carboxymethyl cellulose, microcrystalline cellulose in combination with crosscarmellose sodium, mixtures of any of the foregoing and the like as well as others with which those of ordinary skill in the art will be familiar, most of which are listed in standard references, for example, Remington's Pharmaceutical Sciences, 1985, 17th Edition, Philadelphia College of Pharmacy and Science, Chapter 68, Pharmaceutical Necessities, pages 1278-1320.

Although a single excipient can be used, e.g., microcrystalline cellulose, desirable results may require more care in selecting an appropriate amount of minocycline to be used in the spheres. Therefore, combinations of more than one excipient may be desirable.

Suitable forms of microcrystalline cellulose are, for example, the materials sold as Avicel® PH-101 and Avicel® PH-105 (available from FMC Corporation - American Viscoe Division, Avicel Sales, Marcus Hooks, PA, U.S.A.). Avicel® PH-101 is characterized as having an average particle size of 50 µm, particle size specification of +250 µm (+60 mesh) less than 1 percent and +74 µm (+200 mesh) less than or equal to 30.0 percent, moisture specification of less than 5.0 percent and acceptable flow properties. Avicel® PH-105 is character-

ized as having an average particle size of 20 μm , particle size specification of +37 μm (+400 mesh) less than or equal to 1.0 percent, moisture specification of less than 5.0 percent, and poor flow properties.

A suitable mixture of microcrystalline cellulose and sodium carboxymethyl cellulose is, for example, the material sold as Avicel® RC-581 by FMC Corporation. Avicel® RC-581 is characterized as having an average particle size of less than 0.2 micron, particle size specification of 250 μm (60 mesh) less than or equal to 0.1 percent, and moisture specification of less than 6 percent.

The term "spheres" is well known in the pharmaceutical art, and means spherical granules having a diameter in the range of from 0.1 to 2.5 millimeters, preferably from 0.5 to 2 millimeters, and most preferably from 0.8 to 1.2 millimeters. Preferably, the quick release granules are spherical as well. If spheres having the medicament as a surface layer are to be prepared, coated seeds, e.g., non-pareil seeds or sugar crystals, may be used. Such non-pareil seeds are generally of 0.1 mm to 2.0 mm in size and typically are 1.0 millimeter in size. They can comprise, for example, a blend of sugar and starch. Such crystals are generally 0.01 mm to 0.1 mm in size. The cores of the multi-coated composition are preferably such seeds. However, the cores may comprise minocycline alone or in combination with the excipient as well.

The quick release granules typically are uncoated. However, they may be optionally coated with a polymer coating which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9 and particularly in the human stomach, thereby leaving their immediate or quick release characteristics relatively unchanged.

The film forming polymer, if used, can vary widely in type and amount which correlates into film or coating thickness. Illustrative but not limiting quick release spherical granule coating polymers are methyl cellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, hydroxypropyl methylcellulose succinate, polymers and copolymers of (meth)acrylic acid or (meth)acrylic acid methyl ester, polyvinyl acetate phthalate or polymers or copolymers of polyvinyl acetate, cellulose acetate, fatty acids and esters thereof, cellulose acetate trimellitate, and mixtures of any of the foregoing, adapted to substantially completely dissolve in a medium having a pH of less than 3.9. The coatings can include conventional additives, such as plasticizers, pigments and colorants. The plasticizers include mineral oil; high boiling esters and vegetable oils.

Commercial coating compositions found to be useful include Eudragit®, a product of Rohm Pharma, Westerstadt, Germany, which comprises an anionic polymerizate of methacrylic acid and methyl methacrylate; Surelease® a product of Colorcon, Inc., West Point, PA, which comprises an aqueous dispersion of ethylcellulose, dibutyl sebacate, oleic acid, fumed silica, and ammonium hydroxide; Aquacoat®, a product of FMC Corp., which comprises an aqueous dispersion of ethylcellulose; Coateric®, a product of Colorcon, Inc., which comprises polyvinyl acetate phthalate; Aquateric®, a product of FMC Corp., which comprises cellulose acetate phthalate; Eastman® C-A-P™, a product of Eastman Kodak Company, Rochester, New York, which comprises cellulose acetate phthalate; and Eastman® C-A-T, a product of Eastman Kodak Company, which comprises cellulose acetate trimellitate. Preferred as a coating material for the quick release granules is hydroxypropyl methylcellulose.

Although up to 1 to 10 parts by weight gain due to the coating based upon the weight of the uncoated quick release granules is suitable, from 2 to 5 parts by weight gain is preferred and 2 parts by weight gain is most preferred.

This polymer coating may also optionally include a precoat, an overcoat or a combination of the foregoing. For best results, a 1 to 10 parts by weight gain level is preferred in addition to the standard coating when using aqueous coating formulations.

The polymer coating of the coated spherical granules is pH sensitive and is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5, particularly in the human upper small intestine and most particularly in the duodenum, thereby inhibiting erosion in a pH outside that range such as in the human stomach but leaving the rapid, controlled release characteristics of the coated spherical granules unaffected after the polymer coating is eroded in the upper small intestine, i.e. duodenum.

This pH sensitive film forming polymer can also vary widely in type and amount which correlate to film or coating thickness.

Illustrative but not limiting coated spherical granule pH sensitive coating polymers are methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, hydroxypropyl methylcellulose succinate, a polymer or copolymer of (meth)acrylic acid or (meth)acrylic acid methyl ester, polyvinyl acetate phthalate or polymers or copolymers of polyvinyl acetate, cellulose acetate, fatty acids and esters thereof, cellulose acetate trimellitate, and mixtures of any of the foregoing

adapted to dissolve substantially completely in a medium having a pH of from 4.0 to 7.5 and preferably from 4.0 to 6. These coatings can include any of the conventional coating additives from above as well.

Commercial coating compositions found to be useful include Eudragit® (Rohm Pharma, Weststadt, Germany), Surelease® (Colorcon, Inc., West Point, PA), Aquacoat® (FMC Corp.), Coateric® (Clorcon, Inc.), and Aquateric® (FMC Corp.), Eastman® C-A-P™ (Eastman Kodak Company), and Eastman® C-A-T (Eastman Kodak Company). A suitable form of ethylcellulose is one having a viscosity in the range of 5 to 100 cps at 20°C (U.S. National Formulary XIII) (content of ethoxy groups 44 to 51 percent by weight), and more particularly a viscosity of 50 cps at 20°C (content of ethoxy groups 48 to 49 percent by weight). A suitable form of hydroxypropyl methylcellulose is one having a viscosity in the range of 3 to 100 cps at 20°C (U.S. National Formulary XIII), and more particularly a viscosity of 6 cps at 20°C. Preferred as the coating is hydroxypropyl methylcellulose phthalate or a combination of hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose, and most preferably, these coatings will be adapted to dissolve substantially completely in a medium having a pH of 5.0 or greater than 5.5.

Although from 5 to 35 parts by weight gain due to the pH sensitive polymer coating based upon the weight of the uncoated spherical granules (precursors of coated spherical granules) or core is suitable, from 5 to 25 parts by weight gain is preferred and from 10 to 25 parts by weight is most preferred.

The polymer coating may also independently include a precoat, an overcoat, or a combination of the foregoing. For best results, a 1 to 10 parts by weight gain level is preferred in addition to the standard coating when using an aqueous formulation.

The amounts of minocycline and excipient which comprise the quick release granules can vary broadly but will usually be in the range of from 10 to 70 parts by weight of minocycline and from 90 to 30 parts by weight of excipient based upon 100 parts by weight of minocycline and excipient combined. Preferably, the quick release granules comprise about 50 parts by weight of minocycline and about 50 parts by weight of excipient based upon 100 parts by weight of minocycline and excipient combined.

The amounts of minocycline and excipient which comprise the precursors of the pH sensitive polymer coated spherical granules or the core of the multi-coated compositions can also vary broadly but will usually be in the range of from 10 to 80 parts by weight of minocycline and from 90 to 20

parts by weight of excipient based upon 100 parts by weight of minocycline and excipient combined. The amount of pH sensitive polymer coating on the precursors or the core varies broadly as well and is described above. Preferably, the coated spherical granules or core will comprise about 60 parts by weight of minocycline and about 40 parts by weight of excipient based upon 100 parts by weight of minocycline and excipient combined, and the pH sensitive polymer coating will comprise a weight gain of 10 to 25 parts by weight based upon 100 parts by weight of minocycline and excipient combined.

Additionally, the amount of quick release granules or initial loading component and the amount of pH sensitive polymer coated spherical granules, single coated core or secondary loading component in the pharmaceutical delivery systems, oral dosage unit forms or multi-coated compositions will vary broadly, but will generally be in the range of 20 to 80 parts by weight of quick release granules or initial loading component and 80 to 20 parts by weight of pH sensitive polymer coated spherical granules, single coated core or secondary loading components, based upon 100 parts by weight of quick release granules or initial loading component and pH sensitive polymer coated spherical granules, single coated core or secondary loading component combined. Most preferably, the quick release granules or initial loading component comprise from 30 to 70 parts by weight and the pH sensitive polymer coated spherical granules, single coated core, or secondary loading component comprise from 70 to 30 parts by weight based upon 100 parts by weight of quick release granules or initial loading component and pH sensitive polymer coated spherical granules, single coated core or secondary loading component combined.

The pH sensitive polymer coating in the multi-coated compositions generally comprises from 5 to 35 parts by weight gain based upon the weight of the core, preferably comprises from 5 to 25 parts by weight gain and most preferably from 10 to 25 parts by weight gain.

The optional overcoat comprises from 1 to 10 parts by weight gain in addition to the standard polymer coating when using an aqueous coating formulation.

The multi-coated compositions or the initial loading and/or the secondary loading components of the pharmaceutical delivery systems, separately or in combination, independently can be mixed with a pharmaceutically acceptable liquid carrier known to one of ordinary skill in the pharmaceutical arts such as diluting agents, emulsifying agents and suspending agents alone or with additional active medicaments, colorants, pigments, flavorings, additional excipients or a combination of any of the

foregoing to provide an oral dosage unit form. The multi-coated spheronized pharmaceutical compositions are preferably suspended in a high density liquid pharmaceutical carrier to form a fluid suspension delivery system.

The multi-coated compositions or the components of the pharmaceutical delivery systems, separately or in combination, can also independently be filled into either hard shell gelatin or soft shell gelatin capsules alone or with additional active medicaments, lubricants, disintegrants, plasticizers, colorants, pigments, flavoring, additional excipients or a combination of any of the foregoing by any conventional capsule forming and/or filling machine and optionally may be sealed by any means commonly known to one of ordinary skill in the pharmaceutical arts including but not limited to spot-welding, gelatin bands and matched locking rings.

The hard shell capsules used in the present invention are generally comprised of gelatin, water and optionally, FD&C colorants, opacifying agents such as titanium oxide, sulfur dioxide to prevent any decomposition or a combination of any of the foregoing. They generally comprise two sections, one slipping over the other, completely surrounding the filling.

The soft shell capsules used in the present invention are generally a soft, globular, gelatin shell somewhat thicker than the shell of the hard shell capsule. The gelatin is usually plasticized by the addition of glycerin, sorbitol, or a similar polyol. They may also contain a preservative to prevent the growth of fungi.

The multi-coated compositions or the components of the pharmaceutical delivery systems, separately or in combination, can also independently be formed alone, or with the addition of lubricants, disintegrants, plasticizers, colorants, pigments, flavorings, additional active medicaments, pharmaceutically acceptable excipients, or a combination of any of the foregoing, into tablet oral dosage unit forms by conventional means known to one of ordinary skill in the pharmaceutical arts, e.g. compressing or pressing. The tablet may then, optionally, be coated with an overcoat as explained above.

All of the pharmaceutical delivery systems, compositions or oral dosage unit forms of the present invention can be prepared using any conventional pharmaceutical production equipment.

FIG. 1 illustrates the typical steps in the preparation of uncoated spherical granules for use as either uncoated quick release granules or as precursors of pH sensitive polymer coated spherical granules. Firstly, an effective amount of at least one pharmaceutically acceptable excipient and an effective antibacterial amount or 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid

addition salt thereof are blended in a mixer. The resultant blend of the first step is granulated with a liquid medium, e.g. an aqueous solution or an organic solvent and preferably water, until the proper consistency for extrusion is realized. The resultant granulated mass is then extruded in an extruder or extruder/spheronizer, through a suitably sized, e.g. 1.0 mm, perforated plate and is spheronized at high speed for a time sufficient to form spherical granules. The wet spherical granules are then dried in conventional equipment at suitable temperatures, e.g. such as tray dryers at 55 to 65°C or a conventional fluid bed dryer system at 65 to 70°C to a low moisture level, e.g. 1 to 7 percent and preferably 2 to 5 percent.

FIG. 2 illustrates that the quick release granules then, optionally, may be coated with a substantially uniform polymer coating which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9 with an aqueous or organic solvent, e.g. methylene chloride and/or methanol, solution of the desired coating forming polymer, using fluid bed technology, pan-coating or the like. Preferably, fluid beds are used. FIG. 2 also illustrates that the precursors of coated spherical granules are independently coated with a substantially uniform polymer coating which is rapidly and substantially completely erodible in a medium having a pH of from 4.0 to 7.5 in a manner as explained above.

An initial loading therapeutically effective number of uncoated quick release granules, coated quick release granules, an initial loading therapeutically effective amount of minocycline, or a combination thereof may then be mixed in a low shear mixer with a secondary loading therapeutically effective number of pH sensitive polymer coated spherical granules.

FIG. 3 illustrates the typical steps in the preparation of the multi-coated compositions of the present invention. Firstly, a core is prepared comprising a dried spherical granule as illustrated in FIG. 1, minocycline coated non-pareil seeds, sugar crystals, or minocycline in combination with a suitable binder or pharmaceutically acceptable excipient. The core is then coated with a substantially uniform polymer coating which is rapidly and substantially completely erodible in a medium having a pH of from 4.0 to 7.5 in a manner as described above. An initial loading therapeutically effective amount of minocycline is then coated onto the single coated core in a manner as described above. Optionally, a polymer coating, an overcoating or a combination of the foregoing is sequentially applied in a manner as described above.

FIG. 4 illustrates the multi-coated composition prepared with a minocycline (1) core coated with a pH sensitive polymer coating (3) in turn coated with

a quick release minocycline coating (5) and finally coated with an optional polymer coating which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9 (7).

FIG. 5 illustrates the multi-coated composition prepared from a non-pareil seed or sugar crystals (9) coated with minocycline (1) core, which is coated with a pH sensitive polymer coating (3), subsequently coated with a quick release minocycline coating (5), and finally coated with an optional polymer coating which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9 (7).

The mixture or separate units of initial and secondary loading components, or the multi-coated compositions may then optionally be mixed with a pharmaceutically acceptable liquid carrier.

Alternatively, a hard shell or a soft shell capsule may be at least partially filled and optionally sealed, as previously described, to form a capsule oral dosage unit form.

Tablet oral dosage unit forms may be prepared by optionally adding a lubricant or other pharmaceutically acceptable excipient and then compressing or pressing.

The pharmaceutical delivery systems, spheronized pharmaceutical compositions, multi-coated compositions or oral dosage unit forms containing them may be administered by ingestion, thereby maintaining a therapeutic minocycline level in the blood stream of a warm blooded mammal for 24 hours, and thereby providing a 24 hour therapeutic blood level from a once-a-day dosaging system.

The following examples illustrate the invention without limitation. All parts are given by weight unless otherwise indicated. Bioavailability is a function of, and is an absolute term that indicates measurement of, both the true rate and the total amount (extent) of drug that reaches the blood stream from an administered dosage form.

EXAMPLE 1

A blend is prepared by mixing 2500 grams of minocycline hydrochloride powder (Minocin® - Lederle Laboratories) and 2500 grams of microcrystalline cellulose (Avicel® PH-101, FMC Corporation) in a Hobart mixer at low speed. The powder blend is then granulated to an extrudable consistency by adding 3000 ml of water slowly and mixing. The resultant granulate is extruded at high speed through a 1.0 mm plate in a NICA extruder/spheronizer Model S450, and subsequently is spheronized at high speed. The wet spheres are dried in an Aeromatic fluid bed dryer at 70°C air input until the moisture content is about 1 to 7 percent to form uncoated quick release granules

having a smooth surface and a homogeneous tetracycline compound distribution.

EXAMPLE 2

A polymer coating is prepared by mixing 71 parts of hydroxypropyl methylcellulose adapted to dissolve in a medium having a pH of less than about 3.9, 4 parts of sodium lauryl sulfate and 25 parts of mineral oil and then by adding 7 to 9 times the total weight of the above solids of water. The coating solution is substantially completely dissolvable in a medium having a pH of less than about 3.9. The solution is sprayed onto uncoated quick release granules prepared by the method of Example 1 to a 2 to 10 parts by weight gain based upon the weight of the uncoated quick release granules to form quick release granules having a coating which is adapted to erode rapidly and substantially completely in a medium having a pH of less than about 3.9.

EXAMPLE 3

A blend is prepared by mixing 3000 grams of minocycline hydrochloride powder (Minocin® - Lederle Laboratories), 1650 grams of microcrystalline cellulose (Avicel® PH-101, FMC Corporation) and 350 grams of AC-DI-SOL (crosscarmellose sodium) in a Hobart mixer at low speed. The powder blend is then granulated to an extrudable consistency by adding 3000 ml of water slowly and mixing. The resultant granulate is extruded at high speed through a 1.0 mm plate in a NICA extruder/spheronizer Model S450, and subsequently is spheronized at high speed. The wet spheres are dried in an Aeromatic fluid bed dryer at 70°C air input until the moisture content is about 1 to 7 percent to form precursors of coated spherical granules.

A pH sensitive polymer coating dissolvable in a medium having a pH of 5.0 is prepared by mixing 75 parts of hydroxypropyl methylcellulose phthalate (HP-50, Shin-Etsu Chemical, Tokyo, Japan) adapted to dissolve in a medium having pH of 5.0, 15 parts of mineral oil, and 10 parts of orange colorant (Opaspray K-1-2562, Colorcon, Inc., West Point, PA) and dissolving the mixture in an organic solvent.

The polymer coating solution is sprayed onto 900 grams of dried precursors of coated spherical granules at an initial rate of 7 ml/min which is gradually increased to 9 ml/min in an Uni-Glatt Model 82/E fluid bed until a 16 parts by weight gain based upon the weight of the precursors of coated spherical granules is achieved. Input air is adjusted to 54°C while output air is adjusted between 22 and 25°C.

pH sensitive polymer coated spherical granules having a polymer coating adapted to erode rapidly and substantially completely in a medium having a pH of 5.0 are formed.

Dissolution profiles of the minocycline hydrochloride are determined by U.S.P. XXI test methods using dissolution media of simulated gastric fluid having a pH of 1.2, of buffered media having pH's of 4.5 and 6.0, and of simulated intestinal fluid having a pH of 7.2. The results appear in FIG. 6 in graph form.

EXAMPLE 4

The procedure of Example 3 is followed, however, before the pH sensitive polymer coating is applied to the precursors of coated spherical granules, a precoating of hydroxypropyl methylcellulose is applied by spraying until about 1 to about 5 parts by weight gain based upon the weight of precursors of coated spherical granules is achieved. This provides a smooth surface on the precursors for subsequent pH sensitive polymer coating.

EXAMPLE 5

Coated spherical granules are prepared according to the procedure of Example 3. Subsequently, an overcoating of hydroxypropyl methylcellulose is applied by spraying until 1 to 5 parts by weight gain based upon the weight of the precursors of coated spherical granules is achieved.

EXAMPLE 6

pH sensitive polymer coated spherical granules with an undercoating are prepared according to the procedure of Example 4. Subsequently, an overcoating of hydroxypropyl methylcellulose is applied by spraying until 1 to 5 parts by weight gain based upon the weight of the non-overcoated but undercoated, precursors of coated spherical granules is achieved.

EXAMPLE 7

The procedure of Example 3 is followed substituting a pH sensitive polymer coating dissolvable at a pH of greater than 5.5 which is prepared by mixing 75 parts of hydroxypropyl methylcellulose phthalate (HP-55, Shin-Etsu Chemical, Tokyo, Japan) adapted to dissolve in a medium having a pH of greater than about 5.5, 15 parts of mineral oil and 10 parts of orange colorant (Opaspray K-1-2562, Colorcon, Inc.) and dissolving the mixture in an organic solvent.

Dissolution profiles of the minocycline hydrochloride are determined by U.S.P. XXI test methods using dissolution media of simulated gastric fluid having a pH of 1.2, of buffered media having pH's of 4.5 and 6.0, and of simulated intestinal fluid having a pH of 7.2. The results appear in FIG. 7 in graph form.

EXAMPLE 8

The procedure of Example 3 is followed substituting a pH sensitive polymer coating dissolvable in a medium having a pH of from 4.0 to 7.5 which is prepared by mixing 71.25 parts of hydroxypropyl methylcellulose phthalate (HPMCP-50, Shin-Etsu Chemical, Tokyo, Japan), 3.75 parts of hydroxypropyl methylcellulose (Shin-Etsu Chemical), 15 parts of mineral oil and 10 parts of orange colorant (Opaspray K-1-2562, Colorcon, Inc.) and dissolving the mixture in an organic solvent and spraying the polymer coating solution until a 10 parts by weight gain based upon the weight of the coated spherical granules is achieved.

Dissolution profiles of the minocycline hydrochloride are determined by U.S.P. XXI test methods using buffered media having pH's of 4.0, 4.5 and 6.0. The results appear in FIG. 8 in graph form.

EXAMPLE 9

The procedure of Example 8 is followed, however the pH sensitive polymer coating is applied until a 20 parts by weight gain based upon the weight of the precursors of coated spherical granule is achieved.

EXAMPLE 10

The procedure of Example 3 is followed substituting a pH sensitive polymer coating dissolvable in a medium having a pH of from about 4.0 to about 7.5 which is prepared by mixing 60 parts of hydroxypropyl methylcellulose phthalate (HPMCP-50, Shin-Etsu Chemical, Tokyo, Japan), 15 parts of hydroxypropyl methylcellulose (Shin-Etsu Chemical), 15 parts of mineral oil and 10 parts of orange colorant (Opaspray K-1-2562, Colorcon, Inc.) and dissolving the mixture in an organic solvent and spraying the polymer coating solution until a 10 parts by weight gain based upon the weight of the precursors of coated spherical granules is achieved.

EXAMPLE 11

The procedure of Example 10 is followed, however the pH sensitive polymer coating is applied until a 20 parts by weight gain based upon the

weight of the precursors of coated spherical granules is achieved.

Dissolution profiles of the minocycline hydrochloride are determined by U.S.P. XXI test methods using buffered media having pH's of 4.0, 4.5 and 6.0. The results appear in FIG. 9 in graph form.

EXAMPLE 12

pH sensitive polymer coated spherical granules are prepared according to the method of Example 3. The resultant coated spherical granules are mixed with a pharmaceutically acceptable liquid medium to yield an oral dosage unit form.

EXAMPLE 13

pH sensitive polymer coated spherical granules are prepared according to the method of Example 3. The resultant coated spherical granules are filled into a hard shell capsule to yield an oral dosage unit form.

EXAMPLE 14

pH sensitive polymer coated spherical granules are prepared according to the method of Example 3. The resultant coated spherical granules are filled into a soft shell capsule to yield an oral dosage unit form.

EXAMPLE 15

pH sensitive polymer coated spherical granules are prepared according to the method of Example 3. The resultant coated spherical granules are compressed into a tablet to yield an oral dosage unit form.

EXAMPLE 16

The procedure of Example 3 is followed substituting an anionic polymerizate of methacrylic acid and methyl methacrylate (Eudragit® - Rhom Pharma) for the pH sensitive polymer coating to form pH sensitive polymer coated spherical granules.

A 185 mg sample of minocycline hydrochloride prepared according to the procedure of Example 16 is administered to a human subject, and serum concentration levels of minocycline hydrochloride are measured over a 24 hour period. The results appear in FIG. 10 in the curve referred to as "Example 16". These results show that in the absence of a quick release initial loading dose of minocycline, the blood level of minocycline drops below minimum therapeutically effective amounts desired for the majority of minocycline therapies

after about 10-12 hours.

EXAMPLE 17

690 grams of quick release granules prepared by the method of Example 1 and 810 grams of the pH sensitive polymer coated spherical granules prepared by the method of Example 3 are mixed in a low shear blender at low speed for 15 minutes to form a spheronized pharmaceutical composition mixture.

EXAMPLE 18

The mixture prepared by the method of Example 17 is mixed with a pharmaceutically acceptable liquid carrier to form oral dosage unit forms having a total minocycline content of 185 mg, with 85 mg of minocycline contained in the quick release granules and 100 mg of the tetracycline compound contained in the pH sensitive polymer coated spherical granules.

EXAMPLE 19

The mixture prepared by the method of Example 17 is filled into hard shell gelatin capsules to form oral dosage unit forms having a total minocycline content of 185 mg, with 85 mg of minocycline contained in the quick release granules and 100 mg of the tetracycline compound contained in the pH sensitive polymer coated spherical granules.

Dissolution profiles of the minocycline are determined by U.S.P. XXI test methods using dissolution media with pH's of 1.2 and of 7.2. The results appear in FIG. 11 in graph form.

Serum concentration levels of minocycline over the initial 12 hour period also appear in FIG. 13 in the curve referred to as "Example 19".

The once-a-day regimen is carried out for three days, and serum concentration levels for the twenty-four hour period commencing with the beginning of day three are measured over that subsequent 24 hour period. The results appear in FIG. 12 in the curve referred to as "Example 19".

COMPARATIVE EXAMPLE 19A*

Two capsules, each containing 100 mg of minocycline hydrochloride powder (Minocin® - Lederle Laboratories), are administered as a loading dose to a human subject. Over the following three days, one capsule containing 100 mg of minocycline hydrochloride powder (Minocin®) is administered every 12 hours.

Serum concentration levels are measured over the initial 12 hour period of administration. The

results appear in FIG. 13 in the curve identified as "Comparative Example 19A".

Serum concentration levels for the 24 hour period commencing with the beginning of day three are measured over the subsequent 24 hour period. The results appear in FIG. 12 in the curve referred to as "Comparative Example 19A".

EXAMPLE 20

The mixture prepared by the method of Example 17 is pressed into tablets to form oral dosage unit forms having a total minocycline content of 185 mg, with 85 mg of minocycline contained in the quick release granules and 100 mg of the tetracycline compound contained in the pH sensitive polymer coated spherical granules.

EXAMPLE 21

690 grams of the quick release granules prepared by the method of Example 1 and 810 grams of the pH sensitive polymer coated spherical granules prepared by the method of Example 7 are mixed in a low shear blender at low speed for 15 minutes to form a spheronized pharmaceutical composition mixture.

EXAMPLE 22

The mixture prepared by the method of Example 21 is filled into hard shell gelatin capsules to form oral dosage unit forms having a total minocycline content of 185 mg, with 85 mg of the minocycline contained in the quick release granules and 100 mg of the tetracycline compound contained in the pH sensitive polymer coated spherical granules.

Bioavailability is determined to be 76 percent by measuring the area under the plasma concentration curve and comparing that area to that of a reference curve from Comparative Example 22A.

Dissolution profiles of the minocycline are determined by U.S.P. XXI test methods using dissolution media with pH's of 1.2 and of 7.2. The results appear in FIG. 14 in graph form.

One capsule is administered to a human subject, and serum concentration levels of minocycline are measured over a 24 hour period. The results appear in FIG. 10 in the curve referred to as "Example 22". A maximum serum concentration of minocycline of 1.9 mcg/ml of serum is reached after 3.8 hours.

One capsule is administered to each of a fasting subject and a subject who eats regularly. Serum concentration levels of tetracycline compound are measured over a 24 hour period. The results illustrating that plasma concentration levels of

minocycline of greater than a minimum therapeutically effective serum concentration were maintained for over about 24 hours appear in FIG. 15 in graph form.

COMPARATIVE EXAMPLE 22A*

One capsule containing 100 mg of minocycline hydrochloride powder (Minocin® - Lederle Laboratories) is administered to a human subject, and serum concentration levels of minocycline hydrochloride are measured over a twelve hour period. A second capsule containing 100 mg of minocycline hydrochloride powder (Minocin®) is administered to the subject at the end of the twelve hour period, and serum concentration levels of minocycline hydrochloride are measured over the next twelve hour period. The results appear in FIG. 10 in the curve identified as "Comparative Example 22A".

Bioavailability is 100 percent as this is the reference for comparison.

A maximum serum concentration of minocycline hydrochloride during the first twelve hour period of 1.78 mcg/ml of serum is reached after 1.5 hours, and a maximum serum concentration of minocycline hydrochloride during the second twelve hour period of 2.65 mcg/ml is reached 1.8 hours after the administration of the second capsule. Minocycline hydrochloride plasma level concentration fluctuates broadly can result in undesirable side effects such as nausea and gastrointestinal.

EXAMPLE 23

A multi-coated composition as illustrated in FIG. 4 is prepared.

A core is formed from minocycline (1).

A pH sensitive polymer coating (3) dissolvable in a medium having a pH of about 5.0 is prepared by mixing 75 parts of hydroxypropyl methylcellulose phthalate (HP-50, Shin-Etsu Chemical, Tokyo, Japan) adapted to dissolve in a medium having a pH of about 5.0, 15 parts of mineral oil, and 10 parts of orange colorant (Opaspray K-1-2562, Colorcon, Inc., West Point, PA) and dissolving the mixture in an organic solvent.

The polymer coating solution is sprayed onto the core coated at an initial rate of 7 ml/min which is gradually increased to 9 ml/min in a Uni-Glatt Model 82/E dryer until a 16 percent weight gain based upon the weight of the core is achieved. Input air is adjusted to 54°C while output air is adjusted between 22 and 25°C.

The single coated core is then coated with a quick release coating (5) containing 85 mg of minocycline.

A polymer coating (7) is then prepared by mixing 71 parts of hydroxypropyl methylcellulose adapted to dissolve in a medium having a pH of less than 3.9, 4 parts of sodium lauryl sulfate and 25 parts of mineral oil and then by adding 7 to 9 times the total weight of the above solids of water. The coating solution is substantially completely dissolvable in a medium having a pH of less than 3.9. The solution is sprayed onto the quick release dry coated core to a 2 to 10 weight gain based upon the weight of the quick release dry coated core.

EXAMPLE 24

A multi-coated composition as illustrated in FIG. 5 is prepared. A nonpareil seed (9) is formed from a sucrose crystal. The seed is coated with 100 mg of minocycline (1) to form a core which is then coated with a pH sensitive polymer coating (3) dissolvable in a medium having a pH of 5.0. The pH sensitive polymer coating is prepared by mixing 75 parts of hydroxypropyl methylcellulose phthalate (HP-50, Shin-Etsu Chemical, Tokyo, Japan) adapted to dissolve in a medium having a pH of 5.0, 15 parts of mineral oil, and 10 parts of orange colorant (Opaspray K-1-2562, Colorcon, Inc., West Point, PA) and dissolving the mixture in an organic solvent.

The polymer coating solution is sprayed onto the core at an initial rate of 7 ml/min which is gradually increased to 9 ml/min in a Uni-Glatt Model 82/E dryer until a 16 percent weight gain based upon the weight of the core is achieved. Input air is adjusted to 54°C while output air is adjusted between 22 and 25°C.

The single coated core is then coated with a quick release coating (5) containing 85 mg of minocycline.

A polymer coating (7) is then prepared by mixing 71 parts of hydroxypropyl methylcellulose adapted to dissolve in a medium having a pH of less than 3.9, 4 parts of sodium lauryl sulfate and 25 parts of mineral oil and then by adding 7 to 9 times the total weight of the above solids of water. The coating solution is substantially completely dissolvable in a medium having a pH of less than 3.9. The solution is sprayed onto the quick release dry coated core to a 2 to 10 parts by weight gain based upon the weight of the quick release dry coated core.

Examples 3 (FIG. 6), 7 (FIG. 7), 8 (FIG. 8), and 11 (FIG. 9) demonstrate the selective release properties of pH sensitive polymer coated release spherical granules.

Example 22 demonstrates the ability of compositions and oral dosage unit forms of the present invention to maintain superior prolonged and controlled release of minocycline and thusly the ability

to provide a relatively even, at least minimum therapeutic blood concentration level of minocycline for up to 24 hours with only once-a-day administration.

Comparative Examples 19A* and 22A* illustrate the uneven release rate and the broad fluctuations in blood levels of minocycline that result from conventional minocycline dosages.

Example 22 further demonstrates that the prolonged controlled release properties are also maintained in a fasting patient, thereby obviating the need for a patient to eat regularly for a therapeutic effect.

Example 19 also demonstrates that the prolonged controlled release properties of dosage unit forms of the present invention are maintained even after three days of continued administration and showing that continued use of the present invention does not impair its prolonged controlled release properties. Comparative Example 19A*, in contrast, demonstrates that traditional dosage forms of minocycline, even after three days of administration still give uneven release with great blood level fluctuations and may consequently result in undesirable side effects.

Comparative Examples 19A* and 22A* further illustrate the inability of conventional oral dosage unit forms to maintain minimum therapeutic concentration levels for prolonged periods of time. The effectiveness of the initial dosaging rapidly subsides after about 12 hours as evidenced by the relatively slight increases over initial concentration achieved after the administration of a second dosage at approximately 12 hours.

Comparative Example 19A* illustrates, when compared with Examples 19 and 22, that the relatively low dosages of the present invention provide relatively even therapeutically effective concentration levels of minocycline.

Examples 20 and 22 demonstrate the pH sensitive properties of the compositions and oral dosage unit forms of the present invention.

Claims

Claims for the following Contracting States :
AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE

1. A pharmaceutical delivery system adapted to provide a therapeutically effective blood concentration level of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof for a sustained period of time of up to about twenty-four hours comprising:

(I) a multiple delivery vehicle system comprising

(A) an initial loading therapeutically effective number of quick release granules which comprise

A polymer coating (7) is then prepared by mixing 71 parts of hydroxypropyl methylcellulose adapted to dissolve in a medium having a pH of less than 3.9, 4 parts of sodium lauryl sulfate and 25 parts of mineral oil and then by adding 7 to 9 times the total weight of the above solids of water. The coating solution is substantially completely dissolvable in a medium having a pH of less than 3.9. The solution is sprayed onto the quick release dry coated core to a 2 to 10 weight gain based upon the weight of the quick release dry coated core.

EXAMPLE 24

A multi-coated composition as illustrated in FIG. 5 is prepared. A nonpareil seed (9) is formed from a sucrose crystal. The seed is coated with 100 mg of minocycline (1) to form a core which is then coated with a pH sensitive polymer coating (3) dissolvable in a medium having a pH of 5.0. The pH sensitive polymer coating is prepared by mixing 75 parts of hydroxypropyl methylcellulose phthalate (HP-50, Shin-Etsu Chemical, Tokyo, Japan) adapted to dissolve in a medium having a pH of 5.0, 15 parts of mineral oil, and 10 parts of orange colorant (Opaspray K-1-2562, Colorcon, Inc., West Point, PA) and dissolving the mixture in an organic solvent.

The polymer coating solution is sprayed onto the core at an initial rate of 7 ml/min which is gradually increased to 9 ml/min in a Uni-Glatt Model 82/E dryer until a 16 percent weight gain based upon the weight of the core is achieved. Input air is adjusted to 54°C while output air is adjusted between 22 and 25°C.

The single coated core is then coated with a quick release coating (5) containing 85 mg of minocycline.

A polymer coating (7) is then prepared by mixing 71 parts of hydroxypropyl methylcellulose adapted to dissolve in a medium having a pH of less than 3.9, 4 parts of sodium lauryl sulfate and 25 parts of mineral oil and then by adding 7 to 9 times the total weight of the above solids of water. The coating solution is substantially completely dissolvable in a medium having a pH of less than 3.9. The solution is sprayed onto the quick release dry coated core to a 2 to 10 parts by weight gain based upon the weight of the quick release dry coated core.

Examples 3 (FIG. 6), 7 (FIG. 7), 8 (FIG. 8), and 11 (FIG. 9) demonstrate the selective release properties of pH sensitive polymer coated release spherical granules.

Example 22 demonstrates the ability of compositions and oral dosage unit forms of the present invention to maintain superior prolonged and controlled release of minocycline and thusly the ability

to provide a relatively even, at least minimum therapeutic blood concentration level of minocycline for up to 24 hours with only once-a-day administration.

Comparative Examples 19A* and 22A* illustrate the uneven release rate and the broad fluctuations in blood levels of minocycline that result from conventional minocycline dosages.

Example 22 further demonstrates that the prolonged controlled release properties are also maintained in a fasting patient, thereby obviating the need for a patient to eat regularly for a therapeutic effect.

Example 19 also demonstrates that the prolonged controlled release properties of dosage unit forms of the present invention are maintained even after three days of continued administration and showing that continued use of the present invention does not impair its prolonged controlled release properties. Comparative Example 19A*, in contrast, demonstrates that traditional dosage forms of minocycline, even after three days of administration still give uneven release with great blood level fluctuations and may consequently result in undesirable side effects.

Comparative Examples 19A* and 22A* further illustrate the inability of conventional oral dosage unit forms to maintain minimum therapeutic concentration levels for prolonged periods of time. The effectiveness of the initial dosaging rapidly subsides after about 12 hours as evidenced by the relatively slight increases over initial concentration achieved after the administration of a second dosage at approximately 12 hours.

Comparative Example 19A* illustrates, when compared with Examples 19 and 22, that the relatively low dosages of the present invention provide relatively even therapeutically effective concentration levels of minocycline.

Examples 20 and 22 demonstrate the pH sensitive properties of the compositions and oral dosage unit forms of the present invention.

Claims

Claims for the following Contracting States :
AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE

1. A pharmaceutical delivery system adapted to provide a therapeutically effective blood concentration level of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof for a sustained period of time of up to about twenty-four hours comprising:

(I) a multiple delivery vehicle system comprising

(A) an initial loading therapeutically effective number of quick release granules which comprise



- (a)
- (i) an effective amount of at least one pharmaceutically acceptable excipient; and
 - (ii) an effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof, on or in said quick release granules; and optionally
- (b) a substantially uniform polymer coating, on said quick release granules and which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9; said quick release granules being adapted to release substantially completely said minocycline in a medium having a pH of less than 3.9;
- (A-1) an initial loading therapeutically effective amount of finely divided powder comprising
- (a) an effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof; and optionally
 - (b) an independent effective amount of at least one pharmaceutically acceptable excipient which may be the same as or different than (I)(A)(a)(i); or
- (A-2) an initial loading therapeutically effective combination of (A) and (A-1); and
- (B) a secondary loading therapeutically effective number of pH sensitive polymer coated spherical granules which comprise
- (a)
 - (i) an independent effective amount of at least one pharmaceutically acceptable excipient which may be the same as or different than (I)(A)(a)(i) or (I)(A-1)(b); and
 - (ii) an independent effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof, on or in said coated spherical granules; and
 - (b) a substantially uniform pH sensitive polymer coating, the polymer of which may be the same as or different than (I)(A)(b), on said coated spherical granules and which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5; said coated spherical granules thereby being adapted to re-

- lease substantially completely said minocycline in a medium having a pH in the range of from 4.0 to 7.5; or
- (II) one or more multi-coated spheronized pharmaceutical single delivery vehicle compositions comprising:

- (A) a core comprised of
 - (a) a full or a partial secondary loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof; or
 - (b) at least one granule comprised of
 - (i) an effective amount of at least one pharmaceutically acceptable excipient; and
 - (ii) a full or a partial secondary loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof, on or in said granule; having applied thereon

- (B) a substantially uniform pH sensitive polymer coating which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5; said core thereby being adapted to release substantially completely said minocycline in a medium having a pH in the range of from 4.0 to 7.5; having applied thereon

- (C) a quick release coating comprising a full or partial initial loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof; and optionally having applied thereon

(D)

- (a) a substantially uniform polymer coating, the polymer of which may be the same as or different than (B), and which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9;
- (b) a polymer overcoat, the polymer of which may be the same or different than (B) or (D)(a), or
- (c) a combination of (a) and thereon (b).

2. A pharmaceutical delivery system as defined in Claim 1 comprising a mixed blend of (I)(A), (I)(A-1), or (I)(A-2) and (I)(B).



3. A pharmaceutical delivery system as defined in Claim 1 comprising separate administration units of initial loading component (I)(A), (I)(A-1), or (I)(A-2) for initial administration and secondary loading component (I)(B) for administration up to 120 minutes after administration of (I)(A), (I)(A-1) or (I)(A-2). 5
 4. A pharmaceutical delivery system as defined in Claim 1 wherein said minocycline in said quick release granules (I)(A) comprises from 10 to 70 parts by weight and said at least one pharmaceutically acceptable excipient in said quick release comprises from 90 to 30 parts by weight based upon 100 parts by weight of said minocycline and said excipient combined and said optional polymer coating on said quick release granules comprises from zero to 10 parts by weight based upon 100 parts by weight of said minocycline and said excipient combined. 10 15 20
 5. A pharmaceutical delivery system as defined in Claim 1 containing from 25 to 400 mg of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof. 25
 6. A pharmaceutical delivery system as defined in Claim 5 wherein said initial loading (I)(A), (I)(A-1), (I)(A-2) or (II)(C) contains from 20 to 200 mg of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof. 30
 7. A controlled release pharmaceutical composition in oral dosage unit form comprising a pharmaceutical delivery system as defined in Claim 1 mixed with a pharmaceutically acceptable liquid carrier. 35 40
 8. A method for the preparation of a pharmaceutical delivery system comprising the steps of
 - (A) forming an initial loading component by
 - (a) blending
 - (i) an effective amount of at least one pharmaceutical acceptable excipient; and
 - (ii) an effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof;
 - (b) granulating the resultant blend in the presence of a granulating liquid;
 - (c) extruding the resultant granulate;
 - (d) spheronizing the resultant extrudate to form quick release granules which are adapted to release substantially completely said minocycline in a medium having a pH of less than 3.9;
 - (e) drying said quick release granules; and optionally
 - (f) coating said quick release granules with a substantially uniform polymer coating which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9; or
 - (A-1) forming an initial loading component by
 - (a) dividing 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof into a fine powder; and optionally
 - (b) mixing said powder with an effective amount of a pharmaceutically acceptable excipient; and
 - (B) forming a secondary loading component by
 - (a) blending
 - (i) an independent amount of at least one pharmaceutical acceptable excipient which may be the same as or different than (A)(a)(i) or (A-1)(b); and
 - (ii) an independent effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof;
 - (b) granulating the resultant blend in the presence of a granulating liquid;
 - (c) extruding the resultant granulate;
 - (d) spheronizing the resultant extrudate to form precursors of coated spherical granules;
 - (e) drying said precursors;
 - (f) coating said precursors with a substantially uniform polymer coating, the polymer of which may be the same as or different than that in optional step (A)(f) and which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5.
9. A method for the preparation of a multi-coated composition pharmaceutical delivery system comprising
 - (A) forming a core from one or more spherical granules prepared by
 - (a) blending
 - (i) an effective amount of at least one pharmaceutical acceptable excipient; and
 - (ii) a full or a partial initial loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof;



- (b) granulating the resultant blend in the presence of a granulating liquid;
 (c) extruding the resultant granulate;
 (d) spheronizing the resultant extrudate to form one or more spherical granules; and
 (e) drying said spherical granules;
 (A-1) forming a core from a full or a partial secondary loading effective antibacterial amount of 7-dimethylamino-6-deoxy-demethyltetracycline non-toxic acid addition salt thereof; or
 (A-2) forming a core by coating a non-pareil seed or a sugar crystal with a full or a partial secondary loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof;
 (B) coating said core with a substantially uniform pH sensitive polymer coating which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5; said core thereby being adapted to release substantially completely said minocycline in a medium having a pH in the range from 4.0 to 7.5 to form a single coated core;
 (C) coating said single coated core with a quick release coating comprising a full or a partial initial loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof to form a multi-coated composition; and optionally
 (D) coating said multi-coated composition with (a) a substantially uniform polymer coating, the polymer of which may be the same as or different than (B) and which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9; (b) a polymer overcoat, the polymer of which may be the same as or different than (B) or (D)(a); or (c) a combination of (a) and thereon (b).
10. A pharmaceutical delivery system comprising
 (A) an initial loading therapeutically effective number of quick release granules which comprise
 (a)
 (i) an effective amount of at least one pharmaceutically acceptable excipient; and
 (ii) an effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof, on or in said

- quick release granules; and optionally
 (b) a substantially uniform polymer coating, on said quick release granules and which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9;
 said quick release granules being adapted to release substantially completely said minocycline in a medium having a pH of less than 3.9; and
 (B) a secondary loading therapeutically effective number of pH sensitive polymer coated spherical granules which comprise
 (a)
 (i) an independent effective amount of at least one pharmaceutically acceptable excipient which may be the same as or different than (A)(a)(i); and
 (ii) an independent effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof, on or in said coated spherical granules; and
 (b) a substantially uniform pH sensitive polymer coating, the polymer of which may be the same as or different than (A)-(b), on said coated spherical granules and which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5;
 said coated spherical granules thereby being adapted to release substantially completely said minocycline in a medium having a pH in the range of from 4.0 to 7.5.

11. A pharmaceutical delivery system adapted to provide a therapeutically effective blood concentration level, of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof for a sustained period of time of up to about twenty-four hours comprising one or more multi-coated spheronized pharmaceutical compositions comprising:

- (A) a core comprised of
 (a) a full or a partial secondary loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof; or
 (b) at least one granule comprised of
 (i) an effective amount of at least one pharmaceutically acceptable excipient; and
 (ii) a full or a partial secondary loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-



6-demethyltetracycline or a non-toxic acid addition salt thereof, on or in said core;

having applied thereon

- (B) a substantially uniform pH sensitive polymer coating which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5; said core thereby being adapted to release substantially completely said minocycline in a medium having a pH in the range of from 4.0 to 7.5; having applied thereon
- (C) a quick release coating comprising a full or partial initial loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof; and optionally having applied thereon
- (D)
- (a) a substantially uniform polymer coating, the polymer of which may be the same as or different than (B), and which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9;
- (b) a polymer overcoat, the polymer of which may be the same or different than (B) or (D)(a), or
- (c) a combination of (a) and thereon (b).

12. A spheronized pharmaceutical composition comprising a secondary loading therapeutically effective number of pH sensitive polymer coated spherical granules which include
- (a)
- (i) an effective amount of at least one pharmaceutically acceptable excipient; and
- (ii) an effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof, on or in said coated spherical granules; and
- (b) a substantially uniform pH sensitive polymer coating, on said coated spherical granules, which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5; said coated spherical granules thereby being adapted to release substantially completely said minocycline in a medium having a pH in the range of from 4.0 to 7.5.

Claims for the following Contracting States : ES, GR

1. A method for the preparation of a pharmaceutical delivery system comprising the steps of
- (A) forming an initial loading component by
- (a) blending
- (i) an effective amount of at least one pharmaceutical acceptable excipient; and
- (ii) an effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof;
- (b) granulating the resultant blend in the presence of a granulating liquid;
- (c) extruding the resultant granulate;
- (d) spheronizing the resultant extrudate to form quick release granules which are adapted to release substantially completely said minocycline in a medium having a pH of less than 3.9;
- (e) drying said quick release granules; and optionally
- (f) Coating said quick release granules with a substantially uniform polymer coating which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9; or
- (A-1) forming an initial loading component by
- (a) dividing 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof into a fine powder; and optionally
- (b) mixing said powder with an effective amount of a pharmaceutically acceptable excipient; and
- (B) forming a secondary loading component by
- (a) blending
- (i) an independent amount of at least one pharmaceutical acceptable excipient which may be the same as or different than (A)(a)(i) or (A-1)(b); and
- (ii) an independent effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof;
- (b) granulating the resultant blend in the presence of a granulating liquid;
- (c) extruding the resultant granulate;
- (d) spheronizing the resultant extrudate to form precursors of coated spherical granules;
- (e) drying said precursors;
- (f) coating said precursors with a substantially uniform polymer coating, the



polymer of which may be the same as or different than that in optional step (A)(f) and which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5.

2. A method for the preparation of a multi-coated composition pharmaceutical delivery system comprising

(A) forming a core from one or more spherical granules prepared by

(a) blending

(i) an effective amount of at least one pharmaceutical acceptable excipient; and

(ii) a full or a partial initial loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof;

(b) granulating the resultant blend in the presence of a granulating liquid;

(c) extruding the resultant granulate;

(d) spheronizing the resultant extrudate to form one or more spherical granules; and

(e) drying said spherical granules;

(A-1) forming a core from a full or a partial secondary loading effective antibacterial amount of 7-dimethylamino-6-deoxy-demethyltetracycline non-toxic acid addition salt thereof; or

(A-2) forming a core by coating a non-pareil seed or a sugar crystal with a full or a partial secondary loading therapeutically effective antibacterial amount of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof;

(B) coating said core with a substantially uniform pH sensitive polymer coating which is rapidly and substantially completely erodible in a medium having a pH in the range of from 4.0 to 7.5; said core thereby being adapted to release substantially completely said minocycline in a medium having a pH in the range from 4.0 to 7.5 to form a single coated core;

(C) coating said single coated core with a quick release coating comprising a full or a partial initial loading therapeutically effective antibacterial amount Of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof to form a multi-coated composition; and optionally

(D) coating said multi-coated composition with (a) a substantially uniform polymer coating, the polymer of which may be the

same as or different than (B) and which is rapidly and substantially completely erodible in a medium having a pH of less than 3.9; (b) a polymer overcoat, the polymer of which may be the same as or different than (B) or (D)(a); or (c) a combination of (a) and thereon (b).

3. A method as defined in Claim 1 wherein said minocycline in said quick release granules of step (A) comprises from 10 to 70 parts by weight and said at least one pharmaceutically acceptable excipient in said quick release comprises from 90 to 30 parts by weight based upon 100 parts by weight of said minocycline and said excipient combined and said optional polymer coating on said quick release granules comprises from zero to 10 parts by weight base upon 100 parts by weight of said minocycline and said excipient combined.

4. A method according to Claim 1 which provides a pharmaceutical delivery system containing from 25 to 400 mg of 7-dimethylamino-6-deoxy-6-demethyltetracycline or a non-toxic acid addition salt thereof.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE

1. Pharmazeutisches Abgabesystem, angepaßt zur Bereitstellung eines therapeutisch wirksamen Blutkonzentrationsspiegels von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon für einen anhaltenden Zeitraum bis zu etwa 24 Stunden, umfassend:

(I) ein Mehrfachabgabesystem, umfassend

(A) eine anfängliche Beladung einer therapeutisch wirksamen Anzahl an Körnern mit rascher Freisetzung, umfassend

(a)

(i) eine wirksame Menge mindestens eines pharmazeutisch verträglichen Exzipienten und

(ii) eine wirksame antibakterielle Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon, auf oder in den Körnern zur raschen Freisetzung und gegebenenfalls

(b) eine im wesentlichen gleichförmige Polymerbeschichtung auf den Körnern mit rascher Freisetzung und



die rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert von weniger als 3,9 zerfällt;

wobei die Körnchen mit rascher Freisetzung derart ausgelegt sind, daß die Freisetzung des Minocyclins in einem Medium mit einem pH-Wert von weniger als 3,9 im wesentlichen vollständig ist;

(A-1) eine anfängliche Beladung einer therapeutisch wirksamen Menge an fein verteiltem Pulver, umfassend

(a) eine wirksame antibakterielle Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon; und gegebenenfalls

(b) eine unabhängige wirksame Menge mindestens eines pharmazeutisch verträglichen Exzipienten, der der gleiche oder ein verschiedener sein kann zu (I)(A)(a)(i);

oder (A-2), eine anfängliche Beladung einer therapeutisch wirksamen Kombination von (A) und (A-1) und

(B) eine zweite Beladung einer therapeutisch wirksamen Anzahl an mit pH-empfindlichem Polymer beschichteten kugelförmigen Körnchen, umfassend

(a)

(i) eine unabhängige wirksame Menge von zumindest einem pharmazeutisch verträglichen Exzipienten, der der gleiche oder ein verschiedener sein kann zu (I)(A)(a)(i) oder (I)(A-1)(b); und

(ii) eine unabhängige wirksame antibakterielle Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon auf oder in den beschichteten kugelförmigen Körnchen und

(b) eine im wesentlichen gleichförmige pH-empfindliche Polymerbeschichtung, wobei das Polymer davon das gleiche oder ein verschiedenes sein kann zu (I)(A)(b) auf den beschichteten kugelförmigen Körnchen und das rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 zerfällt, wobei die beschichteten kugelförmigen Körnchen derart ausgelegt sind, um im wesentlichen vollständig Minocyclin in einem Medium mit einem pH im Bereich von 4,0 bis 7,5 freizusetzen; oder

(II) eine oder mehrere mehrfach beschichtete sphäronisierte pharmazeutische Vehiculzusammensetzungen zur Einzelabgabe, umfassend:

(A) einen Kern, umfassend

(a) eine vollständige oder teilweise zweite Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon oder

(b) mindestens ein Körnchen, umfassend

(i) eine wirksame Menge von mindestens einem pharmazeutisch verträglichen Exzipienten; und

(ii) eine vollständige oder teilweise zweite Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon auf oder in den Körnchen, die darauf aufgebracht wurde;

(B) eine im wesentlichen gleichförmige pH-empfindliche Polymerbeschichtung, die rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 zerfällt, wobei der Kern derart ausgelegt ist, daß das Minocyclin im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 freigesetzt wird, die darauf aufgetragen ist,

(C) eine Beschichtung zur raschen Freisetzung, umfassend eine vollständige oder teilweise anfängliche Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon; und gegebenenfalls darauf aufgebracht

(D)

(a) eine im wesentlichen gleichförmige Polymerbeschichtung, wobei das Polymer davon das gleiche sein kann oder verschieden sein kann zu (B) und rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert von weniger als 3,9 zerfällt;

(b) eine Polymerbeschichtung, wobei das Polymer davon gleich oder verschieden sein kann zu (B) oder (D)(a) oder



- (c) eine Kombination von (a) und darauf (b).
2. Pharmazeutisches Abgabesystem nach Anspruch 1, umfassend eine Mischung aus (I)(A), (I)(A-1) oder (I)(A-2) und (I)(B). 5
 3. Pharmazeutisches Abgabesystem nach Anspruch 1, umfassend getrennte Verabreichungseinheiten von anfänglicher Beladungskomponente (I)(A), (I)(A-1) oder (I)(A-2) zur anfänglichen Verabreichung und eine zweite Beladungskomponente (I)(B) zur Verabreichung bis zu 120 Minuten nach der Verabreichung von (I)(A), (I)(A-1) oder (I)(A-2). 10 15
 4. Pharmazeutisches Abgabesystem nach Anspruch 1, wobei das Minocyclin in den Körnchen zur raschen Freigabe (I)(A) 10 bis 70 Gewichtsteile umfaßt und der mindestens eine pharmazeutisch verträgliche Exzipient in dem Mittel zur raschen Freisetzung 90 bis 30 Gewichtsteile umfaßt, bezogen auf 100 Gewichtsteile der Kombination aus Minocyclin und dem Exzipienten und die gegebenenfalls vorliegende Polymerbeschichtung auf dem Körnchen zur raschen Freisetzung 0 - 10 Gewichtsteile, bezogen auf 100 Gewichtsteile der Kombination aus Minocyclin und dem Exzipienten, ausmacht. 20 25 30
 5. Pharmazeutisches Abgabesystem nach Anspruch 1, enthaltend 25 bis 400 mg 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder ein nicht toxisches Säureadditionssalz davon. 35
 6. Pharmazeutisches Abgabesystem nach Anspruch 5, wobei die anfängliche Beladung (I)(A), (I)(A-1), (I)(A-2) oder (II)(C) 20 bis 200 mg 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder ein nicht toxisches Säureadditionssalz davon enthält. 40
 7. Arzneimittel zur kontrollierten Freigabe in oraler Einheitsdosierungsform, umfassend ein pharmazeutisches Abgabesystem nach Anspruch 1, vermischt mit einem pharmazeutisch verträglichen flüssigen Träger. 45
 8. Verfahren zur Herstellung eines pharmazeutischen Abgabesystems, umfassend die Schritte von 50
 - (A) Herstellen einer anfänglichen Beladungskomponente durch
 - (a) Vermischen 55
 - (i) einer wirksamen Menge mindestens eines pharmazeutisch verträglichen Exzipienten und

- (ii) einer wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon;
- (b) Granulieren des erhaltenen Gemisches in Gegenwart einer Granulierungsflüssigkeit;
- (c) Extrudieren der erhaltenen Körnchen;
- (d) Sphäronisieren des erhaltenen Extrudats unter Herstellung von Körnchen zur raschen Freisetzung, die derart ausgelegt sind, daß die rasche Freisetzung von Minocyclin in einem Medium mit einem pH-Wert von weniger als 3,9 vollständig erfolgt;
- (e) Trocknen der Körnchen zur raschen Freisetzung und gegebenenfalls
- (f) Beschichten der Körnchen zur raschen Freisetzung mit einem im wesentlichen gleichförmigen Polymerüberzug, der rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert von weniger als 3,9 zerfällt; oder
- (A-1) Herstellen einer anfänglichen Beladungskomponente durch
 - (a) Zerteilen von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon zu feinem Pulver; und gegebenenfalls
 - (b) Vermischen des Pulvers mit einer wirksamen Menge eines pharmazeutisch verträglichen Exzipienten; und
- (B) Herstellen einer zweiten Beladungskomponente durch
 - (a) Vermischen
 - (i) einer unabhängigen Menge mindestens eines pharmazeutisch verträglichen Exzipienten, der der gleiche oder verschieden sein kann zu (A)(a)(i) oder (A-1)(b); und
 - (ii) einer unabhängigen wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon;
 - (b) Granulieren des erhaltenen Gemisches in Gegenwart einer Granulierungsflüssigkeit;
 - (c) Extrudieren der erhaltenen Körnchen;
 - (d) Sphäronisieren des erhaltenen Extrudats unter Herstellung von Vorstufen von beschichteten sphärischen Körnchen,
 - (e) Trocknen der Vorstufen;
 - (f) Beschichten der Vorstufen mit einer im wesentlichen gleichförmigen Polymerbeschichtung, wobei das Polymer davon gleich oder verschieden sein kann zu



dem im gegebenenfalls vorliegenden Schritt (A)(f) und das rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 zerfällt.

9. Verfahren zur Herstellung einer mehrfach beschichteten Zusammensetzung eines pharmazeutischen Abgabesystems, umfassend

(A) Bilden eines Kerns aus einem oder mehreren sphärischen Körnchen, hergestellt durch

(a) Vermischen

(i) einer wirksamen Menge mindestens eines pharmazeutisch verträglichen Exzipienten; und

(ii) einer vollständigen oder teilweisen anfänglichen Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon;

(b) Granulieren des erhaltenen Gemisches in Gegenwart einer Granulierungsflüssigkeit;

(c) Extrudieren der erhaltenen Körnchen;

(d) Sphäronisieren des erhaltenen Extrudats unter Herstellung von einem oder mehreren kugelförmigen Körnchen und

(e) Trocknen der kugelförmigen Körnchen;

(A-1) Herstellen eines Kerns aus einer vollständigen oder teilweisen zweiten Beladung einer wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-

demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon; oder

(A-2) Herstellen eines Kerns durch Beschichten eines perlenförmigen Keims oder eines Zuckerkristalls mit einer vollständigen oder teilweisen zweiten Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon;

(B) Beschichten des Kerns mit einem im wesentlichen gleichförmigen pH-empfindlichen Polymerüberzug, der rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 zerfällt, wobei der Kern dadurch angepaßt ist zur im wesentlichen vollständigen Freisetzung des Minocyclins in einem Medium mit einem pH-Wert im Bereich von 4,0 und 7,5, unter Herstellung eines einzeln beschichteten Kerns;

(C) Beschichten des einzeln beschichteten Kerns mit einem Überzug zur schnellen Freisetzung, umfassend eine vollständige oder teilweise anfängliche Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon unter Bildung einer mehrfach beschichteten Zusammensetzung und gegebenenfalls

(D) Beschichten der mehrfach beschichteten Zusammensetzung mit (a) einer im wesentlichen gleichförmigen Polymerbeschichtung, wobei das Polymer davon dasselbe ist oder unterschiedlich ist zu (B) und das rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert von weniger als 3,9 zerfällt; (b) einem Polymerüberzug, wobei das Polymer davon das gleiche ist oder unterschiedlich ist zu (B) oder (D)(a); oder (c) einer Kombination von (a) und darauf (b).

10. Pharmazeutisches Abgabesystem, umfassend

(A) eine anfängliche Beladung einer therapeutisch wirksamen Anzahl an Körnchen mit rascher Freisetzung, umfassend

(a)

(i) eine wirksame Menge mindestens eines pharmazeutisch verträglichen Exzipienten und

(ii) eine wirksame antibakterielle Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon, auf oder in den Körnchen zur raschen Freisetzung und gegebenenfalls

(b) eine im wesentlichen gleichförmige Polymerbeschichtung auf den Körnchen mit rascher Freisetzung und die rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert von weniger als 3,9 zerfällt;

wobei die Körnchen mit rascher Freisetzung derart ausgelegt sind, daß die Freisetzung des Minocyclins in einem Medium mit einem pH-Wert von weniger als 3,9 im wesentlichen vollständig ist;

(B) eine zweite Beladung einer therapeutisch wirksamen Anzahl an mit pH-empfindlichem Polymer beschichteten kugelförmigen Körnchen, umfassend

(a)

(i) eine unabhängige wirksame Menge von zumindest einem pharmazeutisch verträglichen Exzipienten, der der gleiche oder ein verschiedener sein kann zu (A)(a)(i); und



- (ii) eine unabhängige wirksame antibakterielle Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon auf oder in den beschichteten kugelförmigen Körnchen und
- (b) eine im wesentlichen gleichförmige pH-empfindliche Polymerbeschichtung, wobei das Polymer davon das gleiche oder ein verschiedenes sein kann zu (A)-
- (b) auf den beschichteten kugelförmigen Körnchen und das rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 zerfällt, wobei die beschichteten kugelförmigen Körnchen derart ausgelegt sind, um im wesentlichen vollständig Minocyclin in einem Medium mit einem pH im Bereich von 4,0 bis 7,5 freizusetzen.
11. Pharmazeutisches Abgabesystem, angepaßt zur Bereitstellung eines therapeutisch wirksamen Blutkonzentrationsspiegels von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon für einen anhaltenden Zeitraum bis zu etwa 24 Stunden, umfassend eine oder mehrere mehrfach beschichtete sphäronisierte pharmazeutische Zusammensetzungen umfassend:
- (A) einen Kern, umfassend
- (a) eine vollständige oder teilweise zweite Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon oder
- (b) mindestens ein Körnchen, umfassend
- (i) eine wirksame Menge von mindestens einem pharmazeutisch verträglichen Exzipienten; und
- (ii) eine vollständige oder teilweise zweite Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon auf oder in den Körnchen, die darauf aufgebracht wurde;
- (B) eine im wesentlichen gleichförmige pH-empfindliche Polymerbeschichtung, die rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 zerfällt, wobei der Kern derart ausgelegt ist, daß das Minocyclin im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 freigesetzt wird, die darauf aufgetragen

ist,

(C) eine Beschichtung zur raschen Freisetzung, umfassend eine vollständige oder teilweise anfängliche Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon; und gegebenenfalls darauf aufgebracht

(D)

- (a) eine im wesentlichen gleichförmige Polymerbeschichtung, wobei das Polymer davon das gleiche sein kann oder verschieden sein kann zu (B) und rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert von weniger als 3,9 zerfällt;
- (b) eine Polymerbeschichtung, wobei das Polymer davon gleich oder verschieden sein kann zu (B) oder (D)(a) oder
- (c) eine Kombination von (a) und darauf (b).

12. Sphäronisierte pharmazeutische Zusammensetzung, umfassend eine zweite Beladung einer therapeutisch wirksamen Anzahl an mit pH-empfindlichem Polymer beschichteten Körnchen, die einschließen

- (a)
- (i) eine wirksame Menge mindestens eines pharmazeutisch verträglichen Exzipienten und
- (ii) eine wirksame antibakterielle Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon, auf oder in den Körnchen zur raschen Freisetzung; und
- (b) eine im wesentlichen gleichförmige pH-empfindliche Polymerbeschichtung auf den beschichteten kugelförmigen Körnchen und die rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 zerfallen;
- wobei die beschichteten kugelförmigen Körnchen derart ausgelegt sind, daß die Freisetzung in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 im wesentlichen vollständig ist.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung eines pharmazeutischen Abgabesystems, umfassend die Schritte von
- (A) Herstellen einer anfänglichen Beladungskomponente durch



- (a) Vermischen
- (i) einer wirksamen Menge mindestens eines pharmazeutisch verträglichen Exzipienten und
 - (ii) einer wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon; 5
- (b) Granulieren des erhaltenen Gemisches in Gegenwart einer Granulierungsflüssigkeit; 10
- (c) Extrudieren der erhaltenen Körnchen;
- (d) Sphäronisieren des erhaltenen Extrudats unter Herstellung von Körnchen zur raschen Freisetzung, die derart ausgelegt sind, daß die rasche Freisetzung von Minocyclin in einem Medium mit einem PH-Wert von weniger als 3,9 im wesentlichen vollständig erfolgt, 15
- (e) Trocknen der Körnchen zur raschen Freisetzung und gegebenenfalls 20
- (f) Beschichten der Körnchen zur raschen Freisetzung mit einem im wesentlichen gleichförmigen Polymerüberzug, der rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert von weniger als 3,9 zerfällt; oder 25
- (A-1) Herstellen einer anfänglichen Beladungskomponente durch 30
- (a) Zerteilen von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon zu feinem Pulver; und gegebenenfalls
 - (b) Vermischen des Pulvers mit einer wirksamen Menge eines pharmazeutisch verträglichen Exzipienten; und 35
- (B) Herstellen einer zweiten Beladungskomponente durch 40
- (a) Vermischen 40
 - (i) einer unabhängigen Menge mindestens eines pharmazeutisch verträglichen Exzipienten, der der gleiche oder verschieden sein kann zu (A)(a)-(i) oder (A-1)(b); und 45
 - (ii) einer unabhängigen wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon; 50
 - (b) Granulieren des erhaltenen Gemisches in Gegenwart einer Granulierungsflüssigkeit;
 - (c) Extrudieren der erhaltenen Körnchen;
 - (d) Sphäronisieren des erhaltenen Extrudats unter Herstellung von Vorstufen von beschichteten sphärischen Körnchen, 55
 - (e) Trocknen der Vorstufen;
- (f) Beschichten der Vorstufen mit einer im wesentlichen gleichförmigen Polymerbeschichtung, wobei das Polymer davon gleich oder verschieden sein kann zu dem im gegebenenfalls vorliegenden Schritt (A)(f) und das rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 zerfällt.
2. Verfahren zur Herstellung einer mehrfach beschichteten Zusammensetzung eines pharmazeutischen Abgabesystems, umfassend
- (A) Bilden eines Kerns aus einem oder mehreren sphärischen Körnchen, hergestellt durch
- (a) Vermischen
 - (i) einer wirksamen Menge mindestens eines pharmazeutisch verträglichen Exzipienten; und
 - (ii) einer vollständigen oder teilweisen anfänglichen Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon oder
 - (b) Granulieren des erhaltenen Gemisches in Gegenwart einer Granulierungsflüssigkeit;
 - (c) Extrudieren der erhaltenen Körnchen;
 - (d) Sphäronisieren des erhaltenen Extrudats unter Herstellung von einem oder mehreren kugelförmigen Körnchen und
 - (e) Trocknen der kugelförmigen Körnchen;
- (A-1) Herstellen eines Kerns aus einer vollständigen oder teilweisen zweiten Beladung einer wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon; oder
- (A-2) Herstellen eines Kerns durch Beschichten eines perlenförmigen Keims oder eines Zuckerkrystals mit einer vollständigen oder teilweisen zweiten Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon;
- (B) Beschichten des Kerns mit einem im wesentlichen gleichförmigen pH-empfindlichen Polymerüberzug, der rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert im Bereich von 4,0 bis 7,5 zerfällt, wobei der Kern dadurch angepaßt ist zur im wesentlichen vollständigen Freisetzung des Minocyclins in einem Medi-



um mit einem pH-Wert im Bereich von 4,0 und 7,5, unter Herstellung eines einzeln beschichteten Kerns;

(C) Beschichten des einzeln beschichteten Kerns mit einem Überzug zur schnellen Freisetzung, umfassend eine vollständige oder teilweise anfängliche Beladung einer therapeutisch wirksamen antibakteriellen Menge von 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder einem nicht toxischen Säureadditionssalz davon unter Bildung einer mehrfach beschichteten Zusammensetzung und gegebenenfalls

(D) Beschichten der mehrfach beschichteten Zusammensetzung mit (a) einer im wesentlichen gleichförmigen Polymerbeschichtung, wobei das Polymer davon dasselbe ist oder unterschiedlich ist zu (B) und das rasch und im wesentlichen vollständig in einem Medium mit einem pH-Wert von weniger als 3,9 zerfällt; (b) einem Polymerüberzug, wobei das Polymer davon das gleiche ist oder unterschiedlich ist zu (B) oder (D)(a); oder (c) einer Kombination von (a) und darauf (b).

3. Verfahren nach Anspruch 1, wobei das Minocyclin in den Körnchen zur raschen Freisetzung von Schritt (A) 10 bis 70 Gewichtsteile umfaßt und der mindestens eine pharmazeutisch verträgliche Exzipient in dem Mittel zur raschen Freisetzung 90 bis 30 Gewichtsteile umfaßt, bezogen auf 100 Gewichtsteile der Kombination aus Minocyclin und dem Exzipienten, und die gegebenenfalls vorliegende Polymerbeschichtung auf dem Körnchen zur raschen Freisetzung 0 - 10 Gewichtsteile, bezogen auf 100 Gewichtsteile der Kombination aus Minocyclin und dem Exzipienten, ausmacht.

4. Verfahren nach Anspruch 1, das ein pharmazeutisches Abgabesystem, enthaltend 25 bis 400 mg 7-Dimethylamino-6-desoxy-6-demethyltetracyclin oder ein nicht toxisches Säureadditionssalz davon, bereitstellt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE

1. Système de libération pharmaceutique conçu pour fournir un niveau de concentration sanguine thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci pendant une durée prolongée pouvant attein-

dre environ 24 heures, comprenant :

(I) un système de véhicules à libération multiple comprenant

(A) une charge initiale d'un nombre thérapeutiquement efficace de granules à libération rapide qui comprennent

(a)

(i) une quantité efficace d'au moins un excipient pharmaceutiquement acceptable, et

(ii) une quantité antibactérienne efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, sur ou dans lesdits granules à libération rapide, et éventuellement

(b) un revêtement polymérique sensiblement uniforme sur lesdits granules à libération rapide et qui peut être érodé rapidement et sensiblement totalement dans un milieu d'un pH inférieur à 3,9, lesdits granules à libération rapide étant conçus pour libérer sensiblement totalement ladite minocycline dans un milieu d'un pH inférieur à 3,9,

(A-1) une charge initiale d'une quantité thérapeutiquement efficace de poudre finement divisée comprenant

(a) une quantité antibactérienne efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, et éventuellement

(b) une quantité efficace indépendante d'au moins un excipient pharmaceutiquement acceptable qui peut être identique à (I)(A)(a)(i) ou différent, ou

(A-2) une charge initiale d'une combinaison thérapeutiquement efficace de (A) et de (A-1), et

(B) une charge secondaire d'un nombre thérapeutiquement efficace de granules sphériques recouverts de polymère sensible au pH qui comprennent

(a)

(i) une quantité efficace indépendante d'au moins un excipient pharmaceutiquement acceptable qui peut être identique à (I)(A)(a)(i) ou (I)(A-1)(b) ou différent, et

(ii) une quantité antibactérienne efficace indépendante de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, sur ou dans lesdits granu-



- les sphériques revêtus, et
- (b) un revêtement polymérique sensible au pH sensiblement uniforme dont le polymère peut être identique à (I)-(A)(b) ou différent, sur lesdits granules sphériques revêtus et qui peut être érodé rapidement et sensiblement totalement dans un milieu de pH compris dans la plage de 4,0 à 7,5, lesdits granules sphériques revêtus étant ainsi conçus pour libérer sensiblement totalement ladite minocycline dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5 ; ou
- (II) une ou plusieurs compositions de véhicules à libération unique pharmaceutiques sphéronisées à revêtements multiples comprenant :
- (A) un noyau constitué par
- (a) une charge secondaire totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, ou
- (b) au moins un granule constitué par
- (i) une quantité efficace d'au moins un excipient pharmaceutiquement acceptable, et
- (ii) une charge secondaire totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, sur ou dans ledit granule, sur lequel est appliqué
- (B) un revêtement polymérique sensible au pH sensiblement uniforme qui peut être érodé rapidement et sensiblement totalement dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5, ledit noyau étant ainsi conçu pour libérer sensiblement totalement ladite minocycline dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5, sur lequel est appliqué
- (C) une composition de revêtement à libération rapide comprenant une charge initiale totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, et sur laquelle est éventuellement appliqué
- (D)

- (a) un revêtement polymérique sensiblement uniforme dont le polymère peut être identique à (B) ou différent, et qui peut être érodé rapidement et sensiblement totalement dans un milieu de pH inférieur à 3,9,
- (b) un sur-revêtement polymérique dont le polymère peut être identique à (B) ou (D) (a) ou différent, ou
- (c) une combinaison de (a) et de (b) sur (a).
2. Système de libération pharmaceutique selon la revendication 1 comprenant une combinaison mélangée de (I)(A), (I)(A-1) ou (I) (A-2) et (I)(B).
 3. Système de libération pharmaceutique selon la revendication 1, comprenant des unités d'administration séparées de charge initiale de constituant (I)(A), (I)(A-1) ou (I)(A-2) pour une administration initiale et de charge secondaire de constituant (I) (B) pour une administration jusqu'à 120 minutes après l'administration de (I)(A), (I)(A-1) ou (I)(A-2).
 4. Système de libération pharmaceutique selon la revendication 1, dans lequel ladite minocycline dans lesdits granules à libération rapide (I)(A) constitue de 10 à 70 parties en poids et ledit ou lesdits excipients pharmaceutiquement acceptables dans lesdits granules à libération rapide (I)(A) constitue de 90 à 30 parties en poids pour 100 parties en poids de ladite minocycline et dudit excipient combinés et ledit revêtement polymérique éventuel sur lesdits granules à libération rapide constitue de 0 à 10 parties en poids pour 100 parties en poids de ladite minocycline et dudit excipient combinés.
 5. Système de libération pharmaceutique selon la revendication 1, contenant de 25 à 400 mg de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci.
 6. Système de libération pharmaceutique selon la revendication 5, dans lequel ladite charge initiale de (I)(A), (I)(A-1), (I)(A-2) ou (II) (C) contient de 20 à 200 mg de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci.
 7. Composition pharmaceutique à libération contrôlée sous forme d'unités de prise orales comprenant un système de libération pharmaceutique selon la revendication 1 en mélange avec un véhicule liquide pharmaceutiquement



acceptable.

8. Procédé de préparation d'un système de libération pharmaceutique comprenant les étapes suivantes :
- (A) former un constituant de charge initiale en
- (a) mélangeant
- (i) une quantité efficace d'au moins un excipient pharmaceutiquement acceptable, et
- (ii) une quantité antibactérienne efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci,
- (b) granulant le mélange résultant en présence d'un liquide de granulation,
- (c) extrudant le granulat résultant,
- (d) sphéronisant l'extrudat résultant pour former des granules à libération rapide qui sont conçus pour libérer sensiblement totalement ladite minocycline dans un milieu de pH inférieur à 3,9,
- (e) séchant lesdits granules à libération rapide, et éventuellement
- (f) revêtant lesdits granules à libération rapide d'un revêtement polymérique sensiblement uniforme qui peut être érodé rapidement et sensiblement totalement dans un milieu de pH inférieur à 3,9, ou
- (A-1) former un constituant de charge initiale en
- (a) réduisant la 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou un sel d'addition d'acide non toxique de celle-ci en une poudre fine, et éventuellement
- (b) mélangeant ladite poudre avec une quantité efficace d'un excipient pharmaceutiquement acceptable, et
- (B) former un constituant de charge secondaire en
- (a) mélangeant
- (i) une quantité indépendante d'au moins un excipient pharmaceutiquement acceptable qui peut être identique à (A)(a)(i) ou (A-1)(b) ou différent, et
- (ii) une quantité antibactérienne efficace indépendante de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci,
- (b) granulant le mélange résultant en présence d'un liquide de granulation,
- (c) extrudant le granulat résultant,
- (d) sphéronisant l'extrudat résultant pour former des précurseurs de granules sphériques revêtus,

(e) séchant lesdits précurseurs,

(f) revêtant lesdits précurseurs d'un revêtement polymérique sensiblement uniforme dont le polymère peut être identique à celui de l'étape éventuelle (A)(f) ou différent et qui peut être érodé rapidement et sensiblement totalement dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5.

9. Procédé de préparation d'un système de libération pharmaceutique de compositions à revêtements multiples comprenant
- (A) la formation d'un noyau à partir d'un ou plusieurs granules sphériques préparés en
- (a) mélangeant
- (i) une quantité efficace d'au moins un excipient pharmaceutiquement acceptable,
- (ii) une charge initiale totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci,
- (b) granulant le mélange résultant en présence d'un liquide de granulation,
- (c) extrudant le granulat résultant,
- (d) sphéronisant l'extrudat résultant pour former un ou plusieurs granules sphériques, et
- (e) séchant lesdits granules sphériques,
- (A-1) la formation d'un noyau à partir d'une charge secondaire totale ou partielle d'une quantité antibactérienne efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, ou
- (A-2) la formation d'un noyau par revêtement d'un grain de nonpareille ou d'un cristal de sucre avec une charge secondaire totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci,
- (B) le revêtement dudit noyau avec un revêtement polymérique sensible au pH sensiblement uniforme qui peut être érodé rapidement et sensiblement totalement dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5, ledit noyau étant ainsi conçu pour libérer sensiblement totalement ladite minocycline dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5 pour former un noyau à revêtement unique,
- (C) le revêtement dudit noyau à revêtement unique avec un revêtement à libération rapi-



de comprenant une charge initiale totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci pour former une composition à revêtements multiples, et éventuellement

(D) le revêtement de ladite composition à revêtements multiples avec (a) un revêtement polymérique sensiblement uniforme dont le polymère peut être identique à (B) ou différent et qui peut être érodé rapidement et sensiblement totalement dans un milieu de pH inférieur à 3,9, (b) un surrevêtement polymérique dont le polymère peut être identique (B) ou (D)(a) ou différent, ou (c) une combinaison de (a) et de (b) sur (a).

10. Système de libération pharmaceutique comprenant

(A) une charge initiale d'un nombre thérapeutiquement efficace de granules à libération rapide qui comprennent

(a)

(i) une quantité efficace d'au moins un excipient pharmaceutiquement acceptable, et

(ii) une quantité antibactérienne efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, sur ou dans lesdits granules à libération rapide, et éventuellement

(b) un revêtement polymérique sensiblement uniforme sur lesdits granules à libération rapide et qui peut être érodé rapidement et sensiblement totalement dans un milieu de pH inférieur à 3,9, lesdits granules à libération rapide étant conçus pour libérer sensiblement totalement ladite minocycline dans un milieu de pH inférieur à 3,9, et

(B) une charge secondaire d'un nombre thérapeutiquement efficace de granules sphériques revêtus de polymère sensible au pH qui comprennent

(a)

(i) une quantité efficace indépendante d'au moins un excipient pharmaceutiquement acceptable qui peut être identique à (A)(a)(i) ou différent, et

(ii) une quantité antibactérienne efficace indépendante de 7-di-méthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci sur ou dans lesdits granules sphériques revêtus, et

(b) un revêtement polymérique sensible au pH sensiblement uniforme dont le polymère peut être identique à (A)(b) ou différent sur lesdits granules sphériques revêtus et qui peut être érodé rapidement et sensiblement totalement dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5, lesdits granules sphériques revêtus étant ainsi conçus pour libérer sensiblement totalement ladite minocycline dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5.

11. Système de libération pharmaceutique conçu pour fournir un niveau de concentration sanguine thérapeutiquement efficace de 7-di-méthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci pendant une durée prolongée pouvant atteindre environ 24 heures, comprenant une ou plusieurs compositions pharmaceutiques sphéronisées à revêtements multiples comprenant :

(A) un noyau constitué par

(a) une charge secondaire totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, ou

(b) au moins un granule constitué par

(i) une quantité efficace d'au moins un excipient pharmaceutiquement acceptable, et

(ii) une charge secondaire totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, sur ou dans ledit noyau, sur lequel est appliqué

(B) un revêtement polymérique sensible au pH sensiblement uniforme qui peut être érodé rapidement et sensiblement totalement dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5, ledit noyau étant ainsi conçu pour libérer sensiblement totalement ladite minocycline dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5, sur lequel est appliqué

(C) un revêtement à libération rapide comprenant une charge initiale totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, et sur lequel est éventuellement appliqué



- (D)
- (a) un revêtement polymérique sensiblement uniforme dont le polymère peut être identique à (B) ou différent et qui peut être érodé rapidement et sensiblement totalement dans un milieu de pH inférieur à 3,9, 5
 - (b) un sur-revêtement polymérique dont le polymère peut être identique à (B) ou (D)(a) ou différent, ou 10
 - (c) une combinaison de (a) et de (b) sur (a).
12. Composition pharmaceutique sphéronisée comprenant une charge secondaire d'un nombre thérapeutiquement efficace de granules sphériques revêtus de polymère sensible au pH qui comprennent
- (a) 15
 - (i) une quantité efficace d'au moins un excipient pharmaceutiquement acceptable, et 20
 - (ii) une quantité antibactérienne efficace de 7-diméthylamino-6-désoxy-6-déméthyl-tétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, sur ou dans lesdits granules sphériques revêtus, et 25
 - (b) un revêtement polymérique sensible au pH sensiblement uniforme, sur lesdits granules sphériques revêtus, qui peut être érodé rapidement et sensiblement totalement dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5, lesdits granules sphériques revêtus étant ainsi conçus pour libérer sensiblement totalement ladite minocycline dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5. 30 35

Revendications pour les Etats contractants : ES, GR 40

1. Procédé de préparation d'un système de libération pharmaceutique comprenant les étapes suivantes :
- (A) former un constituant de charge initiale en 45
 - (a) mélangeant
 - (i) une quantité efficace d'au moins un excipient pharmaceutiquement acceptable, et 50
 - (ii) une quantité antibactérienne efficace de 7-diméthylamino-6-désoxy-6-déméthyl-tétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, 55
 - (b) granulant le mélange résultant en présence d'un liquide de granulation,
 - (c) extrudant le granulat résultant,

- (d) sphéronisant l'extrudat résultant pour former des granules à libération rapide qui sont conçus pour libérer sensiblement totalement ladite minocycline dans un milieu de pH inférieur à 3,9,
- (e) séchant lesdits granules à libération rapide, et éventuellement
- (f) revêtant lesdits granules à libération rapide d'un revêtement polymérique sensiblement uniforme qui peut être érodé rapidement et sensiblement totalement dans un milieu de pH inférieur à 3,9, ou
- (A-1) former un constituant de charge initiale en

- (a) réduisant la 7-diméthylamino-6-désoxy-6-déméthyl-tétracycline ou un sel d'addition d'acide non toxique de celle-ci en une poudre fine, et éventuellement
- (b) mélangeant ladite poudre avec une quantité efficace d'un excipient pharmaceutiquement acceptable, et
- (B) former un constituant de charge secondaire en

(a) mélangeant

- (i) une quantité indépendante d'au moins un excipient pharmaceutiquement acceptable qui peut être identique à (A)(a)(i) ou (A-1)(b) ou différent, et
- (ii) une quantité antibactérienne efficace indépendante de 7-diméthylamino-6-désoxy-6-déméthyl-tétracycline ou d'un sel d'addition d'acide non toxique de celle-ci,

- (b) granulant le mélange résultant en présence d'un liquide de granulation,
- (c) extrudant le granulat résultant,
- (d) sphéronisant l'extrudat résultant pour former des précurseurs de granules sphériques revêtus,
- (e) séchant lesdits précurseurs,
- (f) revêtant lesdits précurseurs d'un revêtement polymérique sensiblement uniforme dont le polymère peut être identique à celui de l'étape éventuelle (A)(f) ou différent et qui peut être érodé rapidement et sensiblement totalement dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5.

2. Procédé de préparation d'un système de libération pharmaceutique de compositions à revêtements multiples comprenant

- (A) la formation d'un noyau à partir d'un ou plusieurs granules sphériques préparés en

(a) mélangeant

- (i) une quantité efficace d'au moins un excipient pharmaceutiquement accep-



table, et

(ii) une charge initiale totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-di-méthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci,

(b) granulant le mélange résultant en présence d'un liquide de granulation,

(c) extrudant le granulat résultant,

(d) sphéronisant l'extrudat résultant pour former un ou plusieurs granules sphériques, et

(e) séchant lesdits granules sphériques,

(A-1) la formation d'un noyau à partir d'une charge secondaire totale ou partielle d'une quantité antibactérienne efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci, ou

(A-2) la formation d'un noyau par revêtement d'un grain de nonpareille ou d'un cristal de sucre avec une charge secondaire totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci,

(B) le revêtement dudit noyau avec un revêtement polymérique sensible au pH sensiblement uniforme qui peut être érodé rapidement et sensiblement totalement dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5, ledit noyau étant ainsi conçu pour libérer sensiblement totalement ladite minocycline dans un milieu dont le pH est compris dans la plage de 4,0 à 7,5 pour former un noyau à revêtement unique,

(C) le revêtement dudit noyau à revêtement unique avec un revêtement à libération rapide comprenant une charge initiale totale ou partielle d'une quantité antibactérienne thérapeutiquement efficace de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci pour former une composition à revêtements multiples, et éventuellement

(D) le revêtement de ladite composition à revêtements multiples avec (a) un revêtement polymérique sensiblement uniforme dont le polymère peut être identique à (B) ou différent et qui peut être érodé rapidement et sensiblement totalement dans un milieu de pH inférieur à 3,9, (b) un surrevêtement polymérique dont le polymère peut être identique à (B) ou (D)(a) ou différent, ou (c) une combinaison de (a) et de (b) sur (a).

3. Procédé selon la revendication 1, dans lequel ladite minocycline dans lesdits granules à libération rapide de l'étape (A) constitue de 10 à 70 parties en poids et ledit ou lesdits excipients pharmaceutiquement acceptables dans lesdits granules à libération rapide constituent de 90 à 30 parties en poids pour 100 parties en poids de ladite minocycline et dudit excipient combinés et ledit revêtement polymérique éventuel sur lesdits granules à libération rapide constitue de 0 à 10 parties en poids pour 100 parties en poids de ladite minocycline et dudit excipient combinés.

4. Procédé selon la revendication 1 qui fournit un système de libération pharmaceutique contenant de 25 à 400 mg de 7-diméthylamino-6-désoxy-6-déméthyltétracycline ou d'un sel d'addition d'acide non toxique de celle-ci.

