once-a-day IR and DR combinations at 70:30 and 80:20 ratios, and twice-a-day 20 mg doxycycline treatment) were determined by in silico modeling, and are shown in FIG. **4**. Using the unique dose (i.e., <50 mg, preferably 40 mg) and composition (IR beads or IR/DR combinations), the steady state blood levels of doxycycline of a minimum of about 0.1 ug/ml, preferably about 0.3 ug/ml and a maximum of about 1.0 ug/ml, more preferably about 0.8 ug/ml, can be achieved to treat such conditions as periodontal and skin diseases.

Example 7

Size 0 capsules containing a ratio of 75:25 of drug-loaded IR pellets to enteric coated DR pellets were prepared as follows. The IR and DR pellets were prepared as set forth in Examples 1 and 2. From the assay value of the doxycycline used to make the pellets, it was determined that 41.26 mg potency of the capsules would correspond to an actual strength of 40 mg. doxycycline. The potency of the IR pellets was 194 mg doxycycline per gram of pellets (mg/g), and for the DR pellets was 133 mg/g. Accordingly, it was calculated that for each capsule the fill weight of IR beads would be 159.5 mg, and for DR beads 77.6 mg, corresponding to 75:25 of IR:DR of a 40 mg capsule.

Example 8

A pharmacokinetic (PK) study was conducted in human subjects to compare a first group taking the extended release doxycycline capsule (see Example 7) (75/25 IR/DR 40 mg) administrated orally once daily versus a second group taking Periostat® tablets (20 mg) administrated orally twice daily, twelve hours apart.

Pharmacokinetic blood draws were collected on Nominal Study Day 1 for first and second groups, and on Day 7 for the first group as follows: 0 (pre dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 (before the post-morning dose, if applicable), 12.5, 13, 13.5, 14, 14.5, 15, 16, 18, 20, and 24 hours after the morning dose.

The data from this study were shown in the following Table 1.

TABLE 1

	75/25 IR/DR Day 1	75/25 IR/DR Day 7 steady state	Periostat ® Day 1
T_{max}	2.2	2.3	1.9/11.9
C_{max}	562	602	100/333
AUC_{0-24} (Hr * ng/ml)	5388	7230	4280

Mean C_{max} at Day 1 from the 75/25 IR/DR 40 mg capsules is comparable to that from the Periostat® tablets, and well below the potential antibiotic effect concentration (1000 ng/ml). The mean C_{min} (177 ng/ml at 24-hour time point) is well above the minimum effective plasma concentration (100 ng/ml). Individual pharmacokinetic data from both 75/25 IR/DR 40 mg capsules and Periostat® 20 mg tablets show that 75/25 IR/DR 40 mg capsules provide more consistent in vivo performance in terms of less frequency of high peak plasma concentration (>1000 ng/ml) and low plasma concentration (<100 ng/ml) at the end of each dosing.

FIGS. **5** and **6** show two aspects of results obtained from the study. FIG. **5** compares the PK profiles of 75:25 IR:DR 40 mg doxycycline formulations over a 24 hour period on Day 1 and also on Day 7 (steady state). FIG. **6** compares the PK profiles of the 75:25 40 mg once daily dosage form and the Periostat® 20 mg (twice daily) dosage forms.

What is claimed is:

1. An oral pharmaceutical composition comprising less than 50 mg of total doxycycline, which at a once-daily dosage will give steady state blood levels of the doxycycline between 0.1 μg/ml and 1.0 μg/ml, and a C_{max} of the doxycycline between 0.4 μg/ml and 0.8 μg/ml, the composition consisting of (i) an immediate release (IR) formulation of the doxycycline, (ii) a delayed release (DR) formulation of the doxycycline comprising at least one enteric polymer, and (iii) one or more pharmaceutically acceptable excipients, wherein the doxycycline in the IR and DR formulations is in a ratio of 75:25.

2. The composition of claim **1**, which at a once-daily dosage will give steady state blood levels of the doxycycline of between 0.3 μg/ml to 0.8 μg/ml.

3. The composition of claim **1**, wherein the IR and/or DR formulation is in the form of a granule, tablet, pellet, powder, sachet, capsule, gel, dispersion or suspension.

4. The composition of claim **1**, which is in a dosage form of a combination of pellets.

5. The composition according to claim **1**, wherein the DR formulation comprises at least one enteric polymer.

6. The composition of claim **5**, wherein the enteric polymer is cellulose acetate phthalate; hydroxypropyl methylcellulose phthalate; polyvinyl acetate phthalate; hydroxypropyl methylcellulose acetate succinate; cellulose acetate trimellitate; hydroxypropyl methylcellulose succinate; cellulose acetate succinate; cellulose acetate hexahydrophthalate; cellulose propionate phthalate; a copolymer of methylmethacrylic acid and methyl methacrylate; a copolymer of methyl acrylate, methylmethacrylate and methacrylic acid; a copolymer of methylvinyl ether and maleic anhydride; ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer; zein; shellac; poly(methacylic acid-co-ethyl acrylate) 1:1, or combinations thereof.

7. The composition according to claim **1**, wherein the DR formulation is in the form of granules, pellets, or tablet.

8. The composition according to claim **1**, wherein the one or more pharmaceutically acceptable excipients is incorporated in the IR formulation, the DR formulation, or both.

9. The composition of claim **8**, wherein the one or more pharmaceutically acceptable excipients is a binder, a disintegration agent, a filling agent, a surfactant, a solubilizer, a stabilizer, and combinations thereof.

10. The composition of claim **9**, wherein the binder is selected from the group consisting of methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and polyvinylpyrrolidone/vinyl acetate copolymer.

11. The composition of claim **9**, wherein the disintegration agent is selected from the group consisting of cornstarch, pregelatinized starch, cross-linked carboxymethylcellulose, sodium starch glycolate, and cross-linked polyvinylpyrrolidone.

12. The composition of claim **9**, wherein the filling agents are selected from the group consisting of lactose, calcium carbonate, calcium phosphate, calcium sulfate, microcrystalline cellulose, dextran, starches, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, and polyethylene glycol.

13. The composition of claim **9**, wherein the surfactants are selected from the group consisting of sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, bile salts, and glyceryl monostearate.

14. The composition of claim **9**, wherein the solubilizers are selected from the group consisting of citric acid, succinic acid, fumaric acid, malic acid, tartaric acid, maleic acid, glutaric acid, sodium bicarbonate, and sodium carbonate.