It would therefore be desirable to provide an improved method for the treatment of peri-implantitits which promotes the healing process of the infected mucosal, while enhancing peri-implant bone formation, improve implant survival rates and enhance the oral health-related quality of life.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions and methods for the treatment of peri-implant diseases, in particular peri-implant disease characterized by the destruction of the crest of the alveolar bone supporting the implant. Specifically, the method comprising the step of applying to a peri-implant bone displaying crestal resorption a pharmaceutical composition comprising biocompatible bone augmentation material coated with a matrix composition which provides local controlled and prolonged release of at least one pharmaceutically active agent at the bone loss site. The pharmaceutically active agent comprises an antibiotic agent, anti-fungal agent, an anti-inflammatory agent, an antiseptic agent, an agent which induces or stimulates bone growth or a combination thereof. According to some preferred embodiments, the pharmaceutically active agent is antibiotic agent.

In one aspect, there is provided use of a pharmaceutical composition comprising a biocompatible bone augmentation material coated with a matrix composition, the matrix composition comprising: (a) a biocompatible polymer; (b) a first lipid comprising at least one sterol; (c) a second lipid comprising at least one phospholipid having fatty acid moieties of at least 14 carbons; and (d) at least one pharmaceutically active agent, said matrix composition provides local sustained release of the pharmaceutically active agent at the peri-implant bone loss site, in the manufacture of a medicament for treating a patient diagnosed with a peri-implant disease associated with crestal peri-implant bone loss.

In one aspect, there is provided use of a pharmaceutical composition comprising coated and non-coated bone augmentation material at a ratio of between about 1:3 - 10: 1, wherein the coated bone augmentation material comprise between about 80-90% (w/w) of bone augmentation material coated with between about 10-20% (w/w) of a matrix composition which comprises: (a) 15-25% (w/w) poly (lactic-co-glycolic acid) (PLGA) (b) 5-15% (w/w) of cholesterol; (c) 50-70% (w/w) of a mixture of 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), wherein the ratio of DPPC to DSPC is between 5: 1 and 2:1 and (d) 7-12% (w/w) of doxycycline or

doxycycline hyclate, in the manufacture of a medicament for treating a patient diagnosed with peri-implantitis associated with crestal peri-implant bone loss.

In one aspect, there is provided use of a pharmaceutical composition comprising (a) 90-95% (w/w) of β-TCP; (b) 1.0-2.0% (w/w) PLGA; (c) 0.4-0.8% (w/w) cholesterol; (d) 2.0-4.0% (w/w) of DPPC; (e) 0.7- 1.3% (w/w) of DSPC; (f) 0.4-2% (w/w) of doxycycline or doxycycline hyclate, in the manufacture of a medicament for treating a patient diagnosed with peri-implantitis associated with crestal peri-implant bone loss.

In one aspect, there is provided use of a pharmaceutical composition comprising a biocompatible bone augmentation material coated with a matrix composition, the matrix composition comprising: (a) a biocompatible polymer; (b) a first lipid comprising at least one sterol; (c) a second lipid comprising at least one phospholipid having fatty acid moieties of at least 14 carbons; and (d) at least one pharmaceutically active agent, said matrix composition provides local sustained release of the pharmaceutically active agent at the peri-implant site, in the manufacture of a medicament for inhibiting oral biofilm formation at a peri-implant site or eradicating an existing oral biofilm at a peri-implant site.

The present invention is based in part on the finding that biocompatible bone augmentation material impregnated or coated with a matrix composition comprising an antibiotic agent according to embodiments of the invention, successfully inhibited biofilm formation in-vitro and completely eradicated an in-vitro established biofilm. Oral biofilm is a recognizable etiologic agent of peri-implantitis.

As used herein "peri-implant bone site displaying crestal resorption" refers to any peri-implant bone deficient region, such as a void, gap, recess, or other discontinuity in a peri-implant bone. According to some embodiments, peri-implant bone site displaying crestal resorption is associated with increased peri-implant pocket probing depths. According to some embodiments, peri-implant bone site displaying crestal resorption is characterized by the loss of the bony support of the implant. According to some embodiments, the loss of bony support is accompanied by inflammation.

As used herein, "treatment of peri-implantitis" relates to enhancing peri-implant bone formation. According to some embodiments, treatment of peri-implantitis relates to reduction of pocket probe depth. According to some embodiments, treating peri-implantitis relates to reduction of mucosal recession. According to some embodiments, treating peri-implantitis

CLAIMS

1. Use of a pharmaceutical composition comprising a biocompatible bone augmentation material coated with a matrix composition, the matrix composition comprising: (a) a biocompatible polymer; (b) a first lipid comprising at least one sterol; (c) a second lipid comprising at least one phospholipid having fatty acid moieties of at least 14 carbons; and (d) at least one pharmaceutically active agent, said matrix composition provides local sustained release of the pharmaceutically active agent at the peri-implant bone loss site, in the manufacture of a medicament for treating a patient diagnosed with a peri-implant disease associated with crestal peri-implant bone loss.
2. The use of claim 1, wherein the peri-implant disease is further associated with clinical attachment loss.
3. The use of claim 1 or 2, wherein the peri-implant disease is further characterized by extensive mucosal recession and/or bleeding on probing.
4. The use of any one of claims 1-3, wherein the peri-implant disease is peri- implantitis.
5. The use of any one of claims 1-4, wherein the subject is human.
6. The use of any one of claims 1-5, wherein the bone augmentation material is selected from the group consisting of allogeneic, xenogeneic, synthetic bone augmentation materials or any combination thereof.
7. The use of any one of claims 1-5, wherein the bone augmentation material comprises beta tri-calcium phosphate (β-TCP) particles.
8. The use of claims 1-7, wherein the bone augmentation material comprises particles having an average particle size of up to about 500 μm inclusive.
9. The use of claim 8, wherein the bone augmentation material comprises particles having an average particle size in the range of about 150 and about 500 μm.
10. The use of any one of claims 1 to 9, wherein the coated bone augmentation material comprise between about 80-90% (w/w) of bone augmentation material and between about 10-20% (w/w) of the matrix composition.

11. The use of any one of claims 1-10, wherein the pharmaceutical composition further comprising non-coated bone augmentation material.
12. The use of claim 11, wherein the non-coated bone augmentation material is selected from the group consisting of allogeneic, xenogeneic, synthetic bone augmentation materials or any combination thereof.
13. The use of claim 11, wherein the non-coated bone augmentation material comprises beta tri-calcium phosphate (β-TCP) particles.
14. The use of any one of claims 11 to 13, wherein the weight ratio between the coated bone augmentation material and the non-coated bone augmentation material is between about 1:3 and about 10: 1.
15. The use of claim 14, wherein the weight ratio between the coated bone augmentation material and the non-coated bone augmentation material is about 1: 1.
16. The use of any one of the preceding claims, wherein the biocompatible polymer is a biodegradable polyester selected from the group consisting of PLA, PGA and PLGA.
17. The use of claim 16, wherein the biodegradable polyester is present at a weight percentage of up to 2% (w/w) of the total weight of the pharmaceutical composition.
18. The use of claim 16 or 17, wherein the biodegradable polyester is PLGA.
19. The method of any one of the preceding claims, wherein the sterol comprises cholesterol.
20. The use of claim 19, wherein the cholesterol is present at a weight percentage of up to 0.8% (w/w) of the total weight of the pharmaceutical composition.
21. The use of any one of the preceding claims, wherein the second lipid comprises a phosphatidylcholine selected from the group consisting of DMPC, DPPC, DSPC or any combination thereof.
22. The use of claim 21, wherein the second lipid comprises a combination of DPPC and DSPC.
23. The use of claim 22, wherein the weight ratio between DPPC and DSPC is between about 10: 1 and 1: 1.

24. The use of claim 22 or 23, wherein the weight of the combination of phosphatidylcholines constitutes at least 2.5% (w/w) of the total weight of the pharmaceutical composition.

25. The use of any one of the preceding claims, wherein the pharmaceutically active agent is selected from the group consisting of an antibiotic agent, anti-fungal agent, an anti-inflammatory agent, an antiseptic agent or a combination thereof..

26. The use of any one of claims 1-24, wherein the pharmaceutically active agent is selected from an antibiotic agent, an anti-inflammatory agent or a combination thereof.

27. The use of any one of claims 1-24, wherein the pharmaceutical composition comprises a plurality of antibiotic agents.

28. The use of any one of claims 1-27, wherein the pharmaceutically active agent is present at 0.4-2% (w/w) of the total weight of the pharmaceutical composition.

29. The use of claim 28, wherein the pharmaceutically active agent is present at 0.4- 0.8% (w/w) of the total weight of the pharmaceutical composition.

30. The use of any one of claim 25 to 29, wherein the pharmaceutically active agent is an antibiotic agent selected from doxycycline and doxycycline hyclate.

31. The use of any one of claims 1 to 30, wherein the pharmaceutical composition is applied at a dose of up to about 5 grams per one peri-implant bone loss site.

32. The use of claim 31, wherein the pharmaceutical composition is applied at a dose ranging from 0.1-2 grams per one peri-implant bone loss site.

33. The use of any one of claims 1 to 32, wherein the pharmaceutical composition further comprises an additional active agent which induces or stimulates bone growth.

34. The use of claim 33, wherein the additional active agent is selected from an osteoinductive factor, a growth factor or a combination thereof.

35. Use of a pharmaceutical composition comprising coated and non-coated bone augmentation material at a ratio of between about 1:3 - 10: 1, wherein the coated bone augmentation material comprise between about 80-90% (w/w) of bone augmentation material

coated with between about 10-20% (w/w) of a matrix composition which comprises: (a) 15-25% (w/w) poly (lactic-co-glycolic acid) (PLGA) (b) 5-15% (w/w) of cholesterol; (c) 50-70% (w/w) of a mixture of 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), wherein the ratio of DPPC to DSPC is between 5: 1 and 2:1 and (d) 7-12% (w/w) of doxycycline or doxycycline hyclate, in the manufacture of a medicament for treating a patient diagnosed with peri-implantitis associated with crestal peri-implant bone loss.

36. Use of a pharmaceutical composition comprising (a) 90-95% (w/w) of β-TCP; (b) 1.0-2.0% (w/w) PLGA; (c) 0.4-0.8% (w/w) cholesterol; (d) 2.0-4.0% (w/w) of DPPC; (e) 0.7- 1.3% (w/w) of DSPC; (f) 0.4-2% (w/w) of doxycycline or doxycycline hyclate, in the manufacture of a medicament for treating a patient diagnosed with peri-implantitis associated with crestal peri-implant bone loss.
37. The use of any one of the preceding claims useful for at least one of enhancing peri-implant bone formation, reduction of pocket probe depth, reduction of mucosal recession, reduction of bleeding on probing, reducing clinical attachment loss, improving implant survival rates.
38. A pharmaceutical composition comprising coated and non-coated bone augmentation material at a ratio of 1:3 - 10: 1, wherein the coated bone augmentation material comprise between about 80-90% (w/w) of bone augmentation material with between 10-20% (w/w) of a matrix composition which comprises: (a) a biocompatible polymer; (b) a first lipid comprising at least one sterol; (c) a second lipid comprising at least one phospholipid having fatty acid moieties of at least 14 carbons; and (d) at least one pharmaceutically active agent, for use in the treatment of peri-implantitis in a subject in need thereof.
39. The pharmaceutical composition of claim 38, wherein the bone augmentation material is selected from the group consisting of allogeneic bone filler, xenogeneic bone filler, synthetic bone filler and a combination thereof.
40. The pharmaceutical composition of claims 38 or 39, wherein the bone augmentation material is a synthetic bone augmentation material, preferably, wherein the synthetic bone augmentation material is Tri-Calcium Phosphate (β-TCP), preferably, wherein the β-TCP has an average particles size of not more than 500 μm.

41. The pharmaceutical composition of any one of claims 38 - 40, wherein the weight ratio between the coated bone augmentation material and non-coated bone augmentation material is 1: 1.

42. The pharmaceutical composition of any one of claims 38-41, wherein the pharmaceutically active agent is an antibiotic agent present at 0.4-2% (w/w) of the total weight of the pharmaceutical composition.

43. The pharmaceutical composition comprising (a) 90-95% (w/w) of β-TCP; (b) 1.0-2.0% (w/w) PLGA; (c) 0.4-0.8% (w/w) cholesterol; (d) 2.0-4.0% (w/w) of DPPC; (e) 0.7-1.3% (w/w) of DSPC; (f) 0.4-2% (w/w) of doxycycline or doxycycline hyclate for use in the treatment of peri-implantitis in a subject in need thereof.

44. The pharmaceutical composition of any one of claims 38-43 useful for at least one of enhancing peri-implant bone formation, reduction of pocket probe depth, reduction of mucosal recession, reduction of bleeding on probing, reducing clinical attachment loss, improving implant survival rates.

45. Use of a pharmaceutical composition comprising a biocompatible bone augmentation material coated with a matrix composition, the matrix composition comprising: (a) a biocompatible polymer; (b) a first lipid comprising at least one sterol; (c) a second lipid comprising at least one phospholipid having fatty acid moieties of at least 14 carbons; and (d) at least one pharmaceutically active agent, said matrix composition provides local sustained release of the pharmaceutically active agent at the peri-implant site, in the manufacture of a medicament for inhibiting oral biofilm formation at a peri-implant site or eradicating an existing oral biofilm at a peri-implant site.