surgical site.

SUMMARY OF THE INVENTION

The present invention provides methods for preventing, inhibiting or treating a surgical site infection associated with a surgical operation comprising the step of applying to the surgical site a biocompatible, biodegradable substrate being impregnated and/or having its surface coated fully or partially with a matrix composition which provides local controlled and prolonged release of at least one pharmaceutically active agent at the surgical site. Specifically, the matrix composition comprises (a) a biocompatible polymer, (b) a first lipid component comprising a sterol, (c) a second lipid component comprising at least one phospholipid having fatty acid moieties of at least 12 carbons; and (d) a pharmaceutically active agent selected from the group consisting of an antibiotic agent, antiseptic agent, an anti-inflammatory agent, anti-fungal agent and any combination thereof.

In one aspect, there is provided use of a biodegradable substrate impregnated or having its surface coated fully or partially with a matrix composition comprising (a) a biocompatible polymer, (b) a first lipid component comprising at least one sterol which is non-covalently associated with the biocompatible polymer, (c) a second lipid component comprising at least one phospholipid having fatty acid moieties of at least 12 carbons; and (d) a pharmaceutically active agent, in the manufacture of a medicament for the treatment or prophylaxis of a surgical site infection associated with surgical operation.

In one aspect, there is provided use of a biodegradable substrate impregnated or having its surface coated fully or partially with a matrix composition 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, wherein the substrate constitutes between about 80-90% (w/w) and the matrix composition constitutes about 10-20% (w/w) of the total weight of the coated substrate, in the manufacture of a medicament for the treatment or prophylaxis of a surgical site infection associated with surgical operation.

In one aspect, there is provided a biodegradable substrate impregnated or having its surface coated fully or partially with a matrix composition comprising (a) a biocompatible polymer, (b) a first lipid component comprising at least one sterol which is non-covalently associated with the biocompatible polymer, (c) a second lipid component comprising at least one phospholipid having fatty acid moieties of at least 12 carbons; and (d) a pharmaceutically active agent for use in the treatment or prophylaxis of a surgical site infection associated with surgical operation in a subject in need thereof.

The substrate being impregnated and/or having its surface coated fully or partially with a matrix composition described herein is intended for local administration to soft tissues and solid organs during surgical procedures and provides localized infection prevention and treatment by reducing the overall infection rate post-surgery and by reducing or eradicating soft tissue infections that may exist prior to surgery. According to some embodiments, the drug coated substrate described herein prevents or inhibits the formation of biofilm that may form at the surgical site and its vicinity, thereby preventing or inhibiting surgical site infections. Inhibition of biofilm formation at the surgical site refers to inhibition of biofilm formation on surfaces such as biological tissues and/or materials or devices that may be used during surgery (e.g. wound tissue, necrotic cells, biomaterials and surgical implants (e.g. sutures and hard ware-stainless steel wires)). According to some embodiments, the drug coated substrate disclosed herein is capable of eradicating an existing biofilm.

Following its application to the surgical site, the substrate being impregnated and/or having its surface coated fully or partially with a matrix composition described herein provides local controlled release of the drug at the surgical site and its surrounding over a predetermined, prolonged period of time, preferably between several days to

CLAIMS:

1. Use of a biodegradable substrate impregnated or having its surface coated fully or partially with a matrix composition comprising (a) a biocompatible polymer, (b) a first lipid component comprising at least one sterol which is non-covalently associated with the biocompatible polymer, (c) a second lipid component comprising at least one phospholipid having fatty acid moieties of at least 12 carbons; and (d) a pharmaceutically active agent, in the manufacture of a medicament for the treatment or prophylaxis of a surgical site infection associated with surgical operation.
2. The use of claim 1, useful for at least one of reducing the overall infection rate post-surgery, eradicating soft tissue infections that may exist prior to surgery, Inhibition of biofilm formation at the surgical site and eradicating an existing biofilm at the surgical site.
3. The use according to claim 1, wherein the surgical operation in selected from orthopedic surgical operations, spine surgical operations, surgical operations on a digestive system organ, cardiac procedures, hernia repair, vascular procedures, caesarian, prostatectomy, obstetric and gynecologic surgical operations, head and neck cancer surgery, transplantation surgeries, neurosurgery and plastic surgeries.
4. The use according to any one of claims 1-3, implemented in addition to standard of care procedures for reduction in the inoculum of bacteria selected from the group consisting of appropriate surgical site preparation, systemic preventive antibiotics, cell based therapy, and enhancement of the host by perioperative supplemental oxygenation, maintenance of normothermia and glycemic control.
5. The use according to claim 1 to 4, wherein the biodegradable substrate is selected from the group consisting of a mineral substrate, a natural polymer material, a water soluble synthetic polymer and a bioabsorbable hydrophobic material.
6. The use according to claim 5, wherein the biodegradable substrate is a mineral substrate selected from the group consisting of hydroxyapatite, fluorapatite, oxyapatite, wollastonite, apatite/wollastonite glass ceramics, anorthite, calcium fluoride, calcium sulfate, calcium carbonate, tetracalcium phosphate, -tricalcium phosphate (α -TCP), β-tricalcium phosphate (β-TCP), amorphous calcium phosphate,

dicalcium phosphate, agrellite, devitrite, canasite, phlogopite, monetite, brushite, octocalcium phosphate, whitlockite, cordierite, berlinite, combeite, phosphoric acid crystals, disodium hydrogen phosphate, and other phosphate salt-based bioceramics.

7. The use according to claim 5, wherein the biodegradable substrate is a natural polymer material selected from the group consisting of gelatin, hyaluronic acid, hyaluronic acid derivatives, such as, a polyionic complex of hyaluronic acid, triethanolamine alginate, casein, keratin, myosin and/or fibroin, collagen, collagen derivatives, such as, succinylated collagen or methylated collagen, chondrotin sulfate, chitosan, chitosan derivatives, such as, methylpyrrolidone-chitosan, polyaminogalactosamine.
8. The use of claim 5, the substrate is a water soluble synthetic polymer.
9. The use of claim 8, wherein the substrate is poly vinyl alcohol (PVA).
10. The use according to any one of claims 1 to 9, wherein the biodegradable substrate consists of particles having an average particle size of less than about 200 microns (μm).
11. The use according to claim 10, wherein the biodegradable substrate consists of particles having an average particle size of less than about 150 microns (μm).
12. The use according to claim 11, wherein the biodegradable substrate consists of particles having an average particle size in the range of 50 - 150 microns (μm).
13. The use according to claim 12, wherein the biodegradable substrate consists of particles having an average particle size in the range of 50 - 100 microns (μm).
14. The use according to anyone of claims 10-13 wherein a majority of the particles are spherical and/or spheroidal.
15. The use according to any one of claims 1 to 14, wherein the matrix composition comprises a phospholipid selected from a phosphatidylcholine or a combination of phosphatidylcholines having fatty acid moieties having at least 12 carbons.
16. The use according to of claim 15, wherein said phospholipid is a phosphatidylcholine or a combination of phosphatidylcholines having fatty acid moieties having 14 - 18 carbons.
17. The use according to any one of claims 1 to 16 wherein the biocompatible

polymer in the matrix composition, is a biodegradable polyester selected from the group consisting of PLA (polylactic acid), PGA (poly glycolic acid) and PLGA (Poly (lactic co glycolic acid).

18. The use according to any one of claims 1 to 16, wherein the biocompatible polymer in the matrix composition is poly ethylene glycol (PEG).
19. The use according to any one of claims 1 to 18, wherein the pharmaceutically active agent is selected from the group consisting of an antibiotic agent, an antiseptic agent, an anti-inflammatory agent, anti-fungal agent and any combination thereof.
20. The use according to any one of claims 1 to 18, wherein the pharmaceutically active agent comprises a plurality of antibiotic agents.
21. The use according to any one of claims 1 to 18, wherein the pharmaceutically active agent comprises at least one antibiotic agent and at least one anti-inflammatory agent.
22. The use according to any one of claims 19-21, wherein the antibiotic agent is selected from the group consisting of penicillin antibiotics, cephem antibiotics, macrolide antibiotics, tetracycline antibiotics, fosfomycin antibiotics, aminoglycoside antibiotics, and new quinolone antibiotics
23. The use according to any one of claims 1-22, wherein the sterol in the matrix composition is a cholesterol.
24. The use according to any one of claims 1 to 23, wherein the weight ratio of total lipids to said biocompatible polymer is between 1 : 1 and 9: 1 inclusive.
25. The use according to any one of the preceding claims wherein the coated substrate comprises between about 60-90% (w/w) of substrate and 10-40% (w/w) of the matrix composition.
26. The use according to claim 25, wherein the coated substrate comprises between about 70-90% (w/w) of substrate and 10-30% (w/w) of the matrix composition.
27. The use according to any one of claims 1 to 26, wherein said matrix composition is substantially free of water.
28. The use according to any one of claims 1 to 27, wherein when the coated substrate is maintained in an aqueous environment, the matrix composition provides

sustained release of said pharmaceutically active agent, wherein at least 30% of said pharmaceutical active agent is released from the composition at zero-order kinetics.

29. Use of a biodegradable substrate impregnated or having its surface coated fully or partially with a matrix composition 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, wherein the substrate constitutes between about 80-90% (w/w) and the matrix composition constitutes about 10-20% (w/w) of the total weight of the coated substrate, in the manufacture of a medicament for the treatment or prophylaxis of a surgical site infection associated with surgical operation.
30. A biodegradable substrate impregnated or having its surface coated fully or partially with a matrix composition comprising (a) a biocompatible polymer, (b) a first lipid component comprising at least one sterol which is non-covalently associated with the biocompatible polymer, (c) a second lipid component comprising at least one phospholipid having fatty acid moieties of at least 12 carbons; and (d) a pharmaceutically active agent for use in the treatment or prophylaxis of a surgical site infection associated with surgical operation in a subject in need thereof.
31. The biodegradable substrate of claim 30 useful for at least one of reducing the overall infection rate post- surgery, eradicating soft tissue infections that may exist prior to surgery, Inhibition of biofilm formation at the surgical site and eradicating an existing biofilm at the surgical site.
32. The biodegradable substrate of claims 30 or 31, wherein the surgical operation in selected from orthopedic surgical operations, spine surgical operations, surgical operations on a digestive system organ, cardiac procedures, hernia repair, vascular procedures, caesarian, prostatectomy, obstetric and gynecologic surgical operations, head and neck cancer surgery, transplantation surgeries, neurosurgery and plastic surgeries.
33. The biodegradable substrate according to any one of claims 30-32, for use in the treatment or prophylaxis of a surgical site infection associated with surgical operation in a subject in need thereof in addition to standard of care procedures for