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, the matrix composition comprising (a) 10-30% (w/w) of a biocompatible polymer selected from the group consisting of PLA (polylactic acid), PGA (poly glycolic acid) and PLGA (Poly (lactic co glycolic acid); (b) 5-30% (w/w) of a first lipid component comprising cholesterol; (c) 40-75% (w/w) of a second lipid component comprising at least one phosphatidylcholine selected from the group consisting of 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) and any combination thereof; and (d) 1-20% (w/w) of an antibiotic agent selected from doxycycline or doxycycline hyclate, in the manufacture of a medicament for the treatment or prophylaxis of a surgical site bacterial infection associated with surgical operation, wherein the bacteria comprises doxycycline resistant bacteria, wherein the biocompatible polymer and the first lipid are non-covalently associated. In one example, there is disclosed 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, said matrix composition comprising: (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 l,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 bacterial infection associated with surgical operation, wherein the bacteria comprises doxycycline resistant bacteria and wherein the PLGA and the cholesterol are non-covalently associated.

CLAIMS:

1. Use of a biodegradable substrate impregnated or having its surface coated fully or partially with a matrix composition, the matrix composition comprising

(a) 10-30% (w/w) of a biocompatible polymer selected from the group consisting of PLA (polylactic acid), PGA (poly glycolic acid) and PLGA (Poly (lactic co glycolic acid);

(b) 5-30% (w/w) of a first lipid component comprising cholesterol;

(c) 40-75% (w/w) of a second lipid component comprising at least one phosphatidylcholine selected from the group consisting of 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) and any combination thereof; and

(d) 1-20% (w/w) of an antibiotic agent selected from doxycycline or doxycycline hyclate,

in the manufacture of a medicament for the treatment or prophylaxis of a surgical site bacterial infection associated with surgical operation, wherein the bacteria comprises doxycycline resistant bacteria, wherein the biocompatible polymer and the first lipid are non-covalently associated.

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, α-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, wherein 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 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 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 when the coated substrate is maintained in an aqueous environment *in vitro*, the matrix composition provides sustained release of said antibiotic agent, wherein at least 30% (w/w) of said antibiotic agent is released from the composition at zero-order kinetics.

16. The use according to any one of claims 1 to 14, wherein the matrix composition further comprises a pharmaceutically active agent selected from the group consisting of an antibiotic agent, an antiseptic agent, an anti-inflammatory agent, anti-fungal agent and any combination thereof, wherein the antibiotic agent is selected from the group consisting of amoxicillin, amoxicillin/clavulanic acid, ampicillin/sulbactam, penicillin, metronidazole, clindamycine, chlortetracycline, dcmeclocycline, oxytetracycline, amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, tobramycin, cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cephradine, cefaclor, cefamandole, cefametazole, cefonicid, cefotetan, cefoxitine, cefpodoxime, cefprozil, cefuroxime, cefdinir, cefixime, cefoperazone, cefotaxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, azithromycin, claforan, clarithromycin, dirithromycin, erythromycin, lincomycin, troleandomycin, bacampicillin, carbenicillin, cloxacillin, dicloxacillin, meticillin, mezlocillin, nafcillin, oxacillin, piperacillin, ticarcillin, cinoxacin, ciprofloxacin, enoxacin, grepafloxacin, levofloxacin, lomefloxacin, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, sulfisoxazole, sulfacytine, sulfadiazine, sulfamethoxazole, sulfisoxazole, dapson, aztreonam, bacitracin, capreomycin, chloramphenicol, clofazimine, colistimethate, colistin, cycloserine, fosfomycin, furazolidone, methenamine, nitrofurantoin, pentamidine, rifabutin, rifampin, spectinomycin, tigecycline, trimethoprim, trimetrexate glucuronate, vancomycin, chlorhexidine and carbapenem antibiotics such as ertapenem.

17. The use according to any one of claims 1 to 14, wherein the matrix composition further comprises at least one anti-inflammatory agent.

18. The use according to claim 16, wherein the additional 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

19. The use according to any one of claims 1 to 18, wherein the lipids and said biocompatible polymer are at a weight ratio of between 1 : 1 and 9: 1 inclusive.

20. The use according to any one of the preceding claims wherein the coated substrate comprises between 60-90% (w/w) of substrate and 10-40% (w/w) of the matrix composition.

21. The use according to claim 20, wherein the coated substrate comprises between 70-90% (w/w) of substrate and 10-30% (w/w) of the matrix composition.

22. The use according to any one of claims 1 to 21, wherein said matrix composition contains less than 5% of water (w/w) of the matrix composition.

23. Use of a biodegradable substrate impregnated or having its surface coated fully or partially with a matrix composition, said matrix composition comprising: (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 l,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 80-90% (w/w) and the matrix composition constitutes 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 bacterial infection associated with surgical operation, wherein the bacteria comprises doxycycline resistant bacteria and wherein the PLGA and the cholesterol are non-covalently associated.