Claims

1. A mucoadhesive layer, preferably mucoadhesive buccal layer, comprising a non-nanoparticulate macrolide.

2. Mucoadhesive layer according to claim 1, wherein the non-nanoparticulate macrolide is selected from macrolide immune suppressants, macrolide antibiotics, and macrolide antifungals;
   wherein, preferably,
   - the macrolide immune suppressant is selected from tacrolimus, sirolimus, everolimus, and pimecrolimus;
   - the macrolide antibiotic is selected from erythromycin, clarithromycin, azithromycin, roxithromycin, josamycin, spiramycin, telithromycin, tylosin, and fidaxomicin; and/or
   - the macrolide antifungal is selected from polyenes, in particular nystatin, natamycin, and amphotericin B,

   wherein, more preferably, said non-nanoparticulate macrolide is non-nanoparticulate tacrolimus or sirolimus, even more preferably non-nanoparticulate tacrolimus.

3. Mucoadhesive layer according to claim 1 or 2, wherein said non-nanoparticulate macrolide is present in said layer in the form of micronized macrolide, preferably micronized crystalline macrolide, and/or in a molecularly dissolved non-nanoparticulate form.

4. Mucoadhesive layer according to claim 3, wherein said micronized macrolide has an average particle size from 1 to 100 μm, preferably from 1.5 to 50 μm, more preferably from 2 to 25 μm.

5. Mucoadhesive layer according to any one of the foregoing claims, wherein the mucoadhesive layer comprises
   - a mucoadhesive polymer, preferably a polymer selected from a) amphiphilic polymers and hydrophilic polymers, b) poly(methacrylates), c) crosslinked polyacrylic acid polymers, d) copolymers of methyl vinyl ether and maleic anhydride, e) polymers comprising polyvinyl acetate and/or polyvinylpyrrolidone, and combinations thereof;
     wherein, preferably,
     the amphiphilic polymers are selected from polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymers, polyoxyl castor oils and D-α-tocopherol-polyethylenglycol-succinate (TPGS), and/or

the poly(methacrylates) are selected from neutral protonizable poly(methacrylates) and cationic poly(methacrylates), preferably selected from copolymers of dialkylaminoethyl methacrylates and methacrylic acid ester(s), and copolymers of trialkylammonioethyl methacrylates and methacrylic acid ester(s), in particular copolymers of dimethylaminoethyl methacrylates and methacrylic acid esters, and copolymers of trimethylammonioethyl methacrylates and methacrylic acid esters;

and wherein the mucoadhesive layer further comprises:

- a cellulose derivative, preferably selected from hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), methyl cellulose (MC), hydroxyethyl methyl cellulose (HEMC), ethyl cellulose (EC), and a combination thereof;
- a plasticizer; preferably selected from glycerol, polyethylene glycol, e.g. low molecular weight polyethylene glycol such as PEG 200 or PEG 400, propylene glycol, sorbitol, triacetin, and tributylcitrate; more preferably glycerol;
- optionally a colorant, preferably TiO_2;
- and the non-nanoparticulate macrolide.

6. Mucoadhesive layer according to any one of claims 3 to 5, wherein said non-nanoparticulate macrolide is present in said layer in the molecularly dissolved non-nanoparticulate form;
and wherein said mucoadhesive polymer and/or said cellulose derivative is a polymer soluble in an organic solvent.

7. Mucoadhesive layer according to any one of the foregoing claims, wherein the mucoadhesive layer comprises
   a) a mucoadhesive polymer, preferably an amphiphilic polymer; hydroxypropyl cellulose (HPC); carboxymethyl cellulose (CMC); a plasticizer, preferably glycerol; and optionally a colorant, preferably TiO_2;
   preferably 10 wt% - 30 wt% of mucoadhesive polymer; 25 wt% - 35 wt% of hydroxypropyl cellulose (HPC); 10 wt% - 25 wt% of carboxymethyl cellulose (CMC); 10 wt% - 16 wt% of said plasticizer; and optionally 1 wt% - 4 wt% of said colorant; or
   b) a mucoadhesive polymer, preferably selected from crosslinked polyacrylic acid polymers and copolymers of methyl vinyl ether and maleic anhydride; hydroxypropyl cellulose (HPC); ethyl cellulose (EC); a plasticizer, preferably glycerol; and optionally a colorant, preferably TiO_2;

preferably 2 wt% - 17 wt% of mucoadhesive polymer; 30 wt% - 70 wt% of hydroxypropyl cellulose (HPC); 5 wt% - 40 wt% of said ethyl cellulose (EC); 3 wt% - 20 wt% of said plasticizer; and optionally 1 wt% - 5 wt% of said colorant.

8. Mucoadhesive layer according to any one of the foregoing claims, wherein said macrolide is present in said mucoadhesive layer at a concentration of at least 2 wt%, preferably at least 3 wt%, e.g. 3.2 wt%; and/or in an amount in the range of from approximately 0.01 mg to approximately 10 mg, with reference to 1 cm^2 of said mucoadhesive layer, preferably in an amount in the range of from approximately 0.1 mg to approximately 5 mg, with reference to 1 cm^2 of said mucoadhesive layer, more preferably in the range of from approximately 1.5 mg to approximately 3.5 mg, with reference to 1 cm^2 of said mucoadhesive layer.

9. A mucoadhesive film, preferably mucoadhesive buccal film, comprising a mucoadhesive layer comprising a non-nanoparticulate macrolide, preferably a mucoadhesive layer as defined in any one of claims 1-8; and further comprising a backing layer, preferably a backing layer impermeable for the macrolide and/or impermeable for water.

10. Mucoadhesive film according to claim 9, wherein the backing layer comprises a plasticizer, preferably selected from glycerol, polyethylene glycol, e.g. low molecular weight polyethylene glycol such as PEG 200 or PEG 400, propylene glycol, sorbitol, triacetin, and tributylcitrate, more preferably glycerol; and/or comprises a water-insoluble polymer and/or a cellulose derivative, e.g. hydroxyethyl cellulose, preferably a water-insoluble cellulose derivative, more preferably ethyl cellulose (EC).

11. Mucoadhesive film according to claim 9 or 10, wherein the mucoadhesive film further comprises an intermediate layer arranged between the mucoadhesive layer and the backing layer;
wherein, preferably, said intermediate layer facilitates adhesion between the mucoadhesive layer and the backing layer;
wherein, optionally, said intermediate layer comprises a plasticizer, preferably selected from glycerol, polyethylene glycol, e.g. low molecular weight polyethylene glycol such as PEG 200 or PEG 400, propylene glycol, sorbitol, triacetin, and tributylcitrate, more preferably glycerol; and a polymer, preferably a polymer comprising polyvinyl acetate and/or polyvinylpyrrolidone, more preferably a vinylpyrrolidone-vinyl acetate copolymer.

12. Mucoadhesive film according to any one of claims 9-11,

wherein said mucoadhesive layer has an area weight in the range of from 70 g/m² to 180 g/m², preferably in the range of from 100 g/m² to 150 g/m²; and/or

wherein said backing layer has an area weight in the range of from 40 g/m² to 100 g/m², preferably in the range of from 40 g/m² to 60 g/m², e.g. 50 g/m²; and/or

wherein, said intermediate layer, if present, has an area weight in the range of from 40 g/m² to 100 g/m², preferably in the range of from 40 g/m² to 70 g/m², e.g. 60 g/m².

13. A mucoadhesive film, preferably mucoadhesive buccal film, comprising a mucoadhesive layer, a backing layer, and an intermediate layer,

wherein said intermediate layer is arranged between the mucoadhesive layer and the backing layer, and wherein said mucoadhesive layer comprises a macrolide, preferably tacrolimus;

wherein, preferably, said intermediate layer facilitates adhesion between the mucoadhesive layer and the backing layer;

wherein, optionally, said intermediate layer comprises a plasticizer, preferably selected from glycerol, polyethylene glycol, e.g. low molecular weight polyethylene glycol such as PEG 200 or PEG 400, propylene glycol, sorbitol, triacetin, and tributylcitrate, more preferably glycerol;

wherein, optionally, said intermediate layer comprises a polymer, preferably a polymer comprising polyvinyl acetate and/or polyvinylpyrrolidone, more preferably a vinylpyrrolidone-vinyl acetate copolymer.

14. Mucoadhesive layer according to any one of claims 1-8, or mucoadhesive film according to any one of claims 9-13, for use as a medicament.

15. Use of the mucoadhesive layer according to any one of claims 1-8, or the mucoadhesive film according to any one of claims 9-13, in the manufacture of a medicament for preventing and/or treating transplant rejection, preferably solid organ transplant rejection such as liver, kidney or heart allograft rejection;

wherein, optionally, said use involves an attachment of said film or layer in the body cavity of a patient, preferably in a buccal cavity of a patient.

16. A method of preparing a mucoadhesive film, comprising

i) providing a micronized macrolide, preferably non-nanoparticulate micronized macrolide; and a polymer mixture, wherein said polymer mixture comprises
   - a mucoadhesive polymer, preferably a polymer selected from a) amphiphilic polymers and hydrophilic polymers, b) poly(methacrylates), c) crosslinked polyacrylic acid polymers, d) copolymers of methyl vinyl ether and maleic anhydride, e) polymers comprising polyvinyl acetate and/or polyvinylpyrrolidone, and combinations thereof;
   - a cellulose derivative, preferably selected from hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), methyl cellulose (MC), hydroxyethyl methyl cellulose (HEMC), ethyl cellulose (EC), and a combination thereof;
   - optionally, a plasticizer; preferably selected from glycerol, polyethylene glycol, e.g. low molecular weight polyethylene glycol such as PEG 200 or PEG 400, propylene glycol, sorbitol, triacetin, and tributylcitrate; more preferably glycerol;
   - optionally a colorant, preferably TiO_2;

ii) optionally, dispersing the micronized macrolide in a liquid medium to obtain a micronized macrolide dispersion and/or dissolving said micronized macrolide in an organic solvent to obtain a micronized macrolide solution;

iii) mixing the micronized macrolide, optionally micronized macrolide dispersion or micronized macrolide solution, with the polymer mixture to obtain a mucoadhesive layer composition;

iv) preparing a mucoadhesive layer using the mucoadhesive layer composition; optionally by coating the mucoadhesive layer composition on a surface, preferably on a process liner, e.g. by coating, hot melt extrusion, and/or casting;

v) optionally, drying said mucoadhesive layer, thereby obtaining the mucoadhesive film comprising said mucoadhesive layer.

17. The method according to claim 16, further comprising preparing a backing layer, comprising

a) providing a backing layer polymer mixture; optionally comprising a plasticizer, preferably glycerol; optionally comprising a water-insoluble polymer and/or a cellulose derivative, e.g. hydroxyethyl cellulose, preferably a water-insoluble cellulose derivative, more preferably ethyl cellulose;

b) preparing a backing layer using the backing layer polymer mixture, optionally on a surface of said mucoadhesive layer, e.g. by coating said polymer mixture on a surface of said mucoadhesive layer;

c) optionally, drying the backing layer.

18. The method according to claim 16 or 17, further comprising preparing an intermediate layer, comprising

1) providing an intermediate layer polymer mixture; optionally comprising a plasticizer, preferably glycerol, and a polymer, preferably a polymer comprising polyvinyl acetate and/or polyvinylpyrrolidone, more preferably a vinylpyrrolidone-vinyl acetate copolymer;
2) preparing an intermediate layer using the polymer mixture, optionally on a surface of said mucoadhesive layer, e.g. by coating said polymer mixture on a surface of said mucoadhesive layer;
3) optionally, drying the intermediate layer.