CLAIMS

1. Transmucosal therapeutic system for the transmucosal administration of an active agent comprising

a mucoadhesive layer structure comprising

A) a backing layer comprising a first film-forming polymer,

B) an adhesive layer comprising

a laminating adhesive; and

a first plasticizer, and

C) an active agent-containing layer comprising

a macrolide immunosuppressant; and

a second film-forming polymer,

wherein

the first film-forming polymer is ethyl cellulose,

the macrolide immunosuppressant is selected from the group consisting of tacrolimus, sirolimus, everolimus and pimecrolimus,

and

the second film-forming polymer is selected from the group consisting of ethyl cellulose, hydroxypropyl cellulose, and any mixtures thereof.

2. Transmucosal therapeutic system according to claim 1, wherein

the macrolide immunosuppressant is tacrolimus and preferably is tacrolimus in amorphous form.

3. Transmucosal therapeutic system according to claim 1 or 2, wherein

the transmucosal therapeutic system comprises a therapeutically effective amount of tacrolimus, and

the active agent-containing layer preferably comprises at least 0.5 mg/cm^2 tacrolimus, more preferably at least 0.8 mg/cm^2 tacrolimus, and most preferably at least 2.0 mg/cm^2 tacrolimus, and/or comprises less than 6.0 mg/cm^2, less than 4.0 mg/cm^2 or less than 2.5 mg/cm^2 tacrolimus.

4. Transmucosal therapeutic system according to any one of claims 1 to 3, wherein

the second film-forming polymer is a mixture of

ethyl cellulose with

a viscosity as measured as a 5% solution at 25 °C in 80:20 toluene:ethanol by weight in accordance with ASTM D914 of from 30 to 60 mPa·s, more preferably from 40 to 52 mPa·s, and/or

a substitution of ethoxyl groups of 48.0 to 49.5 % as measured in accordance with ASTM D914, and/or

a moisture content of 3 % by weight or less,

preferably in an amount of 20 to 40 wt-% and more preferably 25 to 35 wt-% of the active agent-containing layer,

hydroxypropyl cellulose with

a molecular weight (as measured by GPC-size exclusion chromatography) of between 350,000 and 400,000, in particular about 370,000, and/or

a Brookfield Viscosity of 150-400 mPa·s as measured as a 2 % solution in water,

preferably in an amount of 5 to 20 wt-% and more preferably 7 to 15 wt-% of the active agent-containing layer, and

hydroxypropyl cellulose with

a molecular weight (as measured by GPC-size exclusion chromatography) of between 75,000 and 85,000, in particular about 80,000, and/or

a Brookfield Viscosity of 300-600 mPa·s as measured as a 10 % solution in water,

preferably in an amount of 25 to 50 wt-% and more preferably 30 to 45 wt-% of the active agent-containing layer.

5. Transmucosal therapeutic system according to any one of claims 1 to 4, wherein the first film-forming polymer is ethyl cellulose with

a viscosity as measured as a 5% solution at 25 °C in 80:20 toluene:ethanol by weight in accordance with ASTM D914 of from 30 to 60 mPa·s, more preferably from 40 to 52 mPa·s, and/or

a substitution of ethoxyl groups of 48.0 to 49.5 %, and/or

a moisture content of 3 % by weight or less,

preferably in an amount of from 55 to 95 wt- %, and even more preferably in an amount of about 60 wt-% of the backing layer.

6. Transmucosal therapeutic system according to any one of claims 1 to 5, wherein the backing layer is water-insoluble and preferably further comprises

a second plasticizer, preferably in an amount of 5 to 20 wt-%, and even more preferably in an amount of about 10 wt-% of the backing layer, wherein the second plasticizer is preferably selected from the group consisting of mono-, di-, oligo- and polysaccharides and derivatives thereof, polyethylene glycol, triacetin, triethyl citrate, tributyl citrate, propylene glycol, glycerin, medium chain triglycerides and any mixture thereof, and more preferably is triacetin, and/or

a laminating adhesive aid, preferably in an amount of up to 60 wt-%, or more preferably from 10 to 35 wt-% of the backing layer, wherein preferably the laminating adhesive aid is selected from the group consisting of polyvinylpyrrolidone, polyvinylacetate, vinylpyrrolidone-vinyl acetate copolymers, and any mixture thereof, more preferably is a mixture consisting substantially of polyvinylpyrrolidone and polyvinylacetate or a vinylpyrrolidone-vinyl acetate copolymer, and most preferably is identical to the laminating adhesive.

7. Transmucosal therapeutic system according to any one of claims 1 to 6, wherein the adhesive layer is adjacent to the active agent-containing layer on its one side and to the backing layer on its other side.

8. Transmucosal therapeutic system according to any one of claims 1 to 7, wherein

the first plasticizer is selected from the group consisting of mono-, di-, oligo- and polysaccharides and derivatives thereof, polyethylene glycol, triacetin, triethyl citrate, tributyl citrate, propylene glycol, glycerin, medium chain triglycerides and any mixture thereof, and preferably is glycerin or triacetin and more preferably is glycerin.

9. Transmucosal therapeutic system according to any one of claims 1 to 8, wherein

the laminating adhesive is selected from the group consisting of polyvinylpyrrolidone, polyvinylacetate, vinylpyrrolidone-vinyl acetate copolymers, and any mixture thereof, and preferably is a mixture consisting substantially of polyvinylpyrrolidone and polyvinylacetate or a vinylpyrrolidone-vinyl acetate copolymer, wherein more preferably

said mixture comprises

from 10 to 30 wt-%, preferably from 15 to 25 wt-% and more preferably about 19 wt-% polyvinylpyrrolidone,

from 70 to 90 wt-%, preferably from 75 to 85 wt-% and more preferably about 80 wt-% polyvinylacetate, and

about 1 wt-% of one or more stabilizers, and preferably about 0.8 wt-% sodium lauryl sulfate and about 0.2 wt-% of silica as stabilizers, and/or

said mixture has a K-value of from 60 to 68 and/or a glass transition temperature Tg of about 35 °C, and/or

the polyvinylpyrrolidone is selected from soluble polyvinylpyrrolidones and preferably is selected from polyvinylpyrrolidones having a K-Value of from 28 to 32, and/or a molecular weight of from 44,000 to 54,000, and/or

the polyvinylacetate has a molecular weight of from 400,000 to 500,000 and preferably of about 450,000, and/or

the vinylpyrrolidone-vinyl acetate copolymer has a molar ratio of the monomers vinylpyrrolidone and vinyl acetate of about 6:4, a K-Value of from 25 to 31, and/or a molecular weight of from 45,000 to 70,000.

10. Transmucosal therapeutic system according to any one of claims 1 to 9, wherein

the adhesive layer further comprises a film-forming polymer which is preferably identical to the first and/or the second film-forming polymer, and more preferably

the adhesive layer comprises

from 50 to 90 wt-%, preferably from 60 to 85 wt-% of the laminating adhesive,

from 10 to 45 wt-%, preferably about 15 wt-% of the first plasticizer, and

from 0 to 10 wt-%, preferably about 5 wt-% of the first and/or second film-forming polymer each.

11. Transmucosal therapeutic system according to any one of claims 1 to 10, wherein

the active agent-containing layer is a mucosa-contacting layer and preferably further comprises one or more further excipients selected from the group consisting of further film-forming polymers, further plasticizers, colorants, antioxidants, taste-masking agents and stabilizers, and more preferably comprises

at least one further film-forming polymer, preferably in an amount of 1 to 6 wt-%, and even more preferably in an amount of 2 to 5 wt-% of the active agent-

containing layer each, wherein the further film-forming polymer is selected from the group consisting of a mixed calcium/sodium salt of a methyl vinyl ether and maleic anhydride copolymer and a vinylpyrrolidone-vinyl acetate copolymer and any mixture thereof,

a further plasticizer, preferably in an amount of 2 to 10 wt-%, and even more preferably in an amount of 3 to 6 wt-% of the active agent-containing layer, wherein the further plasticizer is selected from the group consisting of mono-, di-, oligo- and polysaccharides and derivatives thereof, polyethylene glycol, triacetin, triethyl citrate, tributyl citrate, propylene glycol, glycerin, medium chain triglycerides and any mixture thereof, and preferably is glycerin, and/or

a colorant, preferably in an amount of 1 to 6 wt-%, and even more preferably in an amount of 2 to 5 wt-% of the active agent-containing layer, wherein the colorant is selected from the group consisting of titanium dioxide, brilliant blue FCF, indigo carmine, fast green FCF, erythrosine, allura red AC, tartrazine and sunset yellow FCF, curcumin, riboflavin, rivoflavin-5'- phosphate, quinoline yellow, orange yellow S, cochineal, carminic acid, azorubine, carmoisine, amaranth, ponceau 4R, cochineal red A, patent blue V, indigotine, chlorophylls, chlorophyllins, copper complexes of chlorophyll and chlorophyllins, green S, plain caramel, caustic sulphite caramel, ammonia caramel, sulphite ammonia caramel, brilliant black BN, black PN, vegetable carbon, brown HT, carotenes, annatto, bixin, norbixin, paprika extract, capsanthian, capsorubin, lycopene, beta-apo-8'-carotenal, lutein, canthaxanthin, beetroot red, betanin, anthocyanins, calcium carbonate, iron oxides and hydroxides, aluminium, silver, gold and litholrubine BK.

12. Transmucosal therapeutic system according to any one of claims 1 to 11, wherein

the backing layer has an area weight of at least 20 g/m^2, preferably at least 40 g/m^2 and more preferably of about 50 g/m^2, or of less than 100 g/m^2, preferably less than 70 g/m^2, and/or

the adhesive layer has an area weight of at least 30 g/m^2, preferably at least 50 g/m^2 and more preferably of about 60 g/m^2, or of less than 100 g/m^2, preferably less than 80 g/m^2, and/or

the active agent-containing layer has an area weight of at least 100 g/m^2, preferably at least 130 g/m^2 and more preferably of about 150 g/m^2, or of less than 250 g/m^2, or of less than 200 g/m^2.

13. Process of manufacture of a transmucosal therapeutic system comprising the steps of:

(a) combining at least

a first film-forming polymer and

a solvent

to obtain a backing layer coating composition,

coating the backing layer coating composition onto a release liner and

drying the coated backing layer coating composition to form a backing layer,

(b) combining at least

an active agent,

a second film-forming polymer, and

a solvent

to obtain an active agent layer coating composition,

coating the active agent layer coating composition onto a release liner and

drying the coated active agent layer coating composition to form a single-layer active agent-containing layer, optionally repeating the coating step by coating the active agent layer coating composition on the coated active agent layer coating composition before drying, or on the dried active agent-containing layer to obtain a double-layer active agent-containing layer,

(c) combining at least

a laminating adhesive, and

a first plasticizer, and

a solvent

to obtain an adhesive layer coating composition,

coating the adhesive layer coating composition onto the backing layer obtained in step (a), and

drying the coated adhesive layer coating composition to form a bi-layer laminate consisting of an adhesive layer and a backing layer on the release liner, and

(d) laminating the bi-layer laminate obtained in step (c) with the single- or double-layer active agent-containing layer obtained in step (b),

wherein

the first film-forming polymer is ethyl cellulose,

the macrolide immunosuppressant is selected from the group consisting of tacrolimus, sirolimus, everolimus and pimecrolimus,

and

the second film-forming polymer is selected from the group consisting of ethyl cellulose, hydroxypropyl cellulose, and any mixtures thereof.

14. Use of a transmucosal therapeutic system according to any one of claims 1 to 12 in the manufacture of a medicament for the treatment and/or prophylaxis of organ rejection after organ transplant in a human patient, and more preferably for the prophylaxis of organ rejection after allogeneic liver, kidney, or heart transplant, in a human patient.

15. An active agent-containing layer for a transmucosal therapeutic system, the active agent-containing layer comprising

i) tacrolimus in amorphous form; and

ii) a film-forming polymer selected from the group consisting of ethyl cellulose, hydroxypropyl cellulose, and any mixtures thereof.

16. An active agent-containing layer according to claim 15, wherein the X-ray diffractogram of the active agent-containing layer is characterized by the absence of reflections of crystalline tacrolimus, and preferably does not comprise reflections at 2-Theta angles of 6.45°, 8.55°, 10.35°, 11.25°, 11.75°, 13.75°, 14.15° and 15.30° ± 0.2° degrees.

17. A mucoadhesive layer structure for a transmucosal therapeutic system comprising

A) the active agent-containing layer according to claim 16 and

B) an adhesive layer comprising

a laminating adhesive; and

a plasticizer.

18. Transmucosal therapeutic system for the transmucosal administration of an active agent comprising

a mucoadhesive layer structure consisting of

A) a backing layer comprising

from 55 to 95 wt- % and preferably about 60 wt-% of ethyl cellulose with a viscosity as measured as a 5% solution at 25 °C in 80:20 toluene:ethanol by weight in accordance with ASTM D914 of from 30 to 60 mPa·s, more preferably from 40 to 52 mPa·s, and a substitution of ethoxyl groups of 48.0 to 49.5 % as measured in accordance with ASTM D914,

from 5 to 20 wt-% and preferably about 10 wt-% triacetin, and

from 10 to 35 wt-% and preferably about 30 wt-% of a mixture consisting of

about 19 wt-% polyvinylpyrrolidone,

about 80 wt-% polyvinylacetate,

about 0.8 wt-% sodium lauryl sulfate and

about 0.2 wt-% of silica,

B) an adhesive layer adjacent to the active agent-containing layer on its one side and to the backing layer on its other side, comprising

from 70 to 90 wt-% and preferably about 80 wt-% of a mixture consisting of

about 19 wt-% polyvinylpyrrolidone,

about 80 wt-% polyvinylacetate,

about 0.8 wt-% sodium lauryl sulfate and

about 0.2 wt-% of silica,

from 10 to 30 wt-%, preferably about 15% of glycerin, and

from 0 to 10 wt-%, preferably about 5 wt-% of ethyl cellulose with a viscosity as measured as a 5% solution at 25 °C in 80:20 toluene:ethanol by weight in accordance with ASTM D914 of from 30 to 60 mPa·s, more preferably from 40 to 52 mPa·s, and a substitution of ethoxyl groups of 48.0 to 49.5 % as measured in accordance with ASTM D914,

C) an active agent-containing layer comprising

at least 0.8 mg/cm^2 of tacrolimus in amorphous form;

ethyl cellulose with a viscosity as measured as a 5% solution at 25 °C in 80:20 toluene:ethanol by weight in accordance with ASTM D914 of from 30 to 60 mPa·s, more preferably from 40 to 52 mPa·s, and a substitution of ethoxyl groups of 48.0 to 49.5 % as measured in accordance with ASTM D914, in an amount of 25 to 35 wt-% of the active agent-containing layer,

hydroxypropyl cellulose with a molecular weight (as measured by GPC-size exclusion chromatography) of about 370,000, and a Brookfield Viscosity of 150-400 mPa·s as measured as a 2 % solution in water, in an amount of 7 to 15 wt-% of the active agent-containing layer, and

hydroxypropyl cellulose with a molecular weight (as measured by GPC-size exclusion chromatography) of about 80,000, and a Brookfield Viscosity of 300-600 mPa·s as measured as a 10 % solution in water, in an amount of 30 to 45 wt-% of the active agent-containing layer,

a mixed calcium/sodium salt of a methyl vinyl ether and maleic anhydride copolymer as a further film-forming polymer in an amount of 2 to 5 wt-% of the active agent-containing layer,

optionally a vinylpyrrolidone-vinyl acetate copolymer in an amount of 1 to 4 wt-% of the active agent-containing layer, and

glycerin in an amount of 3 to 6 wt-% of the active agent-containing layer.