drying. Further, many active agents are less stable in neutral form than in salt form. Therefore, there exists a need for compositions, systems and medicaments having an adhesive matrix as a component layer that can consistently and effectively deliver a therapeutic amount of an active agent over a prolonged period of time.

[0006] The foregoing examples of the related art and limitations related therewith are intended to be illustrative and not exclusive. Other limitations of the related art will become apparent to those of skill in the art upon a reading of the specification and a study of the drawings.

SUMMARY

[0007] The following aspects and examples thereof described and illustrated below are meant to be exemplary and illustrative, not limiting in scope.

[0008] In a first example, a transdermal delivery system is provided, the system comprising a skin contact adhesive layer to attach the system to the skin of a user; a drug reservoir layer comprising an active agent and a drug carrier composition; and a microporous membrane disposed between the adhesive layer and the drug reservoir layer, the microporous membrane comprising a plurality of pores and a membrane treatment composition, wherein the membrane treatment composition occupies at least a portion of the pores.

[0008a] In one aspect, the present disclosure refers to a transdermal delivery system, comprising:

a skin contact adhesive layer to attach the system to the skin of a user;

a drug reservoir layer comprising an adhesive polymer, a salt form of donepezil, and a drug carrier composition; and

a microporous membrane disposed between the adhesive layer and the drug reservoir layer, the microporous membrane comprising a plurality of pores filled with a membrane treatment composition different from the drug carrier composition,

wherein the skin contact adhesive layer comprises an acrylic acid/vinyl acetate copolymer adhesive, a nonionic surfactant, a long-chain aliphatic alcohol, and a citric acid ester,

wherein the drug carrier composition comprises a nonionic surfactant, a long-chain aliphatic alcohol, a citric acid ester and a hydrophilic solvent,

wherein the membrane treatment composition excludes the hydrophilic solvent and comprises sorbitan monolaurate, lauryl lactate, and triethyl citrate.

[0009] In some examples, the microporous membrane is and/or the pores of the microporous membrane are saturated with the membrane treatment composition. In another example, the membrane treatment composition is sequestered in or within the pores of the microporous membrane. In another example, the membrane treatment composition fills the pores of the microporous membrane. In one example, the microporous membrane is a flat sheet microporous membrane.

[0010] In some examples, the drug carrier composition and the membrane treatment composition are the same. In another example, the drug carrier composition and the membrane treatment composition are different. In one example, the drug carrier composition and the membrane treatment composition are different. In one example, the membrane treatment composition and the contact adhesive layer drug carrier composition are the same, and both are different from the drug carrier composition that is disposed in the drug reservoir layer. In one example, the drug carrier composition differs from the membrane treatment composition and the contact adhesive layer drug carrier composition by the presence of a hydrophilic solvent.

[0011] In some examples, the membrane treatment composition comprises a nonionic surfactant, a long-chain aliphatic alcohol, a citric acid ester, and/or combinations thereof.

[0012] In some examples, the active agent is a water insoluble base and the drug carrier composition comprises a nonionic surfactant, a long-chain aliphatic alcohol, a citric acid ester, and/or combinations thereof.

[0013] In some examples, the microporous membrane is a microporous polypropylene.

[0014] In some examples, the microporous membrane has pores with an average pore size of from about 0.001 μm to about 100 μm.

[0015] In some examples, the pore size is from about 0.010 μm to about 0.100 μm.

[0016] In some examples, the pore size is from about 0.040 μm to about 0.050 μm.

[0017] In some examples, the microporous membrane has a porosity of about 30% to about 50%.

[0018] In some examples, the drug reservoir layer additionally comprises glycerine.

[0019] In some examples, the glycerine is present in the amount of about 5 wt% to about 15 wt%.

[0020] In some examples, the membrane treatment composition does not include glycerine.

[0021] In some examples, the drug reservoir layer further comprises a crosslinked polyvinylpyrrolidone.

[0022] In some examples, the crosslinked polyvinylpyrrolidone is present in the amount of about 10 wt% to about 20 wt%.

[0023] In some examples, the active agent to be administered to a subject is generated *in situ* in the drug reservoir layer by reaction of a pharmaceutically acceptable salt of the active agent and an amphoteric base compound.

[0024] In some examples, the amphoteric inorganic compound in the drug reservoir layer is present in the amount of about 2 wt% to about 5 wt% of the drug reservoir layer.

[0025] In some examples, the amphoteric inorganic compound in the drug reservoir layer is an alkaline salt.

[0026] In some examples, the alkaline salt is sodium bicarbonate.

[0027] In some examples, the active agent to be administered to a subject is donepezil base.

[0028] In some examples, the pharmaceutically acceptable salt is donepezil hydrochloride.

[0029] In some examples, the donepezil hydrochloride is present in the drug reservoir layer in the amount of about 5 wt% to about 25 wt% of the drug reservoir layer.

[0030] In some examples, the drug reservoir layer comprises about 5 wt% to about 15 wt% triethyl citrate.

[0031] In some examples, the drug reservoir layer comprises about 0.5 wt% to about 5 wt% sorbitan monolaurate.

[0032] In some examples, the drug reservoir layer comprises about 0.5% to about 5% lauryl lactate.

[0033] In some examples, the drug reservoir layer comprises about 0.1 wt% to about 2 wt% of ascorbic palmitate.

[0034] In some examples, the drug reservoir layer comprises about 35 wt% to about 50 wt% of a copolymer of acrylic acid and vinyl acetate.

[0035] In some examples, the drug carrier composition comprises triethyl citrate, lauryl lactate, sorbitan monolaurate, or combinations thereof.

[0036] In some examples, the drug carrier composition comprises about 60 wt% to about 75 wt% triethyl citrate.

[0037] In some examples, the drug carrier composition comprises about 10 wt% to about 17 wt% sorbitan monolaurate.

[0038] In some examples, the drug carrier composition comprises about 15 wt% to about 25 wt% lauryl lactate.

[0039] In some examples, the drug carrier composition comprises about 66.7 wt% triethyl citrate; about 20.0 wt% lauryl lactate; and about 13.3 wt% sorbitan monolaurate.

[0040] In some examples, the drug reservoir layer comprises about 10 wt% to about 20 wt% of the drug carrier composition.

[0041] In some examples, the drug reservoir layer comprises about 16.0 wt% donepezil hydrochloride; about 2.6 wt% sodium bicarbonate; about 10.0 wt% triethyl citrate; about 3.0 wt% lauryl lactate; about 2.0 wt% sorbitan lacate; about 10.0 wt% glycerine; about 15.0 wt% crosslinked polyvinylpyrrolidone; about 0.5 wt% ascorbic palmitate; and about 40.9 wt% copolymer of acrylic acid and vinyl acetate.

[0042] In some examples, the membrane treatment composition comprises triethyl citrate, lauryl lactate, sorbitan monolaurate, and/or combinations thereof.

[0043] In some examples, the membrane treatment composition comprises about 60 wt% to about 75 wt% triethyl citrate.

[0044] In some examples, the membrane treatment composition comprises about 10 wt% to about 17 wt% sorbitan monolaurate.

[0045] In some examples, the membrane treatment composition comprises about 15 wt% to about 25 wt% lauryl lactate.

[0046] In some examples, the membrane treatment composition comprises about 66.7 wt% triethyl citrate; about 20.0 wt% lauryl lactate; and about 13.3 wt% sorbitan monolaurate.

[0047] In some examples, the system is configured to provide a dose of about 5 mg to about 10 mg of donepezil base per day.

[0048] In some examples, the skin contact adhesive layer comprises a contact adhesive layer drug carrier composition.

[0049] In some examples, the contact adhesive layer drug carrier composition comprises triethyl citrate, lauryl lactate, sorbitan monolaurate, and/or combinations thereof. In one example, the contact adhesive layer drug carrier composition comprises about 66.7 wt% triethyl citrate; about 20.0 wt% lauryl lactate; and about 13.3 wt% sorbitan monolaurate.

[0050] In some examples, the contact adhesive layer drug carrier composition is present in the contact adhesive layer in the amount of about 10 wt% to about 20 wt%.

[0051] In some examples, the active agent is memantine base.

[0052] In some examples, the pharmaceutically acceptable salt is memantine hydrochloride.

[0053] In some examples, the memantine hydrochloride is present in the drug reservoir layer in the amount of about 15 wt% to about 35 wt%.

[0054] In some examples, the drug carrier composition comprises octyldodecanol.

[0055] In some examples, the octyldodecanol is present in the amount of about 5 wt% to about 15 wt%.

[0056] In some examples, the drug reservoir layer comprises about 25 wt% to about 40 wt% of a copolymer of acrylic acid and vinyl acetate.

[0057] In some examples, the skin contact adhesive layer comprises a hydrophilic fumed silica in the amount of about 5 wt% to about 10 wt%.

[0058] In some examples, the membrane treatment composition comprises octyldodecanol.

[0059] In some examples, the system is configured to provide a dose of about 1 mg to about 30 mg of memantine base per day.

[0060] In some examples, the drug reservoir layer comprises about 25 wt% memantine hydrochloride; about 9.73 wt% sodium bicarbonate; about 7.0 wt% octyldodecanol; about 10.0 wt% glycerine; about 15.0 wt% crosslinked polyvinylpyrrolidone; and about 33.27 wt% copolymer of acrylic acid and vinyl acetate.

[0061] In some examples, the skin contact adhesive layer comprises about 5 wt% to about 15 wt% octyldodecanol.

[0062] In some examples, the contact adhesive layer comprises about 10 wt% octyldodecanol.

[0063] In some examples, the active agent is fingolimod.

[0064] In some examples, the pharmaceutically acceptable salt is fingolimod hydrochloride.

[0065] In some examples, the skin contact adhesive layer comprises a copolymer of acrylic acid and vinyl acetate.

[0066] In some examples, the copolymer of acrylic acid and vinyl acetate is present in the amount of about 60 wt% to about 75 wt%.

[0067] In some examples, the skin contact adhesive layer comprises a polyisobutylene.

[0068] In some examples, the polyisobutylene is present in the amount of about 65 wt% to about 90 wt%.

[0069] In some examples, the skin contact adhesive layer further comprises crosslinked polyvinylpyrrolidone.

[0070] In some examples, the crosslinked polyvinylpyrrolidone is present in the amount of about 15 wt% to about 25 wt%.

[0071] In some examples, the transdermal delivery systems described herein can further comprise a first backing layer in contact with the drug reservoir layer; an adhesive overlay in contact with the first backing layer on the side opposite from the drug reservoir layer; and a second backing layer in contact with the adhesive overlay on the side opposite from the first backing layer.

[0072] In some examples, the first backing layer comprises a polyester laminate.

[0073] In some examples, the adhesive overlay comprises a polyisobutylene, a polybutene, a crosslinked polyvinylpyrrolidone, an acrylic adhesive, a copolymer of acrylic acid and vinyl acetate, or combinations thereof.

[0074] In some examples, the adhesive overlay comprises a copolymer of acrylic acid and vinyl acetate.

[0075] In some examples, the second backing layer comprises a woven polyester fabric.

[0076] In some examples, the transdermal delivery systems described herein can further comprise a release liner comprising a film, a non-woven fabric, a woven fabric, a laminate, or combinations thereof wherein the release liner is in contact with the skin contact adhesive layer on the opposite side from the intermediate layer.

[0077] In some examples, the release liner is a silicone-coated polymer film or paper.

[0078] In some examples, the release liner is a silicone-coated polyethylene terephthalate (PET) film, a fluorocarbon film, or a fluorocarbon coated PET film.

[0079] In another example, a method for transdermal delivery of an active agent is provided, comprising providing any one of the above described transdermal delivery systems, securing, or instructing to secure, the system to the skin of a user to deliver the active agent from the system to the skin, whereby (i) the time lag for steady state flux is at least about 20% faster compared to a system with no membrane treatment composition in the pores of the microporous membrane, (ii) the system achieves its steady state equilibrium flux at least 20% faster compared to a system with no membrane treatment composition in the pores of the microporous membrane; and/or (iii) the active agent diffuses from the system to the skin at least 20% faster compared to a system with no membrane treatment composition in the pores of the microporous membrane.

[0079a] In one aspect, the present disclosure refers to a transdermal delivery system as disclosed here for delivery of a base form of donepezil, wherein the transdermal delivery system when secured to the skin of a user delivers the base form of donepezil from the system to the skin, whereby (i) the time to reach steady state flux is at least about 20% faster compared to a system with no membrane treatment composition in the pores of the microporous membrane, (ii) the system achieves its steady state equilibrium flux at least 20% faster compared to a system with no membrane treatment composition in the pores of the microporous membrane; and/or (iii) donepezil diffuses from the system to the skin at least 20% faster compared to a system with no membrane treatment composition in the pores of the microporous membrane.

[0079b] In another aspect, the present disclosure refers to a transdermal delivery system as disclosed herein, for use in treating Alzheimer's disease, wherein the system when applied to skin of a subject generates a base form of the salt form of donepezil for delivery to the skin.

[0079c] In yet another aspect, the present disclosure refers to use of donepezil in the manufacture of a transdermal delivery system as disclosed herein, for treating Alzheimer's disease, wherein the system when applied to skin of a subject generates a base form of the salt form of donepezil for delivery to the skin.

[0080] In yet another example, a method for treating Alzheimer's disease is provided comprising providing any of the transdermal delivery systems comprising an active agent, such as a donepezil base or a memantine base, as described above for administration to the skin of a patient.

[0081] In still another example, a method for treating Alzheimer's disease, obsessive compulsive disorder, anxiety disorder, attention deficit hyperactivity disorder (ADHD), or opioid dependence is

provided comprising providing any of the transdermal delivery systems comprising a memantine compound as described above to the skin of a patient.

[0082] In another example, a method for manufacturing a transdermal delivery system of an active agent is provided comprising providing a skin contact adhesive layer to attach the system to the skin of a user; providing a drug reservoir layer comprising an active agent and a drug carrier composition; treating a microporous membrane having a plurality of pores with a membrane treatment composition to provide a pretreated microporous membrane, wherein at least a portion of the pores of the pretreated microporous membrane contain the membrane treatment composition; and providing an intermediate layer disposed between the skin contact adhesive layer and the drug reservoir layer, wherein the intermediate layer comprises the pretreated microporous membrane;

[0083] In some examples of the manufacturing method, the microporous membrane comprises a microporous polypropylene.

[0084] In some examples of the manufacturing method, the active agent of the drug reservoir layer is generated in situ by reaction of a pharmaceutically acceptable salt of the active agent and an amphoteric base compound.

[0085] In some examples of the manufacturing method, the microporous membrane has an average pore size of from about 0.001 μm to about 100 μm.

[0086] In some examples of the manufacturing method, the pore size is from about 0.010 μm to about 0.100 μm.

[0087] In some examples of the manufacturing method, the pore size is from about 0.040 μm to about 0.050 μm.

[0088] In some examples of the manufacturing method, the microporous membrane has a porosity of about 30% to about 50%.

[0089] In some examples of the manufacturing method, the step of treating a microporous membrane with a membrane treatment composition comprises contacting the microporous membrane with the membrane treatment composition, allowing the microporous membrane to become saturated with the membrane treatment composition, and removing any excess membrane treatment composition from the saturated microporous membrane.

[0090] In some examples of the manufacturing method, the membrane treatment composition comprises a nonionic surfactant, a long-chain aliphatic alcohol, a citric acid ester, or combinations thereof.

[0091] In some examples of the manufacturing method, the amphoteric inorganic base compound is sodium bicarbonate.

[0092] In some examples of the manufacturing method, the active agent is donepezil base and the pharmaceutically acceptable salt is donepezil hydrochloride.

[0093] In some examples of the manufacturing method, the drug carrier composition comprises triethyl citrate, lauryl lactate, sorbitan monolaurate, or any combination thereof.

[0094] In some examples of the manufacturing method, the drug carrier composition comprises about 66.7 wt% triethyl citrate; about 20.0 wt% lauryl lactate; and about 13.3 wt% sorbitan monolaurate.

[0095] In some examples of the manufacturing method, the membrane treatment composition comprises about 66.7 wt% triethyl citrate; about 20.0 wt% lauryl lactate; and about 13.3 wt% sorbitan monolaurate.

[0096] In some examples of the manufacturing method, the active agent is memantine and the pharmaceutically acceptable salt is memantine hydrochloride.

[0097] In some examples of the manufacturing method, the drug carrier composition and the membrane treatment composition both comprise octyldodecanol.

[0100] In some examples of the manufacturing method, the active agent is fingolimod base and the pharmaceutically acceptable salt is fingolimod hydrochloride.

[0101] In some examples, the manufacturing method further comprises the steps of providing a first backing layer in contact with the drug reservoir layer; providing an adhesive overlay in contact with the first backing layer on the side opposite from the drug reservoir layer; and providing a second backing layer in contact with the adhesive overlay on the side opposite from the first backing layer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0102] FIGS. 1A-1D are illustrations of transdermal delivery systems according to several embodiments;

[0103] FIG. 2A is a graph of mean plasma concentration of donepezil, in ng/mL, as a function of time, in days, in human subjects treated with a donepezil transdermal delivery system (circles) for 1 week, or with 5 mg of donepezil administered orally on day 1 and on day 7 (triangles);

[0104] FIG. 2B is a graph showing the mean plasma concentration of donepezil, in ng/mL, in the 24 hour period after oral administration of a 5 mg donepezil tablet (triangles) and after removal of the donepezil transdermal delivery system (circles);

[0105] FIG. 3 is a graph showing the projected mean plasma concentration of donepezil, in ng/mL, over a 28 day (4 week) treatment period with a transdermal delivery system designed to administer 10 mg/day for a week (solid line), with a new patch applied once weekly, and over a 28 day period with a 10 mg daily oral tablet of donepezil (dashed line);

[0106] FIG. 4 is a bar graph of the number of subjects in the group treated with the donepezil transdermal delivery system for 1 week and the observed skin irritation subsequent to patch removal, where the open bars indicate no skin irritation and the filled bars indicate mild skin irritation;

IT IS CLAIMED:

1. A transdermal delivery system, comprising:

a skin contact adhesive layer to attach the system to the skin of a user;

a drug reservoir layer comprising an adhesive polymer, a salt form of donepezil, and a drug carrier composition; and

a microporous membrane disposed between the adhesive layer and the drug reservoir layer, the microporous membrane comprising a plurality of pores filled with a membrane treatment composition different from the drug carrier composition,

wherein the skin contact adhesive layer comprises an acrylic acid/vinyl acetate copolymer adhesive, a nonionic surfactant, a long-chain aliphatic alcohol, and a citric acid ester,

wherein the drug carrier composition comprises a nonionic surfactant, a long-chain aliphatic alcohol, a citric acid ester and a hydrophilic solvent,

wherein the membrane treatment composition excludes the hydrophilic solvent and comprises sorbitan monolaurate, lauryl lactate, and triethyl citrate.

2. The system of claim 1, wherein the plurality of pores are filled with the membrane treatment composition prior to the microporous membrane being disposed between the adhesive layer and the drug reservoir layer.

3. The system claim 1, wherein the hydrophilic solvent in the drug carrier composition is glycerine.

4. The system of claim 1, wherein the nonionic surfactant is sorbitan monolaurate, the long-chain aliphatic alcohol is lauryl lactate or octyldodecanol, and the citric acid ester is triethyl citrate.

5. The system of any one of the preceding claims, wherein the drug reservoir layer further comprises an amphoteric base compound.

6. The system of claim 5, wherein the salt form of donepezil and the amphoteric base compound react *in situ* in the drug reservoir layer after the system is applied to skin of a user to generate a base form of donepezil.

7. The system of claim 1, wherein the skin contact adhesive layer excludes the hydrophilic solvent.

8. The system of claim 7, wherein the hydrophilic solvent is a polyol.

9. The system of claim 8, wherein the drug carrier composition comprises between about 1.5-2.5 wt% sorbitan monolaurate, between about 8-12 wt% triethyl citrate, and between about 5-15 wt% polyol.

10. The system of claim 9, wherein the membrane treatment composition comprises between about 10-17 wt% sorbitan monolaurate, between about 15-25 wt% lauryl lactate, and between about 60-75 wt% triethyl citrate.

11. The system of claim 10, wherein the contact adhesive layer comprises sorbitan monolaurate, lauryl lactate, and triethyl citrate.

12. A transdermal delivery system according to any one of claims 1-11, for use in treating Alzheimer's disease, wherein the system when applied to skin of a subject generates a base form of the salt form of donepezil for delivery to the skin.

13. A transdermal delivery system according to any one of claims 1-11 for delivery of a base form of donepezil,

wherein the transdermal delivery system when secured to the skin of a user delivers the base form of donepezil from the system to the skin, whereby (i) the time to reach steady state flux is at least about 20% faster compared to a system with no membrane treatment composition in the pores of the microporous membrane, (ii) the system achieves its steady state equilibrium flux at least 20% faster compared to a system with no membrane treatment composition in the pores of the microporous membrane; and/or (iii) donepezil diffuses from the system to the skin at least 20% faster compared to a system with no membrane treatment composition in the pores of the microporous membrane.

14. Use of donepezil in the manufacture of a transdermal delivery system according to any one of claims 1-11, for treating Alzheimer's disease, wherein the system when applied to skin of a subject generates a base form of the salt form of donepezil for delivery to the skin.