[0009] Transdermal delivery of basic drugs including memantine can be especially difficult due to poor skin permeability. Further, some active agents have poor or low solubility in the adhesives and/or other components used in typical transdermal formulations. Further, there is a need for stable, long term administration of anti-dementia agents (*e.g.*, 1-10 days or more) that provides a stable and effective release of the agent over the administration period and has suitable adhesion for the long term administration.

[0010] Therefore, there exists a need for transdermal compositions, devices and methods that address these shortcomings.

BRIEF SUMMARY

[0011] The following aspects and examples thereof described and illustrated below are meant to be exemplary and illustrative, not limiting in scope.

[0012] Examples described herein provide for compositions, systems, and methods of treating neurological diseases, such as but not limited to Alzheimer's disease. The present aspects and examples improve upon exiting methods by providing compositions that have been formulated for transdermal delivery of the active ingredients.

[0013] In particular, it is an object and advantage of the present compositions, systems and examples to confer *in situ* synthesis of memantine base by providing components of the synthetic machinery at the site of the application. It is contemplated that use of the *in situ* machinery will not only greatly improve the bioavailability of the drug, but also permit constant and sustained delivery of the drug for various therapeutic applications.

[0014] Additionally, it is contemplated that the delivery systems described herein shall provide for easy titration, optimal constant dosing, improved patience compliance, and better adherence to medication compared to the existing modes of delivery.

[0015] Examples described herein further relate to advantageously treating central nervous system (CNS) disorders, and in particular neurological disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, with the systems and devices. The instant systems and methods may help eliminate or reduce variability in absorption and high first-pass metabolism associated with orally administered memantine in patients suffering from the aforementioned neurological disorders. Additionally, the instant compositions and systems may further confer rapid and extensive drug absorption into the bloodstream without the need for hypodermic needles and injection systems. Furthermore, the ease of delivery conferred by the systems and compositions herein may increase patient adherence, while simultaneously minimizing the risk of misdosing.

Finally, the systems and methods described herein may permit self-treatment by patients without the need for constant supervision from health practitioners.

[0015a] In one aspect, the present disclosure refers to a composition, comprising: a drug reservoir consisting essentially of: a salt of memantine and an alkaline salt; a permeation enhancer; a hydrophilic solvent carrier; a crosslinked polyvinylpyrrolidone and an acrylate copolymer, wherein, after application of the composition to the skin of a subject, memantine base is generated in situ by reaction of the salt of memantine and the alkaline salt.

[0015b] In another aspect, the present disclosure refers to a composition, comprising: a drug reservoir consisting essentially of:

(a) between about 10-30 wt% memantine HCl and between about 5-15 wt% sodium bicarbonate;

(b) about 5-15 wt% octyldodecanol;

(c) about 5-15 wt% glycerol;

(d) about 10-30 wt% crosslinked polyvinylpyrrolidone; and

(e) about 20-50 wt% acrylate polymer.

wherein, after application of the composition to the skin of a subject, memantine base is generated in situ by reaction of the memantine HCl and the sodium bicarbonate.

[0015c] In a further aspect, the present disclosure refers to use of a composition as disclosed herein in the manufacture of a medicament for treating a subject with a CNS disorder.

[0016] In one example, transdermal delivery systems for systemic delivery of memantine base are provided. In examples, the system comprises, in series from the skin facing side, (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprised of an adhesive formulation that optionally does not comprise memantine base and/or a memantine salt; (b) optionally, an intermediate layer directly in contact with the skin contact adhesive layer; (c) a drug reservoir in contact with the intermediate layer; and (d) at least a first backing layer in contact with the drug reservoir. In examples, the system optionally further comprises (e) an adhesive overlay in contact with the first backing layer, and/or (f) a second backing layer in contact with the first backing layer or the adhesive overlay. In examples, the drug reservoir is comprised of (i) an acrylate polymer or copolymer, (ii) a dissolving agent, (iii) a carrier, (iv) an optional disintegrant, and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt. In some examples, the delivery system comprises the intermediate layer.

[0017] In examples, the drug reservoir layer is comprised of (i) an acrylate polymer comprising a copolymer of acrylic acid/vinyl acetate, (ii) at least one dissolving agent, (iii) at least one carrier, (iv) an optional disintegrant, and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt.

[0018] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer comprising vinyl acetate and at least one acrylate selected from the group consisting of 2-ethylhexyl-acrylate, hydroxyethyl acrylate and glycidyl acrylate, (ii) at least one dissolving agent, (iii) at least one carrier, (iv) at least one disintegrant, and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above.

[0019] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug

reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent which is a higher alcohol selected from the group consisting of lauryl alcohol, isostearyl alcohol, octyldodecanol, and oleyl alcohol, (iii) at least one carrier, (iv) an optional disintegrant, and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above.

[0020] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer if present, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent, (iii) at least one carrier selected from the group consisting of glycerol, propylene glycol, and liquid polyethylene glycol, (iv) at least one disintegrant, and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above.

[0021] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent or permeation enhancer, (iii) at least one carrier that is a hydrophilic solvent, (iv) at least one disintegrant, and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above, wherein the skin contact adhesive layer does not comprise the hydrophilic solvent carrier.

[0022] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent, (iii) at least one carrier, (iv) at least one disintegrant selected from the group consisting of polyvinylpyrrolidone (PVP) or polyvinyl alcohol (PVA), or cross-linked derivative thereof, and (v) memantine base generated *in situ* by reaction of a salt of

memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above. In some examples, the disintegrant is cross-linked polyvinylpyrrolidone.

[0023] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer, wherein the intermediate layer is a rate controlling membrane for memantine base; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent, (iii) at least one carrier, (iv) at least one disintegrant, and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above. In some examples, the rate controlling membrane comprises microporous polypropylene. In some examples, the rate controlling membrane comprises non-woven polyester.

[0024] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent, (iii) at least one carrier, (iv) at least one disintegrant, and (v) memantine base generated *in situ* by reaction of a halide salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above. In one example, the halide salt comprises a chloride salt of memantine (memantine HCl).

[0025] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent, (iii) at least one carrier, (iv) at least one disintegrant, and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt selected from the group consisting of sodium acetate, sodium borate, sodium metaborate, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, potassium citrate, potassium acetate, sodium phosphate, potassium phosphate, disodium hydrogen phosphate, sodium oxylate, sodium succinate, sodium citrate, and sodium salicylate; and (d) one or more additional backing

layers, as detailed above. In some examples, the alkaline salt comprises sodium bicarbonate or potassium bicarbonate.

[0026] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent; (iii) at least one carrier; (iv) at least one disintegrant; (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (vi) an additional agent selected from sorbitan monolaurate and lauryl lactate; and (d) one or more additional backing layers, as detailed above.

[0027] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer comprising a higher alcohol and a biocompatible polymer, optionally together with a matrix modifier and further optionally dispersive silica, to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent; (iii) at least one carrier; (iv) an optional disintegrant; and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above. In some examples, the skin contact adhesive layer comprises a higher alcohol, a biocompatible polymer, and a matrix modifier. In another specific example, the skin contact adhesive layer comprises a higher alcohol, a biocompatible polymer, and dispersive silica.

[0028] In another example, a transdermal delivery system for systemic delivery of memantine base comprises (a) a skin contact adhesive layer comprising a higher alcohol selected from the group consisting of lauryl alcohol, isostearyl alcohol, octyldodecanol, and oleyl alcohol, and a biocompatible polymer, optionally together with a matrix modifier and further optionally dispersive silica, to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent; (iii) at least one carrier; (iv) at least one disintegrant; and (v) memantine base

generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above.

[0029] In another example a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer comprising a higher alcohol and a biocompatible polymer selected from the group consisting of polyisobutylene (PIB), a silicone polymer, acrylate copolymers, butyl rubber, polybutylene, styrene-iosprene-styrene block copolymers, styrene-butadiene-styrene block copolymers, ethylene-vinyl acetate (EVA), a mixture thereof or a copolymer thereof, optionally together with a matrix modifier and further optionally dispersive silica, to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent; (iii) at least one carrier; (iv) an optional disintegrant; and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above. In some examples, the biocompatible polymer comprises polyisobutylene or a blend or mixture of polyisobutylene and polybutene.

[0030] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer comprising a higher alcohol and a biocompatible polymer, optionally together with a matrix modifier selected from the group consisting of cross-linked polyvinylpyrrolidone (PVP), soluble PVP, cellulose derivatives, polyacrylamide, polyacrylic acid and clay, and further optionally dispersive silica, to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent; (iii) at least one carrier; (iv) at least one disintegrant; and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above. In some examples, the matrix modifier is a cross-linked polyvinylpyrrolidone.

[0031] In another example, a transdermal delivery system for systemic delivery of memantine comprises (a) a skin contact adhesive layer comprising a higher alcohol and a biocompatible polymer, optionally together with a matrix modifier, and further optionally pharmaceutical grade amorphous anhydrous colloidal silicon dioxide, to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise

memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent; (iii) at least one carrier; (iv) at least one disintegrant; and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) one or more additional backing layers, as detailed above.

[0032] In another example, transdermal delivery systems for systemic delivery of memantine are provided. The delivery system comprises (a) a skin contact adhesive layer to attach the transdermal delivery system to the skin of a user, the skin contact adhesive layer comprising an adhesive formulation that does not comprise memantine; (b) optionally, an intermediate layer directly on the contact adhesive layer; (c) a drug reservoir layer on the intermediate layer, the drug reservoir layer comprised of (i) an acrylate polymer, (ii) at least one dissolving agent, (iii) at least one carrier, (iv) at least one disintegrant, and (v) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; and (d) a first backing layer in contact with the adhesive matrix drug reservoir layer; an adhesive overlay comprising polyisobutylene, polybutene or a mixture thereof in contact with the first backing layer; and a second backing layer in contact with the adhesive overlay. In one particular example, the adhesive overlay is comprised of a first layer and a second layer, the first layer composed of a polyisobutylene, polybutene or a mixture thereof and the second layer composed of an acrylic adhesive. In another example, the adhesive overlay is fused to the drug reservoir matrix, layered on top of the reservoir matrix, or separated from the reservoir matrix by at least one intermediate layer. In another example, the adhesive overlay is a single layer comprised of an acrylate polymer or copolymer.

[0033] In a related example, compositions comprising solid monolithic drug reservoir comprising (i) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; (ii) a carrier and (iii) an acrylate polymer are provided. In one example, the carrier is glycerol.

[0034] In another example, compositions comprising an adhesive matrix comprising (i) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; (ii) at least one carrier; (iii) an acrylate polymer; and at least one dissolving agent are provided. In some examples, the dissolving agent is a higher alcohol selected from the group consisting of lauryl alcohol, isostearyl alcohol, octyldodecanol, and oleyl alcohol.

[0035] In another example, compositions comprising an adhesive matrix comprising (i) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; (ii) at least

one carrier and (iii) an acrylate polymer, wherein adhesive matrix comprises a crosslinked polyvinylpyrrolidone are provided.

[0036] In another example, an adhesive matrix comprising (i) memantine base generated *in situ* by reaction of memantine hydrochloride with an alkaline salt selected from the group consisting of sodium acetate, sodium borate, sodium metaborate, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, potassium citrate, potassium acetate, sodium phosphate, potassium phosphate, disodium hydrogen phosphate, sodium oxylate, sodium succinate, sodium citrate, and sodium salicylate; (ii) a carrier; and (iii) an acrylate polymer is provided.

[0037] In yet another example, compositions comprising an adhesive matrix or polymeric solid monolith consisting essentially of a memantine base generated *in situ* by reaction of a salt of memantine and an alkaline salt; at least one dissolving agent; at least one carrier; and a polymeric, adhesive matrix comprising crosslinked polyvinylpyrrolidone and an acrylate polymer are provided.

[0038] In one example, compositions comprising a drug reservoir consisting essentially of (a) memantine base generated *in situ* by reaction of between about 5-50 wt% or 10-30 wt% memantine salt and between about 5-15 wt% alkaline salt; (b) about 5-15 wt% dissolving agent; (c) about 5-15 wt% carrier; (d) about 10-30 wt% disintegrant; and (e) about 10-65 wt% or 20-65 wt% or 20-50 wt% acrylate copolymer are provided. In some examples, the memantine salt is memantine hydrochloride (memantine HCl); in some examples, the alkaline salt is sodium bicarbonate or potassium bicarbonate; in some examples, the dissolving agent is a higher alcohol selected from the group consisting of lauryl alcohol, isostearyl alcohol, octyldodecanol, and oleyl alcohol; in examples, the carrier is glycerol; in some examples, the disintegrant is crosslinked polyvinylpyrrolidone (PVP-CLM); in examples, the acrylate polymer comprises vinyl acetate and at least one acrylate selected from the group consisting of 2-ethylhexyl-acrylate, hydroxyethyl acrylate and glycidyl acrylate.

[0039] In another example, compositions comprising a drug reservoir consisting essentially of (a) memantine base generated in situ by reaction of between about 22-27wt% memantine salt and between about 7-12 wt% alkaline salt; (b) about 8-12 wt% dissolving agent; (c) about 8-12 wt% carrier; (d) about 13-17 wt% disintegrant; and (e) about 28-35 wt% acrylate polymer are provided. In examples, the memantine salt is memantine hydrochloride (memantine HCl); in some examples, the alkaline salt is sodium bicarbonate or potassium bicarbonate; in some examples, the dissolving agent is a higher alcohol selected from the group consisting of lauryl alcohol, isostearyl alcohol, octyldodecanol, and oleyl alcohol; in some examples, the carrier is glycerol; in some examples, the disintegrant is crosslinked polyvinylpyrrolidone (PVP-CLM); in

some examples, the acrylate polymer comprises vinyl acetate and at least one acrylate selected from the group consisting of 2-ethylhexyl-acrylate, hydroxyethyl acrylate and glycidyl acrylate.

[0040] In another example, compositions comprising (a) one or more of the aforementioned drug reservoirs; (b) a rate controlling membrane or a non-woven layer; and (c) an adhesion matrix; and (d) optionally a permeation enhancer are provided. In some examples, the rate controlling membrane is a microporous polypropylene membrane.

[0041] In one example, the microporous membrane has a plurality of pores. The plurality of pores in the microporous membrane contain a solvent or a solvent composition. In one example, the solvent composition in the pores of the microporous membrane is comprised of one or more of the solvents present in either or both of the drug reservoir and the contact adhesive, exclusive of the hydrophilic solvent or carrier in the drug reservoir.

[0042] In another example, compositions comprising (a) one or more of the aforementioned drug reservoirs; (b) a rate controlling membrane or a non-woven layer; and (c) an adhesion matrix comprising a higher alcohol and a biocompatible polymer, optionally together with a matrix modifier and further optionally dispersive silica are provided. In some examples, the adhesion matrix comprises the higher alcohol, the biocompatible polymer and the matrix modifier. In some examples, the adhesion matrix comprises the higher alcohol, the biocompatible polymer and the dispersive silica. In some examples, the adhesion matrix does not comprise the hydrophilic solvent or carrier in the drug reservoir, and in a specific example does not comprise glycerol.

[0043] In a related example, compositions comprising (a) one or more of the aforementioned drug reservoirs; (b) a rate controlling membrane or a non-woven layer; and (c) an adhesion matrix comprising a higher alcohol selected from the group consisting of lauryl alcohol, isostearyl alcohol, octyldodecanol, and oleyl alcohol and a biocompatible polymer comprising polyisobutylene (PIB), silicone polymers, acrylate copolymers, butyl rubber, polybutylene, styrene-iosprene-styrene block copolymers, styrene-butadiene-styrene block copolymers, ethylene-vinyl acetate (EVA), or a mixture thereof or a copolymer thereof, optionally together with a matrix modifier selected from the group consisting of cross-linked polyvinylpyrrolidone (PVP), soluble PVP, cellulose derivatives, polyacrylamide, polyacrylic acid and clay and further optionally high purity amorphous anhydrous colloidal silicon dioxide are provided.

[0044] In one particular example, compositions comprising (a) one or more of the aforementioned drug reservoirs; (b) a rate controlling membrane or a non-woven layer; and (c) an adhesion matrix comprising about 5-15 wt% of a higher alcohol and about 50-95 wt% of a biocompatible polymer, optionally together with about 10-30 wt% of a matrix modifier and further

optionally about 4-12 wt% of dispersive silica are provided. In some examples, the adhesion matrix comprises a higher alcohol which is octyldodecanol, a biocompatible polymer comprising polyisobutylene, and optionally a matrix modifier comprising cross-linked polyvinylpyrrolidone (PVP) and further optionally dispersive silica comprising high purity amorphous anhydrous colloidal silicon dioxide.

[0045] In another particular example, compositions comprising (a) one or more of the aforementioned drug reservoirs; (b) a rate controlling membrane or a non-woven layer; and (c) an adhesion matrix comprising about 8-12 wt% of a higher alcohol and about 65-90 wt% of a biocompatible polymer, optionally together with about 15-25 wt% of a matrix modifier and further optionally about 5-10 wt% of dispersive silica are provided. In some examples, the adhesion matrix comprises a higher alcohol which is octyldodecanol, a biocompatible polymer comprising polyisobutylene, and optionally a matrix modifier comprising cross-linked polyvinylpyrrolidone (PVP) and further optionally dispersive silica comprising high purity amorphous anhydrous colloidal silicon dioxide.

[0046] In a related example, kits comprising, in one or more packages, (a) one or more of the aforementioned drug reservoirs; (b) a rate controlling membrane or a non-woven layer; and (c) an adhesion matrix, optionally together with instructions for assembling components (a)–(c) into a delivery system, and additionally or optionally together with instructions for administering the composition or the delivery system to a subject in need thereof are provided.

[0047] In an additional example, a kit comprising, in one or more packages, (i) a composition comprising (a) a drug reservoir comprised of an adhesive matrix comprising (i) memantine base generated *in situ* by reaction of a salt of memantine with an alkaline salt; (ii) a carrier, and (iii) an acrylate polymer; (b) a rate controlling membrane or a non-woven layer; and (c) an adhesion matrix, (ii) instructions for assembling the components into a delivery system, and/or (iii) instructions for administering the composition or the delivery system to a subject in need thereof.

[0048] In a further example, methods for delivering memantine to a subject in need thereof comprising contacting a tissue of the subject with a transdermal delivery system as described herein or a transdermal delivery system comprising a composition as described herein are provided. In a particular example, the tissue is skin tissue, *e.g.*, cutaneous skin tissue or mucous skin tissue. In examples, the subject is a human subject who is suffering from or has been diagnosed with a CNS disorder, *e.g.*, Alzheimer's disease, vascular dementia or a combination thereof.

Claims:

1. A composition, comprising: a drug reservoir consisting essentially of:

a salt of memantine and an alkaline salt; a permeation enhancer; a hydrophilic solvent carrier; a crosslinked polyvinylpyrrolidone and an acrylate copolymer, wherein, after application of the composition to the skin of a subject, memantine base is generated in situ by reaction of the salt of memantine and the alkaline salt.

2. The composition of claim 1, wherein the hydrophilic solvent carrier is glycerol.

3. The composition of claim 1, wherein the permeation enhancer is a higher alcohol selected from the group consisting of lauryl alcohol, isostearyl alcohol, octyldodecanol, and oleyl alcohol.

4. The composition of any one of claims 1-3, wherein the salt of memantine is memantine hydrochloride and the alkaline salt is selected from the group consisting of sodium acetate, sodium borate, sodium metaborate, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, potassium citrate, potassium acetate, sodium phosphate, potassium phosphate, disodium hydrogen phosphate, sodium oxylate, sodium succinate, sodium citrate, and sodium salicylate.

5. The composition of claim 1, wherein memantine base is generated in situ in the drug reservoir over a 3-5 day period.

6. The composition of claim 1, wherein the salt of memantine is memantine hydrochloride and the alkaline salt is sodium bicarbonate.

7. The composition of claim 6, wherein the drug reservoir comprises a molar amount of memantine hydrochloride and an equimolar or less than equimolar amount of sodium bicarbonate.

8. The composition of claim 7, wherein the drug reservoir comprises between about 10-30 wt% memantine hydrochloride.

9. The composition of claim 7, wherein the drug reservoir comprises between about 22-27 wt% memantine hydrochloride.

10. The composition of claim 7, wherein the drug reservoir comprises between about 5-15 wt% sodium bicarbonate.

11. The composition of claim 1, further comprising a skin contact adhesive comprised of polyisobutylene (PIB), polybutylene, or a mixture thereof.

12. The composition of claim 11, wherein the skin contact adhesive comprises (i) about 5-15 wt% octyldodecanol; (ii) a mixture of polyisobutylene and polybutylene; and optionally (iii) about 10-30 wt% cross-linked PVP.

13. The composition of claim 11, wherein the skin contact adhesive comprises, (i) about 8-12 wt% octyldodecanol; (ii) about 65-90 wt% of a mixture of polyisobutylene and polybutylene; and optionally (iii) about 15-25 wt% cross-linked PVP.

14. A composition, comprising: a drug reservoir consisting essentially of:

(a) between about 10-30 wt% memantine HCl and between about 5-15 wt% sodium bicarbonate;

(b) about 5-15 wt% octyldodecanol;

(c) about 5-15 wt% glycerol;

(d) about 10-30 wt% crosslinked polyvinylpyrrolidone; and

(e) about 20-50 wt% acrylate polymer.

wherein, after application of the composition to the skin of a subject, memantine base is generated in situ by reaction of the memantine HCl and the sodium bicarbonate.

15. Use of a composition according to any one of claims 1-14 in the manufacture of a medicament for treating a subject with a CNS disorder.

16. The use according to claim 15, wherein the CNS disorder is Alzheimer's disease.