CLAIMS

What is claimed is:

1. A method for improving the stability of a pharmaceutical composition which comprises a high penetration drug substance and a pharmaceutically acceptable carrier, the method comprising:

packaging the high penetration drug substance and the pharmaceutically acceptable carrier in separate containers; and

reconstituting a solution of the pharmaceutical composition by mixing the high penetration drug substance with the pharmaceutically acceptable carrier prior to administration to a patient in need thereof;

characterized in that the pH of the reconstitution solution of the pharmaceutical composition is kept within the range of 2 to 6.

2. The method according to claim 1, wherein the high penetration drug substance comprises one or two protonated amine groups in its molecule, wherein the high penetration drug substance is to be administered ~~when being administered~~ to the patient in need thereof.

3. The method according to claim 1 or 2, wherein the pharmaceutically acceptable carrier is an aqueous carrier.

4. The method according to any one of claims 1 to 3, wherein the pharmaceutically acceptable carrier is water, alcohol, acetone, DMSO, or a mixture thereof.

5. The method according to any one of claims 1 to 4, wherein the pharmaceutically acceptable carrier is an aqueous solution containing 0-70% ethanol by volume.

6. The method according to any one of claims 1 to 5, wherein the pharmaceutically acceptable carrier is an aqueous solution containing 10-35% ethanol by volume.

7. The method according to any one of claims 1 to 6, wherein the reconstitution solution is to be applied transdermally as a spray solution.

8. The method according to any one of claims 1 to 7, further comprising storing the reconstitution solution in a refrigerator at a temperature of 2-8°C.

9. The method according to any one of claims 1 to 8, wherein the pharmaceutical composition further comprises a pH adjusting and buffering agent in the pharmaceutically acceptable carrier.

10. The method according to claim 9, wherein the high penetration drug is high penetration peptide; and the pH adjusting and buffering agent is a sodium, potassium, calcium, lithium, or magnesium salt of an organic acid.

11. The method according to claim 9, wherein the pH adjusting and buffering agent is sodium, potassium, or lithium salt of an organic acid selected from the group consisting of acetic acid, propionic acid, butyric acid, valeric acid, benzoic acid, lactic acid, salicylic acid, citric acid, ascorbic acid, succinic acid, and maleic acid.

12. The method according to any one of claims 1 to 11, wherein the pH of the reconstitution solution of the pharmaceutical composition is in the range of 3 to 6.

13. The method according to any one of claims 1 to 12, wherein the pH of the reconstitution solution of the pharmaceutical composition is in the range of 3 to 5.

14. The method according to any one of claims 1 to 13, wherein the pH of the reconstitution solution of the pharmaceutical composition is 3.5-4.5.

15. The method according to any one of claims 1 to 14, wherein the concentration of the high penetration drug in the reconstitution solution is in the range of 1%-30% by weight.

16. The method according to any one of claims 1 to 15, wherein the concentration of the high penetration drug in the reconstitution solution is in the range of 1%-20% by weight.

17. The method according to any one of claims 1 to 16, wherein the concentration of the high penetration drug in the reconstitution solution is in the range of 3%-10% by weight.

18. The method according to any one of claims 1 to 17, wherein the high penetration drug substance is selected from the group consisting of 2-(diethylamino)ethyl 2-(6-methoxy-2-naphthyl) propionate.HCl, 2-(diethylamino)ethyl (*R,S*)-2-(2-fluoro-4-biphenyl)propionate.HCl, 2-(diethylamino)ethyl 2-(*p*-isobutylphenyl)propionate.HCl, 2-(diethylamino)ethyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetate.HCl, 2-(diethylamino)ethyl 5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1*H*-indene-3-acetate.HCl, 2-(diethylamino)ethyl 1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrole-2-acetate.HCl, 2-(diethylamino)ethyl 5-(4-chlorobenzoyl)-1,4-dimethyl-1*H*-pyrrole-2-acetate.HCl, 2-(diethylamino)ethyl 3-(6-methoxy-2-naphthyl)propionate.HCl, 2-(diethylamino)ethyl 4-(4-chlorophenyl)-2-phenyl-5-thiazoleacetate.HCl, 2-(diethylamino)ethyl 1-(4-chlorobenzoyl-5-methoxy-2-methyl-1H-indole-3-acetoxyacetate.HCl, 2-(diethylamino)ethyl [(1-benzyl-1*H*-indazol-3-yl)oxy]acetate.HCl, 2-(diethylamino)ethyl 2-[(4-chlorophenyl)-5-benzoxazole]propionate.HCl, 2-(diethylamino)ethyl 4,5-diphenyl-2-oxazolepropionate.HCl, 2-(diethylamino)ethyl 4-

[bis(2-chloroethyl)amino]benzenebutyrate.HCl, 2-(diethylamino)ethyl 4-[bis(2-methylsulfonylethyl)amino]benzenebutyrate.HCl, 2-(diethylamino)ethyl acetylsalicylate.HCl, and 2-(diethylamino)ethyl 5-(2,4-difluorophenyl)-2-acetoxybenzoate.HCl.

19. The method according to any one of claims 1 to 13 and 15 to 18, wherein the concentration of the high penetration drug in the reconstitution solution is 3-8% by weight, the pH of reconstitution solution is 3-5, and the pharmaceutically acceptable carrier is 15-35% ethanol in water by volume.

20. The method according to any one of claims 1 to 17, wherein the high penetration drug is selected from the group consisting of H-Val-Pro-Gly-Pro-Arg(NO_2)-OCH(CH_3)$_2$.HCl, H-Ala-Pro-Gly-Pro-Arg(NO_2)-OCH$_2$CH$_3$.HCl, H-Val-Pro-Asp[OCH(CH_3)$_2$]-Pro-Arg(NO_2)-OCH(CH_3)$_2$.HCl, H-Tyr-Gly-Gly-Phe-Leu-OCH(CH_3)$_2$.HCl, and H-Tyr-Gly-Gly-Phe-Met-OCH(CH_3)$_2$.HCl.

21. The method according to claim 20, wherein the concentration of the high penetration drug in the reconstitution solution is 3-8%, the pH of reconstitution solution is 3-5, the pH adjusting and buffering agent is sodium acetate, and the pharmaceutically acceptable carrier is 15-35% ethanol in water by volume.

22. A pharmaceutical composition obtained from any one of the preceding claims 1 to 21.

23. Use of ~~A method of treating a disease or disorder in a subject in need thereof, comprising administering to the subject~~ a therapeutically effective amount of a pharmaceutical composition of claim 22 in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

24. The ~~method~~ use of claim 23, wherein the pharmaceutical composition is a freshly prepared reconstitution solution by mixing the high penetration drug substance with the pharmaceutically acceptable carrier from separate containers.

25. The ~~method~~ use of claim 23 or 24, wherein the disease or disorder is selected from the group consisting of stroke, arthritis, depression, Alzheimer's disease, Parkinson's disease, migraine, sexual dysfunction, sepsis, drug-resistant bacterial infections, epilepsy, diabetes, psoriasis, lupus erythematosus, ulcerative enteritis, asthma, lower and upper respiratory tract infections, allergic rhinitis, allergic conjunctivitis, itchiness, and runny nose.

26. A treatment kit comprising: a high penetration drug substance in a first container, a pharmaceutically acceptable carrier in a second container, and a pH adjusting and buffering agent in the first container, the second container, or a separate third container, wherein the

high penetration drug substance comprises one or two protonated amine groups, and wherein the high penetration drug substance, the pharmaceutically acceptable carrier, and the pH adjusting and buffering agent can be mixed together to form a reconstitution solution ready for administration to a subject in need thereof, wherein the reconstitution solution has a pH in the range of 2 to 6 and is stable for storage at a temperature in the range of 2-20 °C for a period of time prior to administration to the subject in need thereof.

27. The kit of claim 26, wherein the high penetration drug substance is selected from the group consisting of 2-(diethylamino)ethyl 2-(6-methoxy-2-naphthyl) propionate.HCl, 2-(diethylamino)ethyl (*R,S*)-2-(2-fluoro-4-biphenyl)propionate.HCl, 2-(diethylamino)ethyl 2-(*p*-isobutylphenyl)propionate.HCl, 2-(diethylamino)ethyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetate.HCl, 2-(diethylamino)ethyl 5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1*H*-indene-3-acetate.HCl, 2-(diethylamino)ethyl 1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrole-2-acetate.HCl, 2-(diethylamino)ethyl 5-(4-chlorobenzoyl)-1,4-dimethyl-1*H*-pyrrole-2-acetate.HCl, 2-(diethylamino)ethyl 3-(6-methoxy-2-naphthyl)propionate.HCl, 2-(diethylamino)ethyl 4-(4-chlorophenyl)-2-phenyl-5-thiazoleacetate.HCl, 2-(diethylamino)ethyl 1-(4-chlorobenzoyl-5-methoxy-2-methyl-1H-indole-3-acetoxyacetate.HCl, 2-(diethylamino)ethyl [(1-benzyl-1*H*-indazol-3-yl)oxy]acetate.HCl, 2-(diethylamino)ethyl 2-[(4-chlorophenyl)-5-benzoxazole]propionate.HCl, 2-(diethylamino)ethyl 4,5-diphenyl-2-oxazolepropionate.HCl, 2-(diethylamino)ethyl 4-[bis(2-chloroethyl)amino]benzenebutyrate.HCl, 2-(diethylamino)ethyl 4-[bis(2-methylsulfonylethyl)amino]benzenebutyrate.HCl, 2-(diethylamino)ethyl acetylsalicylate.HCl, 2-(diethylamino)ethyl 5-(2,4-difluorophenyl)-2-acetoxybenzoate.HCl, H-Val-Pro-Gly-Pro-Arg(NO_2)-$OCH(CH_3)_2$.HCl, H-Ala-Pro-Gly-Pro-Arg(NO_2)-OCH_2CH_3.HCl, H-Val-Pro-Asp[$OCH(CH_3)_2$]-Pro-Arg(NO_2)-$OCH(CH_3)_2$.HCl, H-Tyr-Gly-Gly-Phe-Leu-$OCH(CH_3)_2$.HCl, and H-Tyr-Gly-Gly-Phe-Met-$OCH(CH_3)_2$.HCl; and the pharmaceutically acceptable carrier is a mixture of an aliphatic C_1-C_6 alcohol and water.

28. The kit of claim 26 or 27, wherein the concentration of the high penetration drug in the reconstitution solution is 3-8%, the pH of reconstitution solution is 3-5, the pH adjusting and buffering agent is sodium acetate, and the pharmaceutically acceptable carrier is 15-35% ethanol in water by volume.