IMPROVED DELIVERY OF LARGE AGENTS

Cross-Reference To Related Applications

[0001] This application claims priority to United States Provisional Patent Application Nos. 62/774,677, filed December 3, 2018, 62/789,407, filed January 7, 2019, and 62/808,274, filed February 20, 2019, the entire contents of all of which are hereby incorporated by reference in their entirety.

Background

[0002] Significant resources are invested in development of effective transdermal delivery technologies. Those skilled in the art are well aware of challenges associated with achieving effective transdermal delivery, particularly for large agents. As molecular size increases, transdermal penetration decreases, to the point where it is de minimis and even non-existent.

Summary

[0002a] In an aspect of the present disclosure, there is provided a use of an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater and a microneedle array having a microneedle density within a range of 2 to 50 microneedles/cm^2 in the manufacture of a kit for treating or preventing a disorder, wherein the emulsion composition is to be applied to a site in combination with microneedle skin conditioning (MSC) of the site with the microneedle array, and wherein the large agent is a botulinum toxin.

[0002b] In a further aspect of the present disclosure, there is provided a use of an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater and a microneedle array having a microneedle hole puncture size within a range of 100 to 35,000 μm^2/microneedle in the manufacture of a kit for treating or preventing a disorder, wherein the emulsion composition is to be applied to a site in combination with microneedle skin conditioning (MSC) of the site with the microneedle array, and wherein the large agent is a botulinum toxin.

[0002c] In a further aspect of the present disclosure, there is provided a use of an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater in the manufacture of a medicament for treating or preventing a disorder, wherein the medicament is to be administered to a site that has been conditioned with microneedle skin conditioning (MSC) with a microneedle array having a microneedle density within a range of 2 to 50 microneedles/cm^2, wherein the large agent is a botulinum toxin.

[0002d] In another aspect of the present disclosure, there is provided a use of an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater in the manufacture of a medicament for treating or preventing a disorder, wherein the medicament is to be administered to a site that has been conditioned with microneedle skin conditioning (MSC) with a microneedle array having a microneedle hole puncture size within a range of 100 to 35,000 μm^2/microneedle, wherein the large agent is a botulinum toxin.

[0002e] In a further aspect of the present disclosure, there is provided a use of an emulsion composition of a product volume of.0001 mls/cm^2 to 0.065 mls/cm^2 comprising a large agent having a molecular weight of 100,000 Da or greater and a microneedle array in the manufacture of a kit for treating or preventing a disorder, wherein the emulsion composition is to be applied to a site in combination with microneedle skin conditioning (MSC) of the site with the microneedle array, and wherein the large agent is a botulinum toxin.

[0002f] In another aspect of the present disclosure, there is provided a non-therapeutic method comprising a step of: applying an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater to a site in combination with microneedle skin conditioning (MSC) of the site with a microneedle array having a microneedle density within a range of 2 to 50 microneedles/cm^2, wherein the large agent is a botulinum toxin.

[0002g] In a further aspect of the present disclosure, there is provided a non-therapeutic method comprising a step of: applying an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater to a site in combination with microneedle skin conditioning (MSC) of the site with a microneedle array having a microneedle hole puncture size within a range of 100 to 35,000 μm^2/microneedle, wherein the large agent is a botulinum toxin.

[0002h] In another aspect of the present disclosure, there is provided a non-therapeutic method comprising a step of: applying an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater to a site that has been conditioned with microneedle skin conditioning (MSC) of the site with a microneedle array having a microneedle density within a range of 2 to 50 microneedles/cm^2, wherein the large agent is a botulinum toxin.

[0002i]In a further aspect of the present disclosure, there is provided a non-therapeutic method comprising a step of: applying an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater to a site that has been conditioned with microneedle skin conditioning (MSC) of the site with a microneedle array having a microneedle hole puncture size within a range of 100 to 35,000 μm^2/microneedle, wherein the large agent is a botulinum toxin.

[0002j]In a further aspect of the present disclosure, there is provided a non-therapeutic method comprising a step of: applying an emulsion composition of a product volume of.0001

mls/cm^2 to 0.065 mls/cm^2 comprising a large agent having a molecular weight of 100,000 Da or greater to a site in combination with microneedle skin conditioning (MSC) of the site with a microneedle array, wherein the large agent is a botulinum toxin.

[0003] Transdermal administration generally has been the subject of research in an attempt to provide an alternative route of administration of agents without undesirable consequences associated with injections and oral delivery. For example, needles often cause localized pain, bleeding and bruising, and potentially expose patients to transmissible diseases; oral administration can suffer from poor bioavailability of medications due to the extremely acidic environment of the patient's stomach. In some examples, transdermal delivery has a more even, regular, and/or consistent pharmacokinetic profile as compared with other routes of administration.

[0004] While having many advantages, transdermal drug delivery poses a number of logistical problems. Only a limited number of drugs have been shown to be administerable by this route. It has been difficult to transdermally deliver active agents including, but not limited to, hydrophilic molecules, large molecular structures (e.g., greater than a few hundred Daltons), genetic treatments, vaccines, etc. Prausnitz, M. R. & Langer, R. "Transdermal drug delivery," Nat Biotechnol. 26(11): 1261–1268 (2008).

[0005] The present disclosure provides improved technologies for transdermal delivery of agents of interest. In some examples, the present disclosure teaches that combination of certain microneedling technologies with topical application of a composition comprising a large agent, can

We claim:

1. Use of an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater and a microneedle array having a microneedle density within a range of 2 to 50 microneedles/cm^2 in the manufacture of a kit for treating or preventing a disorder, wherein the emulsion composition is to be applied to a site in combination with microneedle skin conditioning (MSC) of the site with the microneedle array, and wherein the large agent is a botulinum toxin.

2. The use of claim 1, wherein the microneedle density is within a range of 2 to 10 microneedles/cm^2.

3. The use of claim 1, wherein the microneedle density is within a range of 2 to 35 microneedles/cm^2.

4. The use of claim 1, wherein the emulsion composition comprising a large agent comprises a nanoemulsion comprising the large agent.

5. The use of claim 1, wherein the emulsion composition comprising a large agent comprises a macroemulsion comprising the large agent.

6. The use of any one of claims 1-5, wherein the kit further comprises a penetration enhancing agent.

7. The use of claim 6, wherein the penetration enhancing agent is selected from carrier peptides and co-peptides.

8. The use of any one of claims 6-7, wherein the penetration enhancing agent is selected from a cationic peptide and a positively charged carrier with the sequence RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR.

9. The use of any one of claims 1-8, wherein the MSC of the site is to be performed before the emulsion composition is to be applied to the site.

10. The use of any one of claims 1-8, wherein the MSC of the site is to be performed after the emulsion composition is to be applied to the site.

11. The use of claim any one of claims 1-8, wherein the MSC of the site and applying of the emulsion composition to the site occur at substantially the same time.

12. The use of any one of claims 1-11, wherein the kit further comprises a biologically active agent, and wherein the biologically active agent is to be delivered with botulinum toxin.

13. The use of claim 12, wherein the biologically active agent is selected from steroids, retinoids, anesthetics, fillers, silicone, and/or collagen.

14. The use of claim 13, wherein the biologically active agent is selected from hydrocortisone, retin A, and/or lidocaine.

15. The use of any of any one of claims 1-14, wherein the MSC of the site is accomplished with a device comprising a plurality of needles.

16. The use of claim 15, wherein the device is a patch, a roller, a stamp, or a pen.

17. The use of any one of claims 1-16, wherein the site is a skin surface overlying a muscle or muscle group of a subject.

18. The use of any one of claims 1-17, wherein the site is a skin surface that contains sweat glands.

19. The use of any one of claims 1-18, wherein the site is a skin surface that contains sebaceous glands.

20. The use of any one of claims 1-19, wherein the site is a skin surface that contains hair follicles.

21. The use of any one of claims 15-20, wherein the needles have a length sufficient to project through the stratum corneum of the skin.

22. The use of any one of claims 15-21, wherein the needles have a length insufficient to reach the nerves in the dermis of the skin.

23. The use of any one of claims 15-22, wherein the needles have a length between 10 μm and 4000 μm.

24. The use of any one of claims 15-23, wherein the needles have a length between 10 μm and 800 μm.

25. The use of any one of claims 15-24, wherein the needles have a length between 10 μm and 500 μm.

26. The use of any one of claims 15-23, wherein the needles have a length equal to or greater than 200 μm.

27. The use of any one of claims 15-26, wherein the needles have a length equal to or greater than 300 μm.

28. The use of any one of claims 15-27, wherein the needles have a length equal to or greater than 500 μm.

29. The use any one of claims 15-29, wherein the needles have a length equal to or greater than 200 μm, 300 μm, 500 μm, 800 μm, 1000 μm, 1100 μm, 1200 μm, 1300 μm, 1400 μm, 1500 μm, 1600 μm, 1700 μm, 1800 μm, 1900 μm, 2000 μm, 2100 μm, 2200 μm, 2300 μm, 2400 μm, 2500 μm, 2600 μm, 2700 μm, 2800 μm, 2900 μm, 3000 μm, 3100 μm, 3200 μm, 3300 μm, 3400 μm, 3500 μm, 3600 μm, 3700 μm, 3800 μm, or 3900 μm.

30. The use of any one of claims 15-29, wherein the needles are composed of a biocompatible material.

31. The use of any one of claims 15-29, wherein the needles are composed of a metal.

32. The use of any one of claims 1-31, wherein the MSC comprises administration of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 microneedle or microneedle array impressions, wherein each impression is the time the microneedle(s) is continuously applied to the skin.

33. The use of claim 32, wherein the microneedle array is rotated between one or more impressions.

34. The use of claim 32, wherein the microneedle array is not rotated between one or more impressions.

35. The use of any one of claims 32-34, wherein the impressions are to be made on approximately the same site.

36. The use of any one of claims 32-34, wherein the impressions are to be made on overlapping sites.

37. The use of any one of claims 32-34, wherein the impressions are to be made on different sites.

38. The use of any one of claims 32-37, wherein the microneedle array is in the form of a stamp or roller.

39. The use of claim 38, wherein the impressions are to be made by stamping or rolling.

40. The use of any one of claims 1-39, wherein the large agent penetrates the skin within 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration.

41. The use of any one of claims 1-39, wherein the large agent penetrates the skin within 5 to 60 minutes, 5 to 12 minutes, 5 to 15 minutes, or 15 to 30 minutes of administration.

42. The use of any one of claims 1-39, wherein the large agent penetrates the skin within 1, 2, 3, 4, 5, or 6 hours of administration.

43. The use of any one of claims 15-30, wherein the needles are composed of at least one dissolving polymer.

44. The use of any one of claims 1-43, wherein the emulsion composition comprises a large agent at a lower dose as compared to a reference treatment regimen with MSC of the site using a reference microneedle array having a microneedle density of greater than 50 microneedles/cm^2.

45. The use of any one of claims 1-44, wherein more than one dose of the emulsion composition comprising the large agent is to be administered over time.

46. The use of claim 45, wherein fewer doses of the emulsion composition comprising the large agent is to be administered over a fixed treatment dose interval as compared to the reference treatment regimen with MSC of the site using the reference microneedle array having a microneedle density of greater than 50 microneedles/cm^2 to generate comparable treatment effects.

47. The use of claim 45 or claim 46, wherein each dose of the emulsion composition comprising a large agent is separated by a specified period of time.

48. The use of claim 47, wherein the specified period of time is longer as compared to the specified period of time for administering the reference treatment regimen with MSC of the site using the reference microneedle array having a microneedle density of greater than 50 microneedles/cm^2.

49. The use of any one of claims 44-48, wherein the reference treatment regimen comprises administering the emulsion composition comprising a large agent with the reference microneedle array having a microneedle density of greater than 50 microneedles/cm^2.

50. The use of any one of claims 1-49, wherein the kit is for treating a dermatological disorder.

51. The use of claim 50, wherein the dermatological disorder is selected from acne, unwanted sweating , body odor, hyperhidrosis, bromhidrosis, chromhidrosis, rosacea, hair loss, Raynaud's Syndrome, psoriasis, actinic keratosis, eczematous dermatitis, excess sebum-producing disorders, burns, lupus erythematosus, hyperpigmentation disorders, hypopigmentation disorders, skin cancer, dermal infection, facial wrinkles, unsightly facial expressions, neck lines, hyperfunctional facial lines, hyperkinetic facial lines, platysma bands, and/or combinations thereof.

52. The use of any one of claims 1-50, wherein the kit is for treating or preventing a disorder selected from unwanted sweating, body odor, hyperhidrosis, bromhidrosis, chromhidrosis, hair loss, Raynaud's phenomenon, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, lupus erythematosus, systemic lupus , discoid lupus, drug-induced lupus, neonatal lupus, Crohn's disease, inflammatory bowel disease, ulcerative colitis, pulmonary disorders, asthma, chronic obstructive pulmonary disorder, amyloidosis, systemic amyloidosis, cutaneous amyloidosis, cancer, skin cancer, blood cancer, breast cancer, colon cancer, lung cancer, prostate hyperplasia, dyslipidemia, hypercholesterolemia, infection, *C. difficile* infection, *Staphylococcus* infection, dystonia, headache, pain, arthritis associated pain, rheumatoid arthritis associated pain, psoriatic arthritis associated pain, osteoarthritis associated pain, certain ophthalmologic conditions, certain urologic conditions, neuromuscular disorders, conditions involving muscular spasm and/or contracture, strabismus, hemifacial spasm, tremor, spasticity such as that resulting from multiple sclerosis, retroorbital muscle, neurologic conditions, migraine or other headaches, Alzheimer's Disease, Parkinson's Disease, or stroke.

53. The use of any one of claims 1-52, wherein the emulsion composition comprising a large agent is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

54. Use of an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater and a microneedle array having a microneedle hole puncture size within a range of 100 to 35,000 μm^2/microneedle in the manufacture of a kit for treating or preventing a disorder, wherein the emulsion composition is to be applied to a site in combination with microneedle skin conditioning (MSC) of the site with the microneedle array, and wherein the large agent is a botulinum toxin.

55. The use of claim 54, wherein the emulsion composition comprises a large agent at a lower dose as compared to a reference treatment regimen with MSC of the site using a reference microneedle array having a microneedle hole puncture size of greater than 35,000 μm^2 /microneedle.

56. The use of any one of claims 54-55, wherein more than one dose of the emulsion composition comprising the large agent is to be administered over time.

57. The use of claim 56, wherein fewer doses of the emulsion composition comprising the large agent is to be administered over a fixed treatment dose interval as compared to the reference treatment regimen with MSC of the site using the reference microneedle array having a microneedle hole puncture size of greater than 35,000 μm^2 /microneedle to generate comparable treatment effects.

58. The use of claim 56 or claim 57, wherein each dose of the emulsion composition comprising a large agent is separated by a specified period of time.

59. The use of claim 58, wherein the specified period of time is longer as compared to the specified period of time for administering the reference treatment regimen with MSC of the site using the reference microneedle array having the microneedle hole puncture size of greater than 35,000 μm^2 /microneedle.

60. The use of any one of claims 55-59, wherein the reference treatment regimen comprises administering the emulsion composition comprising a large agent with the reference microneedle array having a microneedle hole puncture size of greater than 35,000 μm^2 /microneedle.

61. Use of an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater in the manufacture of a medicament for treating or preventing a disorder, wherein the medicament is to be administered to a site that has been conditioned with microneedle skin conditioning (MSC) with a microneedle array having a microneedle density within a range of 2 to 50 microneedles/cm^2, wherein the large agent is a botulinum toxin.

62. Use of an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater in the manufacture of a medicament for treating or preventing a disorder, wherein the medicament is to be administered to a site that has been conditioned with microneedle skin conditioning (MSC) with a microneedle array having a microneedle hole puncture size within a range of 100 to 35,000 μm^2/microneedle, wherein the large agent is a botulinum toxin.

63. Use of an emulsion composition of a product volume of .0001 mls/cm^2 to 0.065 mls/cm^2 comprising a large agent having a molecular weight of 100,000 Da or greater and a microneedle array in the manufacture of a kit for treating or preventing a disorder, wherein the emulsion composition is to be applied to a site in combination with microneedle skin conditioning (MSC) of the site with the microneedle array, and wherein the large agent is a botulinum toxin.

64. The use of claim 63, wherein the product volume is within a range of .0001 mls/cm^2 to 0.05 mls/cm^2.

65. The use of claim 63, wherein the emulsion composition comprising a large agent comprises a nanoemulsion comprising the large agent.

66. The use of claim 63, wherein the emulsion composition comprising a large agent comprises a macroemulsion comprising the large agent.

67. The use of any one of claims 63-66, wherein the kit further comprises a penetration enhancing agent.

68. The use of claim 67, wherein the penetration enhancing agent is selected from carrier peptides and co-peptides.

69. The use of any one of claims 67-68, wherein the penetration enhancing agent is selected from a cationic peptide and a positively charged carrier with the sequence RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR.

70. The use of any one of claims 63-69, wherein the MSC of the site is to be performed before the emulsion composition comprising a large agent is to be applied to the site.

71. The use of any one of claims 63-69, wherein the MSC of the site is to be performed after the emulsion composition comprising a large agent is to be applied to the site.

72. The use of any one of claims 63-69, wherein the MSC of the site and applying the emulsion composition comprising a large agent to the site occur at substantially the same time.

73. The use of any one of claims 63-72, wherein the kit further comprises a biologically active agent, and wherein the biologically active agent is to be delivered with botulinum toxin.

74. The use of claim 73, wherein the biologically active agent is selected from steroids, retinoids, anesthetics, fillers, silicone, and/or collagen.

75. The use of claim 74, wherein the biologically active agent is selected from hydrocortisone, retin A, and/or lidocaine.

76. The use of any of any one of claims 63-75, wherein the MSC of the site is accomplished with a device comprising a plurality of needles.

77. The use of claim 76, wherein the device is a patch, a roller, a stamp, or a pen.

78. The use of any one of claims 63-77, wherein the site is a skin surface overlying a muscle or muscle group of a subject.

79. The use of any one of claims 63-78, wherein the site is a skin surface that contains sweat glands.

80. The use of any one of claims 63-79, wherein the site is a skin surface that contains sebaceous glands.

81. The use of any one of claims 63-80, wherein the site is a skin surface that contains hair follicles.

82. The use of any one of claims 76-81, wherein the needles have a length sufficient to project through the stratum corneum of the skin.

83. The use of any one of claims 76-82, wherein the needles have a length insufficient to reach the nerves in the dermis of the skin.

84. The use of any one of claims 76-83, wherein the needles are composed of a biocompatible material.

85. The use of any one of claims 76-83, wherein the needles are composed of a metal.

86. The use of any one of claims 63-85, wherein the microneedle array is rotated between one or more impressions.

87. The use of any one of claims 63-85, wherein the microneedle array is not rotated between one or more impressions.

88. The use of any one of claims 86-87, wherein the impressions are to be made on approximately the same site.

89. The use of any one of claims 86-87, wherein the impressions are to be made on overlapping sites.

90. The use of any one of claims 86-87, wherein the impressions are to be made on different sites.

91. The use of any one of claims 86-87, wherein the microneedle array is in the form of a stamp or roller.

92. The use of claim 91, wherein the impressions are to be made by stamping or rolling.

93. The use of any one of claims 63-92, wherein the large agent penetrates the skin within 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration.

94. The use of any one of claims 63-92, wherein the large agent penetrates the skin within 5 to 60 minutes, 5 to 12 minutes, 5 to 15 minutes, or 15 to 30 minutes of administration.

95. The use of any one of claims 63-92, wherein the large agent penetrates the skin within 1, 2, 3, 4, 5, or 6 hours of administration.

96. The use of any one of claims 76-84, wherein the needles are composed of at least one dissolving polymer.

97. The use of any one of claims 63, 65-96, wherein the emulsion composition comprises a large agent at a lower dose as compared to a reference treatment regimen with MSC of the site using a reference microneedle array having a microneedle length of greater than 700 μm.

98. The use of any one of claims 65-96, wherein the emulsion composition comprises a large agent at a lower dose as compared to a reference treatment regimen with MSC of the site using a reference microneedle array having a microneedle length of greater than 500 μm.

99. The use of any one of claims 63-98, wherein more than one dose of the emulsion composition comprising the large agent is to be administered over time.

100. The use of claim 99, wherein fewer doses of the emulsion composition comprising the large agent is to be administered over a fixed treatment dose interval as compared to the reference treatment regimen with MSC of the site using the reference microneedle array.

101. The use of claim 99 or claim 100, wherein each dose of the emulsion composition comprising a large agent is separated by a specified period of time.

102 The use of claim 101, wherein the specified period of time is longer as compared to the specified period of time for administering the reference treatment regimen with MSC of the site using the reference microneedle array.

103. The use of any one of claims 97, 99-102, wherein the reference treatment regimen comprises administering the emulsion composition comprising a large agent with the reference microneedle array having a microneedle length of greater than 700 μm.

104. The use of any one of claims 100-102, wherein the reference treatment regimen comprises administering the emulsion composition comprising a large agent with the reference microneedle array having a microneedle length of greater than 500 μm.

105. The use of any one of claims 61, 62, or 63-104, wherein the medicament or kit is for treating a dermatological disorder.

106. The use of claim 105, wherein the dermatological disorder is selected from acne, unwanted sweating , body odor, hyperhidrosis, bromhidrosis, chromhidrosis, rosacea, hair loss, Raynaud's Syndrome, psoriasis, actinic keratosis, eczematous dermatitis, excess sebum-producing disorders, burns, lupus erythematosus, hyperpigmentation disorders, hypopigmentation disorders, skin cancer, dermal infection, facial wrinkles, unsightly facial expressions, neck lines, hyperfunctional facial lines, hyperkinetic facial lines, platysma bands, and/or combinations thereof.

107. The use of any one of claims 61, 62, or 63-105, wherein the kit is for treating or preventing a disorder selected from unwanted sweating, body odor, hyperhidrosis, bromhidrosis, chromhidrosis, hair loss, Raynaud's phenomenon, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, lupus erythematosus, systemic lupus , discoid lupus, drug-induced lupus, neonatal lupus, Crohn's disease, inflammatory bowel disease, ulcerative colitis, pulmonary disorders, asthma, chronic obstructive pulmonary disorder, amyloidosis, systemic amyloidosis, cutaneous amyloidosis, cancer, skin cancer, blood cancer, breast cancer, colon cancer, lung cancer, prostate hyperplasia, dyslipidemia, hypercholesterolemia, infection, *C. difficile* infection, *Staphylococcus* infection, dystonia, headache,

pain, arthritis associated pain, rheumatoid arthritis associated pain, psoriatic arthritis associated pain, osteoarthritis associated pain, certain ophthalmologic conditions, certain urologic conditions, neuromuscular disorders, conditions involving muscular spasm and/or contracture, strabismus, hemifacial spasm, tremor, spasticity such as that resulting from multiple sclerosis, retroorbital muscle, neurologic conditions, migraine or other headaches, Alzheimer's Disease, Parkinson's Disease, or stroke.

108. The use of any one of claims 63-107, wherein the emulsion composition comprising a large agent is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

109. A non-therapeutic method comprising a step of:

applying an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater to a site in combination with microneedle skin conditioning (MSC) of the site with a microneedle array having a microneedle density within a range of 2 to 50 microneedles/$cm^{2,}$ wherein the large agent is a botulinum toxin.

110. A non-therapeutic method comprising a step of:

applying an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater to a site in combination with microneedle skin conditioning (MSC) of the site with a microneedle array having a microneedle hole puncture size within a range of 100 to 35,000 μm^2/microneedle, wherein the large agent is a botulinum toxin.

111. A non-therapeutic method comprising a step of:

applying an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater to a site that has been conditioned with microneedle skin conditioning (MSC) of the site with a microneedle array having a microneedle density within a range of 2 to 50 microneedles/cm^2, wherein the large agent is a botulinum toxin.

112. A non-therapeutic method comprising a step of:

applying an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater to a site that has been conditioned with microneedle skin conditioning (MSC)

of the site with a microneedle array having a microneedle hole puncture size within a range of 100 to 35,000 μm²/microneedle, wherein the large agent is a botulinum toxin.

113. A non-therapeutic method comprising a step of:

applying an emulsion composition of a product volume of .0001 mls/cm^2 to 0.065 mls/cm^2 comprising a large agent having a molecular weight of 100,000 Da or greater to a site in combination with microneedle skin conditioning (MSC) of the site with a microneedle array, wherein the large agent is a botulinum toxin.