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.

[0002b] In another aspect of the present disclosure, there is provided a patch comprising a composition comprising a large agent having a molecular weight of 100,000 Da or greater and a plurality of microneedles having a microneedle density within a range of 2 to 50 microneedles/cm^2.

[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 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.

[0002d] In another aspect of the present disclosure, there is provided a kit comprising an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater and a device for microneedle conditioning of a site, wherein the device is a microneedle array having a microneedle density within a range of 2 to 50 microneedles/cm^2.

[0002e] 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.

[0002f] 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.

[0002g] In a further aspect of the present disclosure, there is provided a kit comprising an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater and a device for microneedle conditioning of a site, wherein the device is a microneedle array having a microneedle hole puncture size within a range of 100 to 35,000 μm^2/microneedle.

[0002h] 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 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, wherein between 1 to 13 impressions of the microneedle array are to be made to the site.

[0002i] 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 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, wherein between 1 to 4 impressions of the microneedle array are to be made per square centimeter of the site.

[0002j] 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 and a

microneedle array having a microneedle length within a range of 1 μm to 700 μm 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.

[0002k] 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 length within a range of 1 μm to 500 μm 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.

[0002l] 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.

[0002m] 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.

[0002n] 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.

[0002o] 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.

[0002p] 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.

[0002q] 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 wherein between 1 to 13 impressions of the microneedle array are made to the site.

[0002r] 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 wherein between 1 to 4 impressions of the microneedle array are made per square centimeter of the site.

[0002s] 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 length within a range of 1 µm to 700 µm.

[0002t] 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 length within a range of 1 µm to 500 µm.

[0002u] 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.

[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.

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 large agent is a botulinum toxin.

13. The use of claim 12, wherein the kit further comprises a biologically active agent, and wherein the biologically active agent is to be delivered with botulinum toxin.

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

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

16. The use of any one of claims 1-11, wherein the large agent is an antibody agent.

17. The use of claim 16, wherein the antibody agent is selected from an anti-TNFα antibody, an anti-CD2 antibody, an anti-CD4 antibody, an anti-IL-12 antibody, an anti-IL-17 antibody, an anti-IL-22 antibody, and an anti-IL-23 antibody.

18. The use of any one of claims 16-17, wherein the antibody agent is selected from an antibody having epitope binding elements found in one or more of infliximab, adalimumab, golimumab, etanercept, etanercept-szzs, certolizumab pegol, siplizumab, zanolimumab, briakinumab, secukinumab, brodalumab, fezakinumab, ustekinumab and/or guselkumab.

19. The use of any one of claims 16-17, wherein the kit further comprises a biologically active agent, and wherein the biologically active agent is to be delivered with the antibody agent.

20. The use of any one of claims 16-19, wherein the kit further comprises a penetration enhancing agent, and wherein the penetration enhancing agent is to be delivered with the antibody agent.

21. The use of claim 20, wherein the penetration enhancing agent is selected from co-peptides, and carrier peptides.

22. The use of any of any one of claims 1-21, wherein the MSC of the site is accomplished with a device comprising a plurality of needles.

23. The use of claim 22, wherein the device is a patch, a roller, a stamp, or a pen.

24. The use of any one of claims 1-23, wherein the site is a skin surface overlying a muscle or muscle group of a subject.

25. The use of any one of claims 1-24, wherein the site is a skin surface that contains sweat glands.

26. The use of any one of claims 1-25, wherein the site is a skin surface that contains sebaceous glands.

27. The use of any one of claims 1-26, wherein the site is a skin surface that contains hair follicles.

28. The use of any one of claims 22-27, wherein the needles have a length sufficient to project through the stratum corneum of the skin.

29. The use of any one of claims 22-28, wherein the needles have a length insufficient to reach the nerves in the dermis of the skin.

30. The use of any one of claims 22-29, wherein the needles have a length between 10 μm and 4000 μm.

31. The use of any one of claims 22-30, wherein the needles have a length between 10 μm and 800 μm.

32. The use of any one of claims 22-31, wherein the needles have a length between 10 μm and 500 μm.

33. The use of any one of claims 22-30, wherein the needles have a length equal to or greater than 200 μm.

34. The use of any one of claims 22-33, wherein the needles have a length equal to or greater than 300 μm.

35. The use of any one of claims 22-34, wherein the needles have a length equal to or greater than 500 μm.

36. The use any one of claims 22-30, 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.

37. The use of any one of claims 22-36, wherein the needles are composed of a biocompatible material.

38. The use of any one of claims 22-36, wherein the needles are composed of a metal.

39. The use of any one of claims 1-38, 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.

40. The use of claim 39, wherein the microneedle array is rotated between one or more impressions.

41. The use of claim 39, wherein the microneedle array is not rotated between one or more impressions.

42. The use of any one of claims 39-41, wherein the impressions are to be made on approximately the same site.

43. The use of any one of claims 39-41, wherein the impressions are to be made on overlapping sites.

44. The use of any one of claims 39-41, wherein the impressions are to be made on different sites.

45. The use of any one of claims 39-44, wherein the microneedle array is in the form of a stamp or roller.

46. The use of claim 45, wherein the impressions are to be made by stamping or rolling.

47. The use of any one of claims 1-46, wherein the large agent penetrates the skin within 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration.

48. The use of any one of claims 1-46, 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.

49. The use of any one of claims 1-46, wherein the large agent penetrates the skin within 1, 2, 3, 4, 5, or 6 hours of administration.

50. The use of any one of claims 22-37, wherein the needles are composed of at least one dissolving polymer.

51. The use of any one of claims 1-50, 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.

52. The use of any one of claims 1-51, wherein more than one dose of the emulsion composition comprising the large agent is to be administered over time.

53. The use of claim 52, 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.

54. The use of claim 52 or claim 53, wherein each dose of the emulsion composition comprising a large agent is separated by a specified period of time.

55. The use of claim 54, 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.

56. The use of any one of claims 51-55, 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.

57. The use of any one of claims 1-56, wherein the kit is for treating a dermatological disorder.

58. The use of claim 57, 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.

59. The use of any one of claims 1-57, 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.

60. The use of any one of claims 1-59, wherein the emulsion composition comprising a large agent is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

61. A patch comprising an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater and a plurality of microneedles having a microneedle density within a range of 2 to 50 microneedles/cm^2.

62. The patch of claim 61, wherein the emulsion composition comprising a large agent comprises a nanoemulsion.

63. The patch of claim 61, wherein the emulsion composition comprising a large agent comprises a macroemulsion.

64. The patch of any one of claims 61-63, wherein the needles have a length sufficient to project through the stratum corneum of the skin.

65. The patch of any one of claims 62-64, wherein the needles have a length insufficient to reach the nerves in the dermis of the skin.

66. The patch of any one of claims 62-65, wherein the needles have a length between 10 and 4000 μm.

67. The patch of any one of claims 62-66, wherein the needles have a length equal to or greater than 200 μm.

68. The patch of any one of claims 62-67, wherein the needles have a length equal to or greater than 300 μm.

69. The patch of any one of claims 62-68, wherein the needles have a length equal to or greater than 500 μm.

70. The patch of any one of claims 62-69, wherein the needles are composed of a biocompatible material.

71. The patch of any one of claims 62-70, wherein the needles are composed of a metal.

72. The patch of any one of claims 62-70, wherein the needles are composed of a dissolving polymer.

73. The patch of any one of claims 62-72, wherein the large agent has a molecular weight of 100 KDa or more.

74. The patch of any one of claims 62-73, wherein the large agent is a botulinum toxin.

75. The patch of any one of claims 62-73, wherein the large agent is an antibody agent.

76. 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.

77. The use of claim 76, 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 μm² /microneedle.

78. The use of any one of claims 76-77, wherein more than one dose of the emulsion composition comprising the large agent is to be administered over time.

79. The use of claim 78, 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 μm² /microneedle to generate comparable treatment effects.

80. The use of claim 78 or claim 79, wherein each dose of the emulsion composition comprising a large agent is separated by a specified period of time.

81. The use of claim 80, 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 μm² /microneedle.

82. The use of any one of claims 77-81, 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 μm² /microneedle.

83. A kit comprising an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater and a device for microneedle conditioning of a site, wherein the device is a microneedle array having a microneedle density within a range of 2 to 50 microneedles/cm^2.

84. The kit of any one of claim 83, wherein the emulsion composition comprising a large agent comprises a nanoemulsion.

85. The kit of claim 83 or claim 84, wherein the emulsion composition comprising a large agent comprises a macroemulsion.

86. The kit of any one of claims 83-85, wherein the device is a patch, a roller, a stamp, or a pen.

87. The kit of any one of claims 83-86, comprising a patch of any one of claims 61-75.

88. The kit of claim 83, wherein the emulsion composition comprising a large agent is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

89. 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.

90. 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.

91. A kit comprising an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater and a device for microneedle conditioning of a site, wherein the device is a microneedle array having a microneedle hole puncture size within a range of 100 to 35,000 μm^2/microneedle.

92. The kit of any one of claim 91, wherein the emulsion composition comprising a large agent comprises a nanoemulsion.

93. The kit of claim 91 or claim 92, wherein the emulsion composition comprising a large agent comprises a macroemulsion.

94. The kit of any one of claims 91-93, wherein the device is a patch, a roller, a stamp, or a pen.

95. The kit of any one of claims 91-94, comprising a patch of any one of claims 61-75.

96. The kit of claim 91, wherein the emulsion composition comprising a large agent is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

97. Use of an emulsion composition 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, wherein between 1 to 13 impressions of the microneedle array are to be made to the site.

98. Use of an emulsion composition 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, wherein between 1 to 4 impressions of the microneedle array are to be made per square centimeter of the site.

99. The use of claim 98, wherein between 1 to 3 impressions of the microneedle array are to be made per square centimeter of the site.

100. The use of claim 98, wherein between 1 to 2 impressions of the microneedle array are to be made per square centimeter of the site.

101. 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 length within a range of 1 µm to 700 µm 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.

102. 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 length within a range of 1 µm to 500 µm 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.

103. 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.

104. The use of claim 103, wherein the product volume is within a range of .0001 mls/cm^2 to 0.05 mls/cm^2.

105. The use of any one of claims 101-103, wherein the emulsion composition comprising a large agent comprises a nanoemulsion comprising the large agent.

106. The use of any one of claims 101-103, wherein the emulsion composition comprising a large agent comprises a macroemulsion comprising the large agent.

107. The use of any one of claims 101-106, wherein the kit further comprises a penetration enhancing agent.

108. The use of claim 107, wherein the penetration enhancing agent is selected from carrier peptides and co-peptides.

109. The use of any one of claims 107-108, wherein the penetration enhancing agent is selected from a cationic peptide and a positively charged carrier with the sequence RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR.

110. The use of any one of claims 101-109, 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.

111. The use of any one of claims 101-109, 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.

112. The use of claim any one of claims 101-109, wherein the MSC of the site and applying the emulsion composition comprising a large agent to the site occur at substantially the same time.

113. The use of any one of claims 101-112, wherein the large agent is a botulinum toxin.

114. The use of claim 113, wherein the kit further comprises a biologically active agent, and wherein the biologically active agent is to be delivered with botulinum toxin.

115. The use of claim 114, wherein the biologically active agent is selected from steroids, retinoids, anesthetics, fillers, silicone, and/or collagen.

116. The use of claim 115, wherein the biologically active agent is selected from hydrocortisone, retin A, and/or lidocaine.

117. The use of any one of claims 101-112, wherein the large agent is an antibody agent.

118. The use of claim 117, wherein the antibody agent is selected from an anti-TNFα antibody, an anti-CD2 antibody, an anti-CD4 antibody, an anti-IL-12 antibody, an anti-IL-17 antibody, an anti-IL-22 antibody, and an anti-IL-23 antibody.

119. The use of any one of claims 117-118, wherein the antibody agent is selected from an antibody having epitope binding elements found in one or more of infliximab, adalimumab, golimumab, etanercept, etanercept-szzs, certolizumab pegol, siplizumab, zanolimumab, briakinumab, secukinumab, brodalumab, fezakinumab, ustekinumab and/or guselkumab.

120. The use of any one of claims 117-119, wherein the kit further comprises a biologically active agent, and wherein the biologically active agent is to be delivered with the antibody agent.

121. The use of any one of claims 117-120, wherein the kit further comprises a penetration enhancing agent, and wherein the penetration enhancing agent is to be delivered with the antibody agent.

122. The use of claim 121, wherein the penetration enhancing agent is selected from co-peptides, and carrier peptides.

123. The use of any of any one of claims 101-122, wherein the MSC of the site is accomplished with a device comprising a plurality of needles.

124. The use of claim 123, wherein the device is a patch, a roller, a stamp, or a pen.

125. The use of any one of claims 101-124, wherein the site is a skin surface overlying a muscle or muscle group of a subject.

126. The use of any one of claims 101-125, wherein the site is a skin surface that contains sweat glands.

127. The use of any one of claims 101-126, wherein the site is a skin surface that contains sebaceous glands.

128. The use of any one of claims 101-127, wherein the site is a skin surface that contains hair follicles.

129. The use of any one of claims 123-128, wherein the needles have a length sufficient to project through the stratum corneum of the skin.

130. The use of any one of claims 123-129, wherein the needles have a length insufficient to reach the nerves in the dermis of the skin.

131. The use of any one of claims 123-130, wherein the needles are composed of a biocompatible material.

132. The use of any one of claims 123-130, wherein the needles are composed of a metal.

133. The use of any one of claims 101-132, wherein the microneedle array is rotated between one or more impressions.

134. The use of any one of claims 101-132, wherein the microneedle array is not rotated between one or more impressions.

135. The use of any one of claims 133-134, wherein the impressions are to be made on approximately the same site.

136. The use of any one of claims 133-134, wherein the impressions are to be made on overlapping sites.

137. The use of any one of claims 133-134, wherein the impressions are to be made on different sites.

138. The use of any one of claims 133-137, wherein the microneedle array is in the form of a stamp or roller.

139. The use of claim 138, wherein the impressions are to be made by stamping or rolling.

140. The use of any one of claims 101-139, wherein the large agent penetrates the skin within 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration.

141. The use of any one of claims 101-139, 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.

142. The use of any one of claims 101-139, wherein the large agent penetrates the skin within 1, 2, 3, 4, 5, or 6 hours of administration.

143. The use of any one of claims 123-131, wherein the needles are composed of at least one dissolving polymer.

144. The use of any one of claims 101, 105-143, 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.

145. The use of any one of claims 102, 105-143, 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.

146. The use of any one of claims 101-145, wherein more than one dose of the emulsion composition comprising the large agent is to be administered over time.

147. The use of claim 146, 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.

148. The use of claim 146 or claim 147, wherein each dose of the emulsion composition comprising a large agent is separated by a specified period of time.

149 The use of claim 148, 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.

150. The use of any one of claims 144, 146-149, 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.

151. The use of any one of claims 1467-149, 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.

152. The use of any one of claims 89, 90, or 97-151, wherein the medicament or kit is for treating a dermatological disorder.

153. The use of claim 152, 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.

154. The use of any one of claims 89, 90, or 97-152, 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.

155. The use of any one of claims 101-154, wherein the emulsion composition comprising a large agent is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

156. 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.

157. 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.

158. 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.

159. 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.

160. 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 wherein between 1 to 13 impressions of the microneedle array are made to the site.

161. 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 wherein between 1 to 4 impressions of the microneedle array are made per square centimeter of the site.

162. 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 length within a range of 1 μm to 700 μm.

163. 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 length within a range of 1 μm to 500 μm.

164. 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.