Claims

We claim:

1. A method comprising applying an emulsion composition comprising a large agent having a molecular weight of 100,000 KDa or greater to a site in combination with microneedle skin conditioning (MSC) of the site.

2. The method of claim 1, wherein the composition comprising a large agent comprises a nanoemulsion comprising the large agent.

3. The method of claim 1, wherein the composition comprising a large agent comprises a macroemulsion comprising the large agent.

4. The method of any one of claims 1-3, further comprising the administration of a non-irritating penetration enhancing agent.

5. The method of claim 4, wherein the non-irritating penetration enhancing agent is selected from carrier peptides and co-peptides.

6. The method of any one of claims 4-5, wherein the non-irritating penetration enhancing agent is selected from a cationic peptide and a positively charged carrier with the sequence RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR.

7. The method of any one of claims 1-6, wherein the MSC of the site is performed before applying the composition comprising a large agent to the site.

8. The method of claim any one of claims 1-6, wherein the MSC of the site is performed after applying the composition comprising a large agent to the site.

9. The method of claim any one of claims 1-6, wherein the MSC of the site and applying the composition comprising a large agent to the site occur at substantially the same time.

10. The method of any one of claims 1-9, wherein the large agent is a botulinum toxin.

11. The method of claim 10, further comprising delivering botulinum toxin with a biologically active agent.

12. The method of claim 11, wherein the biologically active agent is selected from steroids, retinoids, anesthetics, fillers, silicone, and/or collagen.

13. The method of claim 12, wherein the biologically active agent is selected from hydrocortisone, retin A, and/or lidocaine.

14. The method of any one of claims 1-9, wherein the large agent is an antibody agent.

15. The method of claim 14, 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.

16. The method of any one of claims 14-15, 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.

17. The method of any one of claims 14-16, further comprising delivering the antibody agent with a biologically active agent.

18. The method of any one of claims 14-17, further comprising delivering the antibody agent with a non-irritating penetration enhancing agent.

19. The method of claim 18, wherein the non-irritating penetration enhancing agent is selected from co-peptides, and carrier peptides.

20. The method of any of any one of claims 1-19, wherein the MSC of the site is accomplished with a device comprising a plurality of needles.

21. The method of claim 20, wherein the device is a patch, a roller, stamp, or pen.

22. The method of any one of claims 1-21, wherein the site is a skin surface overlying a muscle or muscle group of a subject.

23. The method of any one of claims 1-22, wherein the site is a skin surface that contains sweat glands.

24. The method of any one of claims 1-23, wherein the site is a skin surface that contains sebaceous glands.

25. The method of any one of claims 1-24, wherein the site is a skin surface that contains hair follicles.

26. The method of any one of claims 20-25, wherein the needles have a length sufficient to project through the stratum corneum of the skin.

27. The method of any one of claims 20-26, wherein the needles have a length insufficient to reach nerves in the dermis of the skin.

28. The method of any one of claims 20-27, wherein the needles have a length between about 10 and about 4000 μm.

29. The method of any one of claims 20-28, wherein the needles have a length equal to or greater than about 100 μm.

30. The method of any one of claims 20-28, wherein the needles have a length equal to or greater than about 25 μm.

31. The method any one of claims 20-28, wherein the needles have a length equal to or greater than about 300 μm, about 500 μm, about 800 μm, about 1000 μm, about 1500 μm, about 2000 μm, or about 4000 μm.

32. The method of any one of claims 20-31, wherein the needles are composed of a biocompatible material.

33. The method of any one of claims 20-31, wherein the needles are composed of a metal.

34. The method of any one of claims 1-33, 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 MN or MN array impressions.

35. The method of claim 34, wherein the MN array is rotated between one or more impressions.

36. The method of claim 34, wherein the MN array is not rotated between one or more impressions.

37. The method of any one of claims 34-36, wherein the impressions are made on approximately the same site.

38. The method of any one of claims 34-36, wherein the impressions are made on overlapping sites.

39. The method of any one of claims 34-36, wherein the impressions are made on different sites.

40. The method of any one of claims 34-39, wherein the MN array is in the form of a stamp or roller.

41. The method of claim 40, wherein the impressions are made by stamping or rolling.

42. The method of any one of claims 1-41, wherein the large agent penetrates the skin within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration.

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

44. The method of any one of claims 1-41, wherein the large agent penetrates the skin within about 1, 2, 3, 4, 5, or 6 hours of administration.

45. The method of any one of claims 20-32, wherein the needles are composed of a dissolving polymer.

46. The method of any one of claims 1-45, wherein the administering comprises administering the composition comprising a large agent at a lower dose as compared to a reference topical treatment regimen where microneedles are not employed.

47. The method of any one of claims 1-46, comprising administering more than one doses of the composition comprising a large agent over time.

48. The method of claim 47, wherein the administering comprises administering fewer doses of the composition comprising a large agent over a fixed treatment period as compared to a reference treatment regimen where microneedles are not employed to generate comparable treatment effects.

49. The method of claim 47 or claim 48, wherein each dose of the composition comprising a large agent is separated by a specified period of time.

50. The method of claim 49, wherein the specified period of time is longer as compared to the specified period of time for administering a reference treatment regimen where microneedles are not employed.

51. The method of any one of claims 46-50, wherein the reference treatment regimen comprises administering the composition comprising a large agent without MSC.

52. A method of treating a dermatological disorder comprising the method of any one of claims 1-51.

53. The method of claim 52, wherein the dermatological disorder is selected from acne, unwanted sweating , body odor, hyperhidrosis, bromhidrosis, chromhidrosis, rosacea, hair loss , 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.

54. A method of 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, Alzheimer's Disease, Parkinson's Disease, or stroke, comprising the method of any one of claims 1-52.

55. The method of any one of claims 1-54, wherein the composition comprising a large agent is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

56. A patch comprising a composition comprising a large agent and a plurality of microneedles.

57. The patch of claim 56, wherein the composition comprising a large agent comprises a nanoemulsion.

58. The patch of claim 56, wherein the composition comprising a large agent comprises a macroemulsion.

59. The patch of any one of claims 56-58, wherein the needles have a length sufficient to project through the stratum corneum of the skin.

60. The patch of any one of claims 57-59, wherein the needles have a length insufficient to reach nerves in the dermis of the skin.

61. The patch of any one of claims 57-60, wherein the needles have a length between about 10 and about 1000 μm.

62. The patch of any one of claims 57-61, wherein the needles have a length equal to or greater than about 100 μm.

63. The patch of any one of claims 57-62, wherein the needles have a length equal to or greater than about 300 μm.

64. The patch of any one of claims 57-63, wherein the needles are composed of a biocompatible material.

65. The patch of any one of claims 57-64, wherein the needles are composed of a metal.

66. The patch of any one of claims 57-64, wherein the needles are composed of a dissolving polymer.

67. The patch of any one of claims 57-66, wherein the large agent has a molecular weight of 100 KDa or more.

68. The patch of any one of claims 57-67, wherein the large agent is a botulinum toxin.

69. The patch of any one of claims 57-67, wherein the large agent is an antibody agent.

70. A kit comprising a composition comprising a large agent and a patch for use in applying the composition comprising a large agent to a site.

71. The kit of claim 70, wherein the composition comprising a large agent is incorporated into the patch.

72. A kit comprising a composition comprising a large agent and a device for microneedle conditioning of a site.

73. The kit of any one of claims 70-72, wherein the composition comprising a large agent comprises a nanoemulsion.

74. The kit of any one of claims 70-72, wherein the composition comprising a large agent comprises a macroemulsion.

75. The kit of any one of claims 70-74, wherein the device comprises a plurality of needles.

76. The kit of any one of claims 70-75, wherein the device is a patch, a roller, stamp, or pen.

77. The kit of any one of claims 70-76, comprising a patch of any one of claims 56-68.

78. The kit of any one of claims 70 or 72-77, wherein the composition comprising a large agent is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.