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).

**[0004a]** In one 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, wherein the medicament is to be applied to a site in combination with microneedle skin conditioning (MSC) of the site.

**[0004b]** In another aspect of the present disclosure, there is provided 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.

**[0004c]** 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 patch comprising a plurality of needles, for use in applying the emulsion composition to a site.

**[0004d]** In a further aspect of the present disclosure, there is also 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.

**[0005]** The present disclosure provides improved technologies for transdermal delivery of agents of interest. Among other things, the present disclosure provides an insight that certain advantages may be achieved when microneedling technologies are combined with emulsion technologies for transdermal delivery of agents of interest. Alternatively or additionally, in some embodiments, the present disclosure demonstrates that surprising enhancements can be achieved for transdermal delivery of large molecular structures when microneedling technologies are utilized.

**[0006]** A variety of microneedling technologies have been developed that can be useful for administration of certain agents of interest. Microneedling can avoid certain disadvantages (e.g., amount of pain and/or bleeding) that often associated with use of larger needles (e.g., with standard injection technologies). Microneedling technologies may utilize one or more (e.g., an array of) hollow or solid microneedles. An agent of interest may be disposed in (e.g., if the microneedle is hollow and/or if the agent is incorporated into the microneedle material) or on (i.e., on a surface of) microneedle(s), and/or may be applied to a skin site prior to, during, or after microneedling of the site. An agent that is in or on a microneedle may be released, for example, by diffusion or ejection from the microneedle, or by breakage and/or disintegration of the microneedle material after application to a site.

**[0007]** In some embodiments, the present disclosure provides strategies in which microneedling is used to "condition" skin (and specifically to pre-condition skin prior to administration of the large agent) to which a transdermal product has been, is being, or will be applied. The present disclosure provides an insight that such microneedle conditioning, surprisingly, can provide significant benefit in enhancing transdermal delivery of large agents (e.g., having molecular weights above about 100 KDa or more), notwithstanding prior reports that such strategies are only likely to be useful for small molecular weight agents because studies analyzing transdermal delivery of small molecules (specifically, short, hydrophilic peptides having molecular weights in the range of 400-1000 Da) found "[t]he skin permeation of peptides depends on their molecular weight and decreases as the molecular weight increases." Zhang, S., et al., "Enhanced delivery of hydrophilic peptides

## Claims

We claim:

1. 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, wherein the medicament is to be applied to a site in combination with microneedle skin conditioning (MSC) of the site.

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

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

4. The use of any one of claims 1-3, wherein a non-irritating penetration enhancing agent is to be further administered.

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

6. The use 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 use of any one of claims 1-6, wherein the MSC of the site is to be performed before applying the medicament to the site.

8. The use of any one of claims 1-6, wherein the MSC of the site is to be performed after applying the medicament to the site.

9. The use of any one of claims 1-6, wherein the MSC of the site and applying the medicament to the site is to occur at substantially the same time.

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

11. The use of claim 10, wherein the botulinum toxin is to be further delivered with a biologically active agent.

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

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

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

15. The use 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 use 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 use of any one of claims 14-16, wherein the antibody agent is to be further delivered with a biologically active agent.

18. The use of any one of claims 14-17, wherein the antibody agent is to be further delivered with a non-irritating penetration enhancing agent.

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

20. The use of any one of claims 1-19, wherein the MSC of the site is to be performed with a device comprising a plurality of needles.

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

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

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

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

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

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

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

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

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

34. The use of any one of claims 1-33, wherein the MSC 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 is to be administered.

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

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

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

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

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

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

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

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

46. The use of any one of claims 1-45, wherein the medicament is to be administered at a lower dose as compared to a reference topical treatment regimen where microneedles are not employed.

47. The use of any one of claims 1-46, wherein more than one dose of the medicament is to be administered over time.

48. The use of claim 47, wherein fewer doses of the medicament is to be administered over a fixed treatment period as compared to a reference treatment regimen where microneedles are not employed to generate comparable treatment effects.

49. The use of claim 47 or claim 48, wherein each dose of the medicament is separated by a specified period of time.

50. The use 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 use of any one of claims 46-50, wherein the reference treatment regimen comprises administering the medicament without MSC.

52. The use according to any one of claims 1-51, wherein the medicament is for treating a dermatological disorder.

53. The use 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. The use according to any one of claims 1-52, wherein the medicament 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, Alzheimer's Disease, Parkinson's Disease, or stroke.

55. The use of any one of claims 1-54, wherein the medicament is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

56. 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.

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 is a botulinum toxin.

68. The patch of any one of claims 57-66, wherein the large agent is an antibody agent.

69. A kit comprising an emulsion composition comprising a large agent having a molecular weight of 100,000 Da or greater, and a patch comprising a plurality of needles, for use in applying the emulsion composition to a site.

70. The kit of claim 69, wherein the emulsion composition is incorporated into the patch.

71. 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.

72. The kit of any one of claims 69-71, wherein the emulsion composition comprises a nanoemulsion.

73. The kit of any one of claims 69-71, wherein the emulsion composition comprises a macroemulsion.

74. The kit of any one of claims 71-73, wherein the device comprises a plurality of needles.

75. The kit of any one of claims 71-74, wherein the device is a patch, a roller, a stamp, or a pen.

76. The kit of any one of claims 69 or 70, comprising a patch of any one of claims 56-68.

77. The kit of any one of claims 69 or 71-76, wherein the emulsion composition is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.