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 about 2 to about 50 microneedles/cm^2 in the manufacture of a kit, 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 and a plurality of microneedles having a microneedle density within a range of about 2 to about 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 about 100 to about 35,000 μm^2/microneedle in the manufacture of a kit, 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 a composition comprising a large agent and a device for microneedle conditioning of a site, wherein the device is a microneedle array having a microneedle density within a range of about 2 to about 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, 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 about 2 to about 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, 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 about 100 to about 35,000 μm^2/microneedle.

[0002g] In a further aspect of the present disclosure, there is provided a kit comprising a composition comprising a large agent 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 about 100 to about 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, 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 about 1 to about 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, 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 about 1 to about 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 about 1 μm to about 700 μm in the manufacture of a kit, 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 about 1 μm to about 500 μm in the manufacture of a kit, 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 another aspect of the present disclosure, there is provided a use of an emulsion composition of a product volume of about 1/100 of one drop/cm^2 to about 2 drops/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, 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 a further aspect of the present disclosure, there is provided a use of an emulsion composition of a product volume of about .0001 mls/cm^2 to about 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, 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.

[0002n] 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 about 2 to about 50 microneedles/cm^2.

[0002o] 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 about 100 to about 35,000 μm^2/microneedle.

[0002p] 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 about 2 to about 50 microneedles/cm^2.

[0002q] 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 about 100 to about 35,000 μm²/microneedle.

[0002r] 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 about 1 to about 13 impressions of the microneedle array are made to the site.

[0002s] 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 about 1 to about 4 impressions of the microneedle array are made per square centimeter of the site.

[0002t] 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 about 1 μm to about 700 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 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 about 1 μm to about 500 μm.

[0002v] In another 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 about 1/100 of one drop/cm^2 to about 2 drops/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.

[0002w] 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 about .0001

mls/cm^2 to about 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

facilitate and/or otherwise improve delivery of the topical agent. In some examples, such a composition may be or comprise an emulsion (e.g., a nanoemulsion), e.g., comprising the large agent. In some examples, such a composition may or may not comprise an emulsion and/or may be formulated, for example, as a liquid, gel, cream, or other preparation suitable for topical application.

[0006] Recent technologies (see, for example, International Publication No. PCT/US17/53333, incorporated herein by reference) have been developed that achieve various advantages by combining microneedling technologies with emulsion technologies for transdermal delivery of agents of interest; in some examples, these technologies have shown particularly surprising enhancements can be achieved for transdermal delivery of large molecular structures.

[0007] The present disclosure demonstrates that even greater advantages are achieved when microneedling approaches having particular microneedle densities, and/or particular microneedle puncture sizes are utilized. Surprisingly, the present disclosure teaches that particularly desirable results are achieved with relatively low density and/or relatively small puncture size microneedling approaches.

[0008] 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.

[0009] In some examples, 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), e.g. microneedle skin conditioning (MSC), to which a transdermal product has been, is being, or will be applied. The present disclosure provides an insight that such microneedle conditioning as described herein (e.g., relatively low density and/or relatively small puncture size 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), even as compared to higher density and/or larger puncture size

microneedle conditioning approaches. In some examples, the present disclosure teaches that microneedling may provide surprising improvements in delivery of large agents. In some examples, the present disclosure establishes that microneedling treatments may be particularly advantageous for delivery of large agent(s) in emulsion composition(s) (e.g., nanoemulsion).

[0010] Prior reports have found that microneedle conditioning 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 in vitro by transdermal microneedle pretreatment." Acta Pharmaceutica Sinica B. 4(1):100-104 (2014). Furthermore, studies evaluating effects of microneedle densities, microneedle length, and/or microneedle puncture size on such small molecule delivery have established that microneedle density has no effect upon the small molecule delivery and/or bioavailability, and that relatively longer microneedle lengths and larger microneedle puncture sizes improve small molecule delivery and/or bioavailability. Although an early report by Yan (Yan, G., et al., " Evaluation needle length and density of microneedle arrays in the pretreatment of skin for transdermal drug delivery", International Journal of Pharmaceutics, 391: 7-12, 2010) stated that "microneedle arrays with lower needle densities (< 2000 needles/cm^2) were more effective in enhancing drug flux if the microneedles with long enough needle length (> 600 μm)" were used, later work identified defects in the approach used by Yan, including that assays of the type used by Yan "can be prone to artefact" and "may result in biomechanical changes in the tension of the skin and/or level of hydration, which could adversely produce changes in the microchannel dimensions" (see, Donnelly, R.F., et al., Optical coherence tomography is a valuable tool in the study of the effects of microneedle geometry on skin penetration characteristics and in-skin dissolution, Journal of Controlled Release, 147: 333-341, 2010). Moreover, even the lowest microneedle density studied by Yan (400 needles/cm^2) was relatively high. Still further, the data presented by Yan itself showed that there is no significant impact of needle density on small molecule delivery (e.g., "drug flux" through skin) for needle lengths of less than 1100 μm.

[0011] The Donnelly study mentioned above reported that microneedle (MN) penetration depth (rather than density or other factors) is the most significant factor in determining the effective drug permeability. Donnelly also established that "alteration of MN interspacing has no effect upon the depth of penetration achieved". *Id.*

[0012] Thus, prior to the present disclosure, the art indicated that varying microneedle density was not expected to impact delivery of agents across skin, at least at the density levels studied in the literature. On first principles, of course, one might expect that, if microneedling improves delivery, relatively higher microneedle density (and/or relatively larger microneedle puncture size) might be expected to be more effective. As each factor of microneedle density and microneedle diameter increases the aggregate surface area of the skin that has been punctured increases which would be expected to enable more of an active ingredient to penetrate the skin transdermally. The present disclosure, however, documents the surprising finding that, at least for delivery of large agents and/or agents in an emulsion (e.g., a nanoemulsion), relatively lower microneedle density and/or relatively smaller microneedle puncture size achieves better results. That is, it was surprisingly found that as the aggregate surface area of skin that is punctured by the microneedles decreases, the bioavailability of a large agent in an emulsion applied to the skin increases. In some examples, microneedle densities in the range of about 2 to about 50 microneedles/cm^2 can significantly enhance transdermal delivery and/or bioavailability, even when compared to microneedling using relatively higher microneedle densities. Furthermore, the present disclosure surprisingly demonstrates that microneedle conditioning of skin using microneedle puncture sizes in the range of about 100 to about 60,000 μm^2/microneedle can achieve significant transdermal delivery and/or bioavailability. Moreover, the present disclosure further demonstrates that that microneedle conditioning of skin using smaller microneedle puncture sizes (e.g., in the range of about 100 to about 30,000 μm^2/microneedle) can significantly enhance transdermal delivery and/or bioavailability, even when compared to microneedling using relatively larger microneedle puncture sizes. In some examples, microneedle puncture sizes may be in the range of about 100 to about 30,000 μm^2/microneedle.

[0013] Prior to the present disclosure, those skilled in the art would have understood from the literature that microneedle conditioning of skin using any particular microneedle density would not be expected to enhance transdermal delivery of even small molecules, let alone large agents. The present disclosure surprisingly demonstrates that microneedle conditioning of skin using microneedle densities in the range of about 2 to about 50 microneedles/cm^2 can significantly enhance transdermal delivery of agents such as botulinum toxin, which has a molecular weight of about 150,000 Da. Standard antibodies also have a similar molecular weight. Furthermore, the present disclosure surprisingly demonstrates that microneedle conditioning of skin using microneedle puncture sizes in the range of about 100 to about 30,000 μm^2/microneedle can significantly enhance transdermal delivery of such large agents.

[0014] Those skilled in the art, reading the present disclosure, will appreciate that, logically, in addition to decreasing the aggregate surface punctured by decreasing microneedle density and/or decreasing microneedle puncture sizes, one could also achieve a comparable effect by minimizing (e.g., decreasing) the number of impressions made by or with a microneedle array on the skin of the treatment area. Consistent with this understanding, in light of the above-noted surprising observations that reduction in aggregate punctured surface area (which may, for example, by achieved at least in part by small(er) microneedle puncture sizes, which may incidentally have additional advantages), the present disclosure further documents that relatively fewer microneedle array impressions can result in greater bioavailability than relatively higher number of impressions. In some examples, microneedle impressions in the range of about 1 impression/cm^2 to about 5 impressions/cm^2 can achieve significant transdermal delivery and/or bioavailability.

[0015] The present disclosure demonstrates that microneedle conditioning of skin with microneedle impressions in the range of about 1 impression/cm^2 to about 4 impressions/cm^2 can significantly enhance transdermal delivery and/or bioavailability, even when compared to microneedling using relatively higher number of microneedle impressions. In some examples, microneedle impressions in the range of about 1 impression to about 20 impressions made to the treatment site can achieve significant transdermal delivery and/or bioavailability. Furthermore, the present disclosure demonstrates that microneedle conditioning of skin with microneedle impressions in the range of about 1 impression to about 13 impressions made to the treatment site can significantly enhance transdermal delivery and/or bioavailability, even when compared to microneedling using relatively higher number of microneedle impressions.

[0016] Furthermore, those skilled in the art reading the present disclosure will appreciate that decreasing the aggregate surface punctured to which a large agent is applied by decreasing microneedle density, decreasing microneedle puncture sizes, and/or decreasing microneedle array impressions compared to relatively higher surface punctured results in a reduction in the total product volume (i.e., volume of a product formulation comprising a large agent) that is administered to the skin areas that were punctured by the microneedles. Thus the present disclosure teaches a person of ordinary skill in the art that improved transdermal delivery and/or greater bioavailability of a large agent may be achieved by reducing total product volume (*e.g.* of a formulation containing the large agent) applied.

[0017] Absent teachings embodied herein, one of ordinary skill in the art would typically expect that administering more product would result in increased biological effects. Thus, prior to the present disclosure, it would have been expected that application of increasing amounts of a

product containing a biologically active agent (e.g., a large agent), including where such application is performed in conjunction with MSC and/or via a product composition that includes an emulsion (e.g., a nanoemulsion), should achieve increasingly greater biological effects. The present disclosure, however, surprisingly demonstrates that, above a certain "critical" or "threshold" product volume, further *increasing* volume of product composition applied to a given skin treatment area in conjunction with MSC became *less effective* (rather than more effective). Thus, once certain critical product volumes were exceeded, administration (e.g., in conjunction with MSC) of increased volume of a product composition containing a biologically active agent (e.g., a large agent, and including specifically where the product composition comprises an emulsion) *decreased* biological effect, notwithstanding the *increased* dose of biologically active agent administered.

[0018] In some examples, application of a product volume (e.g. of a composition comprising a large agent) in a range of about 1/100 of one drop/cm^2 to about 5 drops/cm^2 to the skin in conjunction with the conditioning of the skin with an impression or impressions of a microneedle array can achieve significant transdermal delivery and/or bioavailability. In some examples, application of a product volume (e.g. of composition comprising a large agent) in a range of about 1/100 of one drop/cm^2 to about 4 drops/cm^2 to the skin in conjunction with the conditioning of the skin with an impression or impressions of a microneedle array can achieve significant transdermal delivery and/or bioavailability. In some examples, application of a product volume (e.g. of a composition comprising a large agent) in a range of about 1/100 of one drop/cm^2 to about 3 drops/cm^2 to the skin in conjunction with the conditioning of the skin with an impression or impressions of a microneedle array can achieve significant transdermal delivery and/or bioavailability. In some examples, application of a product volume (e.g. of a composition comprising a large agent) in a range of about 1/100 of one drop/cm^2 to about 2.5 drops/cm^2 to the skin in conjunction with the conditioning of the skin with an impression or impressions of a microneedle array can achieve significant transdermal delivery and/or bioavailability. The present disclosure demonstrates that application of a product volume (e.g. of a composition comprising a large agent) in a range of about 1/100 of one drop/cm^2 to about 2 drops/cm^2 to skin in conjunction with the conditioning of the skin with an impression or impressions of a microneedle array can significantly enhance transdermal delivery and/or bioavailability, even when compared to using relatively higher product volume (and/or dose) (e.g. of large agent).

[0019] In some examples, application of a product volume (e.g. of a composition comprising a large agent) in a range of about 0.0001 mls/cm^2 to about 0.04 mls/cm^2 to the skin in

conjunction with the conditioning of the skin with an impression or impressions of a microneedle array can achieve significant transdermal delivery and/or bioavailability. In some examples, application of a product volume (e.g. of a composition comprising a large agent) in a range of about 0.0001 mls/cm^2 to about 0.05 mls/cm^2 to the skin in conjunction with the conditioning of the skin with an impression or impressions of a microneedle array can achieve significant transdermal delivery and/or bioavailability. In some examples, application of a product volume (e.g. of a composition comprising a large agent) in a range of about 0.0001 mls/cm^2 to about 0.06 mls/cm^2 to the skin in conjunction with the conditioning of the skin with an impression or impressions of a microneedle array can achieve significant transdermal delivery and/or bioavailability. In some examples, application of a product volume (e.g. of a composition comprising a large agent) in a range of about 0.0001 mls/cm^2 to about 0.065 mls/cm^2 to the skin in conjunction with the conditioning of the skin with an impression or impressions of a microneedle array can achieve significant transdermal delivery and/or bioavailability. Furthermore, the present disclosure demonstrates that application of a product volume (e.g. of a composition comprising a large agent) in a range of about 0.0025 mls/cm^2 to about 0.07 mls/cm^2 to skin in conjunction with the conditioning of the skin with an impression or impressions of a microneedle array can significantly enhance transdermal delivery and/or bioavailability, even when compared to using relatively higher product volume (and/or dose) of large agent.

[0020] Among the advantages provided by certain examples of the present disclosure (e.g., those where volume of applied product composition is reduced) is a reduced time of administration (*e.g.*, of rubbing in) of a topical formulation. As already noted, the present disclosure documents that, surprisingly, *reduced* volume (and/or in some examples reduced *dose*) of a topically applied agent can in fact achieve *greater* delivery (*e.g.*, bioavailability) of the agent across the skin, particularly (but not exclusively) for example, when the agent is applied an emulsion (*e.g.*, a nanoemulsion) formulation.

[0021] As stated previously, studies of microneedle length on small molecule delivery have established that relatively longer microneedle lengths improve small molecule delivery and/or bioavailability. See report by Yan (Yan, G., et al., " Evaluation needle length and density of microneedle arrays in the pretreatment of skin for transdermal drug delivery", International Journal of Pharmaceutics, 391: 7-12, 2010). However, a person of ordinary skill in the art reading the present disclosure will appreciate that reducing aggregate surface punctured improves transdermal delivery and/or active agent (e.g. large agent bioavailability) compared to relatively larger aggregate surface punctured. Thus, logically a person of ordinary skill in the art reading the present disclosure

will appreciate that improved transdermal delivery and/or greater bioavailability of a large agent may be achieved by reducing microneedle length of microneedle skin conditioning array. A person of ordinary skill in the art will appreciate that the longer the microneedle is, the larger the base of the microneedle must be to structurally support the increased length and the larger base of the needle is, the larger the puncture area that is created by that needle. A person of ordinary skill in the art will appreciate that the longer the microneedle is, the greater the surface area of the punctured tissue becomes because of the increase in the surface area of the microneedle itself. The present disclosure surprisingly demonstrates that microneedle skin conditioning using relatively shorter microneedle lengths can result in greater bioavailability than when using relatively longer microneedle lengths. In some examples, microneedle lengths in the range of about 1 μm to about 900 μm can achieve significant transdermal delivery and/or bioavailability. In some examples, microneedle lengths below 1400 μm, and in some examples below about 1100 μm or even 1000 μm are desirable. Indeed, the present disclosure specifically documents surprising effectiveness of microneedle lengths of about 800 μm or less. In some examples, microneedle lengths in the range of about 15 μm to about 800 μm can achieve significant transdermal delivery and/or bioavailability. In some examples, the present disclosure documents surprising effectiveness of microneedle lengths of about 500 μm or less. In some examples, microneedle lengths in the range of about 15 μm to about 500 μm can achieve significant transdermal delivery and/or bioavailability.

[0022] In some examples, microneedle lengths may be in the range of about 50 μm to about 900 μm. In some examples, the present disclosure demonstrates that microneedle conditioning of skin with microneedle lengths in the range of about 50 μm to about 900 μm, or about 100 μm to about 700 μm, made to the treatment site can significantly enhance transdermal delivery and/or bioavailability, even when compared to microneedling using relatively longer microneedle lengths. In some examples, microneedle conditioning of skin with microneedle lengths in the range of about 100 μm to about 800 μm made to the treatment site can significantly enhance transdermal delivery and/or bioavailability, even when compared to microneedling using relatively longer microneedle lengths. In some examples, microneedle conditioning of skin with microneedle lengths in the range of about 15 μm to about 500 μm made to the treatment site can significantly enhance transdermal delivery and/or bioavailability, even when compared to microneedling using relatively longer microneedle lengths. In some examples, microneedle conditioning of skin with microneedle lengths of less than about 800 μm made to the treatment site can significantly enhance transdermal delivery and/or bioavailability, even when compared to microneedling using relatively longer microneedle lengths.

[0023] Among the advantages provided by the unexpected finding, documented herein, that *shorter* needle lengths can achieve more effective delivery (*i.e.,* are described as "increasing bioavailability") is reduced pain to subjects receiving microneedle skin conditioning (*e.g.,* in association with and/or as part of topical treatment) for administration of a large agent. Microneedles of varying lengths (including, for example, within a range of about 500 to about 1400 μm) are readily available, and have been described as useful in particular as bleeding can often be minimized or even avoided with these lengths. However, the present disclosure appreciates that significant pain can be experienced even in the absence of bleeding, particularly for lengths as long as 1400 μm, and sometimes even for shorter lengths. The present disclosure, by documenting effectiveness of microneedle lengths significantly below 1400 μm, and in some examples below even 1100 μm, 1000 μm, 900 μm or shorter, provides a significant advantage in avoiding or reducing pain in topical delivery, even for large agents, and especially (though not exclusively) for agents administered in the context of an emulsion (or even a nanoemulsion) formulation.

[0024] The present disclosure particularly demonstrates that microneedling technologies (e.g., microneedle conditioning of skin using relatively lower needle densities, relatively smaller microneedle puncture size (e.g. puncture size per microneedle), relatively fewer microneedle impressions, relatively smaller product volumes (and/or dose), and relatively shorter needle lengths) can significantly enhance transdermal delivery of large agents, particularly (though not exclusively) in emulsion compositions (e.g., macroemulsion compositions and/or nanoemulsion compositions). As exemplified, for example, pre-conditioning of skin via application of microneedles using a microneedle array having a microneedle density of less than about 31 microneedles/cm^2 prior to any administration of a relevant large agent (botulinum toxin), surprisingly enhanced delivery of the large agent across the skin. Specific examples included herein document such enhanced delivery under various conditions and/or circumstances (e.g., different skin sites, number of applications, etc). Those skilled in the art will be aware of other variations (e.g., to site of application, number of doses, etc) that fall within the scope of the present disclosure.

[0025] Particular nanoemulsion compositions of interest include water-in-oil and oil-in-water nanoemulsions characterized by droplet sizes ranging from about 10 nm to about 300 nm in diameter, a ratio of aqueous dispersion media to oil ranging between about 0.01:1 to about 20:1; oil-to-surfactant ratio in a range that spans about 0.1 to about 40 and/or zeta potential in a range that spans about -80 mV to about +80 mV (see e.g., descriptions of nanoemulsion compositions in one or more of PCT/US2006/26918; PCT US06/46236; PCT/US2012/22276; and PCT/US2012/22279, the disclosures of each of which are herein incorporated by reference in their entireties).

[0026] International Publication No. PCT/US17/53333 already described certain surprising features achieved through combination of microneedling and emulsion (e.g., nanoemulsion) technologies, when considered in light of reports that transdermal delivery of solid nanoparticles of a size (e.g., 105 ± 2.92 nm) comparable to that of the droplets in the nanoemulsion composition utilized herein do not effectively deliver (or enhance delivery of) even small molecule agents transdermally across skin. For example, Gomaa et al described a study in which a solution of rhodamine dye (molecular weight 479 Da) encapsulated in PLGA nanoparticles was applied to skin that had been preconditioned by microneedling, and skin penetration was assessed. *See* Gomaa, Y., et al, "Effect of microneedle treatment on the skin permeation of a nanoencapsulated dye." J Pharm Pharmacol. 2012 November ; 64(11): 1592–1602. The data showed that very small amounts of dye began to permeate the skin after 6 hours of continuous application; no significant increase in permeation was observed until skin had been treated continuously for 24 hours. The researchers explained that "there is an emerging consensus that NPs [nanoparticles] cannot usually penetrate the stratum corneum, although they may well deposit in hair follicles." Thus, prior to the present disclosure, those skilled in the art would expect that use of microneedling technologies with nano-sized vehicles could not effectively deliver even small molecule agents (e.g., rhodamine dye) transdermally; certainly delivery and/or improved bioavailability of large agents would have been considered impossible. International Publication No. PCT/US17/53333 demonstrated that microneedling can significantly enhance transdermal delivery of large agents, particularly when utilized in conjunction with an emulsion (e.g., nanoemulsion) system. The present disclosure further demonstrates that microneedling using microneedle densities in the range of about 2 to about 50 microneedles/cm^2 can significantly enhance transdermal delivery and/or improve bioavailability of large agents when compared to utilizing relatively higher microneedle densities, particularly when utilized in conjunction with an emulsion system (e.g., a nanoemulsion system). In some examples, microneedling using microneedle densities below about 40 microneedles/cm^2 (e.g., in the range of about 2 to about 40 microneedles/cm^2), or better yet microneedling using microneedle densities below about 35 microneedles/cm^2 (e.g., in the range of about 2 to about 35 microneedles/cm^2), or microneedling using microneedle densities below about 32 microneedles/cm^2 (e.g., in the range of about 2 to about 32 microneedles/cm^2), or microneedling using microneedle densities below about 31 microneedles/cm^2 (e.g., in the range of about 2 to about 31 microneedles/cm^2), or microneedling using microneedle densities below about 30 microneedles/cm^2 (e.g., in the range of about 2 to about 30 microneedles/cm^2), or microneedling using microneedle densities below about 29 microneedles/cm^2 (e.g., in the range of about 2 to about 29 microneedles/cm^2), or microneedling using microneedle densities below about 28 microneedles/cm^2

(e.g., in the range of about 2 to about 28 microneedles/cm^2) can significantly enhance transdermal delivery and/or improve bioavailability of large agents when compared to utilizing relatively higher microneedle densities, particularly when utilized in conjunction with an emulsion system (e.g., a nanoemulsion system).

[0027] Furthermore, the present disclosure surprisingly demonstrates that microneedle conditioning of skin using microneedle puncture sizes in the range of about 100 to about 60,000 μm^2/microneedle can achieve significant transdermal delivery and/or bioavailability. Moreover, the present disclosure demonstrates that microneedling using smaller microneedle puncture size, for example in the range of about 100 to about 30,000 μm^2/microneedle can significantly enhance transdermal delivery and/or improve bioavailability of large agents when compared to utilizing relatively larger microneedle puncture sizes, particularly when utilized in conjunction with an emulsion system (e.g., a nanoemulsion system). In some examples, microneedling using microneedle puncture sizes below about 50,000 μm^2/microneedle (e.g., in the range of about 100 to about 50,000 μm^2/microneedle), or microneedling using microneedle puncture sizes below about 45,000 μm^2/microneedle (e.g., in the range of about 100 to about 45,000 μm^2/microneedle), or microneedling using microneedle puncture sizes below about 40,000 μm^2/microneedle (e.g., in the range of about 100 to about 40,000 μm^2/microneedle), or better yet microneedling using microneedle puncture sizes below about 35,000 μm^2/microneedle (e.g., in the range of about 100 to about 35,000 μm^2/microneedle), or microneedling using microneedle puncture sizes below about 30,000 μm^2/microneedle (e.g., in the range of about 100 to about 30,000 μm^2/microneedle), or microneedling using microneedle puncture sizes below about 25,000 μm^2/microneedle (e.g., in the range of about 100 to about 25,000 μm^2/microneedle) can significantly enhance transdermal delivery and/or improve bioavailability of large agents when compared to utilizing relatively larger microneedle puncture sizes, particularly when utilized in conjunction with an emulsion system (e.g., a nanoemulsion system).

[0028] Among other things, the present disclosure demonstrates that microneedling technologies as described herein can enhance transdermal delivery (e.g., of large agents, particularly from macroemulsion or nanoemulsion compositions), when no other disrupting agent (i.e., no chemical penetration enhancing agent and no other technology that disrupts or punctures skin structure) is utilized. Prior studies of transdermal delivery of an agent as large as botulinum toxin (i.e., about 150 kDa) using microneedles have reported that delivery is unsuccessful unless additional treatment is applied to disrupt skin. For example, U.S. Patent Publication No. 2010/0196445 reports that botulinum toxin is not delivered effectively from pre-coated

microneedles unless a skin-digesting enzyme is also applied, so that skin structure is disrupted at the site of microneedling.

[0029] In some examples, the present disclosure provides technologies that achieve enhanced transdermal delivery and/or improved bioavailability of large agents (e.g., botulinum toxin, antibodies, etc) by utilizing microneedling technologies as described herein without the additional use of a penetration enhancing agent. Alternatively or additionally, in some examples, the present disclosure provides technologies that achieve enhanced transdermal delivery and/or improved bioavailability of large agents (e.g., botulinum toxin, antibodies, etc.) by utilizing microneedling technologies without any other disrupting strategy. Provided technologies therefore can achieve effective delivery and/or improved bioavailability without inflammation, irritation, and/or allergic reaction that often accompanies use of skin disrupting agents.

[0030] Alternatively or additionally, the present disclosure identifies the source of a problem with certain prior approaches to associating large agents, and particularly large protein agents (e.g., botulinum toxin, antibodies, etc.), in or on microneedle structures. Typically, such conventional association strategies utilize a liquid solution of the relevant agent, that is applied to a microneedle and allowed to air dry. Such a strategy was utilized to coat microneedles with botulinum toxin in above-noted U.S. Patent Publication No. 2010/0228225. US Patent Publication No. 2017/0209553 describes a microneedle array that is loaded with botulinum into the needles. The present disclosure appreciates that the botulinum coating or loaded material thereby produced is not stable and therefore not commercially viable when used to make a product. Indeed, even if such a liquid is prepared from a powder material, the present disclosure appreciates that, for many large agents (e.g., botulinum toxin), powders and other solid materials that are not formed through a lyophilization process can be highly unstable. For example, per Johnson, E., et al., "Botulinum toxin is very susceptible to denaturation due to surface denaturation, heat, and alkaline conditions. Lyophilization or freeze-drying of botulinum toxin is the most economically sound and practical method of distributing the product in a form that is stable and readily used by the clinician." U.S. Patent No. 5,512,547. Similarly, such an approach would not work for the administration of therapeutic antibodies which have their own stability and storage challenges. The present disclosure provides the insight that use of an emulsion composition (e.g., in some examples, a nanoemulsion composition, and/or in some examples a macroemulsion composition) as described herein can protect or otherwise improve stability of large agents, particularly large protein agents, and specifically including botulinum toxin and/or antibody agents, for association with microneedles.

[0031] The present disclosure provides surprisingly effective technologies for transdermal delivery and/or improved bioavailability of large agents. In particular, the present disclosure teaches that transdermal delivery of such agents can be significantly enhanced through use of certain microneedling technologies. Those skilled in the art, reading the present disclosure, will appreciate that its teachings are likely applicable to any topical formulation of a large agent. In some examples, the present disclosure specifically teaches that particularly advantageous results are achieved when microneedling technologies are combined with emulsion compositions (e.g., in some examples, nanoemulsion compositions, and/or in some examples macroemulsion compositions). In some examples, microneedling technologies are combined with lotion, cream, or liquid compositions, which in turn may be or comprise emulsion compositions (e.g., in some examples with nanoemulsion compositions and/or, in some examples with macroemulsion compositions). In some examples, provided technologies do not utilize skin disrupting technologies, such as chemical penetration enhancing agents.

Brief Description of the Drawing

[0032] Figure 1 depicts the effect of varying microneedle array densities on bioavailability of a botulinum nanoemulsion formulation after MSC ("microneedle skin conditioning") as determined by the survival rates of a rat study.

[0033] Figure 2 depicts the effect of varying microneedle puncture sizes on bioavailability of a botulinum nanoemulsion formulation after MSC as determined by the survival rates of a rat study.

Definitions

[0034] In this application, unless otherwise clear from context, (i) the term "a" may be understood to mean "at least one"; (ii) the term "or" may be understood to mean "and/or"; (iii) the terms "comprising" and "including" may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps; and (iv) the terms "about" and "approximately" may be understood to permit standard variation as would be understood by those of ordinary skill in the art; and (v) where ranges are provided, endpoints are included.

[0035] ***Abrasion:*** The term "abrasion," as used herein refers to any means of altering, disrupting, removing, or destroying the top layer of the skin. In some embodiments, abrasion refers

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 about 2 to about 50 microneedles/cm^2 in the manufacture of a kit, 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 within a range of about 2 to about 10 microneedles/cm^2.

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

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

5. The use of claim 1, wherein the 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 non-irritating penetration enhancing agent.

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

8. The use of any one of claims 6-7, 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.

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 non-irritating penetration enhancing agent, and wherein the non-irritating penetration enhancing agent is to be delivered with the antibody agent.

21. The use of claim 20, wherein the non-irritating 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 nerves in the dermis of the skin.

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

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

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

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

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

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

36. The use any one of claims 22-30, wherein the needles have a length equal to or greater than about 200 μm, about 300 μm, about 500 μm, about 800 μm, about 1000 μm, about 1100 μm, about 1200 μm, about 1300 μm, about 1400 μm, about 1500 μm, about 1600 μm, about 1700 μm, about 1800 μm, about 1900 μm, about 2000 μm, about 2100 μm, about 2200 μm, about 2300 μm, about 2400 μm, about 2500 μm, about 2600 μm, about 2700 μm, about 2800 μm, about 2900 μm, about 3000 μm, about 3100 μm, about 3200 μm, about 3300 μm, about 3400 μm, about 3500 μm, about 3600 μm, about 3700 μm, about 3800 μm, or about 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 MN or MN array impressions, wherein each impression is the time the MN is continuously applied to the skin.

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

41. The use of claim 39, wherein the MN 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 MN 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 about 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 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.

49. The use of any one of claims 1-46, wherein the large agent penetrates the skin within about 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 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 composition comprising the large agent is to be administered over time.

53. The use of claim 52, wherein fewer doses of the 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 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 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 composition comprising a large agent is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

61. A patch comprising a composition comprising a large agent and a plurality of microneedles having a microneedle density within a range of about 2 to about 50 microneedles/cm^2.

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

63. The patch of claim 61, wherein the 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 nerves in the dermis of the skin.

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

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

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

69. The patch of any one of claims 62-68, wherein the needles have a length equal to or greater than about 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 about 100 to about 35,000 μm^2/microneedle in the manufacture of a kit, 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 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 about 35,000 μm^2 /microneedle.

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

79. The use of claim 78, wherein fewer doses of the 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.

80. The use of claim 78 or claim 79, wherein each dose of the 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 μm^2 /microneedle.

82. The use of any one of claims 77-81, wherein the reference treatment regimen comprises administering the composition comprising a large agent with the reference microneedle array having a microneedle hole puncture size of greater than 35,000 μm^2 /microneedle.

83. A kit comprising a composition comprising a large agent and a device for microneedle conditioning of a site, wherein the device is a microneedle array having a microneedle density within a range of about 2 to about 50 microneedles/cm^2.

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

85. The kit of claim 83 or claim 84, wherein the 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 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, 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 about 2 to about 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, 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 about 100 to about 35,000 μm^2/microneedle.

91. A kit comprising a composition comprising a large agent 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 about 100 to about 35,000 μm^2/microneedle.

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

93. The kit of claim 91 or claim 92, wherein the 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 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, 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 about 1 to about 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, 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 about 1 to about 4 impressions of the microneedle array are to be made per square centimeter of the site.

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

100. The use of claim 98, wherein between about 1 to about 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 about 1 μm to about 700 μm in the manufacture of a kit, 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 about 1 μm to about 500 μm in the manufacture of a kit, 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 about 1/100 of one drop/cm^2 to about 2 drops/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, 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. Use of an emulsion composition of a product volume of about .0001 mls/cm^2 to about 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, 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.

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

106. The use of any one of claims 101-104, wherein the composition comprising a large agent comprises a nanoemulsion comprising the large agent.

107. The use of any one of claims 101-104, wherein the composition comprising a large agent comprises a macroemulsion comprising the large agent.

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

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

110. The use of any one of claims 108-109, 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.

111. The use of any one of claims 101-110, wherein the MSC of the site is to be performed before the composition comprising a large agent is to be applied to the site.

112. The use of any one of claims 101-110, wherein the MSC of the site is to be performed after the composition comprising a large agent is to be applied to the site.

113. The use of claim any one of claims 101-110, wherein the MSC of the site and applying the composition comprising a large agent to the site occur at substantially the same time.

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

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

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

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

118. The use of any one of claims 101-113, wherein the large agent is an antibody agent.

119. The use of claim 118, 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.

120. The use of any one of claims 118-119, 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.

121. The use of any one of claims 118-120, wherein the kit further comprises a biologically active agent, and wherein the biologically active agent is to be delivered with the antibody agent.

122. The use of any one of claims 118-121, wherein the kit further comprises a non-irritating penetration enhancing agent, and wherein the non-irritating penetration enhancing agent is to be delivered with the antibody agent.

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

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

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

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

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

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

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

130. The use of any one of claims 124-129, wherein the needles have a length sufficient to project through the stratum corneum of the skin.

131. The use of any one of claims 124-130, wherein the needles have a length insufficient to reach nerves in the dermis of the skin.

132. The use of any one of claims 124-131, wherein the needles are composed of a biocompatible material.

133. The use of any one of claims 124-131, wherein the needles are composed of a metal.

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

135. The use of any one of claims 101-133, wherein the MN array is not rotated between one or more impressions.

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

137. The use of any one of claims 134-135, wherein the impressions are to be made on overlapping sites.

138. The use of any one of claims 134-135, wherein the impressions are to be made on different sites.

139. The use of any one of claims 134-138, wherein the MN array is in the form of a stamp or roller.

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

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

142. The use of any one of claims 101-140, 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.

143. The use of any one of claims 101-140, wherein the large agent penetrates the skin within about 1, 2, 3, 4, 5, or 6 hours of administration.

144. The use of any one of claims 124-132, wherein the needles are composed of at least one dissolving polymer.

145. The use of any one of claims 101, 106-144, wherein the 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 about 700 μm.

146. The use of any one of claims 102, 106-144, wherein the 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 about 500 μm.

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

148. The use of claim 147, wherein fewer doses of the 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.

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

150. The use of claim 149, 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.

151. The use of any one of claims 145, 147-150, wherein the reference treatment regimen comprises administering the composition comprising a large agent with the reference microneedle array having a microneedle length of greater than about 700 μm.

152. The use of any one of claims 147-150, wherein the reference treatment regimen comprises administering the composition comprising a large agent with the reference microneedle array having a microneedle length of greater than about 500 μm.

153. The use of any one of claims 101-152, wherein the kit is for treating a dermatological disorder.

154. The use of claim 153, 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.

155. The use of any one of claims 101-153, 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.

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

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 density within a range of about 2 to about 50 microneedles/cm^2.

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 in combination with microneedle skin conditioning (MSC) of the site with a microneedle array having a microneedle hole puncture size within a range of about 100 to about 35,000 μm^2/microneedle.

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 density within a range of about 2 to about 50 microneedles/cm^2.

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 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 about 100 to about 35,000 μm^2/microneedle.

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 about 1 to about 13 impressions of the microneedle array are made to 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 wherein between about 1 to about 4 impressions of the microneedle array are made per square centimeter of the site.

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 about 1 μm to about 700 μm.

164. 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 about 1 μm to about 500 μm.

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

applying an emulsion composition of a product volume of about 1/100 of one drop/cm^2 to about 2 drops/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.

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

applying an emulsion composition of a product volume of about .0001 mls/cm^2 to about 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.