DELAYING PEAK EFFECT AND/OR EXTENDING DURATION OF RESPONSE

Cross-Reference To Related Applications

[0001] This application claims priority to United States Provisional Patent Application No. 62/847,901, filed May 14, 2019, the entire contents of which are hereby incorporated by reference in their entirety.

Background

[0002] Significant resources are invested in development of technologies for administration of large agents (*e.g.,* biologically active large agents).

Summary

[0003] The present disclosure describes certain technologies for administering large agent(s) (*e.g.,* biologically active large agents such as biologic therapeutics including, for instance, botulinum toxin) to subjects, and furthermore describes unexpected results achieved by such technologies including, for example, delayed peak effect and/or extended duration of response. In some examples, such unexpected results are achieved relative to administration of the same large agent (*e.g.,* botulinum toxin) according to a reference regimen (*e.g.,* via a formulation, route, and/or dosing regimen understood in the art). Those skilled in the art will be aware of relevant (*e.g.,* appropriately comparable) reference regimens, including those for approved products as described herein. Moreover, those skilled in the art will appreciate that, in some examples, an appropriate reference regimen is one that achieves a peak effect that is comparable in magnitude to that of a provided regimen, and furthermore will be familiar with comparing regimens (and/or effects of regimens) that may involve administration of a relevant large agent (*e.g.,* botulinum toxin) via different formulations, different dose amounts, different number of doses, different spacing between doses, different routes of administration, *etc.* To give but one example, those skilled in the art are aware that individual doses of botulinum toxin administered parenterally are typically much lower (*i.e.,*

and unexpected results, which may, in some examples, include one or both of delayed peak effect and/or extended duration of response.

[0006a] In one aspect of the present disclosure, there is provided a use of a composition comprising a large agent having a molecular weight of 100,000 Da or greater in the manufacture of a medicament for treating a site on skin of a subject in combination with microneedle skin conditioning (MSC), wherein the subject is to be treated with a dosing regimen in which at least two successive doses of the medicament are separated from one another by a time period of at least one month.

[0006b] In another aspect of the present disclosure, there is provided a use of a composition comprising a large agent having a molecular weight of 100,000 Da or greater in the manufacture of a medicament for treating a site on skin of a subject in need of treatment in combination with microneedle skin conditioning (MSC), wherein the subject is to be treated with a dosing regimen that achieves a peak effect of the large agent no sooner than about 1 month after the administering.

[0006c] In a further aspect of the present disclosure, there is provided a non-therapeutic method comprising a step of:

administering a plurality of doses of a composition that delivers a large agent having a molecular weight of 100,000 Da or greater to a site on skin of the subject in combination with microneedle skin conditioning (MSC) according to a dosing regimen in which at least two successive doses are separated from one another by a time period of at least one month.

[0006d] In another aspect of the present disclosure, there is provided a non-therapeutic method comprising a step of:

administering a composition that delivers a large agent having a molecular weight of 100,000 Da or greater to a site on skin of the subject in combination with microneedle skin conditioning (MSC) according to a dosing regimen that achieves a peak effect of the large agent no sooner than about 1 month after the administering.

Brief Description of the Drawing

[0007] Figure 1: Figure 1 presents a bar graph comparing responder rates observed with provided technologies as compared with an approved injectable botulinum toxin therapy, and

illustrates, for example, an extended duration of effect achieved by provided technologies as described herein.

[0008] Figure 2: Figure 2 presents a line graph comparing timing of peak effect for two different approved injectable botulinum toxin therapies with provided topical + MSC therapies and documents, for example, a delayed peak effect achieved by provided technologies as described herein.

Definitions

[0009] 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.

[0010] ***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 to a mechanical means of altering, disrupting, removing, or destroying the top layer of the skin. In some embodiments, abrasion refers to a chemical means of altering, disrupting, removing, or destroying the top layer of skin. To give but a few examples, agents such as exfoliants, fine particles (*e.g.* magnesium or aluminum particles), acids (*e.g.* alpha-hydroxy acids or beta-hydroxy acids), alcohols, may cause abrasion. In general, permeation enhancers such as those described, for example, by Donovan (*e.g.* US Publications 2004/009180 and

We claim:

1. Use of a composition comprising a large agent having a molecular weight of 100,000 Da or greater in the manufacture of a medicament for treating a site on skin of a subject in combination with microneedle skin conditioning (MSC), wherein the subject is to be treated with a dosing regimen in which at least two successive doses of the medicament are separated from one another by a time period of at least one month.

2. The use of claim 1, wherein the time period is at least two months.

3. The use of claim 1, wherein the time period is at least four months.

4. The use of claim 1, wherein the time period is at least six months.

5. The use of claim 1, wherein the time period is at least eight months.

6. The use of claim 1, wherein the time period is at least ten months.

7. The use of claim 1, wherein the time period is at least twelve months.

8. The use of claim 1, wherein the dosing regimen comprises at least three doses of the medicament, separated by at least first and second time periods, wherein the average time period is at least one month.

9. The use of claim 8, wherein the average time period is at least two months.

10. The use of claim 8, wherein the average time period is at least four months.

11. The use of claim 8, wherein the average time period is at least six months.

12. The use of claim 8, wherein the average time period is at least eight months.

13. The use of claim 8, wherein the average time period is at least ten months.

14. The use of claim 8, wherein the average time period is at least twelve months.

15. The use of claim 8, wherein each of the time periods is the same.

16. The use of claim 15, wherein each of the time periods is at least one month.

17. The use of claim 15, wherein each of the time periods is at least two months.

18. The use of claim 15, wherein each of the time periods is at least four months.

19. The use of claim 15, wherein each of the time periods is at least six months.

20. The use of claim 15, wherein each of the time periods is at least eight months.

21. The use of claim 15, wherein each of the time periods is at least ten months.

22. The use of claim 15, wherein each of the time periods is at least twelve months.

23. The use of any one of the preceding claims, wherein the treatment comprises topically applying the composition to the site.

24. The use of any one of the preceding claims, wherein the composition comprises a nanoemulsion.

25. The use any one of the preceding claims, wherein the composition comprises a macroemulsion.

26. The use of any one of the preceding claims, wherein a non-irritating penetration enhancing agent is to be further administered to the subject.

27. The use of claim 26, wherein the non-irritating penetration enhancing agent is selected from carrier peptides and co-peptides.

28. The use of any one of claims 26-27, 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.

29. The use of any one of the preceding claims, wherein the subject is to be treated with the medicament, and wherein the MSC is to be performed on the subject prior to the treatment with the medicament.

30. The use of any one of the preceding claims, wherein the subject is to be treated with the medicament, and wherein the MSC is to be performed on the subject after the treatment with the medicament.

31. The use of any one of the preceding claims, wherein the subject is to be treated with the medicament, and wherein the MSC is to be performed on the subject while being treated with the medicament.

32. The use of any one of the preceding claims, wherein the large agent is a botulinum toxin.

33. The use of claim 32, wherein the treatment is further in combination with a cosmetic or therapeutic agent.

34. The use of claim 33, wherein the cosmetic or therapeutic agent is selected from the group consisting of anesthetics, collagen, fillers, retinoids, silicone, steroids, and combinations thereof.

35. The use of claim 34, wherein the cosmetic or therapeutic agent is selected from the group consisting of hydrocortisone, retin A, lidocaine, and combinations thereof.

36. The use of any one of the preceding claims, wherein the large agent is an antibody agent.

37. The use of claim 36, wherein the antibody agent is selected from the group consisting of 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.

38. The use of any one of claims 36-37, wherein the antibody agent is selected from the group consisting of 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.

39. The use of any one of claims 36-38, wherein the treatment is further in combination with a cosmetic or therapeutic agent.

40. The use of any one of claims 36-39, a non-irritating penetration enhancing agent is to be further administered to the subject.

41. The use of claim 40, wherein the non-irritating penetration enhancing agent is selected from co-peptides and carrier peptides.

42. The use of any one of the preceding claims, wherein the MSC is accomplished with a device comprising at least one microneedle (MN).

43. The use of claim 42, wherein the device comprises a plurality of MN.

44. The use of claim 42 or 43, wherein the device is a patch, a roller, a stamp, or a pen.

45. The use of any one of the preceding claims, wherein the site is a skin surface overlying a muscle or muscle group.

46. The use of any one of the preceding claims, wherein the site is a skin surface that contains sweat glands.

47. The use of any one of the preceding claims, wherein the site is a skin surface that contains sebaceous glands.

48. The use of any one of the preceding claims, wherein the site is a skin surface that contains hair follicles.

49. The use of any one of claims 42-47, wherein the MN have a length sufficient to project through the stratum corneum of the skin.

50. The use of any one of claims 42-49, wherein the MN have a length insufficient to reach nerves in the dermis of the skin.

51. The use of any one of claims 42-50, wherein the MN are composed of a biocompatible material.

52. The use of any one of claims 42-51, wherein the MN are composed of a metal.

53. The use of any one of claims 42-51, wherein the MN are composed of at least one dissolving polymer.

54. The use of any one of the preceding claims, wherein during the MSC, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 microneedle (MN) impressions are to be administered, wherein each impression is made in a period of continuous contact between the site and a device that comprises one or more MNs.

55. The use of claim 54, wherein the device is or comprises a stamp that includes the one or more MNs.

56. The use of claim 54, wherein the device is or comprises a roller that includes the one or more MNs.

57. The use of claim 54, wherein the device is or comprises a patch that includes the one or more MNs.

58. The use of any one of claims 54-57, wherein the device comprises a plurality of MNs and MNs of the plurality are arranged in a geometrical pattern.

59. The use of claim 54, wherein during the MSC, a plurality of the impressions is to be administered.

60. The use of any one of claims 59, wherein two or more of the impressions are made on approximately the same site.

61. The use of any one of claims 59, wherein two or more of the impressions are made on overlapping sites.

62. The use of any one of claims 54-59, wherein individual impressions are made on different sites.

63. The use of any one of claims 54-62, wherein the impressions are made by stamping.

64. The use of any one of claims 54-62, wherein the impressions are made by rolling.

65. The use of any one of the preceding claims, wherein the treatment achieves delivery of the large agent into the skin within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes.

66. The use of any one of the preceding claims, wherein the treatment achieves delivery of the large agent into 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.

67. The use of any one of the preceding claims, wherein the treatment achieves delivery of the large agent into the skin within about 1, 2, 3, 4, 5, or 6 hours.

68. The use of any one of the preceding claims, wherein the medicament is for treating a dermatological disease, disorder, or condition.

69. The use of any one of the preceding claims wherein the subject is suffering from or susceptible to a dermatological disease, disorder, or condition and the treatment achieves improvement of one or more features or symptoms of the dermatological disease, disorder, or condition.

70. The use of claim 68 or 69, wherein the dermatological disease, disorder, or condition is selected from acne, actinic keratosis, body odor, bromhidrosis, burns, chromhidrosis, dermal infection, eczematous dermatitis, excess sebum-producing disorders, facial wrinkles, hair loss, hyperfunctional facial lines, hyperhidrosis, hyperkinetic facial lines, hyperpigmentation disorders, hypopigmentation disorders, keloids, linear morphea, lupus erythematosus, neck lines, platysma bands, psoriasis, Raynaud's Syndrome, rosacea, scleroderma, skin cancer, unsightly facial expressions, unwanted sweating, and/or combinations thereof.

71. The use of any one of the preceding claims, wherein the medicament is for treating or preventing a disease, disorder, or condition selected from acne (*e.g.,* which may be associated with excess sebum production, infection, etc), amyloidosis (*e.g.,* cutaneous amyloidosis), asthma, body odor, burns, cancer (*e.g.,* blood cancer, breast cancer, colon cancer, lung cancer, skin cancer), disorders associated with sun exposure (*e.g.,* actinic keratosis, sunburn, skin cancer such as melanoma, etc), inflammatory conditions (*e.g.,* chronic obstructive pulmonary disorder, Crohn's disease, sweating disorders (*e.g.,* bromhidrosis, chromhidrosis, dermal infection, discoid lupus, drug-induced lupus, eczematous dermatitis, excess sebum-producing disorders, facial wrinkles, hair loss, hyperfunctional facial lines, hyperhidrosis, hyperkinetic facial lines, hyperpigmentation disorders, hyperplasia (*e.g.,* prostate hyperplasia), hypopigmentation disorders, inflammatory bowel disease, keloids, linear morphea, lupus erythematosus, neck lines, neonatal lupus, osteoarthritis, platysma bands, psoriasis, psoriatic arthritis, pulmonary disorders, Raynaud's Syndrome, rheumatoid arthritis, rosacea, scleroderma, skin cancer, systemic amyloidosis, systemic lupus , ulcerative colitis, unsightly facial expressions, unwanted sweating, 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, and/or combinations thereof.

72. The use of any one of the preceding claims, wherein the composition is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

73. Use of a composition comprising a large agent having a molecular weight of 100,000 Da or greater in the manufacture of a medicament for treating a site on skin of a subject in need of treatment in combination with microneedle skin conditioning (MSC), wherein the subject is to be treated with a dosing regimen that achieves a peak effect of the large agent no sooner than about 1 month after the administering.

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

administering a plurality of doses of a composition that delivers a large agent having a molecular weight of 100,000 Da or greater to a site on skin of the subject in combination with microneedle skin conditioning (MSC) according to a dosing regimen in which at least two successive doses are separated from one another by a time period of at least one month.

75. The non-therapeutic method of claim 74, wherein the time period is at least two months.

76. The non-therapeutic method of claim 74, wherein the time period is at least four months.

77. The non-therapeutic method of claim 74, wherein the time period is at least six months.

78. The non-therapeutic method of claim 74, wherein the time period is at least eight months.

79. The non-therapeutic method of claim 74, wherein the time period is at least ten months.

80. The non-therapeutic method of claim 74, wherein the time period is at least twelve months.

81. The non-therapeutic method of claim 74, wherein the dosing regimen comprises administering at least three doses, separated by at least first and second time periods, wherein the average time period is at least one month.

82. The non-therapeutic method of claim 81, wherein the average time period is at least two months.

83. The non-therapeutic method of claim 81, wherein the average time period is at least four months.

84. The non-therapeutic method of claim 81, wherein the average time period is at least six months.

85. The non-therapeutic method of claim 81, wherein the average time period is at least eight months.

86. The non-therapeutic method of claim 81, wherein the average time period is at least ten months.

87. The non-therapeutic method of claim 81, wherein the average time period is at least twelve months.

88. The non-therapeutic method of claim 81, wherein each of the time periods is the same.

89. The non-therapeutic method of claim 88, wherein each of the time periods is at least one month.

90. The non-therapeutic method of claim 88, wherein each of the time periods is at least two months.

91. The non-therapeutic method of claim 88, wherein each of the time periods is at least four months.

92. The non-therapeutic method of claim 88, wherein each of the time periods is at least six months.

93. The non-therapeutic method of claim 88, wherein each of the time periods is at least eight months.

94. The non-therapeutic method of claim 88, wherein each of the time periods is at least ten months.

95. The non-therapeutic method of claim 88, wherein each of the time periods is at least twelve months.

96. The non-therapeutic method of any one of the preceding claims, wherein the administering comprises topically applying the composition to the site.

97. The non-therapeutic method of any one of the preceding claims, wherein the composition comprises a nanoemulsion.

98. The non-therapeutic method any one of the preceding claims, wherein the composition comprises a macroemulsion.

99. The non-therapeutic method of any one of the preceding claims, further comprising a step of administering a non-irritating penetration enhancing agent.

100. The non-therapeutic method of claim 99, wherein the non-irritating penetration enhancing agent is selected from carrier peptides and co-peptides.

101. The non-therapeutic method of any one of claims 99-100, 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.

102. The non-therapeutic method of any one of the preceding claims, wherein the step of administering comprises performing the MSC prior to administration of the composition to the site.

103. The non-therapeutic method of claim any one of the preceding claims, wherein the step of administering comprises performing the MSC after administration of the composition to the site.

104. The non-therapeutic method of claim any one of the preceding claims, wherein the step of administering comprises performing the MSC concurrently with administration of the composition to the site .

105. The non-therapeutic method of any one of the preceding claims, wherein the large agent is a botulinum toxin.

106. The non-therapeutic method of claim 105, wherein the step of administering is further in combination with a cosmetic agent.

107. The method of claim 106, wherein the cosmetic agent is selected from the group consisting of anesthetics, collagen, fillers, retinoids, silicone, steroids, and combinations thereof.

108. The non-therapeutic method of claim 107, wherein the cosmetic agent is selected from the group consisting of hydrocortisone, retin A, lidocaine, and combinations thereof.

109. The non-therapeutic method of any one of the preceding claims, wherein the large agent is an antibody agent.

110. The non-therapeutic method of claim 109, wherein the antibody agent is selected from the group consisting of 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.

111. The non-therapeutic method of any one of claims 109-110, wherein the antibody agent is selected from the group consisting of 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.

112. The non-therapeutic method of any one of claims 109-111, wherein the step of administering is further in combination with a cosmetic agent.

113. The non-therapeutic method of any one of claims 109-112, further comprising a step of administering a non-irritating penetration enhancing agent.

114. The non-therapeutic method of claim 113, wherein the non-irritating penetration enhancing agent is selected from co-peptides and carrier peptides.

115. The non-therapeutic method of any one of the preceding claims, wherein the MSC is accomplished with a device comprising at least one microneedle (MN).

116. The non-therapeutic method of claim 115, wherein the device comprises a plurality of MN.

117. The non-therapeutic method of claim 115 or 116, wherein the device is a patch, a roller, a stamp, or a pen.

118. The non-therapeutic method of any one of the preceding claims, wherein the site is a skin surface overlying a muscle or muscle group.

119. The non-therapeutic method of any one of the preceding claims, wherein the site is a skin surface that contains sweat glands.

120. The non-therapeutic method of any one of the preceding claims, wherein the site is a skin surface that contains sebaceous glands.

121. The non-therapeutic method of any one of the preceding claims, wherein the site is a skin surface that contains hair follicles.

122. The non-therapeutic method of any one of claims 115-120, wherein the MN have a length sufficient to project through the stratum corneum of the skin.

123. The non-therapeutic method of any one of claims 115-122, wherein the MN have a length insufficient to reach nerves in the dermis of the skin.

124. The non-therapeutic method of any one of claims 115-123, wherein the MN are composed of a biocompatible material.

125. The non-therapeutic method of any one of claims 115-124, wherein the MN are composed of a metal.

126. The non-therapeutic method of any one of claims 115-124, wherein the MN are composed of at least one dissolving polymer.

127. The non-therapeutic method of any one of the preceding claims, wherein the MSC comprises administration of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 microneedle (MN) impressions, wherein each impression is made in a period of continuous contact between the site and a device that comprises one or more MNs.

128. The non-therapeutic method of claim 127, wherein the device is or comprises a stamp that includes the one or more MNs.

129. The non-therapeutic method of claim 127, wherein the device is or comprises a roller that includes the one or more MNs.

130. The non-therapeutic method of claim 127, wherein the device is or comprises a patch that includes the one or more MNs.

131. The non-therapeutic method of any one of claims 127-140, wherein the device comprises a plurality of MNs and MNs of the plurality are arranged in a geometrical pattern.

132. The non-therapeutic method of claim 127, wherein the MSC comprises administration of a plurality of the impressions.

133. The non-therapeutic method of any one of claims 132, wherein two or more of the impressions are made on approximately the same site.

134. The non-therapeutic method of any one of claims 132, wherein two or more of the impressions are made on overlapping sites.

135. The non-therapeutic method of any one of claims 127-132, wherein individual impressions are made on different sites.

136. The non-therapeutic method of any one of claims 127-135, wherein the impressions are made by stamping.

137. The non-therapeutic method of any one of claims 127-135, wherein the impressions are made by rolling.

138. The non-therapeutic method of any one of the preceding claims, wherein the step of administering achieves delivery of the large agent into the skin within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes.

139. The non-therapeutic method of any one of the preceding claims, wherein the step of administering achieves delivery of the large agent into 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.

140. The non-therapeutic method of any one of the preceding claims, wherein the step of administering achieves delivery of the large agent into the skin within about 1, 2, 3, 4, 5, or 6 hours.

141. The non-therapeutic method of any one of the preceding claims, wherein the composition is formulated as a lotion, cream, powder, ointment, liniment, gel, or drops.

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

administering a composition that delivers a large agent having a molecular weight of 100,000 Da or greater to a site on skin of the subject in combination with microneedle skin conditioning (MSC) according to a dosing regimen that achieves a peak effect of the large agent no sooner than about 1 month after the administering.