methods, considerable practical limitations exist in the design and fabrication associated with microneedle arrays constructed using conventional processes.

SUMMARY

The systems and methods disclosed herein include cutaneous delivery platforms based on dissolvable microneedle arrays that can provide efficient, precise, and reproducible delivery of biologically active molecules to human skin. The microneedle array delivery platforms can be used to deliver a broad range of bioactive components to a patient, including chemotherapeutic agents as disclosed herein for cancer therapy applications.

In one aspect, the present disclosure refers to a dissolvable microneedle array for transdermal insertion into a patient comprising:

a therapeutically effective amount of one or more bioactive components, the one or more bioactive components including at least one chemotherapeutic agent;

a base portion; and

a plurality of microneedles extending from the base portion, wherein substantially all of the one or more bioactive components are located in the plurality of microneedles so that the base portion is substantially formed without any bioactive components contained therein.

In another aspect, the present disclosure refers to a method of fabricating a microneedle array by forming a sheet of material having a plurality of layers, the method comprising:

applying a first solution of a dissoluble biocompatible material having one or more bioactive components contained therein to a microneedle array production mold, the one or more bioactive components including at least one chemotherapeutic agent in a therapeutically effective amount;

applying a second solution of a dissoluble biocompatible material that does not contain one or more active components to the microneedle array production mold; and

drying the first and second solutions to form a solid microneedle array that comprises a base portion and a plurality of microneedles that extend from the base portion, wherein the one or more active components are substantially concentrated in the plurality of microneedles.

In another aspect, the present disclosure refers to a use of at least one chemotherapeutic agent in the manufacture of a medicament for treating skin cancer in a subject, wherein the subject has skin cancer or is at risk for having skin cancer, and wherein the medicament is to be delivered to the subject by the application of the microneedle array as described herein to an area of the subject.

The foregoing and other objects, features, and advantages of the disclosed embodiments will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates exemplary microneedles and their dimensions.

FIG. 2 illustrates an exemplary microneedle array and its dimensions.

FIGS. 3A and 3B illustrate exemplary microneedles with tip-loaded active components.

FIGS. 4A and 4B illustrate exemplary microneedles with tip-loaded active components.

FIGS. 5A and 5B illustrate exemplary microneedles with tip-loaded active components.

FIGS. 6A and 6B illustrate exemplary microneedles with tip-loaded active components.

FIG. 7 illustrates a miniature precision-micromilling system used for fabricating microneedle mastermolds.

FIG. 8 is an SEM image of a micromilled mastermold with pyramidal needles.

FIG. 9 is an SEM image of a pyramidal production mold.

FIG. 10 is an SEM image of an enlarged segment of the production mold, illustrating a pyramidal needle molding well in the center of the image.

FIGS. 11A-11D illustrate exemplary CMC-solids and embedded active components.

FIGS. 12A and 12B illustrate exemplary CMC-solids and embedded active components.

FIG. 13 is a schematic illustration of exemplary vertical multi-layered deposition structures and methods of fabricating the same.

FIG. 14 is a schematic illustration of exemplary microneedle arrays fabricated using layering and spatial distribution techniques of embedded active components.

We claim:

1. A dissolvable microneedle array for transdermal insertion into a patient comprising:

a therapeutically effective amount of one or more bioactive components, the one or more bioactive components including at least one chemotherapeutic agent;

a base portion; and

a plurality of microneedles extending from the base portion, wherein substantially all of the one or more bioactive components are located in the plurality of microneedles so that the base portion is substantially formed without any bioactive components contained therein.

2. The microneedle array of claim 1, wherein the one or more bioactive components comprises doxorubicin.

3. The microneedle array of claim 2, wherein the amount of doxorubicin is about 50 to 200 micrograms.

4. The microneedle array of claim 1, wherein the one or more bioactive component comprises at least two different chemotherapeutic agents.

5. The microneedle array of claim 4, wherein the two different chemotherapeutic agents comprise doxorubicin and at least one other anthracycline agent.

6. The microneedle array of claim 1, wherein the at least one chemotherapeutic agent comprises a cytotoxic agent and an immunostimulant agent.

7. The microneedle array of claim 6, wherein the immunostimulant comprises at least one adjuvant.

8. The microneedle array of claim 6, wherein the immunostimulant comprises at least one TLR antagonist.

9. The microneedle array of claim 6, wherein the immunostimulant comprises at least

one of a ribonucleotide or deoxyribonucleotide.

10. The microneedle array of claim 6, wherein the immunostimulant comprises at least one dsRNA.

11. The microneedle array of claim 6, wherein the immunostimulant comprises at least one Poly(I:C) derviative.

12. The microneedle array of claim 6, wherein the immunostimulant comprises Poly(I:C).

13. The microneedle array of claim 6, wherein the immunostimulant comprises Poly-ICLC.

14. The microneedle array of claim 6, wherein the cytotoxic agent is doxorubicin and the immunostimulant comprises Poly(I:C).

15. The microneedle array of claim 6, wherein the cytotoxic agent is doxorubicin and the immunostimulant comprises Poly-ICLC.

16. The microneedle array of claim 1, wherein the one or more bioactive components are locally concentrated in the plurality of microneedles so that the one or more bioactive components are generally present only in an upper half of respective microneedles in the microneedle array.

17. The microneedle array of claim 1, wherein the plurality of microneedles are pre-formed to have a shape that comprises a first cross-sectional dimension at a top portion, a second cross-sectional dimension at a bottom portion, and a third cross-sectional dimension at an intermediate portion, wherein the intermediate portion is located between the top portion and the bottom portion, and the third cross-sectional dimension is greater than the first and second cross-sectional dimensions.

18. The microneedle array of claim 17, wherein the one or more bioactive components are substantially concentrated in the area at or above the intermediate portion.

19. The microneedle array of claim 18, wherein each microneedle generally tapers to a point above the intermediate portion and each microneedle generally tapers to a smaller cross-sectional dimension below the intermediate portion.

20. The microneedle array of claim 1, wherein each microneedle comprises a plurality of layers of dissoluble biocompatible material.

21. The microneedle array of claim 20, wherein the dissoluble biocompatible material is carboxymethylcellulose.

22. The microneedle array of claim 20, wherein the one or more bioactive component comprises at least two different chemotherapeutic agents, and the at least two different chemotherapeutic agents comprise doxorubicin and at least one other anthracycline agent.

23. The microneedle array of claim 4, wherein the at least two chemotherapeutic agents are selected from the group consisting of a chemotherapeutic agent, an adjuvant, and a chemo attractant for a cancer chemo immunotherapy application.

24. A method of fabricating a microneedle array by forming a sheet of material having a plurality of layers, the method comprising:

applying a first solution of a dissoluble biocompatible material having one or more bioactive components contained therein to a microneedle array production mold, the one or more bioactive components including at least one chemotherapeutic agent in a therapeutically effective amount;

applying a second solution of a dissoluble biocompatible material that does not contain one or more active components to the microneedle array production mold; and

drying the first and second solutions to form a solid microneedle array that comprises a base portion and a plurality of microneedles that extend from the base portion, wherein the one or more active components are substantially concentrated in the plurality of microneedles.

25. The method of claim 24, wherein the one or more bioactive component comprises doxorubicin.

26. The method of claim 25, wherein the amount of doxorubicin is about 50 and 200 micrograms.

27. The method of claim 24, wherein the one or more bioactive component comprises at least two different chemotherapeutic agents.

28. The method of claim 27, wherein the at least two different chemotherapeutic agents comprise doxorubicin and at least one other anthracycline agent, and the dissoluble biocompatible material is carboxymethylcellulose.

29. The method of claim 24, wherein the at least one chemotherapeutic agent comprises both a cytotoxic agent and an immunostimulant agent.

30. The method of claim 29, wherein the immunostimulant comprises at least one adjuvant.

31. The method of claim 29, wherein the immunostimulant comprises at least one TLR antagonist.

32. The method of claim 29, wherein the immunostimulant comprises at least one of a ribonucleotide or deoxyribonucleotide.

33. The method of claim 29, wherein the immunostimulant comprises at least one dsRNA.

34. The method of claim 29, wherein the immunostimulant comprises at least one Poly(I:C) derviative.

35. The method of claim 29, wherein the immunostimulant comprises Poly(I:C).

36. The method of claim 29, wherein the immunostimulant comprises Poly-ICLC.

37. The method of claim 29, wherein the cytotoxic agent is doxorubicin and the immunostimulant comprises Poly(I:C).

38. The method of claim 29, wherein the cytotoxic agent is doxorubicin and the immunostimulant comprises Poly-ICLC.

39. The method of claim 24, wherein the one or more bioactive components are substantially concentrated in an upper half of respective microneedles of the microneedle array.

40. The method of claim 24, further comprising:

removing portions from the sheet of material until the microneedle array is formed having a base portion and plurality of microneedles extending from the base portion, wherein the removal of portions from the sheet array comprises forming the microneedle array so that the one or more bioactive component is concentrated in the respective microneedles of the microneedle array and the one or more bioactive components are substantially absent from the base portion.

41. The method of claim 40, wherein the method of removing portions comprises micromilling the sheet of material to form a microneedle array.

42. ~~A method of treating skin cancer~~Use of at least one chemotherapeutic agent in the manufacture of a medicament for treating skin cancer in a subject, wherein the subject has skin cancer or is at risk for having skin cancer, and wherein the medicament is to be delivered to the subject by the application of the microneedle array of claim 1 to an area of the subject~~, comprising:~~

~~selecting a subject that has skin cancer or is at risk for having skin cancer; and~~

~~applying the microneedle array of claim 1 to an area of the subject to deliver an effective amount of the at least one chemotherapeutic agent to the subject~~.

43. The ~~method~~ use of claim 42, wherein the one or more bioactive components of the microneedle array comprises doxorubicin.

44. The ~~method~~ use of claim 43, wherein the amount of doxorubicin is about 50 and 200 micrograms.

45. The ~~method~~ use of claim 43, wherein the one or more bioactive components of the microneedle array comprise at least two different chemotherapeutic agents.

46. The use~~method~~ of claim 42, wherein the microneedle array comprises a dissoluble biocompatible material.

47. The ~~method~~ use of claim 46, wherein the dissoluble biocompatible material is carobxymethylcellulose.

48. The ~~method~~ use of claim 45, wherein the at least two different chemotherapeutic agents comprise doxorubicin and at least one other anthracycline agent, and the microneedle array comprises a dissoluble biocompatible material.

49. The ~~method~~ use of claim 45, wherein the at least two chemotherapeutic agents comprise a cytotoxic agent and an immunostimulant agent.

50. The use~~method~~ of claim 49, wherein the immunostimulant comprises at least one adjuvant.

51. The use~~method~~ of claim 49, wherein the immunostimulant comprises at least one TLR antagonist.

52. The use~~method~~ of claim 49, wherein the immunostimulant comprises at least one of a ribonucleotide or deoxyribonucleotide.

53. The use~~method~~ of claim 49, wherein the immunostimulant comprises at least one dsRNA.

54. The use~~method~~ of claim 49, wherein the immunostimulant comprises at least one Poly(I:C) derviative.

55. The use~~method~~ of claim 49, wherein the immunostimulant comprises Poly(I:C).

56. The use~~method~~ of claim 49, wherein the immunostimulant comprises Poly-ICLC.

57. The use ~~method~~ of claim 49, wherein the cytotoxic agent is doxorubicin and the immunostimulant comprises Poly(I:C).

58. The use~~method~~ of claim 49, wherein the cytotoxic agent is doxorubicin and the immunostimulant comprises Poly-ICLC.