IMPROVED FLUID DELIVERY APPRATUS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 62/942971 filed December 3, 2019 and entitled "IMPROVED FLUID DELIVERY APPARATUS," the contents of which is incorporated by reference herein in its entirety.

BACKGROUND

~~DESCRIPTION~~

~~INTRODUCTION AND SUMMARY~~

The present disclosure relates generally to a fluid delivery apparatus, and more specifically relates to an injectable fluid delivery apparatus. The present disclosure also relates to methods of applying a fluid delivery apparatus to a subject's skin to deliver a fluidic composition across a dermal barrier of a subject.

Conventionally delivery forms for small-molecule drugs and biological agents in various clinical applications include subcutaneous injections, intravenous infusions, oral tablets, nasal sprays, but these methods present difficulties. Intradermal or subcutaneous administration can be painful. A large first pass effect is seen with oral administration, which causes delayed onset of therapeutic effects. These methods also are not suitable for treatment of diseases of the lymphatics, which requires administration of drugs directly into the lymphatics.

There is a need for intra-lymphatic drug delivery to provide improved efficacy through more effective concentrations in the disease areas, lymphatic system, and lymph nodes, and/or through achieving biological or clinical effects for drugs active in the lymphatics with reduced dose levels. Such intra-lymphatic drug delivery can provide advantages over other methods of drug delivery, including achievement of systemic exposures faster than oral delivery, avoiding the first pass effect, and extended PK profiles for drugs that have a half-life when administered by other routes.

SUMMARY OF INVENTION

In one aspect, the present disclosure provides an injectable fluidic delivery device to improve the efficacy and safety of small molecules and biological agents through tunable pharmacokinetics (PK) and intra-lymphatic drug delivery. The device includes an array of active-hollow micro-sized protrusions covered with a nanopatterned layer with a fluidic distribution assembly that can precisely control the flow out of each protrusion. After device activation, the protrusions penetrate the skin to a depth that is distributed between the epidermal and dermal skin layers proximal to the initial lymphatic capillaries. This location of the protrusions can create a

WHAT IS CLAIMED IS:

1. A device for delivering a fluidic composition across a dermal barrier of a subject, the device comprising:
    a. a fluid distribution assembly comprising:
        i. a base;
        ii. a plurality of protrusions defined on the base, wherein each of the protrusions has a tip and a height at a microscale with a fluidic path defined therein along the height from the base;
        iii. a nanopatterned layer comprising a plurality of nanostructures and covering a surface of the plurality of protrusions;
        iv. a gasket comprising a pressure-sensitive adhesive (PSA) layer;
        v. a fluidic distribution manifold configured to be fluidically connected with the fluidic path of the protrusions and to controllably distribute the fluidic composition among the plurality of protrusions through the fluidic path;
    b. a plenum assembly slidably coupled to the fluidic block and configured to hold the fluidic distribution assembly;
    c. a collet assembly constituting the housing of the device and configured to contact a surface of the subject's skin sufficient for penetration of the plurality of protrusions into the surface of the subject's skin and across the dermal barrier; and
    d. a controller assembly slidably coupled to the fluidic block and configured to control the flow of the fluidic composition during delivery of the fluidic composition through the plurality of protrusions;

    wherein the number of protrusions in the plurality of protrusions is from about 4 to about 3000 protrusions and the device is capable of controllably delivering the fluidic composition to a location below the dermal barrier at a flow rate of greater than about 0.1 µl/hour per protrusion, or at a flow rate ranging from about 0.1 µl/hour to about 10 µl/hour per protrusion.
2. A device for delivering a fluidic composition across a dermal barrier of a subject, the device comprising:
    a. a fluid distribution assembly comprising:
        i. a base;

ii. a plurality of protrusions defined on the base, wherein each of the protrusions has a tip and a height at a microscale with a fluidic path defined therein along the height from the base;

iii. a nanopatterned layer comprising a plurality of nanostructures and covering a surface of the plurality of protrusions;

iv. a gasket comprising a pressure-sensitive adhesive (PSA) layer;

v. a fluidic distribution manifold configured to be fluidically connected with the fluidic path of the protrusions and to controllably distribute the fluidic composition among the plurality of protrusions through the fluidic path, the fluid distribution manifold comprising:

an inlet channel;

a plurality of supply channels and resistance channels, wherein each supply channel is connected to a respective resistance channel that facilitates an increase in the resistance to the flow of the fluid;

an outlet channel aligned with and fluidically connected to the fluidic path of the protrusions;

b. a plenum assembly slidably coupled to the fluidic block and configured to hold the fluidic distribution assembly;

c. a collet assembly constituting the housing of the device and configured to contact a surface of the subject's skin sufficient for penetration of the plurality of protrusions into the surface of the subject's skin and across the dermal barrier; and

d. a controller assembly slidably coupled to the fluidic block and configured to control the flow of the fluidic composition during delivery of the fluidic composition through the plurality of protrusions;

wherein the device is capable of delivering the fluidic composition at a flow rate greater than about 0.1 μl/hour per protrusion, or at a flow rate ranging from about 0.1 μl/hour to about 10 μl/hour per protrusion.

3. A device for delivering a fluidic composition across a dermal barrier of a subject, the device comprising:

a. a fluid distribution assembly comprising:

i. a base;

ii. a plurality of protrusions defined on the base, wherein each of the protrusions has a tip and a height at a microscale with a fluidic path defined therein along the height from the base;

iii. a nanopatterned layer comprising a plurality of nanostructures and covering a surface of the plurality of protrusions;

iv. a gasket comprising a pressure-sensitive adhesive (PSA) layer;

v. a fluidic distribution manifold configured to be fluidically connected with the fluidic path of the protrusions and to controllably distribute the fluidic composition among the plurality of protrusions through the fluidic path;

b. a plenum assembly slidably coupled to the fluidic block and configured to hold the fluidic distribution assembly;

c. a collet assembly constituting the housing of the device and comprising a collet and a collet lock, wherein the collet assembly is configured to contact a surface of the subject's skin sufficient for penetration of the plurality of protrusions into the surface of the subject's skin and across the dermal barrier; and

d. a controller assembly slidably coupled to the fluidic block and configured to control the flow of the fluidic composition during delivery of the fluidic composition through the plurality of protrusions;

e. an attachment band assembly configured to couple to the collet assembly to facilitate contact with a surface of the subject's skin sufficient for penetration of the plurality of protrusions into the surface of the subject's skin and across the dermal barrier, wherein the attachment band assembly comprises:

an annular body comprising a wall defining a hollow inner space and a coupling member to engage with a corresponding coupling member of the collet, wherein the annular body is configured to attach to the collet of the collet assembly; and

a strap assembly removably engaged with the annular body and comprising a hoop-and-loop type fastening strap such that in use, the strap is threaded through a portion of the annular body and folded back to tighten the strap around the skin of the subject.

4. A device for delivering a fluidic composition across a dermal barrier of a subject, the device comprising:

a. a fluid distribution assembly comprising:

i. a base;

ii. a plurality of protrusions defined on the base, wherein each of the protrusions has a tip and a height at a microscale with a fluidic path defined therein along the height from the base;

iii. a nanopatterned layer comprising a plurality of nanostructures and covering a surface of the plurality of protrusions;

iv. a gasket comprising a pressure-sensitive adhesive (PSA) layer;

v. a fluidic block configured to be fluidically connected with the fluidic path of the protrusions and to controllably distribute the fluidic composition among the plurality of protrusions through the fluidic path;

b. a plenum assembly slidably coupled to the fluidic block and configured to hold the fluidic distribution assembly, comprising

a plenum having a center portion removably connected to a tubing system to provide a pressured flow of the fluidic composition from a reservoir for holding the fluidic composition located exterior of the device; and

a plenum cap assembly configured to facilitate gas extraction from the fluid;

c. a collet assembly constituting the housing of the device and comprising a collet and a collet lock, wherein the collet assembly is configured to contact a surface of the subject's skin sufficient for penetration of the plurality of protrusions into the surface of the subject's skin and across the dermal barrier; and

d. an external infusion pump configured to control the flow of the fluidic composition during delivery of the fluidic composition through the plurality of protrusions;

wherein the device is capable of controllably delivering the fluidic composition to a location below the dermal barrier, at a flow rate greater than about 0.1 µl/hour per protrusion, or at a flow rate ranging from about 0.1 µl/hour to about 10 µl/hour per protrusion.

5. A device for delivering a fluidic composition across a dermal barrier of a subject, the device comprising:

a. a fluid distribution assembly comprising:

i. a base;

ii. a plurality of protrusions defined on the base, wherein each of the protrusions has a tip and a height at a microscale with a fluidic path defined therein along the height from the base;

iii. a nanopatterned layer comprising a plurality of nanostructures and covering a surface of the plurality of protrusions;

iv. a gasket comprising a pressure-sensitive adhesive (PSA) layer;

v. a fluidic block configured to be fluidically connected with the fluidic path of the protrusions and to controllably distribute the fluidic composition among the plurality of protrusions through the fluidic path;

b. a plenum assembly slidably coupled to the fluidic block and configured to hold the fluidic distribution assembly, comprising

a plenum component;

a cannula around a center axis coupled in fluid communication with the fluidic block; and

a plenum cap assembly configured to facilitate gas extraction from the fluid;

c. a cartridge assembly comprising a reservoir component includes an upper cavity and an opposing lower cavity coupled together in flow communication with the fluidic block via the cannula of the plenum assembly;

d. a collet assembly constituting the housing of the device and comprising a collet and a collet lock, wherein the collet assembly is configured to contact a surface of the subject's skin sufficient for penetration of the plurality of protrusions into the surface of the subject's skin and across the dermal barrier; and

e. a controller assembly slidably coupled to the fluidic block and configured to control the flow of the fluidic composition during delivery of the fluidic composition through the plurality of protrusions, comprising:

a plunger member positionable in a range from a first position proximal to the plenum, to a second position distant from the plenum; and

a bias assembly positioned between the plenum and the plunger member, the bias assembly being configured to apply a pressure to the plunger member, wherein the pressure applied to the plunger member by the biasing assembly is transmitted to the plenum and facilitates displacing the fluidic composition into the fluidic block~~.~~

wherein the device is capable of penetrating the dermal barrier of the subject and controllably delivering the fluidic composition to a location below the dermal barrier, at a flow rate greater than about 0.1 µl/hour per protrusion, or at a flow rate ranging from about 0.1 µl/hour to about 10 µl/hour per protrusion.

6. The device of any one of claims 1-5, wherein the device is capable of delivering the fluidic composition to a location below the dermal barrier from about 50 µm to about 4000 µm, from about 250 µm to about 2000 µm, or from about 350 µm to about 1000 µm in depth~~.~~; optionally

~~7. The device of any one of claims 1-6,~~ wherein the device is capable of delivering the fluidic composition to a location below the dermal barrier and proximate to the lymphatic vasculature of the subject.

~~8~~7. The device of any one of claims 1-~~7~~6, wherein the dermal barrier comprises the stratum corneum of the subject~~.~~;

~~9. The device of any one of claims 1-7, wherein the dermal barrier comprises~~ a portion of the epidermis of the subject~~.~~; and/or

~~10. The device of any one of claims 1-7, wherein the dermal barrier comprises~~ the entire thickness of epidermis of the subject~~.~~; and/or

~~11. The device of any one of claims 1-7, wherein the dermal barrier comprises~~ at least a portion of the dermis of the subject.

~~12~~8. The device of any one of claims 1-~~11~~7, wherein the device is capable of delivering the fluidic composition having a viscosity from about 1 centipoise to about 100 centipoise~~.~~; optionally,

~~13. The device of any one of claims 1-12, wherein the device is capable of delivering the fluidic composition~~ having a viscosity from about 1 centipoise to about 5 centipoise.

~~14~~9. The device of any one of claims 1-~~13~~8, wherein the device is capable of delivering the fluidic composition having a bioactive (diagnostic or therapeutic) agent in a concentration of from about 5 mg/mL to about 100 mg/mL.

~~15~~10. The device of any one of claims 1-~~14~~9, wherein the plurality of protrusions comprises from about 4 to about 3,000 protrusions; optionally,

~~16. The device of any one of claims 1-15,~~ wherein the plurality of protrusions comprises from about 100 to about 2,500 protrusions, and/or

~~17. The device of any one of claims 1-16,~~ wherein the plurality of protrusions comprises about 100 protrusions~~.~~, and/or

~~18. The device of any one of claims 1-17,~~ wherein the plurality of protrusions comprises about 324 protrusions.

~~19~~11. The device of any one of claims 1-~~18~~10, wherein the device is capable of delivering the flow composition at the flow rate per protrusion ranging from about 0.1 µl/hour to about 10 µl/hour, about 0.5 µl/hour to about 7.5 µl/hour, about 1 µl/hour to about 5 µl/hour, 1.5 µl/hour to about 5 µl/hour, or about 0.15 µl/hour to about 1.5 µl/hour~~.~~; optionally

~~20. The device of any one of claims 1-19,~~ wherein the device is capable of delivering the flow composition at the flow rate per protrusion is about 0.1 µl/hour, 0.15 µl/hour, 0.5 µl/hour, 1 µl/hour, 1.5 µl/hour, 2 µl/hour, 5 µl/hour, 7.5 µl/hour, or 10 µl/hour. .

~~21~~12. The device of any one of claims 1-~~20~~11, wherein the device is capable of delivering the flow composition at the overall device flow rate ranging from about 1 µl/hour to about 25,000 µl/hour, from about 10 µl/hour to about 20,000 µl/hour, from about 100 µl/hour to about 25,000 µl/hour, from about 200 µl/hour to about 15,000 µl/hour, from about 500 µl/hour to about 10,000 µl/hour, or from about 1000 µl/hour to about 5,000 µl/hour~~.~~; optionally

~~22. The device of any one of claims 1-21,~~ wherein the device is capable of delivering the flow composition at the overall device flow rate of about 10 µl/hour, 100 µl/hour, 200 µl/hour, 500 µl/hour, 1000 µl/hour, 1,500 µl/hour, 2,000 µl/hour, 2,500 µl/hour, 3,000 µl/hour, 5,000 µl/hour, 10,000 µl/hour, or 20,000 µl/hour.

~~23~~13. The device of any one of claims 1-~~22~~12, wherein the device is capable of delivering the flow composition at the overall device flow rate of 100 µl/hour~~.~~ or

~~24. The device of any one of claims 1-22, wherein the device is capable of delivering the flow composition at the overall device flow rate of~~ 500 µl/hour.

~~25~~14. The device of any one of claims 1-~~24~~13, wherein the protrusions of the plurality are arranged in an approximately evenly spaced pattern.

~~26~~15. The device of any one of claims 1-~~25~~14, wherein the protrusions are arranged in 2-50 rows and 2-50 columns in an equidistant manner~~.~~;

~~27. The device of any one of claims 1-26, wherein~~ the protrusions are arranged in 10 rows and 10 columns, and the device is capable of delivering the flow composition with the overall device flow rate of about 100 µl/hour~~.~~; or

~~28. The device of any one of claims 1-26, wherein~~ the protrusions are arranged in 18 rows and 18 columns, and the device is capable of delivering the flow composition with the overall device flow rate of about 500 µl/hour.

~~29~~16. The device of any one of claims 1-~~28~~15, wherein the flow rate does not change for at least a predetermined time period~~.~~; or

~~30. The device of any one of claims 1-29, wherein the flow rate of the fluidic composition~~ increases or decreases for a predetermined time period~~.~~; and/or

~~31. The device of any one of claims 1-30, wherein the flow rate~~ changes over time in a sinusoidal, parabolic, triangular, or step-wise manner.

~~32~~17. The device of any one of claims 1-~~31~~16, wherein each of the protrusions has the height ranging from 1 µm to 1 mm, about 200 to about 800 µm, between about 250 to about 750 µm, or between about 300 to about 600 µm~~.~~ and/or

~~33. The device of any one of claims 1-32,~~ wherein the each of the protrusions have a cross-sectional dimension perpendicular to the height, wherein an aspect ratio of the height to the cross-sectional dimension is greater than 2, 3 or 4.

~~34~~18. The device of any one of claims 1-~~33~~17, wherein the fluidic path in the protrusions has a length and a cross-sectional dimension perpendicular to the length, wherein an aspect ratio of the length to the cross-section dimension ranges from about 1 to about 50, about 5 to about 40, or about 10 to about 20 in average.

~~35~~19. The device of any one of claims 1-~~34~~18, wherein the cross-sectional dimension of the fluidic path ranges from about 1 µm to about 100 µm, about 5 µm to about 50 µm, or about 10 µm to about 30 µm.

~~36~~20. The device of any one of claims 1-~~35~~19, wherein the nanostructures comprise a height and a cross-sectional dimension, and at least a portion of the nanostructures have one or more of the following characteristics:

a) center-to-center spacing of from about 50 nanometers to about 1 micrometer;

b) a height of from about 10 nanometers to about 20 micrometers;

c) an aspect ratio of the height to the cross-sectional dimension from about 0.15 to about 30;

d) the plurality of nanostructures constitute a nanopattern having a fractal dimension of greater than about 1;

e) the surface of the protrusion comprising a plurality of nanostructures having an average surface roughness ranging from about 10 nm to about 200 nm; and/or

f) an effective compression modulus ranging from about 4 MPa to about 320 MPa.

~~37~~21. The device of any one of claims 1-~~36~~20, wherein the nanopatterned layer further comprises a plurality of additional nanostructures having a cross-sectional dimension less than the cross-sectional dimension of the nanostructures~~.~~; and/or

~~38. The device of any one of claims 1-37, wherein the nanopatterned layer comprises~~ a polyether ether ketone (PEEK) film.

~~39~~22. The device of any one of claims 1-~~38~~21, comprising a cartridge assembly including a reservoir component having an upper cavity and an opposing lower cavity coupled together in flow communication with the fluidic block.

~~40~~23. The device of any one of claims 1-~~39~~22, comprising a reservoir for holding the fluidic composition located exterior of the device, and fluidically connected to the fluidic block.

~~41~~24. The device of any one of claims 1-~~40~~23, wherein the collet assembly comprises a collet lock coupled to a collet.

~~42~~25. The device of any one of claims 1-~~41~~24, wherein the collet lock is permanently coupled to the collet, optionally wherein the coupling is via a UV-curable adhesive.

~~43~~26. The device of any one of claims 1-~~42~~25, further comprising an attachment band assembly configured to couple to the collet assembly to facilitate contact with a surface of the subject's skin sufficient for penetration of the plurality of protrusions into the surface of the subject's skin and across the dermal barrier~~.~~; optionally

~~44. The device of claim 43,~~ wherein the attachment band assembly comprises:

a. an annular body comprising a wall defining a hollow inner space and a coupling member to engage with a corresponding coupling member of the collet, wherein the annular body is configured to attach to the collet of the collet assembly;

b. a strap assembly removably engaged with the annular body and comprising a hoop-and-loop type fastening strap such that in use, the strap is threaded through a portion of the annular body and folded back to tighten the strap around the skin of the subject.

~~45~~27. The device of any one of claims 1-~~44~~26, wherein the controller assembly includes a plunger member positionable in a range from a first position proximal to the plenum, to a second position distant from the plenum; and a bias assembly positioned between the plenum and the plunger member, the bias assembly being configured to apply a pressure to the plunger member~~.~~; optionally

~~46. The device of claim 45,~~ wherein the pressure applied to the plunger member by the biasing assembly is transmitted to the plenum and facilitates displacing the fluidic composition into the fluidic block.

~~47~~28. The device of any one of claims 1-~~46~~27, wherein the controller assembly includes an external infusion pump and a tubing system to provide a pressured flow of the fluidic composition from a reservoir for holding the fluidic composition located exterior of the device into the device and through the plenum to the fluidic block~~.~~; optionally

~~48. The device of claim 47,~~ wherein the external infusion pump is a syringe pump, an elastomeric pump, or a peristaltic pump~~.~~; and/or

~~49. The device of claim 48,~~ wherein the external infusion pump is portable.

~~50~~29. The device of any one of claims 1-~~49~~28, wherein the device is capable of delivering the flow composition with a protrusion to protrusion variability of a flow rate less than 50%, less than 40%, less than 30%, less than 20%, or less than 10% over at least 75% of the protrusions~~.~~; optionally

~~51. The device of any one of claims 1-50,~~ wherein the device is capable of delivering the flow composition with a protrusion to protrusion variability of the flow rate being about 10% or less.

~~52. A method for delivering a fluidic composition across a dermal barrier of a subject comprising:~~

~~inserting the plurality of protrusions of at least one device of any of the preceding claims across the dermal barrier of the subject; and~~

~~transporting the fluidic composition through the fluidic path of the plurality of protrusions to a location below the dermal barrier.~~

~~53. The method of claim 52, wherein the fluidic composition is delivered at a flow rate greater than about 0.4 µl/hour, or at a flow rate ranging from about 0.4 µl/hour to about 25,000 µl/hour.~~

~~54. A method for delivering a fluidic composition across a dermal barrier of a subject comprising:~~

~~penetrating the dermal barrier with a device having a plurality of protrusions with a nanopatterned layer comprising nanostructures overlaid thereon; and~~

~~transporting the fluidic composition through the fluidic path of the plurality of protrusions to a location below the dermal barrier,~~

wherein the number of protrusions in the plurality of protrusions is from about 4 to about 2,500 protrusions, and the fluidic composition is transported to a location below the dermal barrier at a flow rate greater than about 0.1 µl/hour per protrusion, or at a flow rate ranging from about 0.1 µl/hour to about 10 µl/hour per protrusion.

55. The method of any one of claims 52-54, further comprising transporting the fluidic composition to lymphatic vasculature of the subject.

56. The method of any one of claims 52-55, comprising increasing permeability of the lymphatic vasculature wherein the nanostructures are in contact with, or proximate to, epithelial cells of the subject, thereby opening intercellular junctions between the epithelial cells and facilitating the flow of the fluidic composition during transport to the location below the dermal barrier.

57. A method for delivering a fluidic composition across a dermal barrier of a subject comprising:

applying more than one device of any of the preceding claims at two or more positions of a subject; and

transporting the fluidic composition through the fluidic path of the plurality of protrusions to a location below the dermal barrier.

58. A method for delivering a fluidic composition across a dermal barrier of a subject comprising:

placing a first device of any of the preceding claims on the skin of a subject at a first position proximate to a first location below the dermal barrier; and

placing a second device of any of the preceding claims on the skin of the subject at a second position proximate to a second location below the dermal barrier; and

in one or more steps, inserting the plurality of protrusions of the first device into the subject to a depth whereby an end of at least one of the protrusions is proximate to the first location, and inserting the plurality of protrusions of the second device into the subject to a depth whereby an end of at least one of the protrusions is proximate to the second location; and

in one or more steps, administering via the protrusions of the first device a first dose of the fluidic composition into the first location; and administering via the protrusions of the second device a second dose of the fluidic composition into the second location.

~~59. The method of claim 58, wherein administering the first dose and administering the second dose is simultaneous.~~

~~60. The method of claim 58, wherein administering the first dose and administering the second dose partially overlap in time.~~

~~61. The method of claim 58, wherein administering the first dose and administering the second dose is sequential.~~

~~62. The method of any one of claims 58-61, wherein the first and second devices are different devices.~~

~~63. The method of any one of claims 58-61, wherein the first and second devices are the same device.~~

~~64. The method of any one of claims 58-63, wherein administering the doses cumulatively provides a therapeutically effective dose.~~

~~65. The method of any one of claims 58-64, wherein the first location and the second location are on different limbs of the subject.~~

~~66. The method of any one of claims 58-65, wherein the first location and the second location are each independently proximate to the hands or the feet of the patient.~~

~~67. The method of any one of claims 58-66, wherein the administration step is conducted for at least 4, 6, 8, 10, 12, 16, 24, 36, 48 or 72 hours.~~

~~68. The method of any one of claims 58-67, wherein the device is placed at a location on the skin of the subject having lymphatic capillaries and/or vessels that deliver lymph directly into the lymphatic system in an inflammatory locus in the patient comprising lymph nodes, lymph capillaries, lymph vessel, lymph organs or any combination thereof.~~