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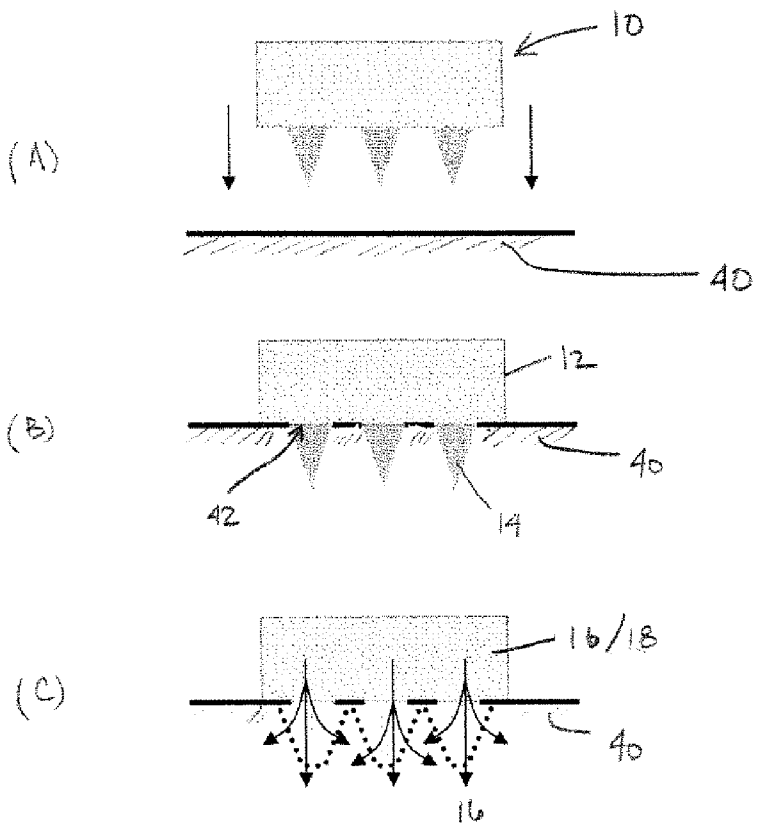
(54) Title: MICRONEEDLE DEVICES AND METHODS OF DRUG DELIVERY OR FLUID WITHDRAWAL



(57) Abstract: Microneedle devices and methods of manufacture and use thereof are provided. In one embodiment, a device is provided for sustained delivery of drug across or into a biological barrier, such as skin. The device may include a base substrate which comprises a drug dispersed in a matrix material; and one or more microneedles extending from the base substrate, wherein the one or more microneedles comprise a water-soluble or water-swellable material, wherein the one or more microneedles will dissolve or swell following insertion into the biological barrier, providing a transport pathway for the drug to pass from the base substrate into the biological barrier.

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MICRONEEDLE DEVICES AND METHODS OF DRUG DELIVERY OR FLUID WITHDRAWAL

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. Provisional Application No. 60/832,479, filed July 21, 2006. The application is incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with U.S. government support under Contract No. 8R01EB00260 awarded by the National Institutes of Health. The U.S. government has certain rights in the invention.

BACKGROUND OF THE INVENTION

This invention is generally in the field of devices and methods for the controlled transport of molecules across skin or other tissue barriers, such as for drug delivery or sampling of biological fluids.

Numerous drugs and therapeutic agents have been developed in the battle against disease and illness. A frequent limitation to the effective and efficient use of these drugs, however, is their delivery, that is, how to transport the drugs across biological barriers in the body (e.g., the skin, the oral mucosa, the blood-brain barrier), which normally do not transport drugs at rates that are therapeutically useful or optimal.

Transdermal drug delivery systems have been shown to be an effective alternative drug pathway for local or systemic drug delivery. Although these systems provide numerous advantages to oral drug delivery routes, development of transdermal delivery devices has been limited by the diffusion of drugs across the stratum corneum of the skin.

To address these problems, microneedles have been developed employing a variety of different fabrication processes and application strategies and may be classified according to the drug delivery strategy. One concept uses microneedles to break the stratum corneum to create pathways through which a drug may enter and thereafter applying a patch to the skin as a drug reservoir. Another concept uses hollow microneedles as a micro duct for the flow of drug in liquid formulations. Still another approach uses coated microneedles to deliver small

amounts of drug loaded onto the microneedle surface. While each of these approaches provides improved drug delivery across the stratum corneum, there still remains a need for improved transdermal drug delivery devices. The first two approaches may be limiting in their requirement of an additional feature or step for drug delivery, while the third approach may be limiting in the amount of drug that may be loaded onto the surface of the coated microneedles. Accordingly, there remains a need to provide improved microneedle devices and methods, particularly for simple and effective transdermal delivery of wide ranges and/or relatively large volumes of drug.

In addition, it would be desirable to have microneedle array devices providing bolus and/or sustained delivery of a macromolecular drug with a relatively large range of therapeutic dose. It would also be desirable to provide a microneedle device with the drug in a stable encapsulated form.

Microneedles also have been proposed for minimally-invasive withdrawal of biological fluids from patients for diagnostic purposes. Some of these device include multiple parts, which may be fragile, costly to produce, and/or difficult to use properly. It would be desirable to provide improved devices which can be made relatively inexpensively and which are relatively simple to use and effective.

SUMMARY OF THE INVENTION

Microneedle devices and methods of use thereof are provided, along with methods of manufacturing the microneedle devices. The devices and methods address one or more of the drawbacks associated with prior microneedle devices.

In one aspect, a device is provided for sustained delivery of drug across or into a biological barrier. In one embodiment, the device includes a base substrate which comprises a drug dispersed in a matrix material; and one or more microneedles extending from the base substrate, wherein the one or more microneedles comprise a water-soluble or water-swellable material, wherein the one or more microneedles will dissolve or swell following insertion into the biological barrier, providing a transport pathway for the drug to pass from the base substrate into the biological barrier. The one or more microneedles may further include a drug dispersed in the water-soluble or water-swellable material.

In one embodiment, the water-soluble or water-swellable material comprises a polysaccharide or a derivative thereof. The water-soluble or water-swellable material may comprise a cellulose derivative. The water-soluble or

water-swellable material may become a hydrogel upon insertion into the biological barrier. In certain embodiments, the water-soluble or water-swellable material may include carboxymethyl cellulose, hydroxypropylmethyl cellulose, amylopectin, starch derivatives, hyaluronic acid, or a combination thereof.

The matrix material of the base substrate may be polymeric, such as a biodegradable polymer. The polymeric matrix material may comprise a water-soluble or water-swellable material, which may be the same as or different from the water-soluble or -swellable material of the one or more microneedles.

The one or more microneedles may each be solid or hollow. In one embodiment, the microneedles each have a length between about 10 μm and about 1500 μm. In one embodiment, the microneedles each have a maximum width between about 10 μm and about 500 μm. The microneedles may have a pyramidal shape.

In one embodiment, the microneedle device includes a backing layer attached to the base substrate distal to the one or more microneedles. In one case, the backing layer has an annular region which surrounds the one or more microneedles. This annular region may include an adhesive substance for contacting a patient's skin or other tissue.

In a particular embodiment, a microneedle array for drug delivery is provided that includes a base substrate comprising a first drug dispersed in a polymeric matrix material; a plurality of microneedles extending from the base substrate, wherein the plurality of microneedles comprises a water-soluble or -swellable material in which a second drug is dispersed, wherein the plurality of microneedles will dissolve following insertion into a biological barrier, providing a transport pathway for the first and second drugs to pass into the biological barrier. The first drug and the second drug may be the same drug or different drugs. In certain variations of this embodiment, the water-soluble or -swellable material of the plurality of microneedles may comprise carboxymethyl cellulose, hydroxypropylmethyl cellulose, amylopectin, starch derivatives, hyaluronic acid, or a combination thereof. In certain variations of this embodiment, the polymeric matrix material of the base substrate may comprise carboxymethyl cellulose, hydroxypropylmethyl cellulose, amylopectin, starch derivatives, or a combination thereof. In one embodiment of these microneedle devices, the drug is a peptide or

protein. In an embodiment, an adhesive substance coating is provided on at least a portion of the surface of the base substrate between/among the microneedles.

In another aspect, a method is provided for delivering a drug across or into the skin or another biological barrier. In one embodiment, the method includes the steps of (i) inserting the one or more microneedles of the device into the biological barrier, to create one or more holes in the biological barrier; (ii) dissolving or swelling the one or more microneedles in the biological barrier; and (iii) transporting the drug from the base substrate through the holes and into the biological barrier. In one particular embodiment, the method further includes dissolving or swelling the one or more microneedles to release the drug from the one or more microneedles into the biological barrier. In a certain embodiment, the drug from the one or more microneedles is substantially released within a period from about a few seconds to about one hour after insertion of the one or more microneedles into the biological barrier. In another certain embodiment, the drug from the base substrate is substantially released within a period from about one hour to about three days after insertion of the one or more microneedles into the biological barrier.

In still another aspect, a method is provided for delivering a drug across or into a biological barrier. In one embodiment, the method includes the steps of: (a) providing a microneedle device that includes (i) a base substrate which comprises a drug dispersed in a polymeric matrix material, and (ii) a plurality of microneedles extending from the base substrate; (b) inserting the microneedles into the biological barrier, to create a plurality of holes in the biological barrier; (c) permitting aqueous fluids from the biological barrier to flow through the holes to hydrate and swell the base substrate, thereby creating fluid pathways within the base substrate for diffusion of the drug within the base substrate; and (d) allowing the drug to diffuse from the base substrate through the holes and into the biological barrier. In a certain embodiment, the one or more microneedles may remain substantially intact during the hydrating and swelling of the base substrate.

In a further aspect, a method is provided for extracting a fluid from a biological barrier. In one embodiment, the method includes: (a) providing a microneedle device that includes (i) a base substrate which comprises a water-swellable polymeric material, and (ii) one more microneedles extending from the base substrate, which one or more microneedles comprise a water-soluble or water-

swellable material; (b) inserting the one or more microneedles into the biological barrier, to create a corresponding one or more holes in the biological barrier; and (c) withdrawing fluid from the biological barrier through the one or more holes and into the base substrate. For example, the biological barrier may comprise the skin or sclera of a human, and the fluid may comprise interstitial fluid and solutes therein.

In another aspect, a method is provided for making a microneedle device. In one embodiment, the method includes (a) providing an inverse mold for at least one microneedle, the mold having base surface in which are located one or more concavities, each in the shape of a microneedle; (b) providing a microneedle structural material in a fluidized form, which comprises a water-soluble or -swellable material; (c) using centrifugation to force the fluidized structural material into the one or more concavities; (d) hardening the structural material into the form of one or more microneedles; (e) forming a base substrate connected to the one or more microneedles, wherein the base substrate comprises a drug dispersed in a polymeric matrix material; and (f) releasing the one or more microneedles from the inverse mold. In one embodiment, the base substrate and the one or more microneedles are formed together in one step by hardening of the fluidized structural material. In one embodiment, the fluidized structural material further comprises a solvent and the hardening step further comprises evaporating the solvent. In a certain embodiment, the inverse mold comprises a plurality of the concavities. In one embodiment, the one or more microneedles do not comprise a drug.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a cross-sectional, side view of a microneedle device according to one embodiment.

FIG. 2 is a cross-sectional, side view of a microneedle device according to another embodiment.

FIG. 3 is a cross-sectional side view of a microneedle patch device according to one embodiment.

FIG. 4 illustrates a method for using an embodiment of the microneedle device according to one embodiment.

FIG. 5 illustrates a method for using an embodiment of the microneedle device according to another embodiment.

FIG. 6 illustrates a process for the fabrication of a microneedle device according to one embodiment.

FIG. 7 illustrates a process for the fabrication of a microneedle device according to another embodiment.

FIGS. 8A-B are graphs of *in vitro* release profiles with Franz cell.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Microneedle devices for the delivery of drugs across or into a biological tissue/barrier are provided, which advantageously may overcome limitations and deficiencies associated with prior art device. The devices may provide sustained release from a drug storage volume that is not limited to the volume of the microneedles alone, in a simple construction which is easy to use. In one embodiment, the microneedle device is in the form of a transdermal patch. In one aspect, the single-use microneedles beneficially leave behind no sharp and rigid needles for disposal or concern about unauthorized re-use. Methods for the manufacture and use of microneedle devices are also provided.

As used herein, the terms "comprise," "comprising," "include," and "including" are intended to be open, non-limiting terms, unless the contrary is expressly indicated.

Microneedle Devices

In one aspect, a microneedle device is provided for sustained release of drug across or into a biological barrier. The biological barrier may be a biological tissue of a patient in need of the drug. The patient may be a human or other mammal, for example. The microneedle device may facilitate transport of one or more drugs through a barrier layer, such as the stratum corneum, and into underlying dermal tissues. The term "biological barrier" may include essentially any cells, tissues, or organs, including the skin or parts thereof, mucosal tissues, vascular tissues, lymphatic vessels, ocular tissues (e.g., cornea, conjunctiva, sclera), and cell membranes. The biological tissue may be in humans or other types of animals (particularly mammals), as well as in plants, insects, or other organisms, including bacteria, yeast, fungi, and embryos. Human skin and ocular tissues may be of particular use with the present devices and methods.

In one embodiment, the device includes a base substrate which comprises a drug dispersed in a matrix material; and one or more microneedles extending from the base substrate, wherein the one or more microneedles comprise or consist of a

water-soluble or water-swellable material, and wherein the one or more microneedles will dissolve or swell following insertion into the biological barrier, providing a transport pathway for the drug to pass from the base substrate into the biological barrier. The matrix material may be a polymer. The drug transport may be by diffusion, alone or enhanced by an active mechanism known in the art, such as electric fields or ultrasound. **FIG. 1** shows one embodiment of a microneedle device **10** which includes a base substrate **12** and three microneedles **14** extending from the base substrate. The base substrate **12** includes drug **16** dispersed in a polymeric matrix material **18**. The microneedles **14** include a water-soluble or -swellable material **15**. In various embodiments, the one or more microneedles may be solid or hollow, may have a length between about 10 μm and about 1500 μm, and may have a maximum width between about 10 μm and about 500 μm. In a preferred embodiment, the one or more microneedles have a pyramidal shape.

In another embodiment, the one or more microneedles further include a drug, which may be dispersed in all of, or a portion of, the water-soluble or -swellable material. The drug provided in the base substrate may be the same as or different from the drug provided in the one or more microneedles. **FIG. 2** shows one embodiment of a microneedle device **20** which includes a base substrate **12** and three microneedles **24** extending from the base substrate. The base substrate **12** includes drug **16** disperse in a matrix material **18**. The matrix material may be polymeric. The microneedles **24** include drug molecules **26** dispersed in the water-soluble or -swellable material **15**. In one embodiment, the one or more microneedles may provide a dose of a drug for immediate release (e.g., by dissolving rapidly upon insertion into the biological tissue) while the base substrate provides a sustaining or maintenance dose of the same drug (e.g., due to the greater time needed for the drug to diffuse from base substrate through the holes in the biological tissue). Alternatively the second drug could be a different drug for the same or a different indication as that of the first drug.

In one embodiment, a microneedle array device is provided for drug delivery. The array device may be part of a transdermal patch. The array device may include a base substrate comprising a first drug dispersed in a matrix material; a plurality of microneedles extending from the base substrate, wherein the plurality of microneedles comprise a water-soluble or -swellable material in which a second drug is dispersed, wherein the plurality of microneedles will dissolve and/or swell

following insertion into a biological barrier, providing a transport pathway for the first and second drugs to pass into the biological barrier. The matrix material may be polymeric. The first drug and the second drug may be the same drug, or they may be different from one another.

In various embodiments, the device may include features for inserting the one or more microneedles into a biological tissue. This feature may be include mechanical or electrical parts, or alternatively, may include a rigid or pliable structure for manually pressing the microneedle into, and the base substrate structure against, skin or other tissues. For example, the device may include a backing layer attached to the base substrate distal to the one or more microneedles. In one case, the backing layer may have an annular region which surrounds the one or more microneedles, wherein the annular region includes an adhesive substance for contacting a patient's skin. Alternatively, or in addition, an adhesive substance is provided (e.g., in a thin film) on the surface of the base substrate, e.g., between some or all of the microneedles. In a preferred embodiment, the backing layer is substantially impervious to the drug in the base substrate, to water vapor, and/or to physiological fluids from the biological barrier. The backing layer may stretch or deform to accommodate swelling/expansion of base substrate during use. **FIG. 3** illustrates one embodiment of a microneedle patch device **30** which includes base substrate **32** from which an array of microneedles **34** extend. The base substrate includes a drug for release. The device **30** further includes backing layer **36** with adhesive **38** for securing the patch to a skin surface during drug delivery. Suitable adhesive substances, such as pressure sensitive adhesives, are well known in the art of adhesive bandages and transdermal drug delivery patches.

Microneedles and Base Substrate

The one or more microneedles extend from the base substrate. The microneedle is formed/constructed of biocompatible materials that will degrade or dissolve, or swell, in the biological barrier, e.g., in physiological fluids present in the biological barrier at the site of insertion of the microneedle. The material(s) of construction and the dimensions of the microneedle are selected to provide, among other things, the mechanical strength to remain substantially intact while being inserted into the skin or into other biological barrier.

In one embodiment, the material of construction of the microneedle includes or consists of a water soluble material. As used herein, a "water soluble"

material is one that dissolves, hydrolyzes, or otherwise breaks down or disintegrates in water or in contact with an aqueous physiological fluid, such as blood, tears, interstitial fluid, mucus, etc., over a period of time following insertion into a biological barrier. The period of time may be rapid, e.g., less than 10 seconds, less than 1 minute, less than 5 minutes, less than 10 minutes, less than 30 minutes, less than 1 hour, less than 4 hours, less than 8 hours, less than 12 hours, or less than 24 hours. In a certain embodiment, the water soluble material comprises a polymer. In one case, it is a polysaccharide or derivative thereof.

In another embodiment, the material of construction of the microneedle includes or consists of a water-swellable material. As used herein, "water-swellable" refers to materials which imbibe aqueous fluids that are in contact therewith, causing the materials to expand. In one embodiment, the material comprises a hydrogel. Hydrogels may be uncrosslinked or crosslinked. Uncrosslinked hydrogels are able to absorb water but may not dissolve due to the presence of hydrophobic and hydrophilic regions. Covalently crosslinked hydrogels may include networks of hydrophilic polymers, including water-soluble polymers. The material may be initially dry and then become a hydrogel upon insertion into the biological barrier. In a certain embodiment, the material is a cross-linked polymer. In various embodiments, the water swellable material may comprise a polyacrylic acid known in the art.

This water-soluble or -swellable material may comprise a polysaccharide or a derivative thereof. In one embodiment, the material is a biocompatible cellulose derivative. In certain embodiments, the water soluble material may be selected from carboxymethyl cellulose, hydroxypropylmethyl cellulose, amylopectin, starch derivatives, hyaluronic acid, or a combination thereof.

The water-soluble or -swellable material also may comprise a polysaccharide, such as alginate, amylose, amylopectin, carrageenan, carboxymethyl cellulose, dextran, gellan, guar gum, polysaccharide conjugate vaccines, hydroxyethyl cellulose, hydroxypropyl cellulose, hyaluronic acid, starch derivatives, xantan, xyloglucan, chitosan-based hydrogel, peptidoglycan, and progeoglycans.

The water-soluble or -swellable material also may comprise a carbohydrate, such as glucose, maltose, lactose, fructose, sucrose, galactose, glucosamine, galactosamine, muramic acid, glucruronate, gluconate, fucose, and trehalose.

The water-soluble or -swellable material also may comprise a synthetic polymer, such as polyvinyl alcohol, polyvinlypyrrolidine, polyethyleneglycol, and polyoxyethylene derivatives. In other cases, the water-soluble or -swellable material may comprise a polypeptide, such as polyvinyl amine or poly(L-lysine).

The base substrate may be made of the same material as that forming the microneedle or it may be made of a different material. In one embodiment, the base substrate comprises a polymeric matrix material which includes or consists of a water soluble or biodegradable polymer. Examples of suitable biodegradable polymers may include poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, polyanhydrides, polyorthoesters, polyetheresters, polycarpolactones, polyesteramides, poly(butyric acid)s, poly(valeric acid)s, polyhydroxyalkanoates, degradable polyurethanes, copolymers thereof, and blends thereof. Alternatively, the polymeric matrix material may be a non-degradable polymer. Examples of non-degradable polymers include polyacrylates, polymers of ethylene-vinyl acetates and other acyl substituted cellulose acetates, non-degradable polyurethanes, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinyl imidazole), chlorosulphonate polyolefins, polyethylene oxide, blends, and copolymers thereof. In certain embodiments, hydrogel materials such as carboxymethyl cellulose (CMC), hydroxypropylmethyl cellulose (HPMC), amylopectin, starch derivatives, hyaluronic acid, or a combination thereof may be used as the base substrate material.

In a preferred embodiment, the microneedles and the base substrate comprise carboxymethyl cellulose.

The base substrate includes one or more drugs. The drug may be located throughout the base substrate material or provided in a sub-component thereof. The drug may be dispersed in the polymer. As used herein, the phrase "dispersed in the polymer" refers to various forms of the drug, including where the drug is dissolved, where the drug is a separate solid or liquid phase, or where the drug is encapsulated into a further material that is within the polymer matrix. For instance, microparticles or nanoparticles of drug may be microencapsulated or nanoencapsulated within another release controlling substance (e.g., a biocompatible polymer, such as a hydrophobic or amphiphilic polymer) and these microcapsules or nanocapsules may be dispersed within the polymer matrix material of the base substrate.

Advantageously, the base substrate simultaneously serves as a platform for the microneedles and storage reservoir for the drug. Beneficially the drug may be stored in a substantially dry, solid form, encapsulated by the matrix material. The drug and polymeric matrix may be a solid solution. In one embodiment, the drug may comprise between about 0.1% and about 70%, such as between 1% and 50% (e.g., between 1 and 25%), by weight of the base substrate and microneedles. Higher or lower loadings may be used, depending upon the particular drug and particular polymeric matrix material used.

In an alternative embodiment, the microneedles may be formed as a composite of two or more degradable or dissolvable materials. The materials may be combined heterogeneously or as a homogeneous mixture. For example, in the heterogeneous embodiments, the materials may be built up in layers, such that the composition varies along the shaft of the microneedle, or the microneedle may have a core of a first material with a coating of a second material formed onto the core. Additional layers of the first or second material may then be included.

The microneedle may have a straight or tapered shaft. In one embodiment, the diameter of the microneedle is greatest at the base end of the microneedle and tapers to a point at the end distal the base. The microneedle can also be fabricated to have a shaft that includes both a straight (i.e., untapered) portion and a tapered portion. The microneedles can be formed with shafts that have a circular cross-section in the perpendicular, or the cross-section can be non-circular. In a preferred embodiment, the microneedle has a pyramidal shape, with a square or triangular base. The tip portion of the microneedles can have a variety of configurations. The tip of the microneedle can be symmetrical or asymmetrical about the longitudinal axis of the shaft. The tips may be beveled, tapered, squared-off, or rounded. The tip portion generally has a length that is less than 50% of the total length of the microneedle.

The dimensions of the microneedle, or array thereof, are designed for the particular way in which it is to be used. The length of the microneedle typically is selected taking into account both the portion that would be inserted into the biological barrier and the base portion that would remain uninserted. In various embodiments, the microneedle may have a length of about 50 μm to about 2000 μm. In an embodiment, the microneedle may have a length of about 150 μm to

about 2000 μm, about 300 μm to about 2000 μm, about 300 μm to about 1500 μm, about 300 μm to about 1000 μm, or about 300 to about 750 μm. In one embodiment, the length of the microneedle is about 500 μm. In various embodiments, the base portion of the microneedle has a maximum width or cross-sectional dimension of about 20 μm to about 500 μm, about 50 μm to about 400 μm, or about 100 μm to about 250 μm. For a hollow microneedle, the maximum outer diameter or width may be about 50 μm to about 400 μm, with an aperture diameter of about 5 μm to about 100 μm. The microneedle may be fabricated to have an aspect ratio (width:length) of about 1:1.5 to about 1:10. Other lengths, widths, and aspect ratios are envisioned.

In various embodiments, the microneedle device includes an array of two or more microneedles. For example, the device may include an array of between 2 and 1000 (e.g., between 4 and 250) microneedles. An array of microneedles may include a mixture of different microneedles. For instance, an array may include microneedles having various lengths, base portion diameters, tip portion shapes, spacings between microneedles, drug coatings, etc.

The single microneedle or array of two or more microneedles may extend from the base substrate of the microneedle device at any angle suitable for insertion into the biological barrier. In a particular embodiment, the base substrate of the microneedle device may be a substantially planar foundation from which the one or more microneedles extend, typically in a direction normal (i.e., perpendicular or 'out-of-plane') to the foundation. Alternatively, the microneedles may be fabricated on the edge of the base substrate 'in-plane' with the substrate. In one case, the microneedles may be fabricated with a flexible base substrate capable of conforming to the shape of the surface of the biological barrier.

Drugs

A wide range of drugs may be formulated for delivery with the present microneedle devices and methods. As used herein, the term "drug" is used broadly to refer to any prophylactic, therapeutic, or diagnostic agent, or other substance that may be suitable for introduction to biological tissues, including pharmaceutical excipients and substances for tattooing, cosmetics, and the like. In one embodiment, the drug is a substance having biological activity, e.g., a therapeutic or prophylactic agent. The drug may be a prodrug. The drug may be formulated

with one or more excipient materials, such as a pharmaceutically acceptable excipient. The drug may be provided in various forms including solids, liquids, liquid solutions, gels, hydrogels, solid particles (e.g., microparticles, nanoparticles), or combinations thereof. The drug may comprise small molecules, large (i.e., macro-) molecules, or a combination thereof.

Non-limiting examples of suitable drugs include amino acids, vaccines, antiviral agents, DNA/RNA, gene delivery vectors, interleukin inhibitors, immunomodulators, neurotropic factors, neuroprotective agents, antineoplastic agents, chemotherapeutic agents, polysaccharides, anti-coagulants, antibiotics, analgesic agents, anesthetics, antihistamines, anti-inflammatory agents, and vitamins. The drug may be selected from suitable proteins, peptides and fragments thereof, which can be naturally occurring, synthesized or recombinantly produced.

A variety of other pharmaceutical agents known in the art may be formulated for administration via the microneedle devices described herein. Examples include β-adenoreceptor antagonists, miotics, sympathomimetics, carbonic anhydrase inhibitors, prostaglandins, anti-microbial compounds, including anti-bacterials and anti-fungals, anti-viral compounds, aldose reductase inhibitors, anti-inflammatory and/or anti-allergy compounds, local anesthetics, cyclosporine, diclofenac, urogastrone and growth factors such as epidermal growth factor, mydriatics and cycloplegics, mitomycin C, and collagenase inhibitors.

In a particular embodiment, the drug may be a vaccine and the water soluble material may include a material which degrades into adjuvants useful for the vaccine. Examples of such materials known in the art include polyphosphazenes and CpG oligonucleotides.

Methods of Using the Microneedle Devices

In another aspect, a method is provided for delivering a drug across or into a biological barrier. In one embodiment, the method includes (i) providing a device that includes a base substrate which comprises a drug dispersed in a polymeric matrix material, and one or more microneedles extending from the base substrate, wherein the one or more microneedles comprises a water-soluble or water-swellable material; (ii) inserting the one or more microneedles into a biological barrier, to create one or more holes (i.e., transport pathways) in the biological barrier; (iii) dissolving and/or swelling the one or more microneedles in

the biological barrier; and (iv) allowing the drug to pass (e.g., diffuse or otherwise be driven) from the base substrate through the holes and into the biological barrier.

In another embodiment, the method includes (i) providing a device that includes a base substrate which comprises a drug dispersed in a polymeric matrix material, and one or more microneedles extending from the base substrate, wherein the one or more microneedles comprises a water-soluble or water-swellable material and a drug dispersed therein; (ii) inserting the one or more microneedles into the biological barrier, to create one or more holes in the biological barrier; (iii) dissolving and/or swelling the one or more microneedles in the biological barrier to release the drug from the one or more microneedles; and (iv) allowing the drug to diffuse (or be driven) from the base substrate through the holes and into the biological barrier.

In one case, the drug from the one or more microneedles may be substantially released within a period from about a few seconds to about one hour after insertion of the one or more microneedles into the biological barrier. In the same or another case, the drug from the base substrate is substantially released within a period from about one hour to about three days after insertion of the one or more microneedles into the biological barrier. The devices described herein can provide both rapid and sustained release of drug.

In a certain embodiment, the method for delivering a drug includes providing a microneedle array device that includes (i) a base substrate which comprises a drug dispersed in a polymeric matrix material, and (ii) a plurality of microneedles extending from the base substrate; inserting the microneedles into the biological barrier, to create a plurality of holes in the biological barrier; permitting aqueous fluids from the biological barrier to flow through the holes to hydrate and swell the base substrate, thereby creating fluid pathways within the base substrate for diffusion of the drug within the base substrate; and transporting the drug from the base substrate through the holes and into the biological barrier. The one or more microneedles may remain substantially intact during the hydration and swelling of the base substrate. The drug transport may occur by solely or partially by diffusion. Transport may be enhanced, e.g., by the use of electrical fields or ultrasound techniques known in the art.

FIG. 4 illustrates one embodiment of the drug delivery method. The method generally comprises applying device **10** to biological barrier **40**, to insert

the array of microneedles **14** into the biological barrier **40** to create holes **42** in the biological barrier (Steps A and B). Then, the microneedles dissolve/degrade and the drug **16** diffuses from the base substrate **12** through the holes **42** and into the biological barrier **40**. Alternatively, the microneedles may swell without appreciable dissolution and the drug diffuses (or is driven) through the swollen microneedle.

FIG. 5 illustrates another embodiment of the drug delivery method. The method generally comprises applying device **10** to biological barrier **40**, to insert the array of microneedles **14** into the biological barrier **40** to create holes **42** in the biological barrier (Steps A and B). Aqueous fluids from the biological barrier flow/diffuse through the holes and/or microneedles, causing the base substrate to hydrate and swell (Steps C and D). This occurs while or following dissolution of the microneedles. The drug **16** diffuses from the base substrate **12** through the holes **42** and into the biological barrier **40**.

In particular embodiments, the hydrating, degrading, or dissolving of the one or more microneedles may also provide rapid release of drug molecules dispersed or encapsulated in the microneedles. Thus, it is envisioned that embodiments of the device may provide for only the sustained release of drug molecules or for both the rapid release and sustained release of drug molecules. The sustained release may include a lag time of, for example, 1 to 2 hours following insertion of the microneedles into the biological tissue. A bolus release from the microneedles may be completed within one hour or another period required for complete dissolution of the microneedles.

The microneedle device is capable of delivering drug across the skin at a therapeutically useful rate. The rate of delivery may be controlled by manipulating a variety of factors, including the characteristics of the materials forming the microneedles and base substrate, the characteristics of the drug formulation to be delivered, the dimensions of each microneedle and the base substrate, and the number of microneedles in the device.

The delivery of the drug from the base substrate and microneedles into/through the barrier tissue may be enhanced by using known techniques and devices for increasing the permeability of the biological barrier and/or for augmenting molecule transport. For example, methods using electric fields (e.g.,

iontophoresis), ultrasound, chemical enhancers, vacuum, viruses, pH, and select application of heat and/or light may be employed in the delivery.

In another method of use, dissolvable microneedles as described herein are made wherein the microneedles and base substrate comprise no drug. After microneedle insertion and removal of the remaining substrate, a transdermal patch may be applied to the permeabilized skin.

In another aspect, the microneedle device is used for fluid extraction from the skin or other biological barrier. For example, the device may be used to collect interstitial fluid (and its solutes) from a patient, and then the fluid may be assayed for diagnostic purposes. In a particular embodiment, a method of extracting a fluid from a biological barrier is provided that includes the steps of (a) providing a microneedle device that includes (i) a base substrate which comprises a water-swellable polymeric material, and (ii) one more microneedles extending from the base substrate, which one or more microneedles comprise a water-soluble or -swellable material; (b) inserting the one or more microneedles into the biological barrier, to create a corresponding one or more holes in the biological barrier; and (c) withdrawing fluid from the biological barrier through the one or more holes and into the base substrate.

In one embodiment, the microneedle device is part of a skin patch, which can be worn by a person over a period of time, such as a few hours, a day, or a week, and then removed and the withdrawn fluid contained in the patch can be analyzed. This application may be particularly useful, for example, in an occupational setting to test workers for exposure to various environmental substances (e.g., potential carcinogens). In other cases, the patch can be used to test residents in a particular location for exposure to a certain biological agent of concern in that locale, for example.

Microneedle Fabrication Methods

In still another aspect, method of making microneedle devices are provided. In one embodiment, the method includes a moderate-temperature, water-based fabrication process for forming the microneedles, which advantageously may be used to incorporated drug compounds that may be damaged by high processing temperatures or certain organic solvents. The methods may produce polymeric microneedle devices that have sufficient mechanical strength to penetrate the biological barrier while also being capable of rapidly degrading or dissolving

within the biological barrier, for example, in less than about one hour, less than about 30 minutes, or less than 15 minutes.

In a certain embodiment, the microneedle devices described herein may be produced using a modified solvent cast-molding method. In this method, a microneedle master structure is made, for example using lithographic and etching techniques known in the art. The master structure may be an array or a single microneedle. In one case, the microneedles each have a pyramidal shape. Then, the master structure is used to make a reusable inverse mold, for example from polydimethylsiloxane. Next, a water soluble material for forming the microneedle is added into the mold in a fluidized form. For example, the water soluble material may be in an aqueous solution. Alternatively, the material may be melted, i.e., in liquid form. Alternatively, the material may be in suspension with a non-solvent liquid. A drug optionally may be included with the fluidized material. Finally, the water soluble material is hardened into the inverse shape of the microneedle mold. This hardening may include drying to remove substantially all of any solvent or non-solvent liquid used to fluidize the water soluble material. Such evaporation processes may involve increasing the temperature of the process material and/or lowering the ambient pressure, relative to room temperature and atmospheric pressure.

In a particular embodiment, the evaporation and/or mold filling steps may be carried out during centrifugation or using another method capable of compacting the material to minimize or prevent the formation of voids in the microneedle. To facilitate rapid evaporation, it may be desirable to use as little solvent as feasible. While this may increase the viscosity of the material and may increase the difficulty of mold filling, centrifugation processes (which involve spinning the mold) may be used to forcing the fluidized material into the mold.

The base substrate may be formed simultaneously with the molding of the microneedles. In such a case, the base substrate and microneedles are integrally connected. In an alternative embodiment, all or part of the microneedles are formed in the mold, the mold surface between the microneedles is cleaned off, and then a second material is formed/molded on top of the microneedles.

FIG. 6 illustrates one embodiment of a molding process to make a microneedle device as described herein. In Step A, a dilute solution **50** of a water soluble material for forming the microneedle structure is made by combining the

polymer or other water soluble material (P) with an aqueous solvent (S). Optionally, a drug (D) may be added. In Step B, a concentrated solution **52** is made by evaporating a portion of the solvent. The concentrated solution may be a hydrogel. In Step C, the concentrated solution **52** is applied onto a microneedle mold **54** which includes inverse microneedle-shaped concavities **56**. In Step D, centrifugal force is used to cast the device **58** in the shape of the microneedles by filling the mold cavities. In Step E, the device **58** having microneedles **59** and base substrate **60** is released from the mold. In this embodiment, a drug added to the solution **50** would result in a device **58** having drug in both the microneedle and in the base substrate.

FIG. 7 illustrates another embodiment of a molding process to make a microneedle device described herein. In Step A, a first concentrated solution **62** of water soluble material, optionally with a drug, for forming the microneedle structure (e.g., made in a like manner to that for making concentrated solution **52** as described with reference to **FIG. 6**) is applied onto a microneedle mold **64** which includes inverse microneedle-shaped concavities **63**. In Step B, centrifugal force is used to cast the microneedles **72** by filling the mold cavities **63**, and excess concentrated solution, if any, is removed from surface **65** of mold **64**. In Steps C and D, a second solution **66** comprising a drug and a polymeric matrix material (or precursor therefor) is applied onto the mold **64** to cast the base substrate **70** in attachment with the microneedles **72**. The base substrate may be cast using centrifugal force. In Step E, the device **68** having microneedles **72** and base substrate **70** is released from the mold.

The present invention may be further understood with reference to the following non-limiting examples.

Example 1: Fabrication of Dissolvable Microneedles

Microneedle master structures were made using lithographic and etching techniques adapted from the microelectronics industry that are well known to those in the art. Carboxymethyl cellulose (CMC) microneedles were then fabricated using a centrifuge casting method at room temperature, as illustrated in **FIG. 6**.

The CMC was hydrated to form a viscous hydrogel which was placed on the surface of a mold and spun in a centrifuge at a temperature from about 25 to 40 °C. The centrifugal force drove the CMC solution into the microneedle cavities in the mold. While continuing to spin the molds at elevated temperature, the water

was dried from the CMC solution, leaving behind solid CMC microneedles. A model drug, sulforhodamine B fluorescent dye, was added to the viscous CMC solution and was thereby incorporated into the microneedles and into the base substrate for sustained delivery. Alternatively, the molds were filled with a solution of CMC and sulforhodamine and the mold surface wiped clean prior to placing a pure CMC solution onto the mold to form a base substrate of CMC microneedles with sulforhodamine only within the microneedles.

Compared to melting methods for polymeric microneedles, the centrifuge casting technique was able to produce perfect replicas without bubbles inside the microneedle structure. The microneedles were of a pyramidal shape having a height of about 500-600 microns and a maximum width of about 250-300 microns. The tip of the microneedle had a radius of curvature of about 25 microns.

Example 2: Drug Delivery with Dissolvable Microneedles

The CMC microneedles made in Example 1 were inserted by hand into full-thickness swine skin affixed to a flat surface. After fixing and sectioning, sites of microneedle insertion and drug release were imaged by Brightfield and fluorescence microscopy. To quantify delivery rates, *in vitro* tests were performed with Franz cells containing human cadaver epidermis pierced with microneedles. Model drug release was measured by spectrofluorometry.

The CMC microneedles dissolved within 5 minutes after insertion into the swine skin. Brightfield imaging of histological sections showed the sites of microneedles insertion as an indented skin surface with a breached stratum corneum and a hole penetrating across the epidermis. Fluorescence microscopy showed intense sulforhodamine release at the sites of needle insertion. It is anticipated that if these experiments were conducted *in vivo*, a release in this manner near the dermal-epidermal junction would result in rapid uptake by the rich capillary bed located in the superficial dermis. Given the small size of microneedles, bolus release from an array of CMC microneedles would be expected to be particularly useful with drugs requiring sub-milligram doses.

The histological cross section of swine skin following a sustained delivery of sulforhodamine for 12 hours from the CMC microneedle device with encapsulated model drug in both the microneedles and the base substrate was evaluated (data not shown). While the microneedles rapidly hydrated and dissolved, the base substrate hydrated more slowly and caused swelling. While not

wishing to be bound by any theory, it is believed that the swelling provided fluid pathways for the sulforhodamine to diffuse within the base substrate, through residual channels left by the dissolved microneedles, and into the skin.

The release rates for sustained delivery are shown in **FIGS. 8A-B**. Although this particular example delivered drug at the microgram level, it is believed that higher loading of the base substrate of the microneedle device with drug molecules would permit delivery of milligrams of drug per day.

Modifications and variations of the methods and devices described herein will be obvious to those skilled in the art from the foregoing detailed description. Such modifications and variations are intended to come within the scope of the appended claims.

We claim:

1. A device for sustained delivery of drug across or into a biological barrier comprising:

a base substrate which comprises a drug dispersed in a matrix material; and

one or more microneedles extending from the base substrate, wherein the one or more microneedles comprise a water-soluble or -swellable material,

wherein the one or more microneedles will dissolve or swell following insertion into the biological barrier, providing a transport pathway for the drug to pass from the base substrate into the biological barrier.

2. The device of claim 1, wherein the water-soluble or -swellable material comprises a polysaccharide or a derivative thereof.

3. The device of claim 1, wherein the water-soluble or -swellable material comprises a cellulose derivative.

4. The device of claim 1, wherein the water-soluble or -swellable material becomes a hydrogel upon insertion into the biological barrier.

5. The device of claim 1, wherein the water-soluble or -swellable material comprises carboxymethyl cellulose, hydroxypropylmethyl cellulose, amylopectin, starch derivatives, hyaluronic acid, or a combination thereof.

6. The device of claim 1, wherein the matrix material comprises a polymer.

7. The device of claim 1, wherein the matrix material comprises a water-soluble or -swellable material.

8. The device of claim 7, wherein the water-soluble or -swellable material of the base substrate is the same as the water-soluble or -swellable material of the one or more microneedles.

9. The device of any one of claims 1 to 8, wherein the one or more microneedles further comprise a drug dispersed in the water-soluble or -swellable material.

10. The device of claim 1, wherein the one or more microneedles are solid.

11. The device of claim 1, wherein the one or more microneedles are hollow.

12. The device of claim 1, wherein the one or more microneedles each have a length between about 10 μm and about 1500 μm.

13. The device of claim 1, wherein the one or more microneedles each have a maximum width between about 10 μm and about 500 μm.

14. The device of claim 1, wherein the one or more microneedles have a pyramidal shape.

15. The device of claim 1, further comprising a backing layer attached to the base substrate distal to the one or more microneedles.

16. The device of claim 15, wherein the backing layer having an annular region which surrounds the one or more microneedles, said region comprising an adhesive substance for contacting a patient's skin.

17. A microneedle array for drug delivery comprising:

a base substrate comprising a first drug dispersed in a matrix material;

a plurality of microneedles extending from the base substrate, wherein the plurality of microneedles comprises a water-soluble or -swellable material in which a second drug is dispersed,

wherein the plurality of microneedles will dissolve following insertion into a biological barrier, providing a transport pathway for the first and second drugs to pass into the biological barrier.

18. The microneedle array of claim 17, wherein the first drug and the second drug are the same drug.

19. The microneedle array of claim 17, wherein the water-soluble or -swellable material of the plurality of microneedles comprises carboxymethyl cellulose, hydroxypropylmethyl cellulose, amylopectin, starch derivatives, hyaluronic acid, or a combination thereof.

20. The microneedle array of any one of claims 17 to 19, wherein the matrix material of the base substrate comprises carboxymethyl cellulose, hydroxypropylmethyl cellulose, amylopectin, starch derivatives, or a combination thereof.

21. The microneedle array of any one of claims 17 to 20, wherein the drug is a peptide or protein.

22. The microneedle array of any one of claims 17 to 21, further comprises an adhesive substance coating at least a portion of the surface of the base substrate between/among the microneedles.

23. A method of delivering a drug across or into a biological barrier comprising:

inserting the one or more microneedles of the device of claim 1 into the biological barrier, to create one or more holes in the biological barrier;

dissolving or swelling the one or more microneedles in the biological barrier; and

transporting the drug from the base substrate through the holes and into the biological barrier.

24. A method of delivering a drug across or into a biological barrier comprising:

inserting the one or more microneedles of the device of claim 9 into the biological barrier, to create one or more holes in the biological barrier;

dissolving or swelling the one or more microneedles in the biological barrier to release the drug from the one or more microneedles; and

transporting the drug from the base substrate through the holes and into the biological barrier.

25. The method of claim 24, wherein the drug from the one or more microneedles is substantially released within a period from about a few seconds to about one hour after insertion of the one or more microneedles into the biological barrier.

26. The method of claim 24, wherein the drug from the base substrate is substantially released within a period from about one hour to about seven days after insertion of the one or more microneedles into the biological barrier.

27. A method of delivering a drug across or into a biological barrier comprising:

providing a microneedle device that includes (i) a base substrate which comprises a drug dispersed in a matrix material, and (ii) a plurality of microneedles extending from the base substrate;

inserting the microneedles into the biological barrier, to create a plurality of holes in the biological barrier;

permitting aqueous fluids from the biological barrier to flow through the holes to hydrate and swell the base substrate, thereby creating fluid pathways within the base substrate for diffusion of the drug within the base substrate; and

allowing the drug to diffuse from the base substrate through the holes and into the biological barrier.

28. The method of claim 27, wherein the microneedles are solid.

29. The method of claim 27 or 28, wherein the microneedles comprise a water-soluble or -swellable material.

30. The method of any one of claims 27 to 29, wherein the one or more microneedles remain substantially intact during the hydrating and swelling of the base substrate.

31. The method of any one of claims 23 to 29, wherein the microneedles comprise a carboxymethyl cellulose.

32. A method of extracting a fluid from a biological barrier comprising:

providing a microneedle device that includes (i) a base substrate which comprises a water-swellable polymeric material, and (ii) one more microneedles extending from the base substrate, which one or more microneedles comprise a water-soluble or -swellable material;

inserting the one or more microneedles into the biological barrier, to create a corresponding one or more holes in the biological barrier; and

withdrawing fluid from the biological barrier through the one or more holes and into the base substrate.

33. The method of claim 32, wherein the fluid comprises interstitial fluid and solutes therein.

34. The method of any one of claims 23 to 33, wherein the biological barrier comprises the skin or sclera of a human.

35. A method for making a microneedle device comprising:

providing an inverse mold for at least one microneedle, the mold having base surface in which are located one or more concavities, each in the shape of a microneedle;

providing a microneedle structural material in a fluidized form, which comprises a water-soluble or -swellable material;

using centrifugation to force the fluidized structural material into the one or more concavities;

hardening the structural material into the form of one or more microneedles;

forming a base substrate connected to the one or more microneedles, wherein the base substrate comprises a drug dispersed in a matrix material; and

releasing the one or more microneedles from the inverse mold.

36. The method of claim 35, wherein the fluidized structural material further comprises a solvent and the hardening step further comprises evaporating the solvent.

37. The method of claim 35 or 36, wherein the inverse mold comprises a plurality of the concavities.

38. The method of any one of claims 35 to 37, wherein the base substrate and the one or more microneedles are formed together in one step by hardening of the fluidized structural material.

39. The method of any one of claims 35 to 37, wherein the one or more microneedles do not comprise a drug.

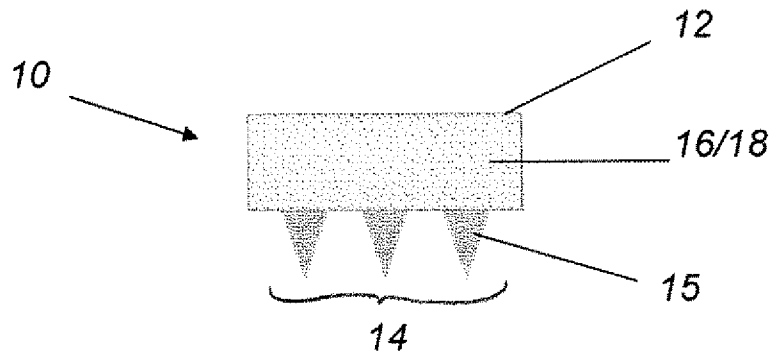


FIG. 1

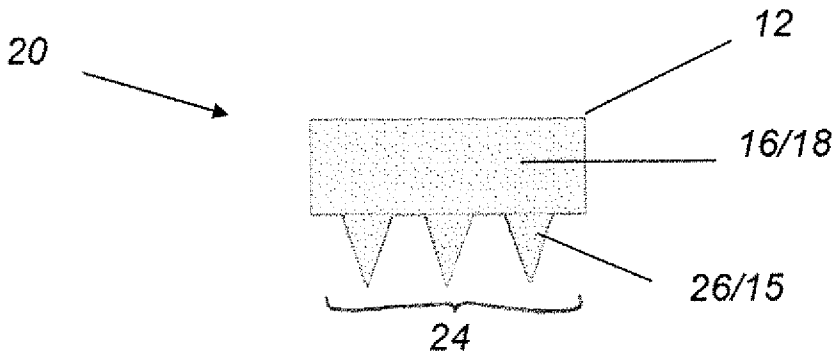


FIG. 2

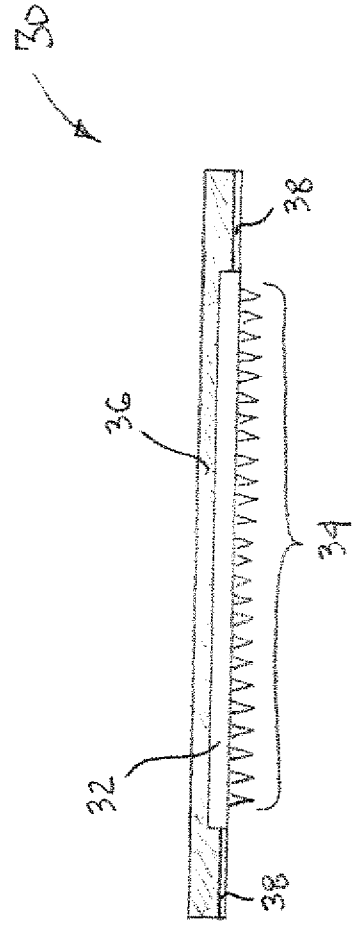


FIG. 3

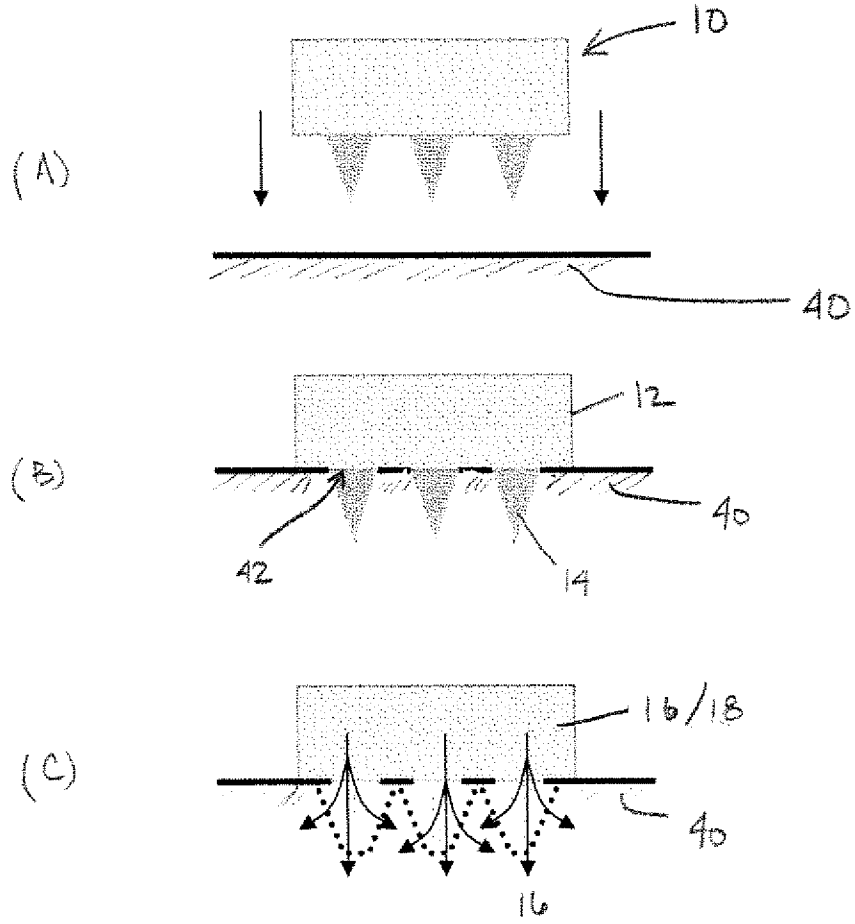


FIG. 4

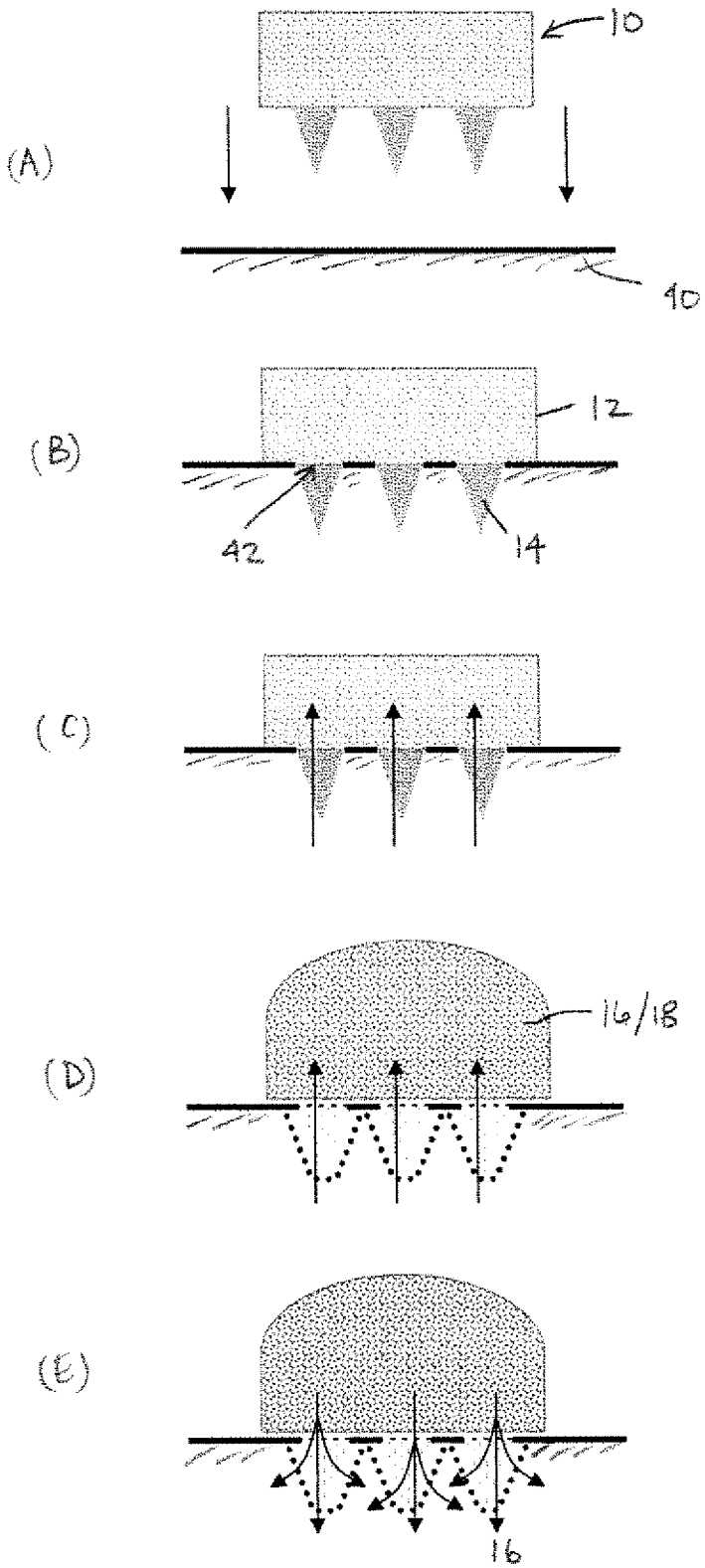


FIG. 5

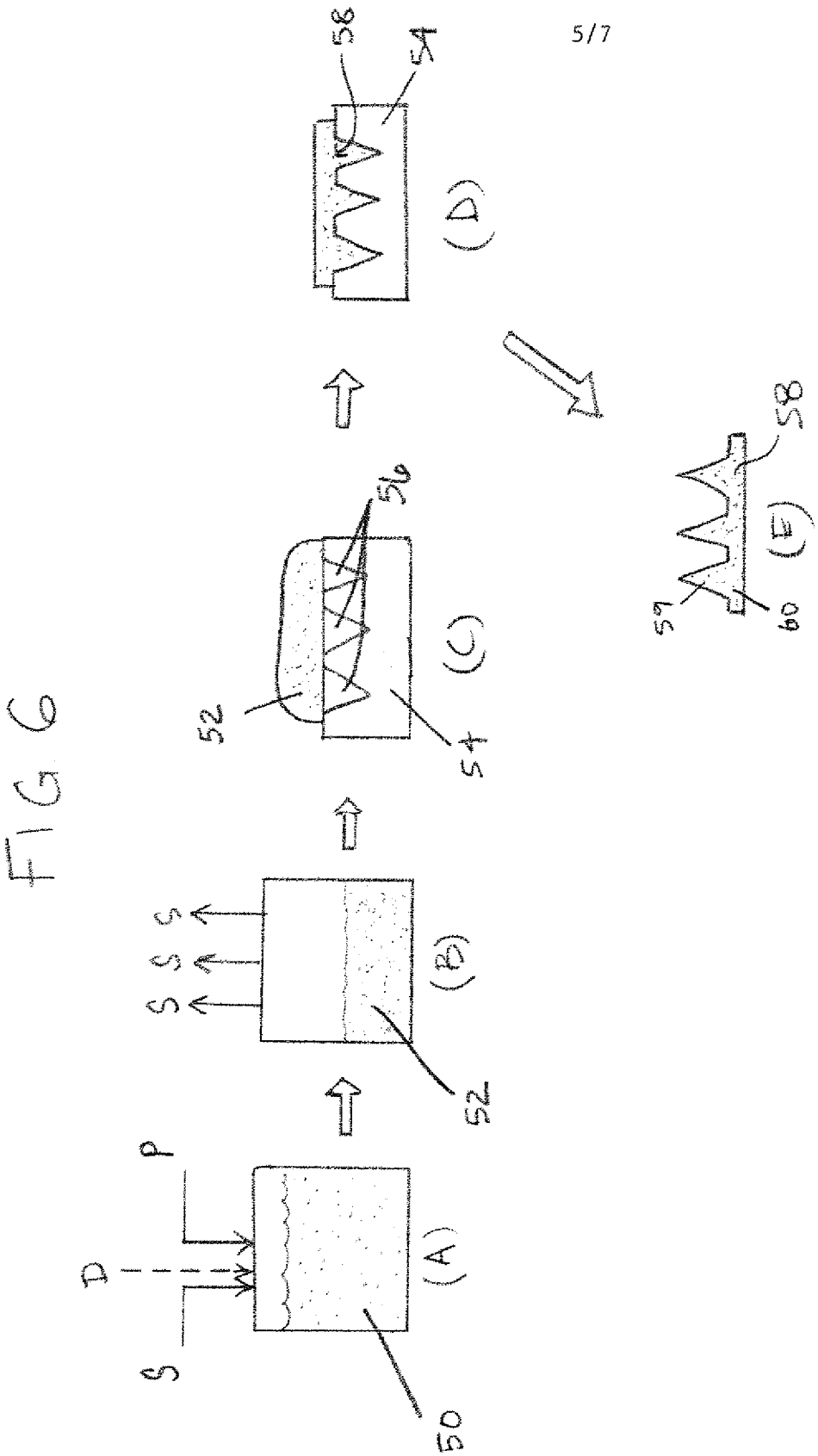
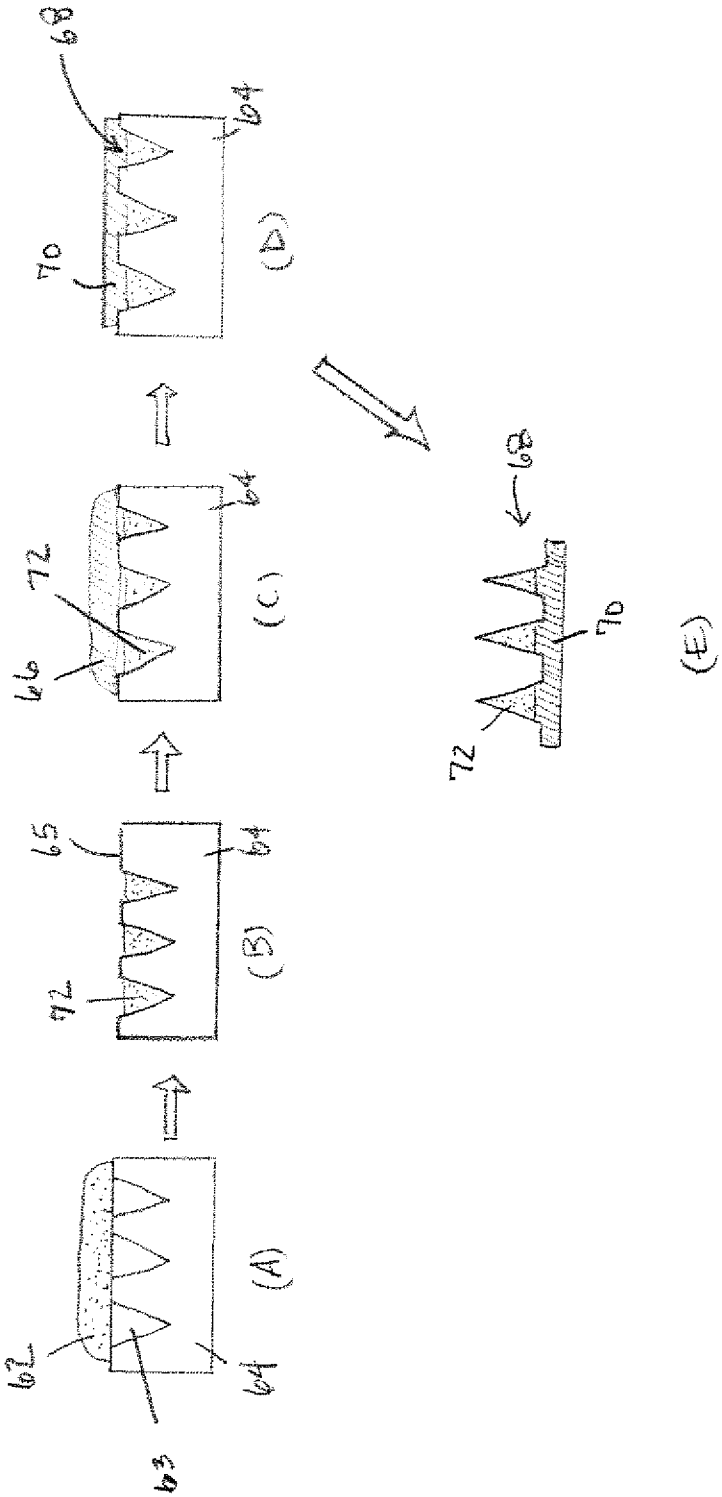


FIG 6

FIG. 7



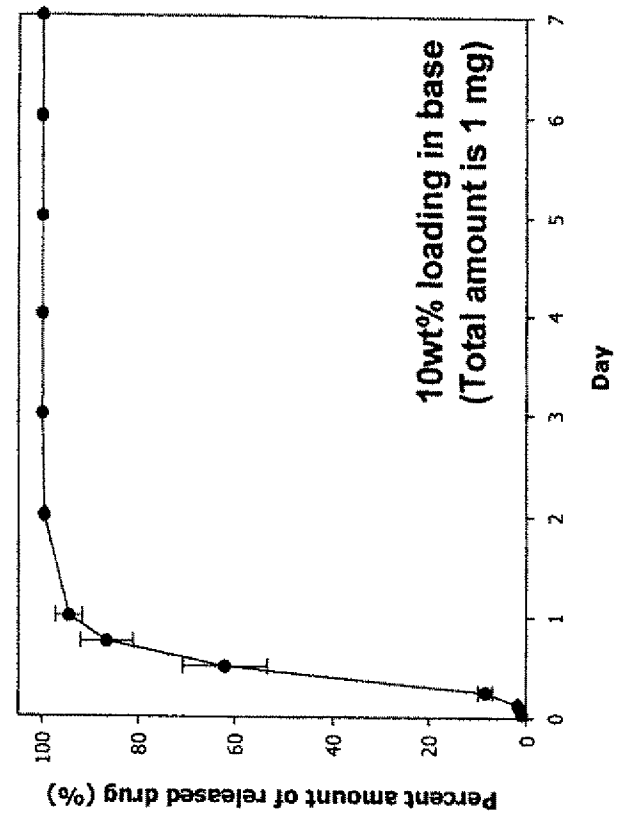

10wt% loading in base
(Total amount is 1 mg)
Percent amount of released drug (%)
Day
0
20
40
60
80
100
0
1
2
3
4
5
6
7

FIG. 8B

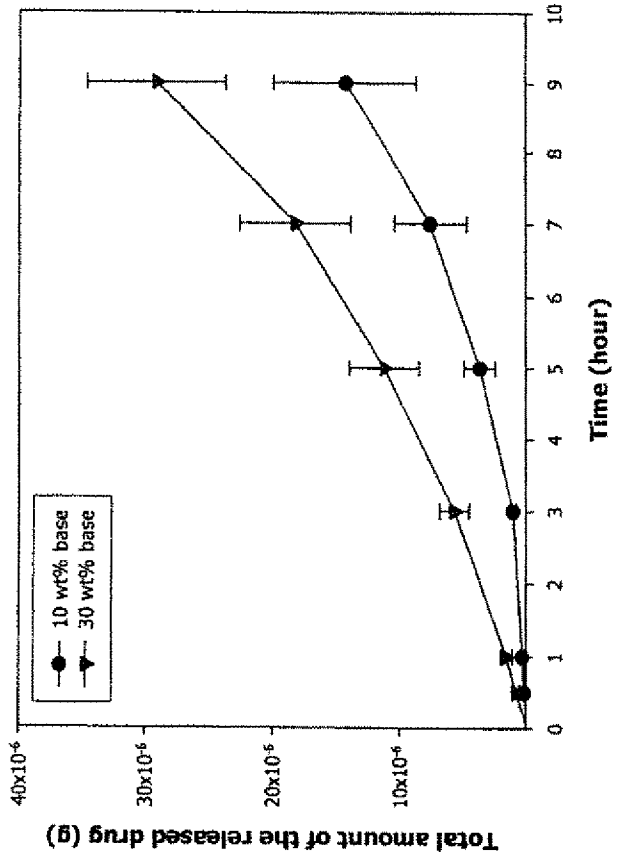

10 wt% base
30 wt% base
Total amount of the released drug (g)
Time (hour)
10x10⁻⁶
20x10⁻⁶
30x10⁻⁶
40x10⁻⁶
0
1
2
3
4
5
6
7
8
9
10

FIG. 8A