Abstract: Methods are provided for applying an active agent to a microneedle wherein the methods utilize a deposition enhancing component to facilitate the deposition of active agent onto the surface of a microneedle.
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
METHODS FOR COATING MICRONEEDLES

Cross-Reference to Related Applications

This application claims priority to International Patent Application Serial No. US2005/041858, filed on November 18, 2005, U.S. Provisional Application Serial Nos. 60/753617, filed on December 23, 2005, 60/754786, filed on December 29, 2005, 60/747618, filed on May 18, 2006, all of which are incorporated herein by reference.

Field

The present invention relates to methods for coating microneedles with an active agent using a deposition enhancing component.

Background

Some therapeutic molecules can be transported through the skin. The principal barrier to the transport of molecules through the skin is the outermost layer of the skin known as the stratum corneum. Devices or "microarrays" equipped with one or more microneedles have been disclosed for use in the delivery of active agents through the skin.

In use, the microarray is pressed against the skin with sufficient force to cause the microneedles to puncture the stratum corneum to create a plurality of microscopic slits through which the transdermal delivery of an active agent may be accomplished. The sampling of certain bodily fluids may also be facilitated by the creation of such microscopic slits.

In delivering a therapeutic molecule or active agent through the stratum corneum, a microarray is sometimes associated with a fluid reservoir that can temporarily retain a liquid formulation of active agent prior to its delivery through the stratum corneum. In such constructions, the microneedles can be hollow structures that provide a flow path for the liquid active agent to flow directly from the fluid reservoir and through the microneedles to deliver the active agent through the skin. In other constructions, a dried coating comprising one or more active agents may be provided on at least a portion of the
microneedles of a microarray so that the active agent can be delivered through the skin after the *stratum corneum* has been punctured. Once in contact with interstitial fluids, the coating of active agent dissolves, and the active agent is free to enter the body and perform its therapeutic function.

In order to place a dried coating of an active agent onto a microneedle, the active agent is typically included as a component of a coatable composition, and the coatable composition is coated over the microneedles and dried. It may be desirable to position the active agent onto the tips or the distal-most portions of the microneedles so that the active agent can more readily be dissolved into the interstitial fluid when the coated microneedle is inserted through the *stratum corneum*.

**Summary**

Improvements in coating methods are desired, including improvements in the formulation of coatable compositions comprising at least one active agent for providing dry coatings that comprise active agent. The present invention provides coatable compositions and methods that facilitate the deposition of active agent from the coatable composition to a microneedle.

In one aspect, the present invention provides a method comprising:

A) Applying a coatable composition to the surface of a microneedle to deposit active agent from the coatable composition onto the surface of the microneedle, the coatable composition comprising

(i) active agent,

(ii) solvent,

(iii) deposition enhancing component; and

B) Drying the coatable composition to leave a coating on the surface of the microneedle, the coating comprising active agent.

In another aspect, the invention provides a method comprising:
A) Applying a first coatable composition to the surface of a microneedle, the first coatable composition comprising

(i) deposition enhancing component,
(ii) solvent;

B) Drying the first coatable composition to leave a first coating on the surface of the microneedle, the first coating comprising deposition enhancing agent;

C) Applying a second coatable composition to the first coating on the surface of the microneedle, the second coatable composition comprising

(i) active agent,
(ii) solvent; and

D) Drying the second coatable composition to leave a final coating on the surface of the microneedle, the final coating comprising active agent.

In still another aspect, the invention provides a method comprising:

A) Applying an initial coating to the surface of a microneedle, the initial coating comprising the deposition enhancing component;

B) Applying a coatable composition to the initial coating, the coatable composition comprising

(i) active agent,
(ii) solvent; and

C) Drying the coatable composition to provide a final coating on the surface of the microneedle, the final coating comprising active agent.

As used herein, certain terms will be understood to have the meanings set forth below.

As used herein, the terms "a," "an," "the," "at least one," and "one or more" will be understood as being interchangeable. For example, a formulation comprising "an effective amount of an active agent" will be understood to mean that the composition includes at least one active agent.
"Active agent" refers to one or more pharmacologically or pharmaceutically effective molecules, compounds, materials or substances producing one or more local or systemic effects in mammals, including humans. Examples of active agents include, without limitation, small molecules, polypeptides, proteins, oligonucleotides, nucleic acids, polysaccharides, drugs, vaccines or other immunologically active agents, agents capable of triggering the production of an immunologically active agent, a composition of matter or mixture containing a drug that is pharmacologically effective when administered in a therapeutically effective amount.

Further examples of "active agents" include, without limitation, leutinizing hormone releasing hormone (LHRH), LHRH analogs (such as goserelin, leuprolide, buserelin, triptorelin, gonadorelin, and napfarelin, menotropins (urofollitropin (FSH) and LH), vasopressin, desmopressin, corticotropin (ACTH), ACTH analogs such as ACTH (1-24), calcitonin, vasopressin, deamino [Val4, D-Arg8] arginine vasopressin, interferon alpha, interferon beta, interferon gamma, erythropoietin (EPO), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), interleukin-10 (IL-10), glucagon, growth hormone releasing factor (GHRF), insulin, insulinotropin, calcitonin, octreotide, endorphin, TRN, NT-36 (chemical name: N-[(s)-4-oxo-2-azetidinyl]carbonyl]-L-histidyl-L-prolinamide), liprecin, aANF, bMSH, somatostatin, bradykinin, somatotropin, platelet-derived growth factor releasing factor, chymopapain, cholecystokinin, chorionic gonadotropin, epoprostrenol (platelet aggregation inhibitor), glucagon, hirulog, interferons, interleukins, menotropins (urofollitropin (FSH) and LH), oxytocin, streptokinase, tissue plasminogen activator, urokinase, ANP, ANP clearance inhibitors, angiotensin II antagonists, antiuretic hormone agonists, bradykinin antagonists, ceredase, CSFs, calcitonin gene related peptide (CGRP), enkephalins, FAB fragments, IgE peptide suppressors, IGF-I, neurotrophic factors, colony stimulating factors, parathyroid hormone and agonists, parathyroid hormone antagonists, prostaglandin antagonists, pentetide, protein C, protein S, renin inhibitors, thymosin alpha-1, thrombolitics, TNF, vasopressin antagonists analogs, alpha-1 antitrypsin (recombinant), TGF-beta, fondaparinux, ardeparin, dalteparin, defibrotide, enoxaparin, hirudin, nadroparin, reviparin, tinzaparin, pentosan polysulfate, oligonucleotides and oligonucleotide derivatives such as formivirsen, alendronic acid, clodronic acid, etidronic
acid, ibandronic acid, incadronic acid, paniidronic acid, risedronic acid, tiludronic acid, zoledronic acid, argatroban, RWJ 445167, and RWJ-671818.

Active agents can be in any of a variety of forms, such as free bases, acids, charged or uncharged molecules, components of molecular complexes or nonirritating, pharmacologically acceptable salts, simple derivatives of the active agents (such as ethers, esters, amides, etc.) that are easily hydrolyzed at body pH, enzymes, etc., can be employed.

"Active agent", when referring to a composition of matter or mixture containing a "vaccine," refers to conventional and/or commercially available vaccines, including, but not limited to, flu vaccines, Lyme disease vaccine, rabies vaccine, measles vaccine, mumps vaccine, chicken pox vaccine, small pox vaccine, hepatitis vaccine, pertussis vaccine, diphtheria vaccine, recombinant protein vaccines, DNA vaccines and therapeutic cancer vaccines. The term "vaccine" includes, without limitation, antigens in the form of proteins, peptides, DNA, polysaccharides, oligosaccharides, lipoproteins, weakened or killed viruses such as cytomegalovirus, hepatitis B virus, hepatitis C virus, human papillomavirus, rubella virus, and varicella zoster, weakened or killed bacteria such as bordetella pertussis, Clostridium tetani, corynebacterium diphtheriae, group A streptococcus, legionella pneumophila, neisseria meningitides, pseudomonas aeruginosa, streptococcus pneumoniae, treponema pallidum, and vibrio cholerae and mixtures thereof.

It will be understood that "active agent" may refer to one, two or more such active agents included within a coatable composition or a coating according to the present invention.

"Coatable composition" refers to liquid mixtures such as solutions, emulsions, dispersions and the like that can be applied to a substrate and dried to form a dry coating.

"Deposition enhancing component" or "DEC" refers to compounds or components that are soluble or otherwise miscible in a coatable composition and which are more readily soluble or miscible in the solvent of the coatable composition than a particular
active agent. An appropriate DEC in a coatable composition tends to facilitate the deposition of active agent onto a substrate (e.g., a microneedle) at a more rapid rate and/or in larger quantities than when the DEC is not present.

"Effective amount," when referring to the amount of active agent, refers to an amount that is sufficient to provide a local or systemic therapeutic (e.g., physiological or pharmacological) result. In a particular instance, the actual amount of active agent that is needed to provide a desired therapeutic effect will depend on a number of factors including the nature and identity of the active agent, the severity of the condition being treated, the site of delivery and the like.

"Microneedle" refers to one or more piercing elements that are microscopic needle-like structures adapted to pierce or cut through the stratum corneum into the underlying epidermis layer, or epidermis and dermis layers, of the skin of a mammal and including a human.

"Microarray" refers to the medical devices described herein that include one or more microneedles arranged in an array for piercing the stratum corneum to facilitate the transdermal delivery of therapeutic agents or the sampling of fluids through the skin.

Those skilled in the art will further appreciate details of the various embodiments of the invention upon consideration of the remainder of the disclosure.

**Brief Description of the Drawings**

Embodiments of the invention will be described in greater detail below with reference to the various Figures in which structural features are identified with reference numerals with like reference numerals indicating like structure, and wherein:

Figure 1 is an elevated sectional view of a portion of an uncoated microarray;

Figure 2 is an elevated sectional view, in schematic, showing a masking fluid applied to a microarray;
Figure 3A is an elevated sectional view, in schematic, showing a masking fluid applied to a microarray with a coatable composition applied over the masking fluid;

Figure 3B is an elevated sectional view, in schematic, showing a masking fluid applied to a microarray with a coatable composition applied over the masking fluid as in Figure 3A but after coatable composition has partially evaporated;

Figure 3C is an elevated sectional view, in schematic, showing a masking fluid applied to a microarray as in Figure 3B and after the coatable composition has dried to form a dry coating;

Figure 3D is an elevated sectional view, in schematic, showing the microarray of Figure 3C after a portion of masking fluid has evaporated;

Figure 3E is an elevated sectional view, in schematic, showing the microarray of Figure 3D after masking fluid has evaporated;

Figure 4 is an elevated sectional view, in schematic, of a microarray with a masking fluid applied to the substrate according to an aspect of the invention;

Figure 5 is an elevated sectional view, in schematic, of a microarray with a masking film applied to the microarray, according to another embodiment of the invention;

Figures 6A is an elevated sectional view, in schematic, of a microarray with a masking film applied to the microarray and a dry coating applied to the distal portions of the microneedles;

Figure 6B is a top plan view of the microarray of Figure 6A;
Figure 6C is an elevated sectional view, in schematic, of the microarray and masking film of Figure 5 with a dry coating on the distal portions of the microneedles; and

Figure 7 is a perspective view of a microarray in the form of a patch.

**Detailed Description**

The present invention provides coatable compositions and methods for depositing coatable compositions onto at least one microneedle within a microarray to form a dry coating comprising active agent. In some embodiments, coatable compositions include active agent, deposition enhancing component (DEC) and a solvent such as water. The coatable composition is formulated with at least one DEC to facilitate the deposition of active agent from the coatable composition onto the surface of a microneedle. The coatable composition is applied to a microneedle or to an entire microarray. Once deposited, solvent in the coatable composition is driven off or allowed to evaporate, resulting in a dry coating on the surface of the microneedle, the dry coating comprising active agent. In some embodiments, the dry coating of active agent is deposited along the entire surface of at least one microneedle. In other embodiments, dry coating of active agent is on at least the distal-most one half of the surface area of at least one microneedle. In still other embodiments, the dry coating of active agent is on at least the distal-most one third of the surface area of at least one microneedle. In still other embodiments, active agent is on portions of the microneedle surface in proximity of the distal end or tip of at least microneedle.

In some embodiments, one or more DEC(s) can be applied separately to a microneedle. In some embodiments, DEC is applied to a microneedle in a first coatable composition that is subsequently dried to provide a first dry coating on the surface of the microneedle. Active agent is provided in a second coatable composition comprising the active agent in a solvent (e.g., water), and the second coatable composition is applied to the first dry coating of DEC on the microneedle. The second coatable composition remains in liquid form long enough to dissolve at least a portion of the DEC from the first dry coating on the microneedle, thereby increasing the concentration of DEC in the second
coatable composition and causing active agent(s) to precipitate onto the microneedle. Thereafter, the remaining water or other solvent is removed from the second coatable composition, leaving a dry coating comprising active agent adhered or affixed to the surface of at least one microneedle. In some embodiments, the dry coating of active agent is deposited along the entire surface of at least one microneedle. In other embodiments, dry coating of active agent is deposited on at least the distal-most one half of the surface area of at least one microneedle. In still other embodiments, the coating of active agent is deposited on at least the distal-most one third of the surface area of at least one microneedle. In still other embodiments, active agent is deposited on portions of the microneedle surface in proximity of the distal end or tip of at least one microneedle.

In some embodiments, DEC is included in a coatable composition with at least one active agent and a solvent. The DEC is selected to promote the deposition of the active agent (e.g., a protein) onto the surface of the microneedle. In embodiments of the invention, one or more suitable DEC(s) are selected to enhance the efficiency of the coating process by essentially driving active agent from a coatable composition and onto the surface of the microneedle. In some embodiments, a separate first coatable composition is prepared comprising DEC and solvent with no active agent. In such embodiments, the DEC will again be selected to be compatible with whatever active agent will later be coated onto the microneedle.

Suitable compositions for use as deposition enhancing components include inorganic salts. Suitable salts include, without limitation, sodium chloride, sodium sulfate or combinations thereof. In some embodiments, DECs include non-ionic compounds. Such nonionic compounds may include, without limitation, sugars, for example. In some embodiments, suitable DECs include solvent-like compounds such as, for example, ethanol. A coatable composition will include a single DEC or it can include a combination of two or more DECs formulated to have a DEC concentration that will facilitate the deposition of active agent to the surface of the microneedle. In some embodiments, the concentration of the DEC in a coatable composition is at least about 0.001%. In some embodiments, the concentration of DEC within a coatable composition is within the range from about 0.001% to about 99.99% by weight. In specific
embodiments, the maximum amount of DEC in a coatable composition corresponds 
approximately to the maximum solubility of the DEC in a selected solvent.

As previously mentioned, some embodiments of the invention utilize more than 
one coatable composition wherein a first coatable composition comprises DEC and a 
solvent with no active agent. A second coatable composition comprises active agent in a 
second solvent. The first and second solvents may be the same or different but will 
generally be compatible in that each solvent will be capable of dissolving the DEC and the 
active agent therein. In other embodiments, the invention utilizes a single coatable 
composition comprising DEC and active agent in a solvent.

Active agents suitable for use in the invention include virtually any molecule, 
compound, material or substance that is capable of producing one or more local or 
ystemic effects in mammals, including humans, when delivered through the stratum 
corneum. Combinations of one or more active agents are also contemplated within the 
scope of the invention. In some embodiments, the active agent is a vaccine. The 
concentration of active agent in the coatable compositions of the invention will depend on 
the identity of the active agent being used, the identity and concentration of the DEC(s) 
being used, and the transdermal dosage desired for the active agent. Other possible 
considerations for determining the concentration of an active agent will be known to those 
skilled in the art.

The solvent for the coatable compositions is typically provided at concentration 
levels sufficient to dissolve the active agent and/or DEC. In some embodiments, a 
minimal amount of solvent is used in order to facilitate a rapid evaporation or removal of 
solvent after the coatable composition has been deposited onto the surface of a 
microneedle or a microarray. However, the invention is not limited in any way to the use 
of a specific amount of solvent in a coatable composition. The solvent is typically a 
liquid, or is liquid at the temperature used for applying coatable composition to a 
microarray. In embodiments of the invention, the solvent will be capable of dissolving 
active agent and the DEC into solution at the concentrations desired. In some 
embodiments, the solvent will be volatile to some degree so that, at ambient temperatures
(e.g., between about 20°C and about 250°C), a dried coating can be formed on a microneedle by allowing the solvent to evaporate without the application of additional heat. In some embodiments, the solvent may be evaporated by the application of heat after the coatable composition has been deposited onto a microneedle.

Suitable solvents include those that are capable of dissolving or dispersing the active agent therein. Examples of suitable solvents include water, ethanol, methanol, isopropanol, ethyl acetate, hexane, and heptane.

Coatable compositions of the present invention may contain additional optional components that may include viscosity modifiers, stabilizers, and other additives. Suitable additional excipients include sucrose, and hydroxyethyl cellulose.

Coatable compositions as described herein can be applied to various coating techniques including without limitation mask coating, suspended drop coating and the like. Specific embodiments of coating processes will now be described. It will be appreciated that the embodiments described in the various Figures are not to scale and absolute or relative dimensions depicted in the Figures are not to be taken as limiting in any way.

Referring generally to the Figures, embodiments of the invention are shown and will now be described. A portion of an uncoated microarray 200 is schematically depicted in Figure 1. The array 200 includes a substrate 220 with microneedles 210 extending from the substrate 220. Each microneedle includes a proximal portion, generally indicated at 214, nearest to the substrate 220 and a distal or tip portion 212 furthest from the substrate 220. In an embodiment of a mask coating process, a masking fluid 230 is applied to the microneedle array 200 in an amount sufficient to cover the substrate 220 and at least the proximal portions 214 of the microneedles 210 extending from the substrate 220 (see Figure 2) to approximately halfway between the substrate 220 and the distal portion 212. As shown in Figure 3A, a coatable composition 235 is applied over the masking fluid 230 in a manner that avoids significantly disturbing the masking fluid 230. In embodiments where the placement of the coatable composition is to be limited to the tips or distal portions 212 of the microneedles 210, the coatable composition 235 and the masking fluid
230 are typically not readily miscible within one another so that, as shown, the coatable composition 235 forms a separate layer over the masking fluid 230, covering or nearly covering the distal portions 212 of the microneedles 210.

In embodiments of the invention, the coatable composition 235 comprises a DEC and an active agent (e.g., a protein) in a solvent such as water, for example. The solvent molecules (e.g., water) within the coatable composition will become associated with the smaller of the two other ingredients, typically the DEC. As a result, the larger sized molecules of active agent(s) (e.g., proteins) tend to be driven out of solution in amounts proportional to the concentration of the smaller sized DEC molecules. As the molecules of active agent leave the coatable composition, they become adsorbed onto the outer surfaces of the microneedles 210. Consequently, higher concentrations of DEC in a coatable composition tends to drive a larger amount of active agent from the coatable composition and onto the surface of a microneedle. In embodiments of the invention, the outer surface of a microneedle 210 can comprise a hydrophobic surface that repels an aqueous coatable composition. In such embodiments, the higher DEC concentration in an aqueous coatable composition is believed to cause the active agent to leave the coatable composition and become adsorbed onto the outer surface of the microneedle. When the coatable composition is applied only to the distal portion of a microneedle (e.g., the potion that includes distal portion 212), the DEC concentration in the coating formulation is provided at a level that will facilitate the deposition of active agent on the distal portion 212. Because different active agents (e.g. proteins) exhibit different solubilities in water, the optimal DEC and the optimal DEC concentration in an aqueous coatable composition can vary for different active agents.

After the coatable composition 235 has been deposited over the masking fluid 230, the solvent (e.g., water) in the coatable composition is removed. Removal of the solvent can be accomplished by allowing the solvent to evaporate at ambient conditions, for example, or by the application of heat. In the embodiment shown schematically in Figure 3B, the coatable composition 235 has partially evaporated, and a dry coating 240 has begun to form at the distal-most portions 212 of the microneedles 210. As the solvent of the coatable composition is allowed to fully evaporate, a more fully formed coating 240
remains on the surface of each microneedle. Use of the masking fluid 230, limits the area on which the coating 240 is deposited so that the coating 240 forms primarily at or near the distal portion 212, as shown in Figure 3C. Following the evaporation of the coatable composition, the masking fluid 230 remains over the substrate 220 and the proximal portions 214 of the microneedles 210.

In another aspect of the foregoing process, the masking fluid 230 is allowed to evaporate or is heated to facilitate evaporation. Figure 3D illustrates the masking fluid 230 after partial evaporation. Coating 240 continues to dry and remains adhered to the distal portions 212 of the microneedles 210. After additional evaporation, as shown in Figure 3E, the substrate 220 is free of masking fluid. The dried coatings 240 are shown as laminar coatings formed on the distal portions 212 of the microneedles 210. The dry coatings 240 comprise active agent that can subsequently be delivered though the *stratum corneum*.

It will be understood by those in the art that the exact sequence of steps process described above need not occur in such a discrete, step-wise fashion. For example, the coatable composition and masking fluid may simultaneously evaporate so that the level of masking fluid drops at the same time the coatable composition is evaporating. Additionally, as mentioned previously, embodiments of the invention utilize a process in which one or more DEC(s) can be applied separately to microneedle 210 in a first coatable composition that is subsequently dried to provide a first dry coating on the surface of the microneedle. In such embodiments, the foregoing process is applicable to the deposition first of DEC and can be repeated to deposit the active agent on the microneedles. As a result, the above described process can be understood to first describe the deposition of a first coatable composition comprising DEC, wherein the first coatable composition 235 is applied over the masking fluid 230 and wherein the resulting coating 240 comprises DEC in a first dry coating on the distal portion 212 of microneedles 210.

A second coatable composition is then formulated comprising the active agent in a solvent (e.g., water). The second coatable composition may be applied in a suitable manner to the dry first coating 240 on the distal portions 212 of microneedles 210. The
second coatable composition remains in liquid form long enough to dissolve at least a portion of the DEC from the first dry coating 240 on the microneedle, thereby increasing the concentration of DEC in the second coatable composition. Once DEC is dissolved in the second coatable composition, the active agent(s) will precipitate onto the microneedle. Thereafter, the remaining water is removed from the second coatable composition, leaving a dry coating comprising active agent adhered or affixed to the surface of microneedles 210. In the foregoing embodiment, the second coatable composition comprising active agent can be applied to the dry coating 240 of DEC prior to the removal of masking fluid 230 from the array 200. Following a suitable time period to allow the active agent to be adsorbed to the microneedles 210, the second coatable composition is removed from the array 200 by, for example, removing the solvent from the second coatable composition or by allowing the solvent to evaporate. Following evaporation of the solvent from the second coatable composition, the masking fluid 230 is removed from the substrate 220. A final dry coating will remain on the distal portions 212 of the microneedles 210 comprising active agent.

In aspects of the foregoing embodiments, dry coating of active agent may be deposited on at least the distal-most one half of the surface area of the microneedle. In other aspects, the coating of active agent is deposited on at least the distal-most one third of the surface area of the microneedle. In still other aspects, active agent is deposited on portions of the microneedle surface in proximity of the distal end or tip of a microneedle. In any of the foregoing aspects, the level of masking fluid can be adjusted initially set to a level that leaves the correct portion of the microneedles exposed and extending above the masking fluid, available for coating by a coatable composition.

It will also be understood that the invention is not limited to the laminar form of the coating 240 depicted in Figure 3E. A dried coating comprising active agent may take on any of a number of different shapes such as a droplet-like shape of the coating 340, as shown schematically in Figure 6A. Coating 340 may be obtained by, for example, drop coating of a coatable composition on to the distal portions of the microneedles in a microarray. In some embodiments, it may be desirable to adjust the relative rates of
evaporation and/or mixing of the masking and coatable compositions to adjust the location of the dried coating. Portions of the dried coating may also be deposited on the substrate.

The thickness of a dry coating may vary. In some embodiments, the dry coating thickness is less than about 50 microns. In some embodiments, the dry coating has a thickness less than about 20 microns. In some embodiments, the dry coating has a thickness less than about 10 microns. In some embodiments, it may be desirable for the dry coating to be thinner near the distal end or tip of each microneedle so that the coating will not significantly interfere with the ability of the microneedle to pierce the stratum corneum.

In some embodiments, the masking fluid 230 may form a meniscus, as shown in Figure 4, caused by surface tension effects and the like. Although the meniscus is shown in Figure 4 in a concave orientation, it will be appreciated that the meniscus may also be convex and that the shape of the meniscus may be adjusted by control of, for example, the type of masking fluid used, the viscosity of the masking fluid, the type of material used in the manufacture of the substrate and microneedles of a microarray, the size (e.g., height) of the microneedles, the spacing between the microneedles, and by surface treatment of the substrate and/or microneedles, for example.

The type of masking fluid selected may vary widely and may depend on a number of factors, including the type of material of the substrate and microneedles, the size of the microneedles, the spacing between the microneedles, any surface treatments of the substrate and/or microneedles, the components included in a coatable composition and the application for which the dry-coated microneedle array is intended. In some embodiments, the density of the masking fluid layer is higher than the density of the coatable composition. In embodiments of the invention, the masking fluid and the coatable composition are substantially immiscible in one another.

In some embodiments, the masking fluid has a vapor pressure lower than that of the coatable composition so that the coatable composition will substantially evaporate before the masking fluid evaporates. In some embodiments, the vapor pressure of the
masking fluid is adjusted to allow it to evaporate at about the same rate as the coatable composition or at a rate faster than that of the coatable composition so that, for example, the entire surface of each microneedle may be coated with active agent to at least some extent. In some embodiments, the masking fluid may be poured off of the substrate after forming a coating from the coatable composition.

Fluorinated solvents, such as hydrofluoroethers or hydrofluoroalkanes may be particularly suitable for use as the masking fluid as they have a relatively high density and are relatively immiscible with water and/or many conventional organic solvents. An example of a suitable hydrofluoroether is commercially available under the trade designation "3M Novec" Engineered Fluid HFE-7500 (available from 3M Company of St. Paul, Minnesota).

Water may be suitable as a masking fluid, for example, when the coatable composition comprises a lower density organic solvent such as hexane or heptane.

In some embodiments, a second masking fluid may be added after addition of a first masking fluid to the microarray. For example, a hydrofluoroether masking fluid may be added to the microarray followed by the addition of ethanol as a second masking fluid so that the overall masking layer comprises two different fluids. The coatable composition may then be applied as previously described. The second masking fluid may aid in altering the relative rates of evaporation of the various fluids or by adjusting surface tensions between the fluids.

In another embodiment, a solid masking layer may be used such as a masking film 300, as schematically depicted in Figure 5 and in Figure 6C. Such a film 300 may be, for example, a thin polymeric film pierced by the microneedles 210 so that a predetermined portion of the distal region of each microneedle 210 is exposed. A coatable composition may be applied over the distal portion of the microneedles 210 to obtain a coating comprising active agent as previously described. The solid masking layer or film 300 can comprise a polymeric film. In embodiments of the invention, the film 300 is a liquid impermeable polymeric film. Examples of polymeric films suitable for use in the
invention include polypropylene, such as biaxially oriented polypropylene, polyethylene, or polyethylene terephthalate. The masking film may also have a surface coating such as a silicon or fluoro carbon release coating, which may repel an aqueous coatable composition from the masking film and cause a coating solution to bead up on the exposed needle tips. Alternatively, the masking film may have a hydrophilic coating which may repel an organic coatable composition from the masking film.

In embodiments of the invention, the masking film 300 is removed after the solvent in the coatable composition has evaporated to leave a dried coating of active agent on each microneedle, such as coating 240 in Figure 6C or coating 340 in Figure 6A. As shown in Figures 6A and 6B, for example, the dry coating 340 resides on the uppermost or distal portions of the microneedles 310. In some embodiments, the masking film 300 may be left in place and the dry-coated microneedle array with masking film 300 can be directly applied to a skin surface.

Also, the masking film 300 may be used in embodiments, as previously described, in which a first coatable composition is used to separately deposit a coating of DEC on the microneedles. After the DEC is deposited and a first dry coating forms on the microneedles, a second coatable composition comprising active agent may be applied to the first dry coating to exchange DEC for active agent. Following deposition of the second coatable composition of active agent, solvent is removed and the resulting dry coating comprises active agent in a form that is available and ready for delivery through the stratum corneum.

In still other embodiments, a masking layer may comprise a semi-solid or solid layer that may be transformed into a liquid and subsequently removed. Examples of suitable masking layers include thermo-responsive gels, electrorheological fluids, reversible gels, such as a silica or polymeric gels that are sensitive to either pH or ions, or any other suitable transient or reversible gel.

An exemplary thermo-responsive gel that may be useful as a masking layer is a gel formed of a propylene oxide-ethylene oxide block copolymer, such as that available under
the trade designation PLURONIC V-II, commercially available from BASF. An aqueous
gel of about 1% solids may be prepared and placed on the microneedle array by applying a
solution of the thermo-responsive propylene oxide-ethylene oxide block copolymer to the
substrate and then heating the array to a temperature of 34 °C or higher to form a gel. The
coating solution may be applied to the exposed microneedles and subsequently dried. The
dry-coated array can then be cooled to room temperature thereby returning the gel to a
liquid state which may be poured off of the array. Other examples of suitable thermo-
responsive gels are provided in U.S. Patent No. 4,474,751, the entire disclosure of which
is incorporated herein by reference thereto.

Low solids content hydrogel solutions may be used to provide a masking layer that
gels when exposed to salts, such as those described in U.S. Patents Nos. 5,340,572 and
5,192,535, the entire disclosures of which are incorporated herein by reference thereto.
The coatable compositions may be applied to the gelled masking layer and allowed to dry,
thereby leaving a dried, coated microneedle array on the exposed portions of the
microneedles. The pH or ionic content of the gelled masking layer may be altered to
return the gel to a liquid state that can be easily removed from the microneedle.

In another embodiment, a charged colloidal fluid may be applied as the masking
layer. Upon application of an electric field the colloidal fluid may form a gel that can
serve as a semi-solid masking layer. The coatable composition may be applied over the
gelled masking layer and allowed to dry thereby leaving a dried coating on at least one of
the microneedles in a microarray. When the electric field is removed, the gel returns to a
liquid state and the liquid may be poured off of the array and/or evaporated.

In any of the foregoing embodiments, any number of conventional coating
methods may be used to apply a coatable composition to the masked microarray including
dip coating, brush coating, gravure coating and spray coating, for example.

Figure 7 illustrates a microneedle device comprising a combination of a microarray
22, pressure sensitive adhesive 24 and backing 26 arranged in the form of a transdermal
patch 20. A portion of the array 22 is illustrated with microneedles 10 protruding from a
microneedle substrate surface 14. The microneedles 10 may be arranged in any desired pattern or distributed randomly over the microneedle substrate surface 14. As shown, the microneedles 10 are arranged in uniformly spaced rows. In one embodiment, arrays of the present invention have a distal-facing surface area of more than about 0.1 cm² and less than about 20 cm², preferably more than about 0.5 cm² and less than about 5 cm². As shown, a portion of the substrate surface 16 of the patch 20 is non-patterned. In one embodiment, the non-patterned surface has an area of more than about 1 percent and less than about 75 percent of the total area of the device surface that faces a skin surface of a patient. In one embodiment the non-patterned surface has an area of more than about 0.10 square inch (0.65 cm²) to less than about 1 square inch (6.5 cm²). In another embodiment (not shown), the microneedles are disposed over substantially the entire surface area of the array 22.

The microneedle devices useful in the various embodiments of the invention may comprise any of a variety of configurations, such as those described in the following patents and patent applications, the disclosures of which are incorporated herein by reference thereto. One embodiment for the microneedle devices comprises the structures disclosed in United States Patent Application Publication No. 2003/0045837. The disclosed microstructures in the aforementioned patent application are in the form of microneedles having tapered structures that include at least one channel formed in the outside surface of each microneedle. The microneedles may have bases that are elongated in one direction, and the channels may extend from one of the ends of the elongated bases towards the tips of the microneedles. Channels formed along the sides of the microneedles may optionally be terminated short of the tips of the microneedles. The microneedle arrays may also include conduit structures formed on the surface of the substrate on which the microneedle array is located. The channels in the microneedles may be in fluid communication with the conduit structures.

Another embodiment for the microneedle devices comprises the structures disclosed in co-pending United States Patent Application, Serial No. 10/621620 filed on July 17, 2003 which describes microneedles having a truncated tapered shape and a controlled aspect ratio. Still another embodiment for the microneedle devices comprises
the structures disclosed in United States Patent No. 6,091,975 (Daddona, et al.) which describes blade-like microprotrusions for piercing the skin. Still another embodiment for the microneedle devices comprises the structures disclosed in United States Patent No. 6,313,612 (Sherman, et al.) which describes tapered structures having a hollow central channel. Still another embodiment for the micro arrays comprises the structures disclosed in International Publication No. WO 00/74766 (Garstein, et al.) which describes hollow microneedles having at least one longitudinal blade at the top surface of tip of the microneedle.

Microneedle devices suitable for use in the present invention may be used to deliver drugs (including any pharmacological agent or agents) through the skin in a variation on transdermal delivery, or to the skin for intradermal or topical treatment, such as vaccination. In one aspect, drugs that are of a large molecular weight may be delivered transdermally. Increasing molecular weight of a drug typically causes a decrease in unassisted transdermal delivery. Microneedle devices suitable for use in the present invention have utility for the delivery of large molecules that are ordinarily difficult to deliver by passive transdermal delivery. Examples of such large molecules include proteins, peptides, nucleotide sequences, monoclonal antibodies, DNA vaccines, polysaccharides, such as heparin, and antibiotics, such as ceftriaxone.

In other embodiments, microneedle devices suitable for use in the present invention may have utility for enhancing or allowing transdermal delivery of small molecules that are otherwise difficult or impossible to deliver by passive transdermal delivery. Examples of such molecules include salt forms; ionic molecules, such as bisphosphonates, preferably sodium alendronate or pamedronate; and molecules with physicochemical properties that are not conducive to passive transdermal delivery.

In still other embodiments, microneedle devices suitable for use in the present invention may have utility for enhancing delivery of molecules to the skin, such as in dermatological treatments, vaccine delivery, or in enhancing immune response of vaccine adjuvants.
Microneedle devices may be used for immediate delivery, that is where they are applied and immediately removed from the application site, or they may be left in place for an extended time, which may range from a few minutes to as long as 1 week. In one aspect, an extended time of delivery may from 1 to 30 minutes to allow for more complete delivery of a drug than can be obtained upon application and immediate removal. In another aspect, an extended time of delivery may be from 4 hours to 1 week to provide for a sustained release of drug.

For suspended-drop coating, it is desirable to coat the microneedle tips before the drop of coatable composition settles to the base of the array. Increased solute concentration in the coating formulation will generally enable faster/greater coating of the needle tip.

For mask coating, it is desirable to coat the needle tips before the mask solvent evaporates, and the coating formulation falls to the base of the array. Increased solute concentration in the coating formulation will generally enable faster/greater coating of the needle tip. The formulation can include surfactant to promote spreading of the formulation across the microneedle array. The array can be masked with HFE-7500, which will evaporate rapidly enough to enable differentiation of enhanced rates of adsorption of the protein to the needle tip area.

**EXAMPLES**

The following examples are presented merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however, that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention.

Tetanus toxoid total-array content by high performance liquid chromatography (HPLC)
A sample extraction solvent was prepared containing 50 mM potassium perchlorate, 50 mM potassium citrate, 20 mM sodium phosphate, 376 mM sodium chloride, and 100 µg/mL bovine serum albumin. An HPLC sample solution was prepared by placing an array into a polypropylene cup, adding 1.0 mL of the sample extraction solvent to the cup, snapping a cap onto the sample cup, and sonicating for 30 minutes. Gradient elution HPLC (Mobile phase A): 0.2% (v/v) perchloric acid; Mobile phase B: 10% water, 88% acetonitrile, 2% isopropanol, 0.2% perchloric acid (70%); Solvent Program: 0.00 min, 22% B, 1.0 mL/min; 6.00 min, 58% B, 1.0 mL/min; 6.01 min, 100% B, 1.0 mL/min; 6.50 min, 100% B, 0.5 mL/min; 10.0 min, 0% B, 0.5 mL/min; Injection Volume: 100 µL; Column: Zorbax 300SB-C8 50 x 4.6mm, 3.5 micron) was used to quantify tetanus toxoid in the HPLC sample solution. Non-adjuvanted tetanus toxoid (TT) vaccine (Aventis) was calibrated against a lyophilized TT primary standard (List Biologies) and used as a working standard. The working standard was used to obtain a calibration curve from approximately 1 µg-TT/mL to 28 µg-TT/mL. The correlation coefficient for the linear regression of the calibration curve was typically greater than 0.999. Tetanus toxoid content results are the average of between 6 and 10 replicates.

**Tetanus toxoid tip-content by high performance liquid chromatography (HPLC)**

Tetanus toxoid content on the tips of the microneedles was measured by fixing the toxoid in place on the substrate and lower portions of the microneedles so that it could not be extracted into the HPLC sample solution. A microneedle array was placed on a flat surface with the needles pointing upward and 10 µL of an oil-based polyurethane coating solution (Minwax Fast-Drying Polyurethane) was applied to the array and allowed to coat the substrate of the array. The polyurethane was allowed to cure for at least 3 hours at ambient conditions. The array was subsequently extracted and analyzed as described in the total content method.
Preparation of microneedle arrays

Microneedle arrays were prepared as follows. A circular disk (area 2 cm², thickness 1.02 mm) that was partially patterned with an array of microneedles (37 x 37) in a square shape (1 cm²) centered on one side of the disk was prepared. The needles were regularly spaced with a distance of 275 microns between the tips of adjacent needles in a square-shaped pattern. Individual needles were pyramidal in shape with a height of 250 microns and a square base having a side-length of 83.3 microns. The tips were truncated with a flat, square-shaped top having a side-length of 5 microns. Arrays were injection molded according to the general description provided in International Patent Application Publication No. WO 05/82596 and made from polycarbonate (LEXAN HPSIR-1 125, GE Plastics, Pittsfield, MA). The center of the disk was then die cut to provide a microneedle array (area = 1 cm²) having microneedles on approximately 90% of the surface of the patterned side of the disk. The microneedle array had approximately 1200 microneedles.

Example 1

A polyvinylpyrrolidone (PVP) stock solution was prepared by adding 825 mg PVP (PLASTONE K-29/32, Povidone USP, ISP Technologies, Wayne, NJ) to 25 mL water and mixing until the PVP was dissolved. A stock solution was prepared by adding 50 mg polysorbate 80 (TWEEN 80, Sigma Chemical Co., St. Louis, MO) to 25 mL ethanol. A diluted stock solution was prepared by adding 2 mL of the polysorbate stock solution to 18 mL ethanol. A PVP coating solution was prepared by adding 1 mL of the PVP stock solution to 9 mL of the diluted polysorbate stock solution. A microneedle array was placed on a flat surface with the needles pointing upward and an aliquot of 30 µL of the PVP coating solution was applied to the center of the array using a pipette and allowed to spread across the array. The PVP coating solution was allowed to dry at ambient conditions.

TWEEN -80 (90 mg) was added to water (30 mL) to prepare a TWEEN -80 stock solution with a concentration of 3 mg/mL. PVP (1.8 g) was added to water (20 mL) to prepare a PVP stock solution with a concentration of 90 mg/mL. Sucrose (1.8 g) was added to water (20 mL) to prepare a sucrose stock solution with a concentration of 90 mg/mL. Potassium citrate (1.8 g) was added to water (20 mL) to prepare a potassium
citrate stock solution with a concentration of 90 mg/mL. An antigen coating formulation was prepared by mixing tetanus toxoid (Statens Serum Institute Lot 92-1, 888 Lf/niL) with aliquots of the TWEEN -80, PVP, sucrose and potassium citrate stock solutions.

An aliquot (15 µL) of masking fluid (FC-43 FLUORINERT Electronic Liquid) was applied to the center of the array using a pipette and allowed to spread across the array. A 10 µL aliquot of the antigen coating formulation was applied to the center of the masking fluid on the array using a pipette. The nominal amount of tetanus toxoid in the applied antigen coating formulation was 10 µg. The nominal amount of TWEEN -80 in the applied antigen coating formulation was 6 µg. The nominal amounts of PVP, sucrose, and potassium citrate were 100 µg. The volatile components of the antigen coating formulation and the masking fluid were allowed to evaporate at ambient conditions for approximately 30 minutes to provide an antigen-containing coating on the array. Tetanus toxoid total-array content as measured by reversed phase HPLC was 11.9 µg (st. dev.=0.5 µg). Tetanus toxoid tip-content was measured as 5.0 µg (st. dev.=1.2 µg).

**Examples 2-5**

Coated arrays were prepared according to the procedure described in Example 1 with the exception that the nominal amounts of PVP, sucrose and potassium citrate were varied, as shown in Table 1. Tetanus toxoid content of the coated array as measured by reversed phase HPLC and tetanus toxoid content on the tips of the microneedles was measured. The results are shown in Table 1.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>PVP [µg]</th>
<th>Sucrose [µg]</th>
<th>Potassium citrate [µg]</th>
<th>Total-array, Mean (st. dev) [µg]</th>
<th>Tip-content, Mean (st. dev) [µg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>11.9 (0.5)</td>
<td>5.0 (1.2)</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>100</td>
<td>10</td>
<td>13.1 (0.4)</td>
<td>8.5 (0.5)</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>10</td>
<td>100</td>
<td>11.6 (0.8)</td>
<td>9.3 (1.3)</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>100</td>
<td>10</td>
<td>11.5 (0.3)</td>
<td>9.1 (1.4)</td>
</tr>
</tbody>
</table>
In vivo tetanus toxoid deposition

Microneedle devices were prepared by adhering antigen coated arrays as described in Examples 1 to 5 to an adhesive backing. The arrays were applied to hairless guinea pigs using an applicator as generally described in U. S. Patent Application Serial No. 60/578,651, the disclosure of which is hereby incorporated by reference. The applicator piston mass was 5.08 g and the devices were applied at a velocity of 8.07 meters/second. The devices were applied to sites on the soft tissue of the abdomen and muscle on the lower back below the ribs and just above the pelvis. The application sites were cleaned with 70% isopropyl alcohol and allowed to air dry for at least 30 seconds prior to device application. Devices (N = 5) were removed at specified time points and the tetanus toxoid content remaining on the arrays was measured by HPLC. The results are summarized in Table 2.

<table>
<thead>
<tr>
<th>Array Example No.</th>
<th>T = 0 min</th>
<th>T = 1 min</th>
<th>T = 5 min</th>
<th>T = 10 min</th>
<th>T = 20 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.9</td>
<td>9.8</td>
<td>10.3</td>
<td>8.6</td>
<td>8.1</td>
</tr>
<tr>
<td>2</td>
<td>13.1</td>
<td>10.9</td>
<td>10.1</td>
<td>8.2</td>
<td>8.1</td>
</tr>
<tr>
<td>3</td>
<td>11.6</td>
<td>9.1</td>
<td>8.1</td>
<td>7.6</td>
<td>6.3</td>
</tr>
<tr>
<td>4</td>
<td>11.5</td>
<td>9.9</td>
<td>8.6</td>
<td>8.2</td>
<td>7.0</td>
</tr>
<tr>
<td>5</td>
<td>12.3</td>
<td>11.1</td>
<td>9.8</td>
<td>10.0</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Example 6

A polyvinyl alcohol coating solution was prepared as follows. An amount (250 mg) of polyvinyl alcohol (80% hydrolyzed, typical MW = 9,000 - 10,000, CAS 9002-89-5, Aldrich, St. Louis, MO) was added to water (25 mL) to prepare a polyvinyl alcohol stock solution. An aliquot of polyvinyl alcohol stock solution (2 mL) was added to ethanol (18 mL) to prepare a polyvinyl alcohol coating solution. A microneedle array was
placed on a flat surface with the needles pointing upward and an aliquot of 30 µL of the polyvinyl alcohol coating solution was applied to the center of the array using a pipette and allowed to spread across the array. The polyvinyl alcohol coating solution was allowed to dry at ambient conditions. An aliquot (15 µL) of masking fluid (FC-43 FLUORINERT Electronic Liquid) was then applied to the center of the array using a pipette and allowed to spread across the array. A 10 µL aliquot of the antigen coating formulation was applied to the center of the masking fluid on the array using a pipette. Antigen coating formulations were prepared according to the general procedure described in Example 1. The nominal amount of tetanus toxoid in the applied antigen coating formulation was 10 µg. The nominal amount of TWEEN-80 in the applied antigen coating formulation was 6 µg. The nominal amounts of PVP, sucrose, and potassium citrate were 100 µg. The volatile components of the antigen coating formulation and the masking fluid were allowed to evaporate at ambient conditions for approximately 30 minutes to provide an antigen-containing coating on the array. Tetanus toxoid total-array content as measured by reversed phase HPLC was 10.4 µg (st. dev. = 0.7 µg). Tetanus toxoid tip-content was measured as 9.3 µg (st. dev. = 0.4 µg).

Examples 7-14

Coated arrays were prepared according to the procedure described in Example 6 with the exception that the nominal amounts of PVP, sucrose and potassium citrate were varied, as shown in Table 3. Tetanus toxoid content of the coated array as measured by reversed phase HPLC and tetanus toxoid content on the tips of the microneedles was measured. The results are shown in Table 3.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>PVP [µg]</th>
<th>Sucrose [µg]</th>
<th>Potassium citrate [µg]</th>
<th>Total-array, Mean (st. dev) [µg]</th>
<th>Tip-content, Mean (st. dev) [µg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>10.4 (0.7)</td>
<td>9.3 (0.4)</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>100</td>
<td>10</td>
<td>10.4 (0.3)</td>
<td>8.2 (0.8)</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>10</td>
<td>100</td>
<td>10.2 (0.6)</td>
<td>9.1 (0.3)</td>
</tr>
</tbody>
</table>
Example 15

A coated array was prepared according to the procedure described in Example 7. Tetanus toxoid total-array content as measured by reversed phase HPLC was 10.7 µg (st. dev.= 0.9 µg). Tetanus toxoid tip-content was measured as 8.7 µg (st. dev.= 0.6 µg). Arrays were applied to hairless guinea pigs as described above in the section "in vivo tetanus toxoid deposition". The amount of tetanus toxoid remaining on the array after removal from the hairless guinea pig was measured by HPLC. The results are summarized in Table 4.

Example 16

A coated array was prepared according to the procedure described in Example 8. Tetanus toxoid total-array content as measured by reversed phase HPLC was 11.4 µg (st. dev.= 0.3 µg). Tetanus toxoid tip-content was measured as 8.6 µg (st. dev.= 0.5 µg). Arrays were applied to hairless guinea pigs as described above in the section "in vivo tetanus toxoid deposition". The amount of tetanus toxoid remaining on the array after removal from the hairless guinea pig was measured by HPLC. The results are summarized in Table 4.

Example 17

A coated array was prepared according to the procedure described in Example 9. Tetanus toxoid total-array content as measured by reversed phase HPLC was 10.8 µg (st. dev.= 0.3 µg). Tetanus toxoid tip-content was measured as 6.8 µg (st. dev.= 0.9 µg).
Arrays were applied to hairless guinea pigs as described above in the section "in vivo tetanus toxoid deposition". The amount of tetanus toxoid remaining on the array after removal from the hairless guinea pig was measured by HPLC. The results are summarized in Table 4.

**Example 18**

A coated array was prepared according to the procedure described in Example 13. Tetanus toxoid total-array content as measured by reversed phase HPLC was 11.7 µg (st. dev. = 0.3 µg). Tetanus toxoid tip-content was measured as 5.3 µg (st. dev. = 1.0 µg).

<table>
<thead>
<tr>
<th>Array Example No.</th>
<th>T = 0 min</th>
<th>T = 1 min</th>
<th>T = 5 min</th>
<th>T = 10 min</th>
<th>T = 20 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>10.7</td>
<td>10.6</td>
<td>8.8</td>
<td>7.8</td>
<td>6.3</td>
</tr>
<tr>
<td>16</td>
<td>11.4</td>
<td>10.2</td>
<td>8.4</td>
<td>8.1</td>
<td>7.3</td>
</tr>
<tr>
<td>17</td>
<td>10.8</td>
<td>9.3</td>
<td>9.2</td>
<td>8.4</td>
<td>7.5</td>
</tr>
<tr>
<td>18</td>
<td>11.7</td>
<td>9.7</td>
<td>9.7</td>
<td>8.3</td>
<td>7.9</td>
</tr>
</tbody>
</table>

**Example 19: Solute-Induced Coating used in the Suspended-Drop Process**

Coatable compositions were prepared comprising active agent (ovalbumin) in phosphate buffered saline (PBS) were prepared that contained increasing concentrations of DEC (sodium chloride), from 0.0M to 1.4M. The formulations were coated onto microneedles in a microarray by a suspended drop technique, using a micropipette to place
droplets of formulation onto the distal tips of the microneedles. The droplets were suspended on the microneedle tips due to the surface tension of the formulation. As the formulation dried at ambient temperature, the ovalbumin was adsorbed to the microneedles.

Ovalbumin Stock Solution (15 mg/mL)
150mg ovalbumin qslOmL water

PBS Stock Solution (IPX)
1 packet pre-weighed PBS powder (for 1.0L PBS) qslO0mL water

Coating Formulation - Ovalbumin/ Max-PBS
1mL Ovalbumin Stock Solution
4mL PBS Stock Solution (IPX)
5mL Ovalbumin (3 mg/mL)/ PBS-8X

Coating Formulation - Ovalbumin/ Min-PBS
1mL Ovalbumin Stock Solution
4mL water
5mL Ovalbumin (3 mg/mL)/ PBS-none

Coating Formulation - Ovalbumin/ Mid-PBS
1mL Ovalbumin/ Max-PBS
1mL Ovalbumin/ Min-PBS
2mL Ovalbumin (3 mg/mL)/ PBS-4X

Array Coating
untreated microneedle array
1µL coating formulation
allow to dry at room temperature overnight
Example 20: Solute-Induced Coating used in the Mask Process

Coatable compositions were prepared comprising an active agent (ovalbumin) in phosphate buffered saline (PBS) and surfactant with increasing concentrations of DEC (sodium chloride), from 0.0M to 1.4M. The coatable compositions were coated onto the microneedles of microarrays using the mask coating technique. An aliquot of fluorocarbon was used to mask the lower portion of a microarray, and a micropipette was used to place an aliquot of formulation onto the distal ends or tips of the microneedles. The fluorocarbon solvent suspended the coatable composition on the microneedle tips due to the insolubility of fluorocarbon and aqueous solutions, and the greater density of the fluorocarbon. As the coatable composition dried at ambient temperature, the ovalbumin was adsorbed to the microneedles.

Ovalbumin Stock Solution (15 mg/mL)
150mg ovalbumin
qslOmL water/ 0.7% surfactant

PBS Stock Solution (10X)
1 packet pre-weighed PBS powder (for 1.0L PBS)
qslOOmL water/ 0.7% surfactant

Coating Formulation - Ovalbumin/ Max-PBS/surfactant
1mL Ovalbumin Stock Solution
4mL PBS Stock Solution (IPX)___
5mL Ovalbumin (3 mg/mL)/ PBS-8X

Coating Formulation - Ovalbumin/ Min-PBS/surfactant
1mL Ovalbumin Stock Solution
4mL water____________________
5mL Ovalbumin (3 mg/mL)/ PBS-none
Coating Formulation - Ovalbumin/ Mid-PBS/ surfactant

ImL Ovalbumin/ Max-PBS

ImL Ovalbumin/ Min-PBS

2mL Ovalbumin (3 mg/mL)/ PBS-4X

Array Coating
untreated microneedle array

20mcL FC-43

10 mcL coating formulation/surfactant
allow to dry at room temperature

While embodiments of the invention have been described in some detail, those skilled in the art will appreciate that changes and modifications to the embodiments, both foreseeable and unforeseeable, may be made without departing from the spirit and scope of the invention.
What is claimed:

1. A method comprising:
   A) Applying a coatable composition to the surface of a microneedle to deposit active agent from the coatable composition onto the surface of the microneedle, the coatable composition comprising
      (i) active agent,
      (ii) solvent, and
      (iii) deposition enhancing component; and
   B) Drying the coatable composition to leave a coating on the surface of the microneedle, the coating comprising active agent.

2. The method of claim 1 further comprising:
   prior to step A), preparing the coatable composition comprising
      (i) active agent
      (ii) solvent, and
      (iii) deposition enhancing component.

3. The method of claim 1 wherein drying under step B) is accomplished in an oven.

4. The method of claim 1 wherein drying under step B) is accomplished under ambient conditions.

5. The method of claim 1 wherein the deposition enhancing component is selected from the group consisting of sodium chloride, sodium sulfate, and combinations of two or more of the foregoing.

6. The method of claim 1 wherein the deposition enhancing component is a sugar.

7. The method of claim 1 wherein the deposition enhancing component is ethanol.
8. The method of claim 1 wherein step A) comprises applying a masking fluid to mask at least a portion of the microneedle, and applying the coatable composition to a portion of the microneedle not masked by the masking fluid.

9. The method of claim 1 wherein step A) comprises applying a masking film to mask at least a portion of the microneedle, and applying the coatable composition to a portion of the microneedle not masked by the masking film.

10. The method of claim 1 wherein the active agent is a vaccine.

11. A method comprising:
   A) Applying a first coatable composition to the surface of a microneedle, the first coatable composition comprising
      (iii) deposition enhancing component, and
      (iv) solvent;
   B) Drying the first coatable composition to leave a first coating on the surface of the microneedle, the first coating comprising deposition enhancing agent;
   C) Applying a second coatable composition to the first coating on the surface of the microneedle, the second coatable composition comprising
      (ii) active agent, and
      (ii) solvent; and
   D) Drying the second coatable composition to leave a final coating on the surface of the microneedle, the final coating comprising active agent.

12. A method comprising:
   A) Applying an initial coating to the surface of a microneedle, the initial coating comprising the deposition enhancing component;
   B) Applying a coatable composition to the initial coating, the coatable composition comprising
      (iii) active agent, and
      (iv) solvent;
C) Drying the coatable composition to provide a final coating on the surface of the microneedle, the final coating comprising active agent.
Fig. 6A

Fig. 6B
A. **CLASSIFICATION OF SUBJECT MATTER**

* A61M 37/00(2006.01), C09D 7/12(2006.01) *

According to International Patent Classification (IPC) or to both national classification and IPC

B. **FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

- IPC 8 A61M 5/00, A61M 37/00, A61B 17/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

- Korean Patents and Applications for Invention since 1975
- Korean Utility models and Application for Utility model since 1975
- Japanese Patents and Application for Invention since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

- eKIPASS(KIPO internal), Delphion, Pubmed (microneedle array&coating&active agent)

C. **DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Widera G et al., Effect of delivery parameters on immunization to ovalbumin following intracutaneous administration by a coated microneedle array patch system</td>
<td>1-4, 11, 12</td>
</tr>
<tr>
<td>A</td>
<td>Vaccine 24(10) 1653-1664 6 October 2005 (Epubhshed) See Materials and Methods (2 2 Microneedle arrays and coating)</td>
<td>5-7, 10, 8, 9</td>
</tr>
<tr>
<td>Y</td>
<td>US2005153873A1 (CHAN KEITH T, CORMIER MICHEL J, LIN WEIQI) 14 July 2005 See page 5 (paragraphs 49, 63 and 66)</td>
<td>5-7, 10</td>
</tr>
<tr>
<td>A</td>
<td>Cormier M et al., Transdermal delivery of desmopressin using a coated microneedle array patch system J Control Release 97(3) 503-1 1 7 July 2004 See Materials and Methods (2 3 Desmopressin coating)</td>
<td>1-12</td>
</tr>
<tr>
<td>A</td>
<td>Xie Y et al., Controlled transdermal delivery of model drug compounds by MEMS microneedle array Nanomedicine 1(2) 184-190 June 2005 See the whole document, especially abstract</td>
<td>1-12</td>
</tr>
</tbody>
</table>

- Further documents are listed in the continuation of Box C
  - See patent family annex

- Special categories of cited documents
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier application or patent but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

- Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- Document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- Document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- Document member of the same patent family

- Date of the actual completion of the international search: 14 MARCH 2007 (14 03 2007)
- Date of mailing of the international search report: 15 MARCH 2007 (15.03.2007)

Name and mailing address of the ISA/KR

- Korean Intellectual Property Office
- 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No 82-42-472-7140

Authorized officer

- CHO, Kyung Joo

Telephone No 82-42-481-8287

Form PCT/ISA/210 (second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US20030135166A1 (Robert R Gonnelh) 17 July 2003 See the whole document, especially abstract</td>
<td>1-12</td>
</tr>
<tr>
<td>A</td>
<td>US6334856B1 (Georgia Tech Research Corporation) 01 January 2002 See the whole document, especially abstract and figures 1 to 9</td>
<td>1-12</td>
</tr>
<tr>
<td>A</td>
<td>US6835184B1 (Becton, Dickinson and Company) 28 December 2004 See the whole document, especially abstract and figures 2 to 4</td>
<td>1-12</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP1706176A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR1020060134050</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W02005069758A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W02005069758A3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W02005069758A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP14517300A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EPO1086719B1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP1086719A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP20011157715A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US2003199811AA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US2006264893AA</td>
</tr>
</tbody>
</table>