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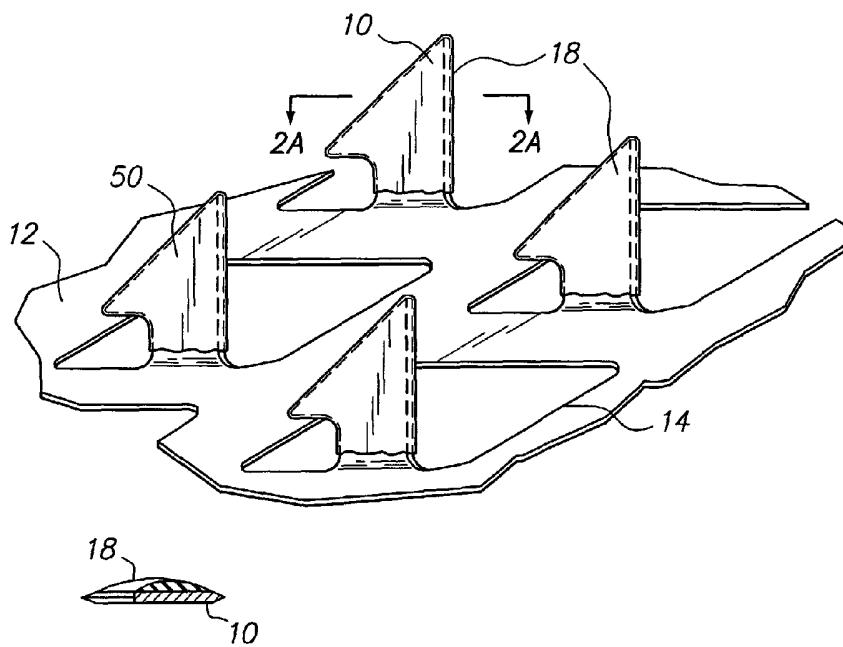
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[Continued on next page]

(54) Title: MICROPROJECTION ARRAY HAVING A BENEFICIAL AGENT CONTAINING COATING



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(57) Abstract: The device including a plurality of stratum corneum-piercing microprojections, and a solid coating disposed upon the microprojections, wherein the solid coating includes at least one beneficial agent and a biocompatible carrier is provided. The device is applied to the skin of a living animal (e.g., a human), causing the microprojections to pierce the stratum corneum and deliver an effective dose of the agent to the animal.



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**MICROPROJECTION ARRAY
HAVING
A BENEFICIAL AGENT CONTAINING COATING**

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TECHNICAL FIELD

[0001] The present invention relates to administering and enhancing transdermal delivery of an agent across the skin. More particularly, the invention relates to a drug delivery system for administering a biologically active agent through the stratum corneum using skin-piercing microprojections, which have a substantially dry coating disposed thereupon, wherein a beneficial agent is contained within the coating. The microprojections pierce the skin to only a very shallow depth, preferably too shallow to reach blood carrying capillaries. Delivery of the agent is accomplished when the microprojections pierce the outermost layer(s) of the skin of a patient and release the active agent contained in the coating into the patient's skin tissue.

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BACKGROUND ART

[0002] Drugs are most conventionally administered either orally or by injection. Unfortunately, many medicaments are completely ineffective or of radically reduced efficiency when orally administered since they either are not absorbed or are adversely affected before entering the blood stream and thus do not possess the desired activity. Transdermal delivery when compared to oral delivery avoids the harsh environments of the digestive tract, bypasses gastrointestinal drug metabolism, reduces first-pass effects, and avoids the possible deactivation by digestive and liver enzymes. Conversely, the digestive tract is not subjected to the drug during transdermal administration. On the other hand, the direct injection of the medicament into the bloodstream, while assuring no modification of the medicament in administration, is a difficult, inconvenient, painful and uncomfortable procedure, sometimes resulting in poor patient compliance. This is particularly true for vaccination of children, where the vaccinations must be delivered intramuscularly in a series of injections.

[0003] Hence, in principal, transdermal delivery provides for a method of administering drugs that would otherwise need to be delivered via hypodermic injection or intravenous infusion.

5 **[0004]** The word "transdermal" is used herein to mean the delivery of an agent (e.g., a therapeutic agent such as a drug) into or through the skin for local or systemic therapy. Transdermal agent delivery includes delivery via passive diffusion as well as by other external energy sources including electricity (e.g., iontophoresis) and ultrasound (e.g. phonophoresis). While drugs do diffuse
10 across both the stratum corneum and the epidermis, the rate of diffusion through the intact stratum corneum is often the limiting step. Many compounds require higher delivery rates than can be achieved by simple passive transdermal diffusion. When compared to injections, transdermal agent delivery eliminates the associated pain and reduces the possibility of infection. Theoretically, the
15 transdermal route of agent administration could be advantageous in the delivery of many therapeutic proteins, because proteins are susceptible to gastrointestinal degradation and exhibit poor gastrointestinal uptake. Additionally transdermal devices are more acceptable to patients than injections. However, the transdermal flux of medically useful peptides and proteins is often insufficient to
20 be therapeutically effective due to the large size/molecular weight of these molecules. Often the delivery rate or flux is insufficient to produce the desired effect or the agent is degraded prior to reaching the target sight, for example the patient's blood stream.

25 **[0005]** Passive transdermal drug delivery systems generally rely on passive diffusion to administer the drug while active transdermal drug delivery systems rely on an external energy source (e.g., electricity) to deliver the drug. Passive transdermal drug delivery systems are more common. Passive transdermal systems have a drug reservoir containing a high concentration of drug adapted to
30 contact the skin where the drug diffuses through the skin and into the body tissues or bloodstream of the patient. The transdermal drug flux is dependent

upon the condition of the skin, the size and physical/chemical properties of the drug molecule, and the concentration gradient across the skin. Because of the low skin permeability to many drugs, transdermal delivery has had limited applications. This low permeability is attributed primarily to the stratum corneum, 5 the outermost skin layer which consists of flat, dead cells filled with keratin fibers (keratinocytes) surrounded by lipid bilayers. The highly ordered structure of the lipid bilayers confers a relatively impermeable character to the stratum corneum.

[0006] One common method of increasing the passive transdermal diffusional 10 drug flux, involves pre-treating the skin with, or co-delivering with the drug, a skin permeation enhancer. A permeation enhancer, when applied to a body surface through which the drug is delivered, enhances the flow of the drug therethrough. However, the efficacy of these methods in enhancing transdermal protein 15 transport has been limited, at least for the larger proteins, due to their size. Active transport systems use an external energy source to assist the drug flux 20 through the stratum corneum. One such enhancement for transdermal drug delivery is referred to as "electrotransport." This mechanism uses an electrical potential, which results in the application of electric current to aid in the transport of the agent through the body surface, such as skin. Other active transport systems use ultrasound (phonophoresis) or heat as the external energy source.

[0007] There also have been many attempts to mechanically penetrate or 25 disrupt the outermost skin layers, thereby creating pathways into the skin in order to enhance the amount of agent being transdermally delivered. Early vaccination devices known as scarifiers generally had a plurality of tines or needles, which are applied to the skin to scratch or make small cuts in the area of application. The vaccine was applied either topically on the skin, such as described in U.S. 30 Patent No. 5,847,726 issued to Rabenau, or alternatively, as a wetted liquid that may be applied to the tines of the scarifier as shown and described in U.S. Patent No. 4,453,926, issued to Galy; or U.S. Patent No. 4,109,655 issued to Charcornac, or U.S. Patent No. 3,136,314 issued to Kravitz. Scarifiers have

been suggested for intradermal vaccine delivery in part because only very small amounts of the vaccine need to be delivered into the skin to be effective in immunizing the patient. Further, the amount of vaccine delivered is not particularly critical since a minimum amount achieves satisfactory immunization

5 as well as an excess amount. However, a serious disadvantage in using a scarifier to deliver a drug is the difficulty in determining the transdermal drug flux and the resulting dosage delivered because it cannot be determined if the minimum amount was delivered. For example, in many instances, the agent disposed upon the skin piercing tines of an intradermal vaccination device is

10 pushed off the tines during skin piercing. Further, many beneficial agents do not have good adhesion characteristics, after being coated onto tines or other skin piercing microprojections, so that the beneficial agent is easily dislodged from the surface of the microprojections. For example, a portion of the beneficial agent may be dislodged from the microprojections during use and not delivered to the

15 patient, resulting in a situation where the patient may not receive the full dosage needed or required. Also, due to the elastic, resilient, and deforming nature of skin that allows it to deflect and resist puncturing, the tiny piercing elements often do not uniformly penetrate the skin and/or are wiped free of a liquid coating of an agent upon skin penetration. Additionally, due to the self healing process of the

20 skin, the punctures or slits made in the skin tended to close up after removal of the piercing elements from the stratum corneum. Thus, the skin acts to remove active agent coating the tiny piercing elements upon penetration. Furthermore, the tiny slits formed by the piercing elements heal quickly after removal of the device, thus, limiting the passage of the agent through the passageways created

25 by the piercing elements and in turn limiting the transdermal flux of such devices.

[0008] Other devices that use tiny skin piercing elements to enhance transdermal drug delivery are disclosed in European Patent 0407063A1; U.S. No. Patent 5,879,326 issued to Godshall et al.; U.S. Patent No. 3,814,097 issued

30 to Ganderton et al.; U.S. Patent No. 5,279,544 issued to Gross et al.; U.S. Patent No. 5,250,023 issued to Lee et al.; U.S. Patent No. 3,964,482 issued to Gerstel

et al.; U.S. Patent No. Reissue 25,637 issued to Kravitz et al.; and PCT Publications No. WO 96/37155, WO 96/37256, WO 96/17648, WO 97/03718, WO 98/11937, WO 98/00193, WO 97/48440, WO 97/48441, WO 97/48442, WO 98/00193, WO 99/64580, WO 98/28037, WO 98/29298, and WO 98/29365; all 5 incorporated by reference in their entirety. These devices use piercing elements of various shapes and sizes to pierce the outermost layer (i.e. the stratum corneum) of the skin. The piercing elements disclosed in these references generally extend perpendicularly from a thin, flat member, such as a pad or sheet. The piercing elements in some of these devices are extremely small, 10 some having dimensions (i.e., microblade length and width) of only about 25-400 micro-meters and a microblade thickness of only about 5-30 micro-meters. These tiny piercing/cutting elements make correspondingly small microslits in the stratum corneum for enhanced transdermal agent delivery therethrough.

15 **[0009]** Generally these systems include a reservoir for holding the drug and also a delivery system to transfer the drug from the reservoir through the stratum corneum, such as by hollow tines of the device itself. One example of such a device is disclosed in WO 93/17754, which has a liquid drug reservoir. The reservoir must be pressurized to force the liquid drug through the tiny tubular 20 elements and into the skin. Disadvantages of devices such as these include the added complication and expense of adding a pressurizable liquid reservoir and complications due to the presence of a pressure-driven delivery system. Another disadvantage of these systems is that they have a limited shelf life due to degradation of the beneficial agent within the liquid reservoir.

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DISCLOSURE OF THE INVENTION

[0009] The device and method of the present invention overcome these limitations by transdermally delivering a biologically active agent using a microprojection array including a plurality of microprojections, which are coated 30 with a solid substantially dry coating containing a beneficial agent therein. The present invention is directed to a device and method for delivering a beneficial

agent, which may be a pharmacologically active agent through the stratum corneum, of preferably, a mammal and most preferable a human, by coating a plurality of stratum corneum piercing microprojections with an amorphous glassy coating that protects the beneficial agent prior to deployment in the stratum corneum. The beneficial agent is selected to be sufficiently potent to be effective when delivered from a solid coating on a plurality of skin piercing microprojections. The coating preferably has sufficient water solubility such that when the microprojections are disposed within the patient's tissue the coating is easily and quickly dissolved, thereby releasing the beneficial agent. Further, the coating is sufficiently adhered to the surfaces of the microprojections so that the coating is not dislodged from the microprojections during insertion of the array into the patient's tissue.

[00010] A preferred embodiment of this invention consists of a device for delivering a beneficial agent through the stratum corneum, the device including a plurality of stratum corneum-piercing microprojections; and a solid coating disposed upon the microprojections, wherein the solid coating includes at least one beneficial agent and a biocompatible carrier.

[00011] In another preferred embodiment of this invention, there is provided a device for forming a plurality of microslits through the stratum corneum for delivering a beneficial agent therethrough, the device including a plurality of microprojections extending from a substrate, the microprojections being sized and arranged to pierce human skin to a depth of less than about 500 micrometers, and a solid coating disposed upon the microprojections, wherein the solid coating includes a beneficial agent and a biocompatible carrier.

[00012] In another preferred embodiment of this invention there is provided a device for forming a plurality of microslits through the stratum corneum for delivering a beneficial agent therethrough, the device including a plurality of microprojections extending from a substrate, the microprojections being sized

and arranged to pierce human skin to a depth of less than about 500 micrometers, and a solid coating disposed upon the microprojections, wherein the solid coating includes a beneficial agent and an albumin carrier.

5 [00013] In another preferred embodiment of this invention, there is provided a method for delivering a beneficial agent through the stratum corneum layer of skin, the method including, providing a microprojection array having a plurality of stratum corneum-piercing microprojections, the microprojections being coated with a biocompatible coating containing a beneficial agent and a biocompatible carrier, and causing the microprojections to pierce the stratum corneum layer of a 10 predetermined skin site, whereby the beneficial agent is released into the skin tissue.

15 [00014] In another preferred embodiment of this invention, there is provided an apparatus for delivering a plurality of beneficial agents to a patient, the apparatus including, a microprojection array comprising a plurality of solid coatings disposed upon the microprojections in the array. Preferably the different coatings are disposed on separate regions of the array. Each of the coatings contains a biocompatible carrier and a different beneficial agent. The 20 microprojection array has a plurality of microprojections sized, shaped and configured to form a plurality of microslits through a stratum corneum layer when the array is applied to skin, wherein the beneficial agents are delivered into the skin tissue.

25 [00015] In another preferred embodiment of this invention there is provided an apparatus for delivering a plurality of beneficial agents to a patient, the apparatus including a microprojection array comprising a plurality of solid coatings disposed upon the microprojections in the array. Preferably the different coatings are disposed on separate regions of the array. Each of the coatings 30 contains an albumin carrier and a different beneficial agent. The microprojection array has a plurality of microprojections sized, shaped and configured to form a

plurality of microslits through a stratum corneum layer when the array is applied to skin, wherein the beneficial agents are delivered into the skin tissue.

[00016] In another preferred embodiment of this invention there is provided

5 an apparatus for delivering a plurality of beneficial agents to a patient, the apparatus including a microprojection array comprising a plurality of solid coatings disposed upon the microprojections in the array. Preferably the different coatings are disposed on separate regions of the array. Each of the coatings contains a biocompatible carrier and a different beneficial agent. The

10 microprojection array has a plurality of microprojections sized, shaped and configured to form a plurality of microslits through a stratum corneum layer when the array is applied to skin, wherein the beneficial agents are delivered into the skin tissue.

15 **[00017]** In another preferred embodiment of this invention there is provided a composition useful for forming a solid coating on microprojections in a microprojection array, the composition including a beneficial agent and a biocompatible carrier, wherein the composition is applied to the microprojections in a liquid form and forms a solid coating on the microprojection array, and

20 wherein the solid coating allows release of the beneficial agent from the coating upon hydration of the coating.

[00018] In another preferred embodiment of this invention there is provided a composition useful for forming a solid coating on microprojections in a

25 microprojection array, said composition comprising a beneficial agent and an albumin carrier, wherein said composition is applied to the microprojections in a liquid form and forms a solid coating on said microprojection array, and wherein the solid coating allows release of the beneficial agent from the coating upon hydration of the coating.

[00019] The coating thickness is preferably less than the thickness of the microprojections, more preferably the thickness is less than 50 micrometers and most preferably less than 25 micrometers. Generally, the coating thickness is an average thickness measured over the surfaces of the microprojections. The 5 coating thickness can generally be increased by applying multiple coats of the coating liquid, allowing the coats to substantially dry between successive coatings.

[00020] The biocompatible carrier for coating the microprojections is 10 selected to have sufficient adhesion characteristics and to avoid adverse interactions with the beneficial agent. The biocompatible carrier preferably also possesses good solubility properties. The most preferred biocompatible carrier is selected from the group consisting of albumin, polyglutamic acid, polyaspartic acid, polyhistidine, pentosan polysulfate, and polyamino acids. The beneficial 15 agent must have sufficient biological activity to be effective in quantities of up to 1000 micrograms. The preferable beneficial agent is chosen from the group consisting of potent drugs, vaccines and desensitizing agents.

[00021] The coating can be applied to the microprojections using known 20 coating methods. For example, the microprojections can be immersed into an aqueous coating solution containing the biocompatible carrier and the beneficial agent. Alternatively, the coating may be applied by spray coating and/or microfluidic dispensing techniques. More preferably, the coating may be applied using the apparatuses and methods disclosed in U.S. Patent Application Serial 25 No. 60/276,762 filed March 16, 2001, the disclosure of which is hereby incorporated by reference in its entirety.

[00022] In another aspect of the invention, the stratum corneum piercing 30 microprojections are formed from a sheet, preferably a metal sheet, wherein the microprojections are formed by etching or punching the sheet and then the microprojections are folded or bent out of the plane of the sheet. While the

coating can be applied to the sheet before formation of the microprojections, preferably the coating is applied after the microprojections are cut or etched out but prior to being folded out of the plane of the sheet. More preferred is coating after the microprojections have been folded or bent from the plane of the sheet.

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BRIEF DESCRIPTION OF THE DRAWINGS

[00023] The invention will now be described in greater detail with reference to the preferred embodiments illustrated in the accompanying drawings and figures wherein:

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[00024] FIG. 1 is a perspective view of a portion of one example of a microprojection array;

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[00025] FIG. 2 is a perspective view of the microprojection array of Figure 1 with a coating deposited onto the microprojections;

[00026] FIG. 2A is a cross sectional view of a single microprojection 10 taken along line 2A-2A in FIG. 2;

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[00027] FIG. 3 is a view of a skin proximal side of a microprojection array illustrating the division of the microprojection array into various portions;

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[00028] FIG. 4 is a side sectional view of a microprojection array illustrating an alternative embodiment wherein different coatings may be applied to different microprojections; and

[00029] FIG. 5 is a side sectional view of a microprojection array having an adhesive backing.

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MODES FOR CARRYING OUT THE INVENTION

DEFINITIONS:

[00029] Unless stated otherwise the following terms used herein have the following meanings.

5 [00030] The term "transdermal" means the delivery of an agent into and/or through the skin for local or systemic therapy.

[00031] The term "transdermal flux" means the rate of transdermal delivery.

[00032] The term "co-delivering" as used herein means that a supplemental agent(s) is/are administered transdermally either before the agent is delivered, before and during transdermal flux of the agent, during transdermal flux of the agent, during and after transdermal flux of the agent, and/or after transdermal flux of the agent. Additionally, two or more agents may be coated onto the microprojections resulting in co-delivery of the agents.

15 [00033] The terms "biologically active agent", and "beneficial agent" as used herein refer to an agent, such as a drug, vaccine, desensitizing agent, allergen or composition of matter or mixture containing a drug, vaccine, desensitizing agent or allergen, which is therapeutically effective when administered in an amount of less than about 1 milligram and preferably less than about 0.25 milligrams. Thus, the terms "biologically active agent", and "beneficial agent" encompass only agents that are effective at very low doses. These terms specifically include potent drugs, polypeptides, proteins, desensitizing agents, vaccines and allergens. Examples of such agents include, 20 without limitation, polypeptide and protein drugs such as 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 25 analogs such as ACTH (1-24), calcitonin, parathyroid hormone (PTH), 30 vasopressin, deamino [Val4, D-Arg8] arginine vasopressin, interferon alpha, interferon beta, interferon gamma, erythropoietin (EPO), granulocyte

macrophage colon stimulating factor (GM-CSF), interleukin-10 (IL-10) and glucagon; analgesic drugs such as fentanyl, sufentanil, and remifentanyl; antigens used in vaccines such as influenza vaccines, Lyme disease vaccine, rabies vaccine, measles vaccine, mumps vaccine, chicken pox vaccine, small 5 pox vaccine and diphtheria vaccine; and desensitizing agents such as cat, dust mite, dog, and pollen allergens.

[00034] The term "effective amount" or "the effective rate" refers to the amount or rate of the pharmacologically active agent needed to effect the 10 desired, often beneficial, result. The amount of beneficial agent employed in the coating will be that amount necessary to deliver an effective amount of the beneficial agent to achieve the desired result. In practice, this will vary widely depending upon the particular beneficial agent being delivered, the site of delivery, the severity of the condition being treated, the desired effect (e.g., a 15 pharmacological effect versus the stimulation of an immune response) and the dissolution and release kinetics for delivery of the agent from the coating into skin tissues. It is not practical to define the precise range for the effective amount of the beneficial agent incorporated into the coating on the microprojections and delivered transdermally according to the methods described herein. However, 20 generally such agents utilized in the device of the present invention are defined as potent agents since the microprojections are sized with a limited surface area for carrying the coating. In general, the amount of the agent needed to achieve the desired therapy is less than about 1 milligram, more preferably less than about 0.25 milligram.

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[00035] The term "microprojections " or "microblades" refers to the piercing elements which are adapted to pierce or cut through the stratum corneum into the underlying epidermis layer, or epidermis and dermis layers, of the skin of a living animal, particularly a human. The piercing elements should not pierce the 30 skin to a depth that will cause significant bleeding and preferably pierce the skin to a depth which causes no bleeding. Typically the piercing elements have a

blade length of less than 500 micrometers, preferably less than 250 micrometers. The microprojections typically have a width and thickness of about 5 micrometers to about 50 micrometers. The microprojections may be formed in different shapes, such as needles, hollow needles, blades, pins, punches, and 5 combinations thereof. Furthermore, the microprojections may contain means for receiving a greater amount of coating. For example, the microprojections may contain depressions, reservoirs, grooves, or similar geometric features for retaining the coating.

10 **[00036]** The term "microprojection array" as used herein refers to a plurality of microprojections arranged in an array for piercing the stratum corneum. The microprojection array may be formed by etching or punching a plurality of microprojections from a thin sheet and folding or bending the microprojections out of the plane of the sheet to form a configuration such as that shown in Figure 15 1 and in Trautman et al., US 6,083,196. The microprojection array may also be formed in other known manners, such as by forming one or more strips having microprojections along an edge of each of the strip(s) as disclosed in Zuck, U.S. Patent No. 6,050,988. Other microprojection arrays, and methods of making same, are disclosed in Godshall et al., US 5,879,326 and Kamen, US 5,983,136. 20 The microprojection array may also be in the form of hollow needles that hold a dry pharmacologically active agent.

25 **[00037]** The term "pattern coating" refers to coating an agent onto selected areas of the microprojections. More than one agent may be pattern coated on a single microprojection array. Pattern coatings can be applied to the microprojections using known micro-fluidic dispensing techniques such as micropipetting, and ink jet printing.

30 **[00038]** The term "coating" refers to a composition including a bio-compatible carrier and a beneficial agent, wherein the agent may be suspended or dissolved within the carrier. The coating is selected for its adhesion

properties, its stabilization properties, its ability to be quickly dissolved within the epidermis layer, and its ability to form an amorphous glassy structure which retains soluble agents and insoluble agents when substantially dried onto the microprojections.

5

DETAILED DESCRIPTION

[00039] The present invention provides a device for transdermally delivering a beneficial agent to a patient in need thereof. The device has a plurality of stratum corneum-piercing microprojections extending therefrom. The 10 microprojections are adapted to pierce through the stratum corneum into the underlying epidermis layer, or epidermis and dermis layers, but do not penetrate so deep as to cause significant bleeding. The microprojections have a substantially dry coating thereon which contains the active agent. Upon piercing the stratum corneum layer of the skin, the coating is dissolved by body fluid 15 (intracellular fluids and extracellular fluids such as interstitial fluid) and the beneficial agent is released.

[00040] The kinetics of the coating dissolution and release will depend on many factors including the nature of the drug, the coating process, the coating 20 thickness and the coating composition (e.g., the presence of coating formulation additives). Depending on the release kinetics profile, it may be necessary to maintain the coated microprojections in piercing relation with the skin for extended periods of time (e.g., up to about 1 hour). This can be accomplished by anchoring the microprojection array to the skin using an adhesive or by utilizing 25 anchored microprojections such as those described in WO 97/48440, the disclosure of which is incorporated by reference in its entirety. Alternatively, the coating may be quickly dissolved, in which case the microprojection array only need be in contact with the skin for a relatively small amount of time (e.g., less than 1 minute). Still further, the microprojection array of the present invention 30 may be deployed onto a patient's skin manually, or more preferably using an applicator such as that shown and described in US Patent Applications Serial No.

60/240,307 filed October 13, 2000 and Serial No. 60/240,436 filed October 13, 2000, the disclosures of which are incorporated by reference in their entirety.

[00041] Figure 1 illustrates one embodiment of a stratum corneum-piercing microprojection array for use with the present invention. As shown in Figure 1, a portion of the microprojection array 5 includes a plurality of microprojections 10. The microprojections 10 extend at substantially a 90 degree angle from a sheet 12 having openings 14. As shown in Figure 5, the sheet 12 may be incorporated in a delivery patch including a backing 15 for the sheet 12. The backing 15 may further include an adhesive 16 for adhering the backing 15 and microprojection array 5 to a patient's skin. In this embodiment, the microprojections 10 are formed by either etching or punching a plurality of microprojections 10 out of a plane of the sheet 12. The microprojection array 5 may be manufactured of metals such as stainless steel, titanium, nickel titanium alloys, or similar biocompatible materials such as plastics. The microprojection array 5 is preferably constructed of titanium. Metal microprojection members are disclosed in Trautman et al., U.S. Patent No. 6,038,196; Zuck U.S. Patent No. 6,050,988; and Daddona et al., U.S. Patent No. 6,091,975, the disclosures of which are herein incorporated by reference. Other microprojection members that can be used with the present invention are formed by etching silicon, by utilizing chip etching techniques or by molding plastic using etched micro-molds. Silicon and plastic microprojection members are disclosed in Godshall et al., U.S. Patent 5,879,326, the disclosure of which is incorporated herein by reference.

[00042] Figure 2 illustrates the microprojection array 5 wherein the microprojections 10 have been coated with a biocompatible coating 50. The biocompatible coating 50 may partially or completely cover the microprojections 10. The biocompatible coating 50 can be applied to the microprojections before or after the microprojections are formed.

[00043] The coating 50 on the microprojections can be formed by a variety of known methods. One such method is dip-coating. Dip-coating can be described as a means to coat the microprojections by partially or totally immersing the microprojections into the beneficial agent-containing coating solution. Alternatively, the entire device can be immersed into the coating solution. In many instances, the beneficial agent within the coating may be very expensive, therefore it may be preferable to only coat the tips of the microprojections. Microprojection tip coating apparatus and methods are disclosed in Trautman et al. US Patent Application Serial No. 60/276,762 filed 5 March 16, 2001, the disclosure of which is incorporated herein by reference. As shown in the above referenced application the coating device only applies coating to the microprojections themselves and not upon the substrate/sheet that the microprojections project from. This may be desirable in the case where the cost of the beneficial agent is relatively high and therefore the coating containing 10 the beneficial agent should only be disposed onto parts of the microprojection array that will pierce beneath the patient's stratum corneum layer. This coating technique has the added advantage of naturally forming a smooth coating that is not easily dislodged from the microprojections during skin piercing. The smooth cross section of the microprojection tip coating is more clearly shown in Figure 15 2A. Other coating techniques such as microfluidic spray or printing techniques can be used to precisely deposit a coating 18 on the tips of the microprojections 20 as shown in Figure 2. The microprojections 10 may further include means adapted to receive and/or increase the volume of the coating 18 such as apertures (not shown), grooves (not shown), surface irregularities (not shown), or 25 similar modifications, wherein the means provides increased surface area upon which a greater amount of coating may be deposited.

[00044] Other coating methods include spraying the coating solution onto the microprojections. Spraying can encompass formation of an aerosol 30 suspension of the coating composition. In a preferred embodiment, an aerosol

suspension forming a droplet size of about 10 to about 200 picoliters is sprayed onto the microprojections and then dried.

[00045] Referring now to Figures 3 and 4, there is shown an alternative embodiment of the present invention. As shown in Figure 3 the microprojection array may be divided into portions illustrated at 60-63, wherein a different coating is applied to each portion, thereby allowing a single microprojection array to be utilized to deliver more than one beneficial agent during use. Referring now to Figure 4, there is shown a cross-sectional view of a microprojection array 5, including a plurality of microprojections 10, wherein a "pattern coating" has been applied to the microprojection array 5. As shown, each of the microprojections 10 may be coated with a different biocompatible coating as indicated by reference numerals 61-64. That is, separate coatings are applied to the individual microprojections 10. The pattern coating can be applied using a dispensing system for positioning the deposited liquid onto the surface of the microprojection array. The quantity of the deposited liquid is preferably in the range of 0.1 to 20 nanoliters/microprojection. Examples of suitable precision-metered liquid dispensers are disclosed in Tisone, U.S. Patents 5,916,524; 5,743,960; 5,741,554, and 5,738,728 the disclosures of which are incorporated herein by reference. Microprojection coating solutions can also be applied using ink jet technology using known solenoid valve dispensers, optional fluid motive means and positioning means which are generally controlled by use of an electric field. Other liquid dispensing technology from the printing industry or similar liquid dispensing technology known in the art can be used for applying the pattern coating of this invention. As shown, each of the microprojections 10 may be coated with a different biocompatible coating as indicated by reference numerals 61-64.

[00046] The liquid compositions applied to the microprojections to form the solid coatings used in the present invention are liquid compositions including a biocompatible carrier and a beneficial agent. The agent may be dissolved within

the biocompatible carrier or alternatively, the agent may be suspended within the carrier. The ratio of the biocompatible carrier to the beneficial agent in the solid coating may range from about 0.2:1 weight/weight to about 5:1 weight/weight, preferably about 0.5:1 to about 2:1 weight/weight. The biocompatible carrier may

5 be chosen from the group consisting of human albumin, bioengineered human albumin, polyglutamic acid, polyaspartic acid, polyhistidine, pentosan polysulfate, and polyamino acids. The list above is merely exemplary and should not be considered limiting in any manner, it is contemplated that other biocompatible carriers not listed may be utilized. Known adjuvants may be added to the

10 biocompatible carrier to enhance the qualities of the coating. The biocompatible carrier is chosen such that when the coating is substantially dried it forms an amorphous glassy material. Still further, the biocompatible carrier is chosen for its adhesive properties. That is, when substantially dry, the coating is not easily dislodged from the microprojections. The coatings of the present invention allow

15 for beneficial agents having poor aqueous stability to be retained as a solid coating on the microprojections in a stable manner. Thus a beneficial agent having poor aqueous stability may be coated onto a microprojection array wherein the microprojection array will be placed into storage for use at a latter time. Still further, the biocompatible carrier preferably exhibit good water

20 solubility properties such that when the microprojection array is disposed within the stratum corneum and into contact with aqueous body fluids (e.g., in the epidermis) the beneficial agent is quickly delivered. Speed of beneficial agent delivery from the microprojection coating is enhanced where the solid biocompatible carrier has good water solubility. In such cases the coating is

25 quickly dissolved upon skin piercing, thereby releasing the beneficial agent. This ability allows a physician to determine quickly if the patient is exhibiting signs of an allergic reaction to a beneficial agent particularly those in the form of a vaccine and/or antigen.

30 [00047] The coating thickness is dependent upon the density of the microprojections per unit area and the viscosity and concentration of the coating

composition as well as the coating method chosen. In general, coating thickness must be less than 50 micrometers since thicker coatings have a tendency to slough off of the microprojections upon piercing the stratum corneum. Preferred average coating thicknesses are less than 30 micrometers as measured

5 perpendicularly from the microprojection surface. Generally, average coating thickness is measured over the entire coated portions of the microprojection array. More preferred coating thicknesses are about 1 micrometer to about 10 micrometers.

10 [00048] The beneficial agents utilized with the coating are high potency agents requiring a dose of about 1 milligram or less, preferably about 0.25 milligrams or less. Amounts of the beneficial agent within this range can be coated onto the microprojection array of the type shown in Figure 1. Such a microprojection array may have an area of up to 10 centimeters square and a

15 microprojection density of up to 500 microprojections per centimeter squared of the sheet.

[00049] The liquid compositions used to coat the microprojections are prepared by mixing the biocompatible carrier, the beneficial agent to be

20 delivered, and optionally any coating adjuvants, with a volatile liquid. The volatile liquid can be water, dimethyl sulfoxide, dimethyl formamide, ethanol, isopropyl alcohol, and mixtures thereof. Of these, water is most preferred. The liquid coating solution or suspension will typically have a beneficial agent concentration of about 1 to 30 wt%. The coating is dried after being deposited onto the

25 microprojection array utilizing known drying methods such as air drying, vacuum drying, lyophilization and/or combinations thereof. It shall be understood that the term "dried" means substantially free of the volatile liquid. In the case of aqueous coating solutions or suspensions, the coatings typically retain some moisture, more typically the coatings retain a moisture content that is in equilibrium with the

30 atmosphere surrounding the microprojection array. Thus, those skilled in the art

will appreciate that a "dry" coating need not be anhydrous. Alternatively, the coating may be anhydrous, and therefore containing no water.

[00050] Other known formulation adjuvants may be added to the coating as 5 long as they do not adversely affect the necessary solubility and viscosity characteristics of the coating and the physical integrity of the dried coating.

[00051] The coated microprojection array as described may be utilized to 10 deliver vaccines as described above. It is also contemplated that the coated microprojections may be utilized to deliver allergens for desensitization procedures, or for allergy testing. For example, many people develop allergies to multiple allergens (i.e., dust mite, cats, dogs, pollen, etc.).

[00052] In an alternative embodiment, the biocompatible carrier may be 15 chosen from the group consisting of sucrose, trehalose, melezitose, raffinose, stachyose. Additionally, any of the above may be added to the human albumin biocompatible carrier.

[00053] The following examples are given to enable those skilled in the art 20 to more clearly understand and practice the present invention. They should not be considered as limiting the scope of the invention but merely as being representative thereof.

EXAMPLE 1

25 **Human Albumin Dry Film**

[00054] In order to test the ability of aqueous albumin solutions to form solid 30 coatings on titanium microprojections, a coated microprojection array was prepared in the following manner. Human albumin was utilized as a model biocompatible carrier (Sigma, Fraction V). Solutions containing 40, 20, and 10 percent by weight human albumin were prepared in sterile water. To aliquots of these solutions, fluorescein, a marker added for subsequent visualization of the

dried coating, was added at a final concentration of 1 millimolar. A 1-microliter drop of this solution was spread on titanium foil having an area of about one centimeter square. The solution was allowed to dry at room temperature for about 1 hour. Fluorescence microscopy revealed that the coating, when dry, 5 formed an amorphous glassy surface. Redissolution of the dry film in water was fast and complete.

Particle Suspension

[00055] A microprojection array having a coating containing a drug surrogate, in the form of fine particles, was prepared in the following manner. A 10 40 percent by weight human albumin solution was prepared in water. To 50 microliters of this solution, 50 microliters of a 20 percent by weight suspension of 0.5-micrometer fluorescent beads (i.e., the drug surrogate) was added. A 1-microliter drop of this suspension was spread on titanium foil having an area of approximately 1 square centimeter and allowed to air dry at room temperature for 15 about 1 hour. 50 microliters of this suspension was also spread on a microprojection array and blown dry. Fluorescence microscopy demonstrated that the fluorescent beads were dispersed homogenously in the albumin matrix and that the coating of the microprojection array was effective. The coating prepared with human albumin had glasslike properties at this high particle 20 concentration. In addition, the particles were freed readily following rehydration. A similar experiment was performed with fluorescent beads of various sizes (ranging from 0.02 to 0.5 micrometers). The final bead concentration was 20 percent by weight and the human albumin was 1 percent by weight. Similarly, 25 microscopy revealed that the fluorescent beads are dispersed homogenously in the albumin dry coating. In each of the cases, the particles were readily freed from the dry coating following rehydration. In contrast, when a 10 percent by weight suspension of the 0.5 micrometer fluorescent beads were prepared in water and attempts were made to apply the suspension on a titanium foil, spreading was very poor and, following drying, the coating was found to be very 30 heterogeneous.

EXAMPLE 2

Cyclosporin A (CSA) Suspension

[00056] A coated microprojection array was prepared in the following manner. CSA is a water-insoluble peptide drug (1200 dalton molecular weight) 5 used in therapeutics. 10 milligrams of CSA was dry milled. To this powder, 90 microliters of 20 percent by weight human albumin solution was added and homogenized with the CSA powder prepared in water. To this suspension, fluorescein, a marker added for subsequent visualization, was added at a final concentration of 1 millimolar. A 1 microliter drop of this suspension was spread 10 on titanium foil having an area of 1 square centimeter and allowed to dry at room temperature for about an hour. Fluorescence microscopy demonstrated that the CSA particles were dispersed homogeneously in the albumin matrix. The CSA particles, ranging from 1 micrometer to 25 micrometers, were freed readily following rehydration.

15

EXAMPLE 3

Soluble drugs.

[00057] A 40 percent by weight solution of human albumin was prepared in water. To 50 microliters of this solution, 50 microliters of a 40 percent by weight 20 aqueous solution of lidocaine HCl was added. A control solution containing no albumin was also prepared. 1-microliter drops of these solutions were spread on titanium foil having an area of approximately 1 square centimeter. The solutions were allowed to air dry at room temperature for about 1 hour. An inspection revealed that the dry film of the albumin/lidocaine mixture formed a glassy 25 amorphous surface. Redissolution of the coating in water was fast and complete. By contrast, the lidocaine solution formed a very hygroscopic film unsuitable for subsequent storage

[00058] An aqueous solution containing 20 wt% human growth hormone 30 (20 wt% hGH), and 20 wt% sucrose was prepared. Microprojection arrays (microprojection length 250 μ m, 595 microprojections per array) had a skin

contact area 2 cm². The tips of the microprojections were coated with this solution by passing the arrays over a rotating drum carrying the hGH/sucrose solution using the method and apparatus disclosed in US Patent Application Serial No. 60/276,762 filed March 16, 2001. Four successive coatings were 5 performed on each microprojection array at 4°C. The amount of protein coated on the arrays was evaluated by total protein assay. An average of 9.5 ± 0.9 µg of hGH was coated per array. Scanning electron microscopy revealed good uniformity of coating from microprojection to microprojection, with the coating limited to the first 100 µm of the microprojection tip. On the microprojection itself, 10 the coating was found unevenly distributed. Most of the solid coating appeared to be located in caps centered on the geometric center of the faces of the coated area of the microprojections. Following two days storage in a vacuum chamber, the solid coating presented a very smooth surface with absence of cracking and it was demonstrated to adhere very tightly to the microprojections. The 15 maximum measured thickness of the coating was about 4 µm while the average calculated thickness over the entire coated area was only about 1.7 µm. Overall, the coating presented good aerodynamics and good adhesion, consistent with minimum effect on penetration of the microprojections into the skin and minimal removal of the drug from the microprojection during penetration.

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[00059] Some of the hGH tip-coated arrays were subsequently used for drug delivery studies in hairless guinea pigs. The application of the coated microprojection arrays was done using an impact applicator (total energy = 0.4 Joules, delivered in less than 10 milliseconds) using a spring-driven impact 25 applicator or the type disclosed in US Patent Application Serial No. 60/240,307 filed October 13, 2000. The arrays were left on the skin after application for 5 seconds, 5 minutes, or 1 hour, in groups of three animals. Blood was collected at time intervals for plasma hGH determination by ELISA. The results showed that hGH delivery was the same at all wearing times. On average, 5 µg of hGH 30 was delivered in each animal, which accounts for approximately 50% of the

coated dose. Assuming that the bioavailability from microprojection delivery was similar to that of subcutaneous administration (65%), about 80% of the coated dose was delivered into the skin. In addition, as compared to subcutaneous injection, a quicker onset was observed following microprojection administration 5 (tmax of 60 minutes and 30 minutes, respectively; Cmax of 5 ng/mL and 13 ng/mL, respectively). Finally, the 5 minute wearing time group had the smallest CV (30%), which is even smaller than that observed following subcutaneous injection (50%).

CLAIMS:

1. A device for delivering a beneficial agent through the stratum corneum, the device comprising:

5 a plurality of stratum corneum-piercing microprojections;

wherein the coating includes at least one beneficial agent and at least one water soluble biocompatible carrier; and

wherein said coating is placed in contact with body fluid after the microprojections have pierced the stratum corneum.

10

2. The device according to Claim 1, wherein the at least one biocompatible carrier is human albumin.

15 3. The device according to Claim 1, wherein the at least one biocompatible carrier is bio-engineered human albumin.

4. The device according to Claim 1, wherein the coating is applied to the microprojections as an aqueous solution or suspension.

20 5. The device according to Claim 1 wherein the coating is in an amorphous glassy form.

6. The device according to Claim 1, wherein the at least one beneficial agent is suspended in the at least one biocompatible carrier.

25

7. The device according to Claim 1, wherein the at least one biocompatible carrier includes at least one carrier chosen from the group consisting of polyamino acids, polysaccharides and oligosaccharides.
- 5 8. The device according to Claim 1, wherein the at least one beneficial agent is selected from the group consisting of proteins, glycoproteins, peptides, polysaccharides, oligosaccharides, oligonucleotides, and DNA.
9. The device according to Claim 1, wherein the at least one beneficial agent 10 is selected from the group consisting of vaccines and desensitizing agents.
10. The device according to Claim 1, wherein the at least one biocompatible carrier is selected from the group consisting of human albumin, dextran sulfate, pentosan polysulfate, polyglutamic acid, polyaspartic acid, polyhistidine, and non-15 reducing sugars.
11. The device according to Claim 1, wherein the ratio of all biocompatible carriers to all beneficial agents range from about 0.2:1 to about 5:1 weight/weight.
- 20 12. The device according to Claim 1, wherein the ratio of all biocompatible carriers to all beneficial agents range from about 0.5:1 to about 2:1 weight/weight.

13. The device according to Claim 1, wherein the at least one beneficial agent is suspended in the at least one biocompatible carrier and wherein the at least one biocompatible carrier functions as an adhesive to retain the at least one 5 beneficial agent upon the microprojections.

14. The device according to Claim 1, wherein the at least one biocompatible carrier functions as an adhesive to retain the at least one beneficial agent upon the microprojections.

10

15. The device according to Claim 1, wherein at least a portion of the microprojections further includes a means adapted to retain the coating.

16. The device according to Claim 15, wherein the means adapted to retain 15 the coating includes an aperture formed through the microprojection.

17. The device according to Claim 15, wherein the means adapted to retain the coating includes at least one groove disposed upon the microprojection.

20 18. The device according to Claim 1, wherein the coating has a thickness less than about 50 micrometers.

19. The device according to Claim 1, wherein the coating has a thickness less than about 25 micrometers.

20. The device according to Claim 1, wherein the coating has a thickness
5 between about 1.0 micrometers and about 10 micrometers.

21. The device according to Claim 1, wherein the at least one biocompatible carrier stabilizes the at least one beneficial agent.

10 22. The device according to Claim 1, wherein the at least one biocompatible carrier is a polyamino acid.

23. The device according to Claim 1, wherein the microprojections extend through the stratum corneum into the epidermis.

15

24. The device according to Claim 1, wherein the at least one biocompatible carrier in the coating is water soluble.

20 25. The device according to Claim 1, wherein the coating is soluble in body fluid.

26. The device according to Claim 1, wherein the coating comprises a plurality of beneficial agents.

27. The device according to Claim 27 wherein the each of the plurality of beneficial agents are included on coatings which are on separate portions of the plurality of microprojections.

5

28. A method for delivering a beneficial agent through the stratum corneum layer of skin, the method comprising:

providing a microprojection array having a plurality of stratum corneum-piercing microprojections, the microprojections being coated with a biocompatible 10 coating containing at least one beneficial agent and a biocompatible carrier; and causing the microprojections to pierce the stratum corneum layer of a predetermined skin site, whereby the beneficial agent is released into the skin tissue.

15 29. The method according to Claim 28, wherein the at least one biocompatible carrier is human albumin.

30. The method according to Claim 28, wherein the at least one biocompatible carrier is bio-engineered human albumin.

20

31. The method according to Claim 28, wherein the coating is applied to the microprojections as an aqueous solution or suspension.

32. The method according to Claim 28, wherein the coating is in an amorphous glassy form.

33. The method according to Claim 28, wherein the at least one beneficial 5 agent is suspended in the at least one biocompatible carrier.

34. The method according to Claim 28, wherein the at least one biocompatible carrier includes at least one carrier chosen from the group consisting of polyamino acids, polysaccharides and oligosaccharides.

10

35. The method according to Claim 28, wherein the at least one beneficial agent is selected from the group consisting of proteins, glycoproteins, peptides, polysaccharides, oligosaccharides, oligonucleotides, and DNA.

15 36. The method according to Claim 28, wherein the at least one beneficial agent is selected from the group consisting of vaccines and desensitizing agents.

37. The method according to Claim 28, wherein the at least one biocompatible carrier is selected from the group consisting of human albumin, dextran sulfate, 20 pentosan polysulfate, polyglutamic acid, polyaspartic acid, polyhistidine, and non-reducing sugars.

38. The method according to Claim 28, wherein the ratio of all biocompatible carriers to all beneficial agents range from about 0.2:1 to about 5:1 weight/weight.

5 39. The method according to Claim 28, wherein the ratio of all biocompatible carriers to all beneficial agents range from about 0.5:1 to about 2:1 weight/weight.

10 40. The method according to Claim 28, wherein the at least one beneficial agent is suspended in the at least one biocompatible carrier and wherein the at least one biocompatible carrier functions as an adhesive to retain the at least one beneficial agent upon the microprojections.

15 41. The method according to Claim 28, wherein the at least one biocompatible carrier functions as an adhesive to retain the at least one beneficial agent upon the microprojections.

42. The method according to Claim 28, wherein at least a portion of the microprojections further includes a means adapted to retain the coating.

20

43. The method according to Claim 42, wherein the means adapted to retain the coating includes an aperture formed through the microprojection.

44. The method according to Claim 42, wherein the means adapted to retain the coating includes at least one groove disposed upon the microprojection.

45. The method according to Claim 28, wherein the coating has a thickness
5 less than about 50 micrometers.

46. The method according to Claim 28, wherein the coating has a thickness less than about 25 micrometers.

10 47. The method according to Claim 28, wherein the coating has a thickness between about 1.0 micrometers and about 10 micrometers.

48. The method according to Claim 28, wherein the at least one biocompatible carrier stabilizes the at least one beneficial agent.

15

49. The method according to Claim 28, wherein the at least one biocompatible carrier is a polyamino acid.

20 50. The method according to Claim 28, wherein the microprojections extend through the stratum corneum into the epidermis.

51. The method according to Claim 28, wherein the at least one biocompatible carrier in the coating is water soluble.

52. The method according to Claim 28, wherein the coating is soluble in body fluid.

5 53. The method according to Claim 29, wherein the coating comprises a plurality of beneficial agents.

54. The method according to Claim 29, wherein the each of the plurality of beneficial agents are included on coatings which are on separate portions of the
10 plurality of microprojections.

55. A composition useful for forming a solid coating on microprojections in a microprojection array, said composition comprising a beneficial agent and a biocompatible carrier, wherein said composition is applied to the microprojections
15 in a liquid form and forms a solid coating on said microprojection array, and wherein the solid coating allows release of the beneficial agent from the coating upon hydration of the coating.

56. The composition according to Claim 55, wherein the at least one
20 biocompatible carrier is human albumin.

57. The composition according to Claim 55, wherein the at least one biocompatible carrier is bio-engineered human albumin.

58. The composition according to Claim 55, wherein the composition is applied to the microprojections as an aqueous solution or suspension.

5 59. The composition according to Claim 55, wherein the composition forms a coating having an amorphous glassy form.

60. The composition according to Claim 55, wherein the at least one beneficial agent is suspended in the at least one biocompatible carrier.

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61. The composition according to Claim 55, wherein the at least one biocompatible carrier includes at least one carrier chosen from the group consisting of polyamino acids, polysaccharides and oligosaccharides.

15 62. The composition according to Claim 55, wherein the at least one beneficial agent is selected from the group consisting of proteins, glycoproteins, peptides, polysaccharides, oligosaccharides, oligonucleotides, and DNA.

20 63. The composition according to Claim 55, wherein the at least one beneficial agent is selected from the group consisting of vaccines and desensitizing agents.

64. The composition according to Claim 55, wherein the at least one biocompatible carrier is selected from the group consisting of human albumin,

dextran sulfate, pentosan polysulfate, polyglutamic acid, polyaspartic acid, polyhistidine, and non-reducing sugars.

65. The composition according to Claim 55, wherein the ratio of all
5 biocompatible carriers to all beneficial agents range from about 0.2:1 to about 5:1
weight/weight.

66. The composition according to Claim 55, wherein the ratio of all
biocompatible carriers to all beneficial agents range from about 0.5:1 to about 2:1
10 weight/weight.

67. The composition according to Claim 55, wherein the at least one beneficial
agent is suspended in the at least one biocompatible carrier and wherein the at
least one biocompatible carrier functions as an adhesive to the at least one
15 beneficial agent upon the microprojections.

68. The device according to Claim 55, wherein the at least one biocompatible
carrier functions as an adhesive to retain the at least one beneficial agent upon
the microprojections.

20

69. The composition according to Claim 55, wherein the composition is
capable of being formed into a coating of having a thickness less than about 50
micrometers.

70. The composition according to Claim 55, wherein the composition is capable of being formed into a coating of having a thickness less than about 25 micrometers.

5

71. The composition according to Claim 55, wherein the composition is capable of being formed into a coating of having a thickness between about 1.0 micrometers and about 10 micrometers.

10 72. The composition according to Claim 55, wherein the at least one biocompatible carrier stabilizes the at least one beneficial agent.

73. The composition according to Claim 55, wherein the at least one biocompatible carrier is a polyamino acid.

15

74. The composition according to Claim 55, wherein the at least one biocompatible carrier in the coating is water soluble.

20 75. The composition according to Claim 55, wherein the compositions is capable of forming a coating which is soluble in body fluid.

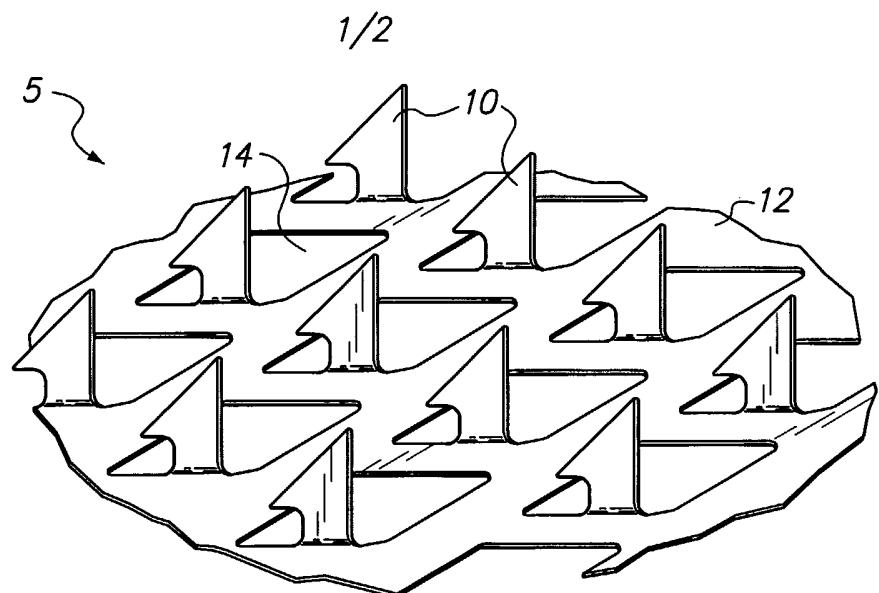


FIG. 1

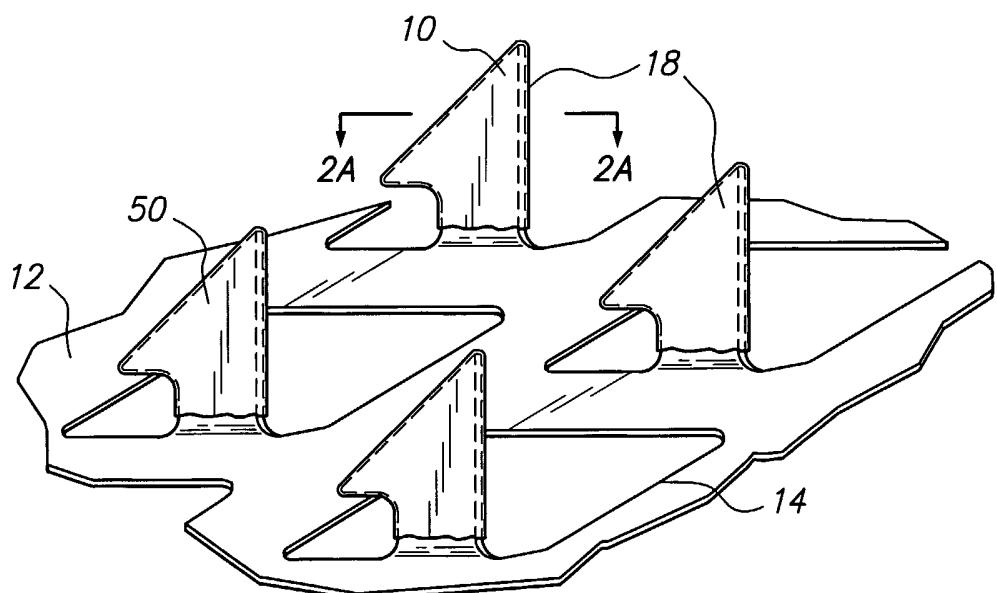


FIG. 2

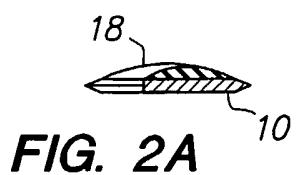
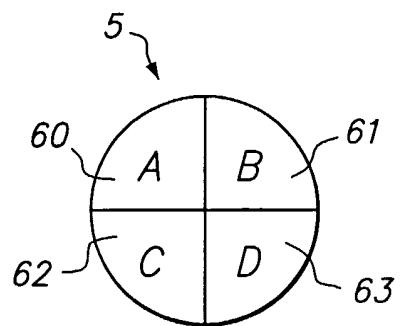
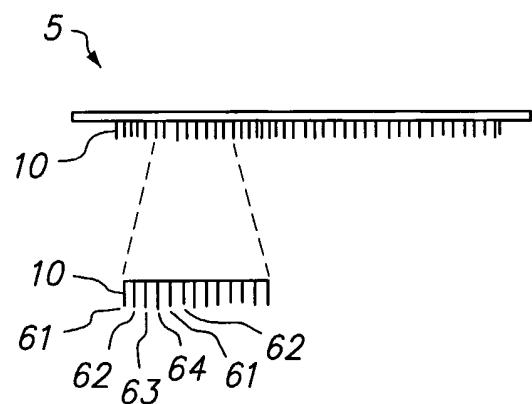
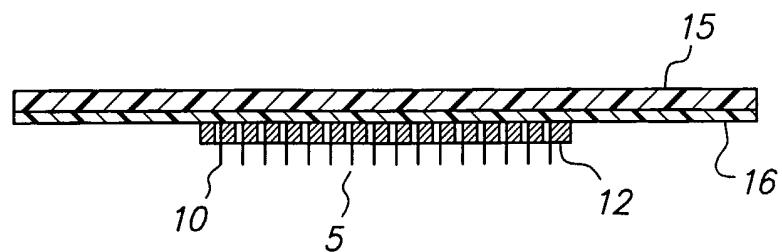


FIG. 2A

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**FIG. 3****FIG. 4****FIG. 5**