(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 January 2017 (05.01.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/004067 A1

(51) International Patent Classification:
A61M 37/00 (2006.01) *A61K 9/00* (2006.01)

(21) International Application Number:
PCT/US2016/039864

(22) International Filing Date:
28 June 2016 (28.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/186,310 29 June 2015 (29.06.2015) US

(71) Applicant: **CORIUM INTERNATIONAL, INC.** [US/US]; 235 Constitution Drive, Menlo Park, California 94025 (US).

(72) Inventors: **SHASTRY, Ashutosh**; 3092 Adams Way, Santa Clara, California 95051 (US). **FAASSE, Adrian**; P.O. Box 547, Carmel Valley, California 93942-0547 (US). **SINGH, Parminder**; 5504 Alvelais Drive, Union City, California 94587 (US).

(74) Agents: **MAHONEY, Jacqueline F.** et al.; 500 North Capitol Street, N.W., Washington, District of Columbia 20001-1531 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: MICROARRAY FOR DELIVERY OF THERAPEUTIC AGENT, METHODS OF USE, AND METHODS OF MAKING

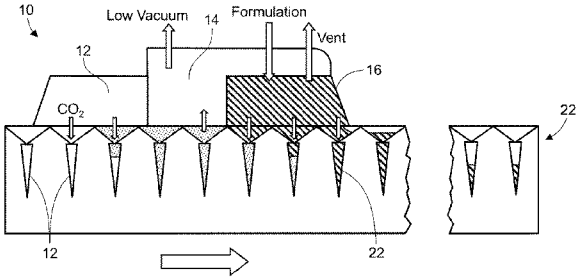

FIG. 1

(57) Abstract: Devices and methods for manufacturing and using microstructure arrays are described. In the methods, formulation is introduced into cavities of a microprojection array mold by means that include a vacuum to achieve a more efficient and uniform filling of the cavities and/or reduce bubble formation in the cavities.

WO 2017/004067 A1

MICROARRAY FOR DELIVERY OF THERAPEUTIC AGENT, METHODS OF USE, AND METHODS OF MAKING

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/186,310, filed June 29, 2015, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The disclosure relates generally to methods for making or fabricating the delivery systems for administering a therapeutic agent or drug using an array of microstructures, methods for using the systems for delivery of an agent, and related features thereof.

BACKGROUND

[0003] Arrays of microneedles were proposed as a way of administering drugs through the skin in the 1970s, for example in expired U.S. Pat. No. 3,964,482. Microneedle or microstructure arrays can facilitate the passage of drugs through or into human skin and other biological membranes in circumstances where ordinary transdermal administration is inadequate. Microstructure arrays can also be used to sample fluids found in the vicinity of a biological membrane such as interstitial fluid, which is then tested for the presence of biomarkers.

[0004] In recent years it has become more feasible to manufacture microstructure arrays in a way that makes their widespread use financially feasible. U.S. Pat. No. 6,451,240 discloses some methods of manufacturing microneedle arrays. If the arrays are sufficiently inexpensive, for example, they may be marketed as disposable devices. A disposable device may be preferable to a reusable one in order to avoid the question of the integrity of the device being compromised by previous use and to avoid the potential need of resterilizing the device after each use and maintaining it in controlled storage.

[0005] Despite much initial work on fabricating microneedle arrays in silicon or metals, there are significant advantages to polymeric arrays. U.S. Patent No. 6,451,240 discloses some methods of manufacturing polymeric microneedle arrays. Arrays made primarily of biodegradable polymers also have some advantages. U.S. Pat. No. 6,945,952 and U.S. Published Patent Applications Nos. 2002/0082543 and 2005/0197308 have some discussion of microneedle arrays made of biodegradable polymers. A further description of the fabrication of a microneedle array made of polyglycolic acid is found in Park *et al.*, "Biodegradable polymer microneedles: Fabrication, mechanics, and transdermal drug delivery," *J. of Controlled Release*, 104:51-66 (2005).

[0006] A method of forming microprotrusion arrays using solvent casting methods is described in U.S. Publication Nos 2008/0269685 and 2014/0272101, which are incorporated in their entirety herein by reference.

[0007] A layered microstructure array has been described in U.S. Publication No. 2011/0276028, incorporated in its entirety herein, for hPTH delivery comprising a fast dissolving drug-in-tip distal layer and a backing layer formed of an insoluble biodegradable polymer.

[0008] Despite these efforts, there is still a need to find simpler and better methods for the manufacture of polymeric delivery systems. A particular need is for systems and methods that provide better, more consistent and easier formation of the arrays as well as providing methods that are useful for commercial manufacture of arrays. A further need is for a method of forming microstructure arrays that is scalable from small scale, aseptic and pilot testing to commercial processes.

[0009] The foregoing examples of the related art and limitations related therewith are intended to be illustrative and not exclusive. Other limitations of the related art will become apparent to those of skill in the art upon a reading of the specification and a study of the drawings.

BRIEF SUMMARY

[0010] The following aspects and embodiments thereof described and illustrated below are meant to be exemplary and illustrative, not limiting in scope.

[0011] In one aspect, a method of making or preparing an array of microstructures. In some embodiments, the method comprises dissolving or suspending at least one therapeutic or active agent in a first solvent to form a therapeutic or active agent solution or suspension. At least one polymer is dissolved in a second solvent, which may be the same or different than the first solvent, to form a polymer matrix solution or suspension. In some embodiments, at least one of the first or second solvent is water or an aqueous solution. The therapeutic or active agent solution or suspension and the polymer solution are mixed to form a polymer matrix solution or suspension.

[0012] In some embodiments, the therapeutic or active agent solution or suspension and/or the polymer solution or suspension includes one or more excipients and/or additives. In some embodiments, the excipient or additive is selected from one or more of a sugar, a surfactant, or an antioxidant. In some embodiments, one or more of the excipients or additives is dissolved in at least one of the first or second solvent. In some embodiments, the sugar is selected from sorbitol, sucrose, trehalose, fructose, or dextrose. In some embodiments, the surfactant is selected from Polysorbate 20 or Polysorbate 80. In some embodiments, the antioxidant is selected from methionine, cysteine, D-alpha tocopherol acetate, EDTA, or vitamin E. Where the excipient is a sugar, in some embodiments the at least one sugar is dissolved in the polymer matrix or suspension after the polymer is dissolved in the solvent.

[0013] In embodiments, the therapeutic or active agent is selected from one or more of a drug, a small molecule, a peptide or a protein, and/or a vaccine.

[0014] A low vacuum is applied to a mold having a plurality of microstructure cavities formed therein. The polymer matrix solution or suspension is dispensed on the mold and the

microstructure cavities in the mold are filled with the polymer matrix solution or suspension. The solution or suspension is dried to form the array of microstructures. In embodiments, the low vacuum is applied to achieve a vacuum pressure of about $1x10^{-3}$ to 760 Torr. In other embodiments, the low vacuum is applied to achieve a vacuum pressure of about 25 to 760 Torr. In some embodiments, the dispensing and/or filling steps are performed outside the low vacuum. In some embodiments, excess polymer matrix solution or suspension is removed from the mold, including the mold surface, after the filling step.

[0015] In some embodiments, the method further comprises dispensing at least one soluble gas into the cavities prior to applying the low vacuum to the mold. In some embodiments, the method further comprises comprising dispensing at least one soluble gas into the cavities prior to dispensing the polymer matrix solution or suspension on the mold. In some embodiments, the soluble gas is selected from CO_2 and CH_4.

[0016] In some embodiments, the polymer matrix solution or suspension is dried at a temperature of about 5-50° C. In some embodiments, the polymer matrix solution or suspension is dried for at least about 30-60 minutes.

[0017] In some embodiments, the method further comprises dispensing a basement or backing layer formulation on the mold surface. In embodiments, the basement or backing layer formulation is dispensed such that the basement or backing layer formulation contacts the polymer matrix to connect the dried microstructure (polymer matrix) portions. In some embodiments, the basement or backing layer formulation is dried in an oven at about 5-50° C. In some embodiments, the basement or backing layer is comprised of at least one non-biodegradable polymer.

[0018] In some embodiments, the basement or backing layer is affixed to a substrate. In some embodiments, the substrate is selected from a pressure sensitive adhesive and a UV cured adhesive.

[0019] In some embodiments, the method further comprises demolding the array from the mold. In some embodiments, the array is demolded from the mold drying the basement or backing layer.

[0020] Additional embodiments of the present microstructures, arrays, methods, apparatuses, devices, and the like, will be apparent from the following description, drawings, examples, and claims. As can be appreciated from the foregoing and following description, each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present disclosure provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment of the present invention. Additional aspects and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying examples and drawings.

BRIEF DESCRIPTION OF DRAWINGS

[0021] FIGURE 1 is an illustration of one embodiment of a method of casting microprojections.

[0022] FIGURE 2 is a flowchart of one method of forming a microprojection array.

[0023] FIGURES 3A-3B are illustrations of molds containing solution without low vacuum (FIG. 3A) and with low vacuum (FIG. 3B).

[0024] It will be appreciated that the thicknesses and shapes for the various microstructures have been exaggerated in the drawings to facilitate understanding of the device. The drawings are not necessarily "to scale."

[0025] Various aspects now will be described more fully hereinafter. Such aspects may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey its scope to those skilled in the art.

DETAILED DESCRIPTION

[0026] The practice of the present disclosure will employ, unless otherwise indicated, conventional methods of chemistry, biochemistry, and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, *e.g.*; A.L. Lehninger, *Biochemistry* (Worth Publishers, Inc., current addition); Morrison and Boyd, *Organic Chemistry* (Allyn and Bacon, Inc., current addition); J. March, *Advanced Organic Chemistry* (McGraw Hill, current addition); *Remington: The Science and Practice of Pharmacy*, A. Gennaro, Ed., 20th Ed.; *Goodman & Gilman The Pharmacological Basis of Therapeutics*, J. Griffith Hardman, L. L. Limbird, A. Gilman, 10th Ed.

[0027] Where a range of values is provided, it is intended that each intervening value between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the disclosure. For example, if a range of 1 μm to 8 μm is stated, it is intended that 2 μm, 3 μm, 4 μm, 5 μm, 6 μm, and 7 μm are also explicitly disclosed, as well as the range of values greater than or equal to 1 μm and the range of values less than or equal to 8 μm.

[0028] As used in this specification, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a "polymer" includes a single polymer as well as two or more of the same or different polymers; reference to an "excipient" includes a single excipient as well as two or more of the same or different excipients, and the like.

[0029] In describing and claiming the present invention, the following terminology will be used in accordance with the definitions described below.

[0030] The terms “microprotrusion”, “microprojection”, “microstructure” and “microneedle” are used interchangeably herein to refer to elements adapted to penetrate or pierce at least a

portion of the stratum corneum or other biological membrane. For example, illustrative microstructures may include, in addition to those provided herein, microblades as described in U.S. Patent No. 6,219,574, edged microneedles as described in U.S. Patent No. 6,652,478, and microprotrusions as described in U.S. Patent Publication No. U.S. 2008/0269685.

[0031] In discussing the applicators and arrays described herein, the term "downward" is sometimes used to describe the direction in which microprotrusions are pressed into skin, and "upward" used to describe the opposite direction. However, those of skill in the art will understand that the applicators can be used where the microprotrusions are pressed into skin at an angle to the direction of the earth's gravity, or even in a direction contrary to that of the earth's gravity. In many applicators, the energy for pressing the microprotrusions is provided primarily by an energy-storage member and so efficiency is not much affected by the orientation of the skin relative to the earth's gravity.

[0032] In this application reference is often made for convenience to "skin" as the biological membrane which the microprojections penetrate. It will be understood by persons of skill in the art that in most or all instances the same inventive principles apply to the use of microprojections to penetrate other biological membranes such as, for example, those which line the interior of the mouth or biological membranes which are exposed during surgery.

[0033] “Biodegradable” refers to natural or synthetic materials that degrade enzymatically, non-enzymatically or both to produce biocompatible and/or toxicologically safe by-products which may be eliminated by normal metabolic pathways.

[0034] “Medium vacuum” refers to a partial pressure that may be achieved with a vacuum pump. A medium pressure may not be measurable using a liquid or mechanical manometer. In embodiments, a medium vacuum refers to a pressure of about 25 to $1x10^{-3}$ Torr.

[0035] The term "microprotrusion array" for purposes herein is intended to denote a two-dimensional or a three-dimensional arrangement of microprotrusions, microstructures, microprojections, or microneedles, which are used interchangeably herein. The arrangement may be regular according to a repeating geometric pattern or it may be irregular. A typical “microstructure array”, “microprojection array”, or “microneedle array” comprises microstructures, microprojections, or microneedles projecting from a base or substrate of a particular thickness, which may be of any shape, for example square, rectangular, triangular, oval, circular, or irregular. An array typically comprises a plurality of microstructures, microprojections, or microneedles. The microstructures, microprojections, or microneedles themselves may have a variety of shapes. While an array could be pressed by hand into skin, a variety of devices may be used to hold the array as it is being applied and/or to facilitate in one way or another the process of application of the array to the skin or other biological membrane. Such devices may broadly be referred to as "applicators." Applicators may for example reduce the variations in force, velocity, and skin tension that occur when an array is

pressed by hand into the skin. Variations in force, velocity and skin tension can result in variations in permeability enhancement.

[0036] "Non-biodegradable" refers to natural or synthetic materials that do not appreciably degrade when inserted into and/or contacted with skin, mucosa, or other biological membrane for a period of time associated with use of microstructure arrays.

[0037] "Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not.

[0038] "Rough vacuum" or "low vacuum" refers to a partial pressure of less than 1 atmosphere (760 Torr). In embodiments, a rough or low vacuum refers to a pressure of about 760 to 25 Torr.

[0039] "Substantially" or "essentially" means nearly totally or completely, for instance, 90-95% or greater of some given quantity.

[0040] "Transdermal" refers to the delivery of an agent into and/or through the skin for local and/or systemic therapy. The same inventive principles apply to administration through other biological membranes such as those which line the interior of the mouth, gastro-intestinal tract, blood-brain barrier, or other body tissues or organs or biological membranes which are exposed or accessible during surgery or during procedures such as laparoscopy or endoscopy.

[0041] A material that is "water-soluble" may be defined as soluble or substantially soluble in aqueous solvents, such that the material dissolves into, within or below the skin or other membrane which is substantially aqueous in nature.

[0042] Where a range of values is provided, it is intended that each intervening value between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the disclosure. For example, if a range of 1 μm to 8 μm is stated, it is intended that 2 μm, 3 μm, 4 μm, 5 μm, 6 μm, and 7 μm are also disclosed, as well as the range of values greater than or equal to 1 μm and the range of values less than or equal to 8 μm.

I. Methods of Making Microstructure Arrays

[0043] Before describing the methods of manufacture in detail, it is to be understood that the methods are not limited to specific solvents, materials, or device structures, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0044] Examples of forming various microstructure arrays using different formulations and configurations are provided in Example 1.

A. Array Molds

[0045] The molds used to form the arrays in the methods herein can be made using a variety of methods and materials. Exemplary molds and methods of making molds are

described, for example, in U.S. Patent Publication No. 2008/2696585. In one exemplary embodiment, the mold is a negative mold formed from a silicone such as polydimethylsilicone. A negative mold is typically formed by preparing a master microprojection array and casting a liquid mold material over the master array. The mold is allowed to dry and harden, which results in a mold comprising cavities corresponding to the microprojections of the master array. It will be appreciated that the molds suitable for use in the present methods may be prepared according to other methods.

[0046] In general, the microprojections have a height of at least about 100 μm, at least about 150 μm, at least about 200 μm, at least about 250 μm, or at least about 300 μm. In general it is also preferred that the microprojections have a height of no more than about 1 mm, no more than about 500 μm, no more than about 300 μm, or in some cases no more than about 200 μm or 150 μm. In embodiments, the microprojections have a height of at least about 50-500 μm. In other embodiments, the microprojections have a height of at least about 100-500 μm, 100-400 μm, 100-300 μm, 100-200 μm, 100-150 μm, 150-500 μm, 150-400 μm, 150-300 μm, 150-200 μm, 200-500 μm, 200-400 μm, 200-300 μm, 300-500 μm, 300-400 μm, or 400-500 μm. It will be appreciated that the microprojections within an array may have a range of heights. The microprojections may have any suitable shape including, but not limited to polygonal or cylindrical. Particular embodiments include pyramidal including a four-sided pyramid, a funnel shape, a cylinder, a combination of funnel and cylinder shape having a funnel tip and a cylindrical base, and a cone with a polygonal bottom, for example hexagonal or rhombus-shaped. Other possible microprojection shapes are shown, for example, in U.S. Published Patent Apps. 2004/0087992 and 2014/0180201. Microprojections may in some cases have a shape which becomes thicker towards the base, for example microprojections which have roughly the appearance of a funnel, or more generally where the diameter of the microprojection grows faster than linearly with distance to the microprojection distal end. It will be appreciate that polygonal microprojections may also have a shape which becomes thicker toward the base or where a radius or diameter grows faster than linearly with distance to the microprojection distal end. Where microprojections are thicker towards the base, a portion of the microprojection adjacent to the base, which may be called the "foundation," may be designed not to penetrate the skin.

[0047] The microprojections may be spaced about 0-500 μm apart. In specific, but not limiting embodiments, the microprojections are spaced about 0 μm, about 50 μm, about 100 μm, about 150 μm, about 200 μm, about 250 μm, about 300 μm, about 350 μm, about 400 μm, about 450 μm, or about 500 μm apart. The space between the microprojections may be measured from the base of the microprojections (base to base) or from the tip (tip to tip). The spacing of the microprojections may be regular or irregular.

[0048] One exemplary master array includes a plurality of diamond shaped projections having a height of about 200 μm, a base of about 70 μm, and spacing between the projections

of about 200 μm. In another exemplary embodiment, the master array includes a plurality of hexagonal or other polygonal shaped projections having a height of about 200 μm, a base of about 70 μm, and spacing between the projections of about 400 μm. In yet another embodiment, the master array includes a plurality of cylindrical shaped projections having a height of about 400 μm, a diameter of about 100 μm, and spacing between the projections of about 200 μm. It will be appreciated that the cylindrical shaped projections may have a funnel shaped, pointed, or sharp distal end.

B. Preparation of Casting Solution or Formulation

[0049] For the active agent containing portion of the microstructures, a casting solution or formulation is formed by dissolving or suspending one or more therapeutic agents, active agents, drugs, APIs, or other substances to be transdermally delivered and one or more polymers in a solvent to form a polymer matrix solution or suspension. The terms active agent, therapeutic agent, agent, drug, API are used interchangeably herein and discussion or reference to one is intended to include and apply to each and all terms. In one embodiment, the casting solution is formed by dissolving or suspending at least one agent and one or more polymers in an aqueous buffer or solvent to form a solution or suspension comprising the active agent and the polymer. In another embodiment, at least one active agent is dissolved or suspended in a solvent to form an active agent solution or suspension. At least one polymer is separately dissolved in a solvent to form a polymer solution or suspension. The suspension may be a liquid in liquid suspension or a solid in liquid suspension depending on the nature of the active agent and/or polymer. The solvent used for the active agent solution and the polymer solution may be the same or different. The active agent solution and the polymer solution are mixed to form a polymer matrix solution or suspension. It will further be appreciated that a solvent mixture may be used to dissolve or suspend the active agent and/or polymer.

[0050] Casting solvents are preferably aqueous solvents. Suitable aqueous solvents include, but are not limited to, water, alcohols (for example, C_1 to C_8 alcohols such as propanol and butanol), alcohol esters, or mixtures of thereof. In other embodiments, the solvents are non-aqueous. Suitable non-aqueous solvents include, but are not limited to, esters, ethers, ketones, nitrites, lactones, amides, hydrocarbons and their derivatives as well as mixtures thereof. In other non-limiting embodiments, the solvent is selected from acetonitrile (ACN), dimethyl sulfoxide (DMSO), water, or ethanol. It will be appreciated that the choice of solvent may be determined by one or more properties of the active agent and/or polymer. It will further be appreciated that the casting solvent may comprise a mixture of solvents.

[0051] Any suitable drug, therapeutic agent, API, or other active agent may be dissolved or suspended in the solvent. The present arrays are suitable for a wide variety of substances or agents. Suitable active agents that may be administered include the broad classes of compounds such as, by way of illustration and not limitation: analeptic agents; analgesic

agents; antiarthritic agents; anticancer agents, including antineoplastic drugs; anticholinergics; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihelminthics; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents such as antibiotics, antifungal agents, antiviral agents and bacteriostatic and bactericidal compounds; antiinflammatory agents; antimigraine preparations; antinauseants; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; antitubercular agents; antiulcer agents; anxiolytics; appetite suppressants; attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular preparations including calcium channel blockers, antianginal agents, central nervous system agents, beta-blockers and antiarrhythmic agents; caustic agents; central nervous system stimulants; cough and cold preparations, including decongestants; cytokines; diuretics; genetic materials; herbal remedies; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; keratolytic agents; leukotriene inhibitors; mitotic inhibitors; muscle relaxants; narcotic antagonists; nicotine; nutritional agents, such as vitamins, essential amino acids and fatty acids; ophthalmic drugs such as antiglaucoma agents; pain relieving agents such as anesthetic agents; parasympatholytics; peptide drugs; proteolytic enzymes; psychostimulants; respiratory drugs, including antiasthmatic agents; sedatives; steroids, including progestogens, estrogens, corticosteroids, androgens and anabolic agents; smoking cessation agents; sympathomimetics; tissue-healing enhancing agents; tranquilizers; vasodilators including general coronary, peripheral and cerebral; vessicants; and combinations thereof.

[0052] In embodiments, the active agent is a biological agent including, but not limited to peptides, polypeptides, proteins, or nucleic acids (e.g. DNA or RNA). In one embodiment, the active agent is a polypeptide such as human parathyroid hormone (e.g. hPTH(1-34)), a protein such as human growth hormone, or an antibody. Examples of peptides and proteins which may be used with the microstructure arrays include, but are not limited to, parathyroid hormone (PTH), oxytocin, vasopressin, adrenocorticotropic hormone (ACTH), epidermal growth factor (EGF), prolactin, luteinizing hormone, follicle stimulating hormone, luliberin or luteinizing hormone releasing hormone (LHRH), insulin, somatostatin, glucagon, interferon, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, kyotorphin, taftsin, thymopoietin, thymosin, thymostimulin, thymic humoral factor, serum thymic factor, tumor necrosis factor, colony stimulating factors, motilin, bombesin, dinorphin, neurotensin, cerulein, bradykinin, urokinase, kallikrein, substance P analogues and antagonists, angiotensin II, nerve growth factor, blood coagulation factors VII and IX, lysozyme chloride, renin, bradykinin, tyrocidin, gramicidines, growth hormones, melanocyte stimulating hormone, thyroid hormone releasing hormone, thyroid stimulating hormone, pancreozymin, cholecystokinin, human placental lactogen, human chorionic gonadotropin, protein synthesis stimulating peptide, gastric inhibitory peptide, vasoactive intestinal peptide, platelet derived growth factor, growth hormone releasing factor, bone morphogenic protein, and synthetic

analogues and modifications and pharmacologically active fragments thereof. Peptidyl drugs also include synthetic analogs of LHRH, e.g., buserelin, deslorelin, fertirelin, goserelin, histrelin, leuprolide (leuprorelin), lutrelin, nafarelin, tryptorelin, and pharmacologically active salts thereof. Administration of oligonucleotides is also contemplated, and includes DNA and RNA, other naturally occurring oligonucleotides, unnatural oligonucleotides, and any combinations and/or fragments thereof. Therapeutic antibodies include Orthoclone OKT3 (muromonab CD3), ReoPro (abciximab), Rituxan (rituximab), Zenapax (daclizumab), Remicade (infliximab), Simulect (basiliximab), Synagis (palivizumab), Herceptin (trastuzumab), Mylotarg (gemtuzumab ozogamicin), CroFab, DigiFab, Campath (alemtuzumab), and Zevalin (ibritumomab tiuxetan).

[0053] In other embodiments, at least a portion of the distal layer comprises an agent suitable for use as a prophylactic and/or therapeutic vaccine. In an embodiment, the vaccine comprises an antigen epitope conjugated on or to a carrier protein. It will be appreciated that vaccines may be formulated with our without an adjuvant. Suitable vaccines include, but are not limited to, vaccines for use against anthrax, diphtheria/tetanus/pertussis, hepatitis A, hepatitis B, Haemophilus influenzae type b, human papillomavirus, influenza, Japanese encephalitis, measles/mumps/rubella, meningococcal diseases (e.g., meningococcal polysaccharide vaccine and meningococcal conjugate vaccine), pneumococcal diseases (e.g., pneumococcal polysaccharide vaccine and meningococcal conjugate vaccine), polio, rabies, rotavirus, shingles, smallpox, tetanus/diphtheria, tetanus/diphtheria/pertussis, typhoid, varicella, and yellow fever.

[0054] Additional agents include those directed against avian (pandemic) influenza virus, *Campylobacter* sp., *Chlamydia* sp., *Clostridium botulinum, Clostridium difficile,* dengue fever virus, *E. coli,* Ebola virus, Epstein Barr virus, nontypeable *Haemophilus influenzae,* hepatitis C, hepatitis E, herpes viruses including herpes zoster, HIV, leishmanial and malarial parasites, meningococcal serogroup B, nicotine, parainfluenza, ragweed allergen, respiratory syncytial virus (RSV), Rift Valley fever virus, SARS-associated coronavirus, *Shigella* sp., *Staphylococcus aureus,* Streptococcus Group A (GAS), Streptococcus Group B (GBS), tick-borne encephalitis, Venezuelan equine encephalitis, and West Nile virus.

[0055] It will be appreciated agents include those typically used for veterinary uses including vaccines for cats, dogs and other small animals as well as those for use with livestock such as cattle, pigs, goats, horses, chickens, *etc.* Veterinary agents include those directed against parvovirus, distemper virus, adenovirus, parainfluenza virus, *Bortadella bronchiseptica*, *Leptospira spp.*, *Borrelia burgdorferi*, feline herpesvirus, feline calcivirus, feline panleukopenia virus, feline leukemia virus, feline immunodeficiency virus, and *Chlamydia felis*. Veterinary agents further include those directed against viral respiratory diseases (infectious bovine rhinotracheitis - IBR, bovine viral diarrhea - BVD parainfluenza-3 virus - PI3, bovine respiratory syncytial virus - BRSV), *Campylobacter fetus* (Vibriosis) *Leptospirosis sp.*, *Trichomoniasis*, *Moraxella bovis* (pinkeye), Clostridial (Blackleg), Brucellosis, *Mannheimia haemolytica*,

Pasteurella multocida, *Haemophilus somni*, *Escherichia coli*, Anaplasmosis, foot-and-mouth disease virus (FMDV), procine parvovirus, swine fever, porcine reproductive and respiratory syndrome virus (PRRS), swine influenza, transmissible gastro enteritis virus (TGE), *Staphylococcus hyicus*, *Actinobacillus pleuropneumonia*, Atrophic rhinitis, Enzootic pneumonia, *Haemophilus parasuis*, Streptococcal meningitis, *Mycoplasma gallisepticum*, Salmonella, Marek's Disease virus, and infectious bronchitis virus. Further veterinary agents include those directed against Eastern/Western Equine Encephalomyelitis, Equine influenza, Potomac Horse Fever, Strangles, Equine Herpesvirus, and Equine Viral Arteritis.

[0056] It will be appreciated that the vaccines described herein may include one or more antigens and one or more adjuvants. For example, the seasonal flu vaccine typically includes agents directed against several strains of influenza. Where multiple antigens are included in the vaccine, the antigens may be directed to conferring an immune response to one or more bacteria, virus, or microorganism. For example, more than one antigen specific to the same bacteria, virus or microorganism may be included in the vaccine. Alternatively, multiple antigens specific to different bacteria, viruses, or microorganisms may be included in the vaccine. Where the vaccine includes multiple antigens, the vaccine may include multiple adjuvants. The number of adjuvants included in the vaccine may be the same, less or more than the number of corresponding antigens included in the vaccine. In an embodiment, a vaccine including a single antigen may include multiple adjuvants.

[0057] In another embodiment, at least a portion of the distal layer comprises an agent suitable for veterinary uses. Such uses include, but are not limited to, therapeutic and diagnostic veterinary uses.

[0058] Polymers for use in the methods are typically biocompatible. In one embodiment, at least some of the polymers are biodegradable.

[0059] In an embodiment, the polymer is a structure-forming polymer. In an embodiment, the polymer is a hydrophilic water soluble polymer. Suitable polymers are known in the art and described, for example, in U.S. Patent Application No. 2008/0269685. Exemplary biocompatible, biodegradable, or bioerodible polymers include poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid)s (PLGAs), polyanhydrides, polyorthoesters, polyetheresters, polycaprolactones (PCL), polyesteramides, poly(butyric acid), poly(valeric acid), polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), polyethylene glycol (PEG), block copolymers of PEG-PLA, PEG-PLA-PEG, PLA-PEG-PLA, PEG-PLGA, PEG-PLGA-PEG, PLGA-PEG-PLGA, PEG-PCL, PEG-PCL-PEG, PCL-PEG-PCL, copolymers of ethylene glycol-propylene glycol-ethylene glycol (PEG-PPG-PEG, trade name of Pluronic® or Poloxamer®), block copolymers of polyethylene glycol-poly(lactic acid-co-glycolic acid) (PLGA-PEG), dextran, hetastarch, tetrastarch, pentastarch, hydroxyethyl starches, cellulose, hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (Na CMC), thermosensitive HPMC (hydroxypropyl methyl cellulose), polyphosphazene, hydroxyethyl cellulose (HEC),

polysaccharides, polyalcohols, gelatin, alginate, chitosan, hyaluronic acid and its derivatives, collagen and its derivatives, polyurethanes, and copolymers and blends of these polymers. One hydroxyethyl starch may have a degree of substitution of in the range of 0-0.9. An exemplary polysaccharide is dextran including dextran 70, dextran 40, and dextran 10.

[0060] The casting solution may further include one or more excipients dissolved or suspended in the buffer or solvent. Suitable excipients include, but are not limited to, one or more stabilizers, plasticizers, surfactants, and/or anti-oxidants.

[0061] In one embodiment one or more sugars is added to the casting solution. Sugars can stabilize the active ingredient and/or plasticize at least one of the polymers. Sugars may also be used to affect, moderate, or regulate degradation of the polymer(s). Exemplary sugars include, but are not limited to, dextrose, fructose, galactose, maltose, maltulose, iso-maltulose, mannose, lactose, lactulose, sucrose, and trehalose, and sorbitol. In other embodiments, a sugar alcohol as known in the art is included in the casting solution. Exemplary sugar alcohols include, but are not limited to, lactitol, maltitol, sorbitol, and mannitol. Cyclodextrins can also be used advantageously in microprojection arrays, for example α, β, and γ cyclodextrins. Exemplary cyclodextrins include hydroxypropyl-β-cyclodextrin and methyl-β-cyclodextrin. In other embodiments, where Dextran, hetastarch and/or tetrastarch is used as a polymer in the casting solution, sorbitol may preferably be included in the casting solution. In this embodiment, sorbitol may not only stabilize the active agent, but also plasticize the polymer matrix, which reduces brittleness. The biodegradability or dissolvability of the microprojection array may be facilitated by the inclusion of sugars. Sugars and sugar alcohols may also be helpful in stabilization of peptides, proteins, or other biological active agents and in modifying the mechanical properties of the microprojections by exhibiting a plasticizing-like effect. Where the active agent is a biological agent including, but not limited to, peptides, proteins, and antibodies, one or more sugars or sugar alcohols may be used in the casting solution as a stabilizing agent. The sugar may be added to (i) the therapeutic agent solution or suspension, (ii) the polymer solution or suspension, or (iii) the polymer matrix solution or suspension once (i) and (ii) have been mixed.

[0062] One or more surfactants may be added to the casting solution to change the solutions' surface tension and/or reduce the hydrophobic interactions of proteins. Any suitable surfactant as known in the art may be used. Exemplary surfactants include, but are not limited to, emulsifiers such as Polysorbate 20 and Polysorbate 80.

[0063] One or more antioxidants may be added to the casting solution. Any suitable antioxidant as known in the art may be used. Exemplary antioxidants include, but are not limited to, methionine, cysteine, D-alpha tocopherol acetate, EDTA, and vitamin E.

C. Formation of Microstructure Arrays

[0064] In a general method, a casting solution is dispensed onto the mold or into the mold cavities. The casting solution is moved into the cavities. The casting solution is dried to form a

solid polymer. Optionally, a backing or basement layer is cast on the mold and dried. A further optional substrate layer is applied to the backing or basement layer. A flow chart of an exemplary method of forming a microstructure array is shown in Fig. 2.

[0065] Filling the cavities of the mold with the liquid formulations has been a challenge. In casting a solution on the mold, it is commonly desired to avoid the presence of bubbles of air between the casting solution and the mold during casting. Due to the shape required to produce a sharp tip and/or the surface properties of the mold, bubbles often form/are trapped between the formulation and the mold surface as the liquid casting solution is moved into the mold cavities. This may be more prevalent at the deepest portion of the mold cavities. Air bubbles may be trapped especially at the tip of the cavities. If the formulation does not fill the cavities, the resulting microstructures may not have the desired shape including gaps and/or not have the required sharp tip. The shape of the meniscus for the casting solution in the cavity and/or the extent of filling the cavity is dependent upon the contact angle behavior of the casting solution on the mold surface.

[0066] Various approaches have been used to minimize or remove air bubbles in the cavities. The mold may be treated prior to dispensing the casting solution to improve dispensing of the casting solution and/or to avoid or reduce the presence of air bubbles. The mold itself, or portions of it, may be subject to surface treatments which make it easier for the solution to wet the mold surface. Suitable treatments are known in the art and described, for example, in U.S. Patent Publication No. 2008/0269685, which is incorporated herein in its entirety. U.S. Patent Publication No. 2008/0269685 describes applying a vacuum over the cavities while the casting solution is dispensed into the mold cavities. When the vacuum is removed, the higher pressure over the liquid film will shrink the bubble in the cavity and push the casting solution into the cavity.

[0067] A further approach is described, for example, in U.S. Patent Publication No. 2014/0272101, which is incorporated herein in its entirety, where the mold with the casting solution is pressurized to move the solution into the cavities. The pressurization shrinks the size of the air bubble as expected by Boyle's Law. For example, an air bubble that has a volume of 1 µL at 1 atmosphere will have an approximate volume of 0.2 µL at 50 psig (5 atm). As the bubble size shrinks, further casting solution fills the cavity further into the cavity and the area/volume ratio of the air bubble decreases allowing for a corresponding decrease in time required for the air to diffuse into the mold. While pressurization works well for a batch processes it is difficult and not economical to scale in order while maintaining high drug utilization. The leak pressure for a scaled batch process is an order of magnitude lower than the pressure necessary to effectively reduce air bubble size.

[0068] In a further approach described, for example, in U.S. Patent Publication No. 2008/0269685, a vacuum is applied to the mold after a casting solution is applied over the cavities in the mold. The vacuum causes the air bubbles in the cavities to expand and increase

the force pushing the bubbles up through the casting solution. The air bubbles rise to the surface of the casting solution. Drying must be modulated to allow the air bubbles to rise completely through the casting solution or air voids will be formed within the microstructures as the solution dries.

[0069] Yet a further approach uses a soluble gas such as carbon dioxide (CO_2) to move the casting solution into or further into the cavities as described in U.S. Patent Publication No. 2014/0272101. The soluble gas displaces air in the cavities. Because the solubility and diffusivity of the soluble gas into the mold is significantly greater than air, the time required for any gas bubbles to permeate into the mold is reduced. While the high solubility and diffusivity of soluble gases such CO_2 are effective to reduce bubble size, some casting solution formulations are not compatible with the soluble gas. In particular, the soluble gas may adversely affect the pH or other characteristic of the casting solution and/or mold. For example, CO_2 gas may lower the pH of the casting solution, which presents the risk that the active agent may precipitate out of the solution. Thus, the effectiveness of using a soluble gas such as CO_2 may therefore be dependent upon the formulation of the casting solution. A further method of reducing, removing, or preventing air bubbles that is independent or relatively independent of the casting is therefore desirable.

[0070] In a preferred embodiment, a rough or low vacuum is applied to the mold prior to dispensing the casting solution on or in the mold to reduce the size of any air bubbles by removing the air in the cavities prior to dispensing the casting solution on or into the mold. Rather than applying a vacuum after the casting solution is dispensed onto or into the mold, the vacuum is applied prior to dispensing the casting solution to remove at least some of the air in the cavities prior to fill. In a preferred embodiment, a rough or low vacuum is applied to the mold prior to dispensing the casting solution. A rough or low vacuum is typically a vacuum that is slightly below atmospheric pressure. For convenience, the terms “rough vacuum”, “low vacuum” and “medium” vacuum are used interchangeably hereafter. By “applied” with reference to a vacuum, it is typically intended that the mold is placed into and/or passed through a chamber or other container having the desired partial pressure. In embodiments, a low vacuum has a pressure of less than atmospheric (760 Torr). In embodiments, the low vacuum has a pressure range of less than about 760 to about 25 Torr. In embodiments a vacuum of about 750-25, about 700-25, about 600-25, about 500-25, about 400-25, about 300-25, about 200-25, about 150-25, about 100-25, about 760-100, about 750-100, about 700-100, about 600-100, about 500-100, about 400-100, about 300-100, about 200-100, about 760-150, about 750-150, about 700-150, about 600-150, about 500-150, about 400-150, about 300-150, about 200-150, about 100-150, about 760-200, about 750-200, about 700-200, about 600-200, about 500-200, about 400-200, about 300-200, about 760-300, about 750-300, about 700-300, about 600-300, about 500-300, about 400-300, about 760-400, about 750-400, about 700-400, about 600-400, about 500-400, about 760-500, about 750-500, about 700-500, about 600-500,

about 760-600, about 750-600, or about 700-600 Torr is applied to the mold prior to dispensing the casting solution.

[0071] In embodiments, all or substantially all of the air in the cavities is removed by application of a low vacuum prior to dispensing the casting solution. The reduction in air in the cavities results in a corresponding decrease in the volume of air bubbles trapped between the casting solution and the mold as the cavities are filled. As shown in Fig. 3B, application of a 20% vacuum (0.15 atm) results in a volume of the air bubble 26 at the distal portion of the cavity of 0.15 µL. In comparison, when the casting solution 28 is cast at atmospheric pressure, the air bubble at the distal portion of the cavity 24 has a volume of 1 µL (Fig. 3A). In some embodiments, the cavities have an approximate volume of about 1-5 µL or more. Application of a low vacuum results in an 85% reduction in the volume of the air bubble as compared casting performed at atmospheric pressure. In embodiments, application of a low vacuum results in a 10-100% reduction in the volume of the distal air bubble as compared to the volume of an air bubble formed in the distal portion of the cavity at atmospheric pressure. In embodiments, application of a low vacuum results in a 10-90%, 10-80%, 10-70%, 10-60%, 10-50%, 10-40%, 10-30%, 10-20%, 20-100%, 20-90%, 20-80%, 20-70%, 20-60%, 20-50%, 20-40%, 20-30%, 30-100%, 30-90%, 30-80%, 30-70%, 30-60%, 30-50%, 30-40%, 40-100%, 40-90%, 40-80%, 40-70%, 40-60%, 40-50%, 50-100%, 50-90%, 50-80%, 50-70%, 50-60%, 60-100%, 60-90%, 60-80%, 60-70%, 70-100%, 70-90%, 70-80%, 80-100%, 80-90%, 90-100%, or 95-100% reduction in the volume of any distal air bubble as compared to the volume of an air bubble formed in the distal portion of the cavity at atmospheric pressure.

[0072] It will be appreciated that the step of applying a low vacuum prior to dispending the casting solution may be combined with one or more known methods of reducing or eliminating air bubbles. In one example, the use of a soluble gas may be combined with application of low pressure to further reduce air bubbles. As seen in Fig. 1, a soluble gas such as CO_2 may be dispensed to the cavities to displace air in the cavities. A low vacuum is then applied to the mold to reduce the size of the soluble gas bubbles. A casting solution or formulation is dispensed onto the mold and/or into the mold cavities and dried. The embodiment as shown in Fig. 1 is a continuous or conveyer type system 10 where the mold comprising cavities 18 is moved through sections including the soluble gas (e.g. CO_2) dispensing section 12 (optional), the vacuum application section 14, and the formulation dispensing section 16, as shown. It will be appreciated that further sections including, but not limited to one or more drying sections 20 and further dispensing/vacuum sections may be included with the system. It will further be appreciated that the present methods may be performed sequentially but without the use of a continuous system.

[0073] After the low vacuum is applied, a casting solution or formulation 22 is dispensed onto the mold and/or into the mold cavities 18. It will be appreciated that the casting solution or formulation may be dispensed onto the mold and/or into the mold cavities while the low vacuum

is applied. Where the solution is cast on the mold, the solution is moved into the cavities by any suitable means. In one embodiment, the mold surface with solution thereon is covered to spread the solution or formulation on the mold and at least partially into the cavities. In other embodiments, the solution is spread on the mold without covering. The cavities are filled with the casting solution.

[0074] In one embodiment, the mold is pressurized, with or without a cover, to move the solution into or further into the cavities of the mold. Pressurization may be accomplished by placing the mold with the casting solution into a pressure vessel as known in the art. Pressurization may involve a pressure of at least about 3 psi, about 5 psi, about 10 psi, about 14.7 psi, about 20 psi, or about 50 psi above atmospheric. In other embodiments, pressurization involves a pressure of at least about 3-50 psi above atmospheric. In other embodiments, pressurization involves a pressure of at least about 3-40 psi, about 3-30 psi, about 3-20 psi, about 3-14.7 psi, about 3-10 psi, about 3-5 psi, about 5-50 psi, about 5-30 psi, about 5-20 psi, about 5-14.7 psi, about 5-10 psi, about 10-50 psi, about 10-30 psi, about 10-20 psi, about 10-14.7 psi, about 20-50 psi, about 20-30 psi, or about 30-40 psi above atmospheric. Excess solution may be wiped or otherwise removed from the mold surface by any suitable means.

[0075] The mold with liquid casting solution is then dried using a single or multiple drying steps. Multiple and/or controlled drying steps are used to remove excess solvent and/or dry the microprojections. In one embodiment, the mold with liquid casting solution is dried at a temperature of about 5-50 °C for about 30 minutes to about 2 hours. It will be appreciated that the mold with liquid casting solution may be dried for any appropriate period of time to remove all or substantially all of the casting solution solvent(s). Drying may involve placing the mold with solution in an oven or other temperature controlled chamber. In another embodiment, a two-step primary drying method is used. The first step in a two-step drying method uses a slow drying method in which the mold with casting solution is dried under controlled humidity. Where the drying step involves controlling humidity, the mold is in dried in a chamber or section where humidity in the chamber is controlled from at least about 10% to about 95% relative humidity (RH). The mold with casting solution is initially dried for about 5 minutes to about an hour at a temperature of about 5-50 °C. The second step involves drying without humidity control. In non-limiting embodiments, the second step involves drying the mold and casting solution/formulation at a temperature of about 5-50 °C for about 20-120 minutes or more. In another embodiment, the casting solution is dried in a chamber having a controlled partial pressure of the evaporate. Further, the mold with the liquid casting solution may be dried from beneath, under or below the mold. It will be appreciated that the casting solution may be dried from substantially beneath, under or below the mold. Specific embodiments of drying times, humidity, and/or drying conditions are disclosed in U.S. Patent Publication Nos. 2008/0269685 and 2014/0272101, which are incorporated herein by reference.

[0076] In one embodiment, an optional backing layer, base layer, or basement layer is further cast on the mold. A liquid backing formulation is dispensed on the mold or into the cavities. The liquid backing formulation is typically prepared by dissolving or suspending one or more polymers in a suitable solvent. In a preferred embodiment, the one or more polymers are biocompatible. Typically, but not always, the polymers are non-biodegradable. In another embodiment, the backing formulation may comprise one or more biodegradable and/or non-biodegradable polymers. Suitable biodegradable polymers are described above. Suitable non-biodegradable polymers are known in the art and include, but are not limited to, amphiphilic polyurethanes, polyether polyurethane (PEU), polyetheretherketone (PEEK), poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), polyethylene terephthalate, polycarbonate, acrylic polymers such as those sold under the trade name Eudragit®, polyvinylpyrrolidones (PVP), polyamide-imide (PAI), and/or co-polymers thereof. Further suitable polymers are described in U.S. Patent No. 7,785,301, which is incorporated herein in its entirety. The backing formulation may include one or more excipients as described above for the active agent casting solution. In another embodiment, the backing layer is an adhesive layer. One suitable adhesive is the Dymax® 1187-M UV medical device adhesive. It will be appreciated that any biocompatible adhesive is suitable for use with, in and/or as the backing layer. This layer may also be a nonwoven or porous film double coated with pressure sensitive adhesive. Liquid backing formulations may be moved into the cavities by the same or similar methods as for the active agent casting solution.

[0077] Where a liquid backing layer formulation is used, the solvent of the backing layer formulation is removed by a drying process such that the resulting array has a backing layer with a plurality of microstructures extending at an angle from the backing layer. The drying conditions for drying the backing layer should be controlled so that the backing layer solvent can be removed effectively without affecting the stability of an active agent and/or to properly form (e.g. uniform) the backing layer. It will be appreciated that the conditions and methods for drying the active agent formulations as described above may be used for drying the backing layer formulations. In one embodiment, the mold is placed into a compressed dry air (CDA) box under controlled air flow and then placed in an oven at about 5-50 °C. In further embodiments, the mold is placed in the oven at a temperature of about 5-50 °C. In embodiments, the temperature of the CDA and/or oven is about 5 °C, about 10 °C, about 20 °C, about 30 °C, about 40 °C, about 45 °C, or about 50 °C. In embodiments, the temperature of the CDA and/or oven is about 5-45 °C, 5-40 °C, 5-30 °C, 5-20 °C, 5-15 °C, 5-10 °C, 10-50 °C, 10-45 °C, 10-40 °C, 10-30 °C, 10-20 °C, 10-15 °C, 15-50 °C, 15-45 °C, 15-40 °C, 15-30 °C, 15-20 °C, 20-50 °C, 20-45 °C, 20-40 °C, 20-30 °C, 30-50 °C, 30-45 °C, 30-40 °C, 30-45 °C, 40-50 °C, 40-45 °C, or 45-50 °C. In embodiments, the oven uses convection, conduction, or radiation for drying. In another embodiment, the mold is placed in an oven at about 5-50 °C without prior time in a CDA box. In embodiments, the mold is placed in the CDA and/or oven

for at least about 0-120 minutes, about 30-120 minutes, about 30-90 minutes, about 30-60 minutes, about 30-45 minutes, about 45-120 minutes, about 45-90 minutes, about 45-60 minutes, about 60-120 minutes, about 60-90 minutes, about 90-120 minutes, or longer. Residual solvents in the backing layer can be measured to determine the effectiveness of solvent removal under different drying conditions. The backing layer connects and/or supports the microprojection tips.

[0078] The backing layer with attached microstructures is demolded as described further below and undergoes an optional final drying step to form the microstructure array (MSA). Before or after the microprojection array is removed from the mold a final drying step may be performed. This final drying step may be performed under vacuum. The final drying may be at room temperature or at an elevated temperature. In embodiments, the final drying is at about 5-50 °C. In embodiments, the final drying is at about 5 °C, at about 10 °C, at about 20 °C, at about 25 °C, at about 35 °C, at about 40 °C, at about 45 °C, or at about 50 °C. Further suitable temperatures and ranges are described above with reference to drying the backing layer. In embodiments, the final drying is from about 1-24 hours or longer, from about 4-20 hours, from about 6-10 hours, from about 8-16 hours, from about 8-12 hours, from about 8-10 hours, from about 10-12 hours, from about 10-16 hours, from about 12-16 hours or longer. In other embodiments, the final drying step is overnight. It will be appreciated that the MSA may be demolded prior to undergoing the final drying step.

[0079] Before or after the optional final drying step, the microprojection arrays may further and optionally be positioned on a base or substrate. The substrate may be in addition to or instead of a backing layer. The microprojections may be attached to the substrate by any suitable means. In one, non-limiting embodiment, the microstructures are attached to the substrate using an adhesive. Suitable adhesives include, but are not limited to, acrylic adhesives, acrylate adhesives, pressure sensitive adhesives, double-sided adhesive tape, double sided adhesive coated nonwoven or porous film, and UV curable adhesives. One exemplary double-sided tape is the #1513 double-coated medical tape available from 3M. One exemplary, but non-limiting, UV curable adhesive is the 1187-M UV light-curable adhesive available from Dymax®. It will be appreciated that any medical device adhesive known in the art would be suitable. In one embodiment, the substrate is a breathable nonwoven pressure sensitive adhesive. The substrate is placed on the backing layer where present or a proximal surface of the microprojections. The substrate is adhered or attached to the microprojections. In another embodiment, the substrate is a UV cured adhesive in a polycarbonate film. The UV adhesive is dispensed on the top of the backing layer or the proximal surface of the microprojections, covered with a polycarbonate (PC) film to spread the adhesive and cured using a UV Fusion system. In one embodiment a UV curing dose is about 1.6 J/cm^2. After the substrate is attached or adhered to the microprojections, the microprojection array is removed

from the mold. It will be appreciated where the array includes a backing layer the substrate is attached or adhered to the backing layer as described above for the microstructures.

[0080] Cast microprojection arrays are removed from the mold by any suitable means. In one embodiment, the microprojection array is removed from the mold by using a de-mold tool. A double-sided adhesive is placed on the back of microprojection array with one side for adhering to the array and the other side for adhering to the de-mold tool. The array is removed from the mold by gently rolling the de-mold tool over the adhesive on the back of the array with a slight rolling angle, such as about 1-90 degrees. The microprojection array is then gently peeled off from the de-mold tool. The arrays may be demolded after drying the backing layer or after a final drying step.

[0081] After the microprojection array is removed from the mold, it may be cut to an appropriate size and/or shape. In one embodiment, the microprojection array is die cut with an 11 or 16 mm punch.

II. Microstructure Arrays

[0082] General features of microstructure arrays suitable for use in the instant arrays and methods are described in detail in U.S. Patent Publication No. 2008/0269685, U.S. Patent Publication No. 2011/0006458, and U.S. Patent Publication No. 2011/0276028, the entire contents of which are explicitly incorporated herein by reference.

[0083] The microstructure arrays are preferably stable both during the fabrication process as described above and have a stable shelf life. Short-term stability of the arrays may be evaluated by storing the arrays at various temperatures and/or humidities and analyzing monomer content, composition purity, and deamidation of proteins by SEC-HPLC, RP-HPLC, and IEX-HPLC. The liquid casting solution or formulation is preferably stable during the fabrication process, which typically lasts a few hours. Preferably, the liquid casting solution is stable for a period of 30 minutes to 6 hours. In non-limiting embodiments, the liquid casting solution is stable for a period of at least from 30 minutes to 1 hour, from 30 minutes to 2 hours, from 30 minutes to 3 hours, from 30 minutes to 4 hours, from 30 minutes to 5 hours, from 1-6 hours, from 1-5 hours, from 1-4 hours, from 1-3 hours, from 1-2 hours, from 2-6 hours, from 2-5 hours, from 2-4 hours, from 2-3 hours, from 3-6 hours, from 3-5 hours, from 3-4 hours, from 4-6 hours, from 4-5 hours, or from 5-6 hours. In specific, but not limiting embodiments, the liquid casting solution is stable for at least about 30 minutes, about 45 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, or longer. The microstructure arrays are preferably stable for at least about one day when stored at about room temperature (e.g. about 25 °C). In other embodiments, the arrays are preferably stable for at least about 1 week when stored at about 5 °C. In other embodiments, the arrays are stable when stored at an elevated temperature (e.g. about 40 °C) for at least about 1-12 weeks, about 1-16 weeks, or about 1-32 weeks. In other embodiments, the arrays are stable when

stored at about 5 °C for at least about 1-52 weeks or 1-156 weeks. It will be appreciated that the shelf-life may vary depending on the storage temperature. In embodiments, the arrays are stable when stored at about 5 °C for at least about 1-156 weeks, about 1-12 weeks, about 1-2 weeks, about 1-3 weeks, about 1-4 weeks, about 1-5 weeks, about 2-6 weeks, about 2-5 weeks, about 2-4 weeks, about 2-3 weeks, about 3-6 weeks, about 3-5 weeks, about 3-4 weeks, about 4-6 weeks, about 4-5 weeks, or about 5-6 weeks. In embodiments, the arrays are stable when stored at about 40 °C for at least about 1-26 weeks, about 1-12 weeks, about 1-2 weeks, about 1-3 weeks, about 1-4 weeks, about 1-5 weeks, about 2-6 weeks, about 2-5 weeks, about 2-4 weeks, about 2-3 weeks, about 3-6 weeks, about 3-5 weeks, about 3-4 weeks, about 4-6 weeks, about 4-5 weeks, or about 5-6 weeks. In other embodiments, the arrays are stable when stored at about 25 °C for at least about 1-14 days. In further embodiments, the arrays are stable when stored at about 25 °C for at least about 1-12 weeks, about 1-16 weeks, about 1-104 weeks, or about 1-156 weeks. In specific, but not limiting, embodiments, the arrays are stable when stored at about 5 °C for at least about 5 days, at least about 1 week, at least about 2 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, or longer. In embodiments, the arrays are stable when stored at about 25 °C for at least about 1-2 days, about 1-5 days, about 1-7 days, about 1-10 days, about 2-5 days, about 2-7 days, about 2-10 days, about 2-14 days, about 3-5 days, about 3-7 days, about 3-10 days, about 3-14 days, about 5-14 days, about 5-10 days, about 5-14 days, or about 10-14 days. In specific, but not limiting, embodiments, the arrays are stable when stored at about 25 °C for at least about 12 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about one week, or longer. Stability is typically monitored by measuring the purity of the active agent in the array after storage as compared to an array before storage (time= 0). In embodiments, the array has a purity of at least about 80-100%, about 85-100%, about 90-100%, about 95-100%, about 80-95%, about 85-95%, about 90-95% about 80-90%, about 85-90% or about 80-85% after storage. In non-limiting embodiments, the array has a purity of at least about 80%, about 85%, about 90%, about 92%, about 93%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% after storage.

[0084] Where the active agent is a protein, Methionine-oxidation (Met-oxidation) is preferably less than or equal to 1-20% after storage for about 1-6 weeks at about 5 °C – 40 °C. In embodiments Met-oxidation is less than about 1-10%, about 1-5%, about 1-6%, about 2-3%, about 2-4%, about 2-5%, 2-6%, about 3-5%, or about 3-6%. In specific, but not limiting, embodiments, Met-oxidation is less than about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, or about 10%.

[0085] The microstructure arrays should have sufficient mechanical strength to at least partially penetrate the stratum corneum or other membrane surface of a subject. It will be appreciated that different mechanical strength will be required for application at different sites.

One method for assessing mechanical strength is a skin-penetration efficiency (SPE) study as described U.S. Patent Publication No. 2014/0272101. Preferably, the arrays have a SPE of at least about 50-100%. In other embodiments, the arrays have a SPE of at least about 50-80%, about 50-85%, about 50-90%, about 50-95%, about 60-80%, about 60-85%, about 60-90%, about 60-95%, about 60-100%, about 75-80%, about 75-85%, about 75-90%, about 75-95%, about 75-100%, about 80-85%, about 80-90%, about 80-95%, about 80-100%, about 90-95%, and about 90-100%. In specific, non-limiting, embodiments, the arrays have a SPE of at least about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, and 100%.

[0086] Preferably, at least about 50-100% of the active agent is delivered by the MSAs described herein. Delivery efficiency may be determined by preparing the MSA and applying the MSA in vivo or in vitro. In embodiments, the MSA has a delivery efficiency of at least about 50-60%, about 50-70%, about 50-75%, about 50-80%, about 50-90%, about 50-95%, about 50-99%, about 60-70%, about 60-75%, about 60-80%, about 60-90%, about 60-95%, about 60-99%, about 70-75%, about 70-80%, about 70-90%, about 70-95%, about 70-99%, about 75-80%, about 75-90%, about 75-95%, about 75-99%, about 80-90%, about 80-95%, about 80-99%, about 90-95%, about 90-99%, or about 95-99%.

III. Methods of Use

[0087] The methods, kits, microstructure arrays and related devices described herein may be used for treating any condition. It will be appreciated that the microstructure arrays may be used with any appropriate applicator including the applicator described in U.S. Publication No. 2011/0276027, as well as those described in U.S. Publication No. 2014/0276580 and 2014/0276366, each of which are incorporated herein in their entirety.

IV. Examples

[0088] The following examples are illustrative in nature and are in no way intended to be limiting. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C and pressure is at or near atmospheric.

EXAMPLE 1

PREPARING MICROSTRUCTURE ARRAYS

[0089] A silicone mold comprising a plurality of microstructure cavities is purged with carbon dioxide (CO_2). The mold is placed in a vacuum of less than 1 atm. About 90 µL of a liquid formulation comprising an active agent is dispensed onto the mold from a reservoir using a syringe or fountain type reservoir. The mold containing the formulation is pressurized for 1 minute at about 50 psi. The mold surface is then wiped to remove excess formulation from the mold surface.

[0090] Depending on the physiochemical properties of the liquid formulation (viscosity, solid content, surface interaction between formulation and mold, etc.), the formulation is dried using either one or two primary drying steps. The one step primary drying comprises directly placing the mold comprising the liquid formulation in an incubator oven at 32 °C for about 30 minutes to remove solvents.

[0091] In the two step primary drying, a slow drying step is followed by a second drying step. The mold with the liquid formulation is placed in a chamber where the humidity is controlled to about 50% to 90% relative humidity (RH), at room temperature for about 5 to 30 minutes. The air convection in the chamber may also be controlled. The mold with formulation is then incubated for about 30 minutes in an oven at about 30°C to 35°C.

[0092] A backing layer liquid formulation is then dispensed onto the mold surface from a second reservoir. The backing layer formulation is moved into the mold cavities to contact the dried active agent formulation. The backing layer formulation dried to remove the solvent. The mold with the backing layer formulation is placed into a compressed dry air box for about 30 minutes with controlled air flow, and then placed in a convection oven at about 40°C to 50°C for about 90 minutes. The backing layer formulation contacts the drug formulation to connect and support the drug formulation, which becomes the distal tip or portion of the microstructures.

[0093] A breathable, nonwoven pressure sensitive adhesive is placed on the dried backing layer to form a substrate layer. Alternatively, a UV adhesive is dispensed on the top of the backing layer, covered with 5 ml polycarbonate (PC) film to spread the adhesive, and then cured using a UV Fusion system. The UV curing dose is about 1.6 J/cm^2.

[0094] The microstructure array comprising the drug-in-tip (DIT) layer comprising the active agent, the backing layer, and the substrate is demolded or removed from the mold. The array is die cut with an 11 mm or 16 mm punch. The microstructure array is dried under vacuum (~0.05 torr) at room temperature (~35 °C) overnight.

[0095] Embodiments:

1. A method of making an array of microstructures comprising:

(a) dissolving or suspending at least one therapeutic agent in a first solvent to form a therapeutic agent solution or suspension;

(b) dissolving at least one polymer in a second solvent to form a polymer matrix solution or suspension;

(c) mixing the therapeutic agent solution or suspension and the polymer solution or suspension to form a polymer matrix solution or suspension;

(d) applying a low vacuum to a mold having an array of microstructure cavities;

(e) dispensing the polymer matrix solution or suspension on the mold;

(f) filling the microstructure cavities in the mold;

(g) drying the solution or suspension to form the array of microstructures.

2. The method of embodiment 1, wherein the low vacuum is applied to achieve a vacuum pressure of about $1x10^{-3}$ to 760 Torr.

3. The method of the combined or separate embodiments 1-2, wherein the low vacuum is applied to achieve a vacuum pressure of about 25 to 760 Torr.

4. The method of the combined or separate embodiments 1-3, wherein step (f) is performed outside of the low vacuum.

5. The method of the combined or separate embodiments 1-4, further comprising:

after step (f), removing excess polymer matrix solution or suspension on the mold surface.

6. The method of the combined or separate embodiments 1-5, wherein the polymer matrix solution or suspension is dried at a temperature of about 5-50° C.

7. The method of the combined or separate embodiments 1-6, wherein the polymer matrix solution or suspension is dried for at least about 30-60 minutes.

8. The method of the combined or separate embodiments 1-7, further comprising:
dispensing a basement or backing layer formulation on the mold surface; and
drying the basement or backing layer formulation.

9. The method of the combined or separate embodiments 1-8, wherein the basement or backing layer is comprised of at least one non-biodegradable polymer.

10. The method of the combined or separate embodiments 1-9, wherein drying the basement or backing layer comprising drying in an oven at about 5-50° C.

11. The method of the combined or separate embodiments 1-10, further comprising:

affixing the basement or backing layer to a substrate.

12. The method of the combined or separate embodiments 1-11, wherein the substrate is selected from a pressure sensitive adhesive and a UV cured adhesive.

13. The method of the combined or separate embodiments 1-12, further comprising dispensing at least one soluble gas into the cavities prior to applying the low vacuum to the mold.

14. The method of the combined or separate embodiments 1-13, further comprising dispensing at least one soluble gas into the cavities prior to dispensing the polymer matrix solution or suspension on the mold.

15. The method of the combined or separate embodiments 1-14, wherein the soluble gas is selected from CO_2 and CH_4.

16. The method of the combined or separate embodiments 1-15, wherein at least one of the first or second solvent is water or an aqueous solution.

17. The method of the combined or separate embodiments 1-16, further comprising: demolding the microstructure array.

18. The method of the combined or separate embodiments 1-17, further comprising: demolding the microstructure array after drying the basement or backing layer.

19. The method of the combined or separate embodiments 1-18, further comprising: dissolving at least one of a sugar, a surfactant, or an antioxidant in at least one of the first or the second solvent.

20. The method of the combined or separate embodiments 1-19, wherein the sugar is selected from sorbitol, sucrose, trehalose, fructose, or dextrose.

21. The method of the combined or separate embodiments 1-20, wherein the surfactant is selected from Polysorbate 20 or Polysorbate 80.

22. The method of the combined or separate embodiments 1-21, wherein the antioxidant is selected from methionine, cysteine, D-alpha tocopherol acetate, EDTA, or vitamin E.

23. The method of the combined or separate embodiments 1-22, further comprising: dissolving a sugar in the polymer matrix solution or suspension after step (b).

24. The method of the combined or separate embodiments 1-23, wherein the therapeutic agent is selected from a drug, a small molecule, a peptide or protein, or a vaccine.

[0096] While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, permutations, additions and sub-combinations thereof. It is therefore intended that the following appended claims and claims hereafter introduced are interpreted to include all such modifications, permutations, additions and sub-combinations as are within their true spirit and scope.

[0097] All patents, patent applications, and publications mentioned herein are hereby incorporated by reference in their entireties. However, where a patent, patent application, or publication containing express definitions is incorporated by reference, those express definitions should be understood to apply to the incorporated patent, patent application, or publication in which they are found, and not necessarily to the text of this application, in particular the claims of this application, in which instance, the definitions provided herein are meant to supersede.

WHAT IS CLAIMED IS:

1. A method of making an array of microstructures comprising:

(a) dissolving or suspending at least one therapeutic agent in a first solvent to form a therapeutic agent solution or suspension;

(b) dissolving at least one polymer in a second solvent to form a polymer matrix solution or suspension;

(c) mixing the therapeutic agent solution or suspension and the polymer solution or suspension to form a polymer matrix solution or suspension;

(d) applying a low vacuum to a mold having an array of microstructure cavities;

(e) dispensing the polymer matrix solution or suspension on the mold;

(f) filling the microstructure cavities in the mold;

(g) drying the solution or suspension to form the array of microstructures.

2. The method of claim 1, wherein the low vacuum is applied to achieve a vacuum pressure of about $1x10^{-3}$ to 760 Torr.

3. The method of claim 1 or 2, wherein the low vacuum is applied to achieve a vacuum pressure of about 25 to 760 Torr.

4. The method of any previous claim, wherein step (f) is performed outside of the low vacuum.

5. The method of any previous claim, further comprising:

after step (f), removing excess polymer matrix solution or suspension on the mold surface.

6. The method of any previous claim, wherein the polymer matrix solution or suspension is dried at a temperature of about 5-50° C.

7. The method of any previous claim, wherein the polymer matrix solution or suspension is dried for at least about 30-60 minutes.

8. The method of any previous claim, further comprising:

dispensing a basement or backing layer formulation on the mold surface; and

drying the basement or backing layer formulation.

9. The method of claim 8, wherein the basement or backing layer is comprised of at least one non-biodegradable polymer.

10. The method of claim 8 or 9, wherein drying the basement or backing layer comprising drying in an oven at about 5-50° C.

11. The method of any one of claims 8 to 10, further comprising:

affixing the basement or backing layer to a substrate.

12. The method of claim 11, wherein the substrate is selected from a pressure sensitive adhesive and a UV cured adhesive.

13. The method of any previous claim, further comprising dispensing at least one soluble gas into the cavities prior to applying the low vacuum to the mold.

14. The method of any previous claim, further comprising dispensing at least one soluble gas into the cavities prior to dispensing the polymer matrix solution or suspension on the mold.

15. The method of claim 13 or 14, wherein the soluble gas is selected from CO_2 and CH_4.

16. The method of any previous claim, wherein at least one of the first or second solvent is water or an aqueous solution.

17. The method of any previous claim, further comprising:
demolding the microstructure array.

18. The method of any one of claims 8 to 12, further comprising:
demolding the microstructure array after drying the basement or backing layer.

19. The method of any previous claim, further comprising:
dissolving at least one of a sugar, a surfactant, or an antioxidant in at least one of the first or the second solvent.

20. The method of claim 19, wherein the sugar is selected from sorbitol, sucrose, trehalose, fructose, or dextrose.

21. The method of claim 19 or 20, wherein the surfactant is selected from Polysorbate 20 or Polysorbate 80.

22. The method of any one of claims 19 to 21, wherein the antioxidant is selected from methionine, cysteine, D-alpha tocopherol acetate, EDTA, or vitamin E.

23. The method of any previous claim, further comprising:
dissolving a sugar in the polymer matrix solution or suspension after step (b).

24. The method of any previous claim, wherein the therapeutic agent is selected from a drug, a small molecule, a peptide or protein, or a vaccine.

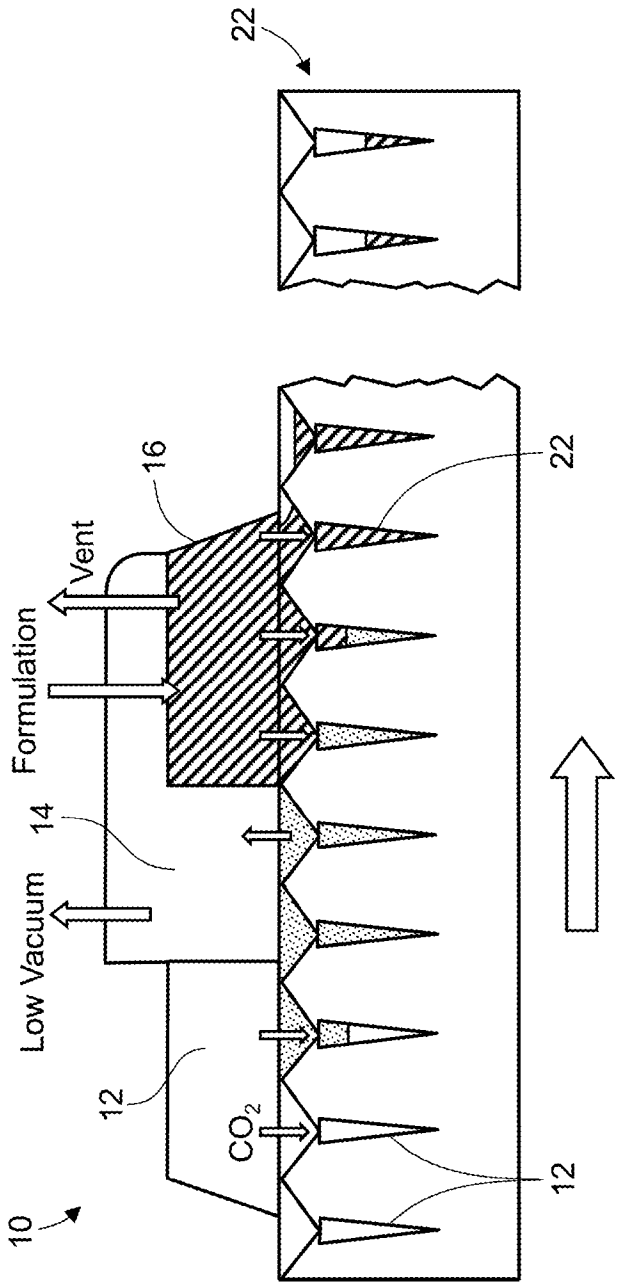

FIG. 1

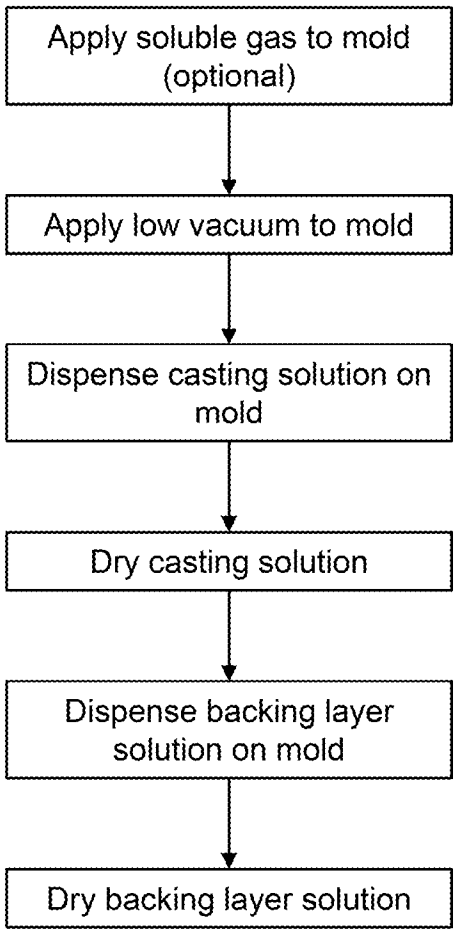
Apply soluble gas to mold (optional)
Apply low vacuum to mold
Dispense casting solution on mold
Dry casting solution
Dispense backing layer solution on mold
Dry backing layer solution

FIG. 2

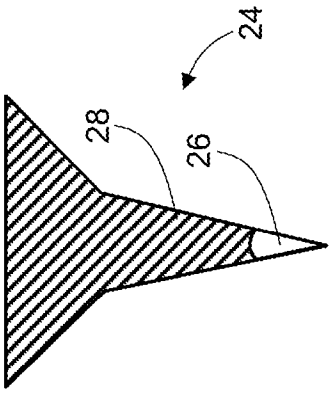

FIG. 3B

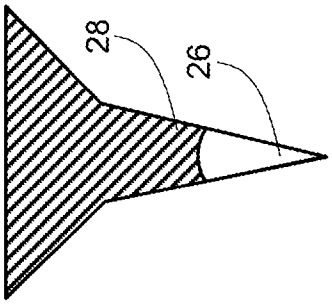

FIG. 3A

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/039864

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M37/00
ADD. A61K9/00

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)
A61M A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/040271 A1 (JIN TUO [CN]) 15 April 2010 (2010-04-15)	1,6, 8-10,17, 18,24
Y	page 5, line 25 - page 6, line 7; claim 15; figures 1-2 page 7, line 22 - line 25 page 8, line 26 - page 9, line 7	2-5, 12-15, 20-22
Y	WO 2012/153266 A2 (UNIV CORK [IE]; MOORE ANNE [IE]; VRDOLJAK ANTO [IE]) 15 November 2012 (2012-11-15) page 6, line 9 - line 17; figures 1-2 page 9, line 6 - line 20 page 15, line 9 - line 12 page 18, line 11 - line 15	1,4, 6-10, 13-21, 23,24

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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 another 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

"T" 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

"X" 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

"Y" 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	Date of mailing of the international search report
15 September 2016	23/09/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Berndorfer, Urs

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/039864

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 2015/238413 A1 (MOCHIZUKI AYA [JP] ET AL) 27 August 2015 (2015-08-27) paragraphs [0094] - [0095], [0101] - [0102], [0114] - [0115], [0125] - [0135], [0148] - [0149]; figures 14A-14D,18	1-3, 5-11, 16-19, 23,24
Y	& WO 2014/077242 A1 (FUJI FILM CORP) 22 May 2014 (2014-05-22) figures 14A-14D,18	1-3, 5-11, 16-19, 23,24
Y	US 2014/272101 A1 (CHEN GUOHUA [US] ET AL) 18 September 2014 (2014-09-18) cited in the application paragraphs [0021], [0072], [0085], [0091], [0107]; claim 1	1,6-12, 16-24

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/039864

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010040271 A1	15-04-2010	CA 2739876 A1	15-04-2010
		CN 102202720 A	28-09-2011
		EP 2346563 A1	27-07-2011
		JP 5879126 B2	08-03-2016
		JP 2012505164 A	01-03-2012
		US 2011195124 A1	11-08-2011
		WO 2010040271 A1	15-04-2010
WO 2012153266 A2	15-11-2012	EP 2707080 A2	19-03-2014
		US 2014188041 A1	03-07-2014
		WO 2012153266 A2	15-11-2012
US 2015238413 A1	27-08-2015	CN 104780967 A	15-07-2015
		EP 2921202 A1	23-09-2015
		US 2015238413 A1	27-08-2015
		WO 2014077242 A1	22-05-2014
US 2014272101 A1	18-09-2014	AU 2014233541 A1	17-09-2015
		CA 2903583 A1	18-09-2014
		EP 2968119 A1	20-01-2016
		JP 2016512754 A	09-05-2016
		US 2014272101 A1	18-09-2014
		WO 2014144973 A1	18-09-2014