

POLYMERIC MICRONEEDLE ARRAY AND APPARATUS AND METHOD FOR MANUFACTURING OF THE SAME

Field of the Invention

[0001] The present invention generally relates to medicine delivery devices and technologies, and more particularly to polymeric microneedle arrays and apparatus and method for manufacturing the same.

Background of the Invention

[0002] Medicine delivery is critical for medical treatments, and different medicines may be delivered via different routes. For example, liquid medicines may be delivered by subcutaneous injection with a needle. While the subcutaneous injection is direct and effective, it causes pain and tissue damages if the needle used for the injection has a big dimension, due to the skin histology. Human skin consists of three layers. The outermost layer is called Stratum corneum (SC) consisting of dead tissue with a thickness of about 10-15 μm . This layer is often the primary barrier to fluid transport to the body. The layer beneath the SC is called Viable epidermis (VE), wherein the VE has a thickness of about 50-100 μm , and it contains living cells, but is devoid of blood vessels and contains few nerves. The layer beneath the VE is called Dermis of about 1-3 mm, wherein the Dermis forms the bulk of the skin volume and contains nerves and blood vessels.

[0003] Hypodermic needles are widely used in the medical field for injection into and extraction from human skin. Hypodermic needles generally have a relatively large diameter. For example, conventional needle is about 20-50mm in length and 0.5-0.7mm in diameter, and it will easily penetrate into the Dermis of the skin, causing pains and tissue damages.

[0004] Furthermore, targeted drug delivery or the application of a high concentration of one or more drugs to a specific target area within the body has become of paramount importance to the fight against tumors, restentosis and similar life threatening medical conditions. For example, it would be very desirable to deliver medicines into the

plaque sites during angioplasty surgery. It is apparent that conventional hypodermic needles cannot be used in such operations.

[0005] There are certain attempts to design and manufacture medicine delivery devices that are capable of delivering medicine directly and effectively but not causing pains or tissue damages. Moreover, the desired medicine delivery devices may be employed to deliver medicine into certain sites inside the body. Microneedle array is one of the desired medicine delivery devices. As used herein, the term “microneedle array” refers to a plurality of elongated structures that are sufficiently long to penetrate through the stratum corneum skin layer and into the epidermal layer, yet are also sufficiently short to not penetrate to the dermal layer. Of course, if the dead cells have been completely or mostly removed from a portion of skin, then a very minute length of microneedle could be used to reach the viable epidermal tissue.

[0006] A microneedle array may have dimensions on the order of 1 cm^2 and may include tens, hundreds or even thousands of microneedles, so that it can inject/extract a requisite amount of drug/liquid even though each microneedle has a relatively small diameter. The use of microneedle arrays has great advantages in that intracutaneous drug delivery can be accomplished without pain, leading to increased patient compliance, and without bleeding. Further, patients may apply the drug delivery devices themselves without extensive training.

[0007] Polymeric materials are suitable for manufacturing of microneedle arrays. However, the polymer microneedle arrays cannot be manufactured in a cost-effective manner using currently available techniques. For example, injection moulding of microneedle arrays requires expensive, dedicated micro-injection moulding machine. In addition, US 2002/0020688 A1 discloses manufacturing procedures for creating plastic arrays of microneedles including “self-moulding,” micromoulding, microembossing, and micro-injection techniques. All techniques need a mould containing a micropillar array so that the melted plastic materials will form the microneedles according to the micropillar array.

[0008] Therefore, there is an imperative need to improve the apparatus and method for manufacturing of microneedle arrays.

Summary of the Invention

[0009] The present invention provides an apparatus for manufacturing a polymeric microneedle array. In one embodiment of the present invention, the apparatus comprises a forming mould having a surrounding wall so as to form a cavity and a bottom integrated with one end of the surrounding wall, wherein the bottom has an array of openings; a top mould having an array of apertures that are aligned with the openings in the forming mould; and a holding plate having a plate and an array of micro pins that are integrated onto the plate so that the micro pins can be moved up or down with the plate.

[0010] The present invention further provides a method for manufacturing a polymeric microneedle array using the apparatus provided herein. The method comprises the steps of providing polymeric materials to the cavity of the forming mould; closing the top mould and the forming mould; moving down the micro pins; curing the melted polymeric materials; withdrawing the top mould; retracting the pins; and obtaining the polymeric microneedle array.

[0011] The present invention further provides a polymeric microneedle array manufactured by the apparatus provided herein. The present invention also provides a medicine delivery device for delivery liquid and/or fine powdered medicines, where the medicine delivery device comprises a polymeric microneedle array manufactured by the apparatus of claim 1; and a medicine reservoir connected to the polymeric microneedle array; thereby the medicines may be stored in the medicine reservoir and ready to be delivered through the microneedles.

[0012] One advantage of the present invention is that the microneedle arrays may have substantially sharp tips which make it easier to penetrate through stratum corneum layer of the skin.

[0013] Another advantage of the present invention is that the microneedles of the microneedle arrays could be of various dimensions and shapes. By changing the design of the forming mould, various geometry and shape of microneedles can be formed, for example, pyramidal shaped needles.

[0014] Yet another advantage of the present invention is that the fabrication procedure does not involve expensive micromachining process or require dedicate micro-

injection machine, resulting in low fabrication cost as compared with other known technologies.

[0015] Yet another advantage of the present invention is that the fabrication requires less steps, resulting in easy implementation.

[0016] The objectives and advantages of the invention will become apparent from the following detailed description of preferred embodiments thereof in connection with the accompanying drawings.

Brief Description of the Drawings

[0017] Preferred embodiments according to the present invention will now be described with reference to the Figures, in which like reference numerals denote like elements.

[0018] FIG 1 is a schematic cross-section view of the apparatus in accordance with one embodiment of the present invention.

[0019] FIG 2 is a schematic cross-section view of a medicine delivery device having the polymeric microneedle array manufactured in accordance with one embodiment of the present invention.

[0020] FIG 3 shows an actual microneedle in a microneedle array made of polypropylene (PP).

[0021] FIG 4 shows another microneedle made of polyvinyl chloride (PVC).

Detailed Description of the Invention

[0022] The present invention may be understood more readily by reference to the following detailed description of certain embodiments of the invention.

[0023] Throughout this application, where publications are referenced, the disclosures of these publications are hereby incorporated by reference, in their entirety, into this application in order to more fully describe the state of art to which this invention pertains.

[0024] In the following detailed description, specific details are set forth in order to provide a thorough understanding of the invention. However, it will be understood by

those skilled in the relevant art that the present invention may be practiced without these specific details. In other instances, well-known methods, procedures, components, and materials have not been described in detail so as not to obscure the present invention.

[0025] The present invention provides an apparatus and method for manufacturing polymeric microneedle arrays. Now referring to FIG 1, there is provided a schematic cross-section view of the apparatus for manufacturing of the polymeric microneedle array in accordance with one embodiment of the present invention. The apparatus comprises a forming mould **10**, a top mould **20**, and a holding plate **30** with an array of precision micro pins **32**. The forming mould **10** comprises a surrounding wall **11** and a bottom having cooling channels **12**, heating channels **13**, and an array of openings. The surrounding wall **11** is configured so that it has two functions. One is to hold the polymeric materials to be moulded into polymeric microneedle arrays when the polymeric materials are melted. Another is to provide an adaptor for the moulded polymeric microneedle arrays so that they can be connected with medicine reservoir for delivery. The cooling channels **12** and heating channels **13** can be arranged alternatively in the undersurface of the forming mould. In another embodiment, the cooling and heating channels are provided in a conformal profile surrounding the array of openings. The heating channels and cooling lines can be on the undersurface of the forming mould **10** or inside the forming mould **10**. It is noted that the configurations of the channels will determine the dimensions of the openings through which the polymeric microneedles are made. In one embodiment, the cooling and heating channels are provided in the same moulding apparatus so that the apparatus will have a heating and cooling process that is evenly distributed across the bottom of the forming mould. The cooling and heating channels may be implemented in any suitable way that is well known to those skilled in the art.

[0026] The top mould **20** comprises a moulding plate **21** with an array of apertures that are in line with the openings of the forming mould when the top mould and the forming mould are closed, and an array of boss **22** that can prevent the melted polymeric material from spilling into the apertures of the top mould, but permit the micro pins (to be discussed later) to penetrate. Boss **22**, a circular rounded projection, is employed to press the melted polymeric material. The press of the boss is immediately followed by pins' penetration. Each boss has one bore in which a pin can slide up/down, where the bore is in line with the aperture of the top mould and the opening of the forming mould, and has

close dimensional tolerance such that the small clearance between the pin and bore can prevent the melted polymeric materials from spilling out. There may have flash after fabrication, which can be easily removed by a deburring process.

[0027] The holding plate **30** with an array of precision micro pins comprises a plate **31** and an array of precision micro pins **32**, wherein the array of micro pins are fixed onto the plate so that, when the plate is moved up or down, the micro pins will move up or down with the plate. The precision micro pins may be made of any suitable material, e.g., tungsten. The movement and the control of the movement of the holding plate can be realized manually, mechanically, or electromechanically. The means for doing so are well known to those skilled in the art. It is to be noted that the array of micro pins are aligned with the apertures of the top mould and the openings in the forming mould. The dimensions of the array of micro pins are determinative of the inner-channel sizes of the resultant microneedles, so that different sized microneedles can be made by adjusting the dimensions of the precision micro pins. It is to be appreciated that the array of precision micro pins may be held in any suitable means so long as the micro pins can be moved up/down simultaneously.

[0028] Now there is provided a brief description of the method of using the aforementioned apparatus to manufacture polymeric microneedle arrays. When the top mould and forming mould are separated, polymeric materials may be introduced into the cavity of the forming mould formed by the surrounding walls. In one embodiment, melted polymeric materials may be directly presented into the cavity of the forming mould. In another embodiment, when the forming mould has the heating channels as shown in FIG 1, polymeric materials in the form of pellets or granules may be put onto the bottom of the cavity of the forming mould, and the polymeric materials will be melted by the heating channels. Alternatively, the melting process may be done after the mould has been closed. In another embodiment, polymeric materials may be pre-cut sheet of plastic which may be directly placed upon the bottom of the cavity of the forming mould, pressed down by the top mould, heated in the mould to a temperature slightly below the melting point, and then penetrated by the pins.

[0029] After the polymeric materials are melted onto the bottom of the cavity of the forming mould, the top mould will be pressured sufficiently so that all the air gaps between the top mould and the forming mould are closed, leaving minute protruding droplets at the

entrance of openings on the bottom of the forming mould. Then, the array of precision micro pins will be inserted through the apertures of the top mould and the openings at the bottom of the forming mould. The micro pins are pushed down together with the holding plate so that the melted polymeric materials are drawn downwards and form the hollow tips of the microneedles. As used herein, the term “hollow” means having one or more substantially annular bores or channels through the interior of the microneedle structure, having a diameter sufficiently large to permit passage of fluid and/or fine powdered materials through the microneedles. Once the melted polymeric materials are cured after a holding and cooling stage, the micro pins are withdrawn with the holding plate, the top mould retracts, and the microneedle array is formed.

[0030] The polymeric materials that are suitable for the present invention may be any commercially available materials. In one embodiment, the polymeric materials are polypropylene (PP) or polyvinyl chloride (PVC). It will be understood that the plastic material may consist of any type of permanently deformable material that is capable of undergoing a gradual deformation as its melting point is reached or slightly exceeded. This “plastic material” could even be some type of metallic substance in a situation where the metallic material would deform at a low enough temperature so as to not harm the mould itself. The preferred material is a polymer such as PP, PVC or nylon, although many other types of polymer material certainly could be used to advantage. Other potential materials include: polyester, polyethylene (PE), acrylonitrile butadiene styrene (ABS) or polymethylmethacrylate (PMMA). Of course, one important criterion is that the material which makes up the microneedles does not chemically react with skin, or with the fluidic substance that is being transported through the hollow interiors of the microneedle array.

[0031] Now referring to FIG 2, there is provided a medicine delivery device **50** comprising a polymeric microneedle array **51** manufactured in accordance with the apparatus and method disclosed herein, a medicine reservoir **52** connected to the polymeric microneedle array, and a medicine **53** is stored within the medicine reservoir and ready to be delivered through the microneedles. The connections between a polymeric microneedle array and medicine reservoir can be achieved by any plastic joining means such as laser transmission welding or ultrasonic welding.

[0032] The devices disclosed herein are useful in transport of material into or across biological barriers including the skin (or parts thereof); the blood-brain barrier;

mucosal tissue (e.g., oral, nasal, ocular, vaginal, urethral, gastrointestinal, respiratory); blood vessels; lymphatic vessels. The biological barriers can be in humans or other types of animals. The microneedle device can be applied to tissue internally with the aid of a catheter or laparoscope. For certain applications, such as for drug delivery to an internal tissue, the devices can be surgically implanted.

[0033] The following example is provided for showing the actual practice of the present invention. The actual dimensions and configuration and materials used are provided for illustration only.

[0034] Examples

[0035] A microneedle array was manufactured with the apparatus shown in FIG 1. The polymeric material is polypropylene (PP). The array of microneedles has about 144 needles. The microneedles are conically shaped with a bore. Length of microneedles is about 0.6-1.0 mm for penetrating into dermis or 0.06-0.1mm for penetrating into VE only. Diameter of microneedles is about 0.08-0.2 for penetrating into dermis or 0.03-0.06mm for penetrating into VE only. Pitch of microneedles is about 0.75-0.8 mm. Patch size is about 15x15 mm².

[0036] FIG 3 shows an actual microneedle in a microneedle array made of polypropylene (PP). The microneedle has a hollow inside and a sharp tip. The precision pins were tungsten micro pins with a tip diameter of 0.1 mm. The microneedle shown has a base diameter of 1 mm, tip diameter of 0.28 mm, and height of 1.49 mm. FIG 4 shows another microneedle made of polyvinyl chloride (PVC), having a base diameter of 1 mm, tip diameter of 0.45 mm, and height of 0.76 mm. It is noted that the tip is not sharp.

[0037] While the present invention has been described with reference to particular embodiments, it will be understood that the embodiments are illustrative and that the invention scope is not so limited. Alternative embodiments of the present invention will become apparent to those having ordinary skill in the art to which the present invention pertains. Such alternate embodiments are considered to be encompassed within the spirit and scope of the present invention. Accordingly, the scope of the present invention is described by the appended claims and is supported by the foregoing description.

CLAIMS

What is claimed is:

1. An apparatus for manufacturing a polymeric microneedle array, comprising:
 - a forming mould having a surrounding wall so as to forming a cavity and a bottom integrated with one end of the surrounding wall, wherein the bottom has an array of openings;
 - a top mould having an array of apertures that are aligned with the openings in the forming mould; and
 - an array of micro pins being able to be moved through array of openings of the forming mould and the array of apertures of the top mould;thereby, when a polymeric material is placed onto the bottom of the cavity of the forming mould, the top mould and the forming mould will be closed so as to seal all the air gaps, and then the micro pins will penetrate the polymer through the apertures, resulting forming microneedles around the micro pins.
2. The apparatus of claim 1, further comprising a holding plate to which the array of micro pins are integrated so that the holding plate will move the micro pins through array of openings of the forming mould and the array of apertures of the top mould.
3. The apparatus of claim 1, wherein, when the polymeric material is placed onto the bottom of the cavity of the forming mould, the polymeric material is in a melted state.
4. The apparatus of claim 1, wherein the forming mould further comprises a plurality of cooling channels and heating channels.
5. The apparatus of claim 4, wherein, when the polymeric material is placed onto the bottom of the cavity of the forming mould, the polymeric material may be in a solid state so that it can be melted within the mould by the heating channels.

6. The apparatus of claim 5, wherein the polymeric material is pellets or granules.
7. The apparatus of claim 5, wherein the polymeric material is a sheet of plastic, thereby the sheet of plastic is heated up to a temperature slightly below the melting point.
8. The apparatus of claim 1, wherein the polymeric material is plastic.
9. The apparatus of claim 1, wherein the top mould further comprises a plurality of boss.
10. A method for manufacturing a polymeric microneedle array using the apparatus with a forming mould having an array of openings, a top mould having an array of apertures that are aligned with the openings of the forming mould, and an array of micro pins being able to be moved through the array of openings of the forming mould and the array of apertures of the top mould, comprising the steps of:
 - providing polymeric materials to the bottom of the cavity of the forming mould;
 - closing the top mould and the forming mould;
 - moving down the micro pins;
 - curing the melted polymeric materials;
 - withdrawing the top mould;
 - retracting the pins; and
 - obtaining the polymeric microneedle array.
11. The method of claim 10, wherein the polymeric materials may be in a melted state when they are provided onto the bottom of the cavity of the forming mould.
12. The method of claim 10, wherein the polymeric materials may be in a solid state when they are provided onto the bottom of the cavity of the forming mould, and will be melted within the mould by a heating means within the mould.
13. The method of claim 12, wherein the heating means may be a plurality of heating channels provided by the forming mould.

14. A polymeric microneedle array manufactured by the apparatus of claim 1.
15. The polymeric microneedle array of claim 14, wherein the polymeric microneedle array is made of plastic.
16. A medicine/liquid delivery device for delivery medicine/liquid and/or fine powdered medicines, comprising:
 - a polymeric microneedle array manufactured by the apparatus of claim 1; and
 - a medicine/liquid reservoir connected to the polymeric microneedle array;thereby the medicine/liquid may be stored in the medicine/liquid reservoir and ready to be delivered through the microneedles.