[Frontiers in Bioscience 13, 1711-1715, January 1, 2008]

Microneedles for transdermal drug delivery: a minireview

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1. ABSTRACT

The stratum corneum is the main barrier for transdermal drug transport. It could be bypassed by microneedles, which have a length of a few tens to a few hundreds of microns. They are usually arranged in arrays and can be used in several ways to enhance transdermal drug transport. Microneedles can be inserted into the skin in order to increase its permeability, after which the drug is applied (poak with patch). Drugs could also be coated onto the microneedles and be inserted into the skin (coat and poke). Hollow microneedles are used to inject drug solutions in to the skin. This review aims to discuss recently published *in vivo* and *in vitro* studies on microneedle aided transdermal drug delivery.

2. INTRODUCTION

The main barrier in trandermal drug delivery is the outer layer of the skin, the stratum corneum. Because of the structure of the stratum corneum, the choice of drug molecules which can be delivered is limited to those which have a rather small size or molecular weight, are rather lipophilic and have a low therapeutic dose. Several techniques have been developed to improve transdermal drug transport, such as electroporation, electrophoresis and phonophoresis (1,2). These techniques have shown, to some extent, to improve the permeability of the stratum corneum and to be able to improve skin penentration of drug molecules with relatively small sizes and molecular weights. Direct injection by a hypodermic needle could

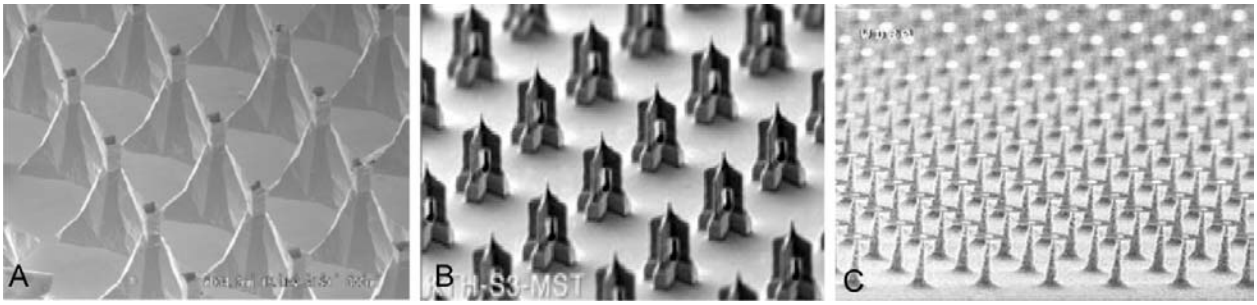

Figure 1. Examples of microneedle arrays: pyramidal (A), cross shaped (B) and flat thin (C).

also be employed to avoid the transcorneal barrier. However, injections are generally not well accepted by patients as they can cause pain.

The developments in microelectronics technology, allowing for the miniaturization of mechanics and structures, have made it possible to produce arrays of microneedles, which, when applied to the skin, can dramatically increase skin permeability. Since the stratum corneum is about 10-20 μm thick, microneedles with a length of few hundreds of microns are able to cross this barrier, as was shown by Henry *et al.* (3). Compared to classical hypodermic needles, these microneedles have the advantage not to cause a painful sensation, although they are inserted at least into the epidermis and sometimes deeper into the superficial dermis where nerves are present (4). Probably, their small size reduces the odds of encountering a nerve or of stimulating it to produce a painful sensation. Other potential advantages are the possibility to deliver higher molecular weight drugs such as peptides, proteins and DNA and the potential of controlled drug delivery by combining the microneedles with a patch system.

Several materials have been used to produce microneedles depending on the production methods available, such as silicon, metal, titanium, glass, ceramic and polymeric materials (5). A multitude of fabrication processes are employed such as litography, spin coating, laser cutting and micro injection molding (6,7). The materials chosen depend on the production techniques available, but other properties such as biocompatibility and mechanical strength of the microneedles should be taken into consideration. Recently, biodegradable materials such as polylactic acids have also been employed, in order to improve safety (8,9). Several shapes, both solid and hollow can be made, from flat thin to cross shaped and pyramidal (Figure1). The geometry of the needle (wall thickness, wall angle, tip radius,) is a factor determining the force needed to insert it into living skin and the force the microneedles can withstand before breaking. In a study of Davis *et al.* the ratio of fracture force to insertion force is defined as the safety ratio. This ratio was found to increase with increasing wall thickness and decreasing tip radius (10). This review aims to discuss recently published scientific work on these delivery systems. The focus is not on the production methods being developed, but on *in vitro* and *in vivo* studies performed with microneedle arrays.

3. MICRONEEDLE AIDED DRUG ADMINISTRATION

There are several ways in which microneedle arrays can be employed to improve transdermal drug delivery, which can be divided into “poke with patch”, “coat and poke”, and injection through hollow microneedles. “Poke with patch” would imply that a microneedle array is used to pierce the skin in order to increase its permeability. The drug is administered afterwards (e.g. as a patch) and penetrates the skin through the channels created by the microneedles. “Coat and poke “ means that the microneedle arrays are coated with the drug, and then pierced into the skin together with the microneedle array. Hollow microneedles can be used as a means to inject a drug into the skin. In combination with miniaturized pumping systems they can be employed to deliver the drug in a controlled way. In some cases other techniques such as electrophoresis or electroporation are combined with microneedles to obtain a controlled drug delivery.

3.1. Poke with patch systems

Verbaan *et al.* recently studied the passage of a range of molecules varying in molecular weight, through human skin *in vitro*. Dermatomed skin was pierced with a 4 × 4 needle patch with needle lenghts of 300, 550, 700 and 900 μm. The skin appeared to be pierced by all needles except the ones of 300 μm, as was shown with tryptan blue staining. After piercing transport studies were performed in Franz type diffusion cells with compounds varying in molecular weight from 538 Da to 72 kDa. For all molecules investigated an increased passive diffusion through the skin was observed. *In vivo* treatment of the skin of healthy volunteers was also performed. Four healthy volunteers were treated on the left forearm with sterilized microneedle arrays for 1 min after which trans epidermal water loss (TEWL) values were measured. An increased TEWL was observed compared to the untreated situation, except for the microneedles with 300 μm length, suggesting that a minimal needle length is needed to effectively increase passive transport through the skin (11).

In another study, Wu *et al.* used an array of 9 acupuncture needles on a silicone sheet, each needle tapered over a 400-μm length to a sharp tip with 28° angle, to pierce excised hairless rat skin. The *in vitro* transport of a series of FITC dextrans (*MW* 3.8 up to 200 kDa) was studied. An increased transcorneal transport was observed, and a linear relationship between log *MW* and log *P* was observed. Additional iontophoresis was shown to even further increase drug transport (12). Both of the above mentioned studies showed the potential of microneedles for the delivery of compounds over a wide range of molecular weights.

Park *et al.* developed a technique to produce microneedles of biodegradable polymers, which are expected to improve safety in case a microneedle might accidentally break off in the skin. A copolymer of lactic acid and glycolic acid (PLGA) was chosen as biocompatible and biodegradable polymer. The authors demonstrated that it was possible to produce PLGA microneedles that showed sufficient mechanical strength. Permeability studies on human cadaver skin showed an improved permeability up to three orders of magnitude, for both a lower molecular weight model drug (calcein) as well as for one with a high molecular weight (albumin) (8).

3.2. Coat and poke systems

Cormier *et al.* coated a microneedle array of 2cm^2 (with 321 needles/cm^2, each microneedle arrowhead-shaped with a length of 200 μm) with different amounts of desmopressin. The arrays were attached to a patch and applied on the skin of hairless guinea pigs. Pharmacologically relevant amounts of desmopressin were delivered after 5 min and bioavailability was as high as 85%. The elimination kinetics for serum desmopressin were similar after transdermal and intravenous (IV) delivery, suggesting the absence of a skin depot. This study showed that transdermal delivery of desmopressin could be a viable alternative for the injectable, intranasal or oral formulation currently used, which show either painful sensations for the patients or low and variable bioavailibility (13).

The previous study shows the possibility to deliver drugs coated onto microneedle arrays. In another study, Xie *et al.* demonstrated that the coating could also be used to influence drug release. They employed a microneedle array with 400 out-of-plane, needleshaped microstructures fabricated using micro-electro-mechanical systems (MEMS). The array was coated with several model drugs: calcein, a small molecule (molecular weight, 623 D) that has little skin penetration, and bovine serum albumin (BSA) (molecular weight, 66,000 D), a hydrophilic biological macromolecule. The coating was done by dispersing the drug in a chitosan solution, which was subsequently coated on the microneedles. The skin of Male Sprague-Dawley rats was used in *in vitro* permeation tests. The authors showed that for both molecules the transport was increased by using the coated microneedles. Moreover, the results showed that the chitosan film acts as a matrix that can regulate the BSA release rate. BSA permeation rate decreased with an increase of the chitosan concentration; the thicker the film, the slower the permeation rate. In addition, a linear relationship between the permeation rate and the square root of the BSA loading dose was established. These results show that the composition and thickness of a coating could be used as a tool to regulate drug release rate (14).

One application of microneedles that shows great potential is vaccination through the skin. Hooper *et al.* used a combination of skin electroporation and plasmid DNA-coated microneedle arrays to deliver an experimental smallpox DNA vaccine. Plasmid DNA was dried onto the tips of the microneedles. These microneedles (≤ 1 mm long) were inserted into the skin where the DNA dissolves in interstitial fluid and is then transfected into the surrounding cells by electroporation. When applied to female BALB/c mice, the authors demonstrated a complete protection against a lethal (>10 LD50) intranasal challenge with vaccinia virus strain IHD-J. This demonstrates that a protective immune response can be achieved by microneedle-mediated skin electroporation (15).

Another study in which microneedles were tested to induce an immune response was performed by Widera *et al.* They used a microneedle array coated with ovalbumin (OVA) as a model antigen in order to study the effect of delivery parameters on the resulting immune responses. Microneedle arrays were 2 cm^2 in size. Several arrays were compared with different microneedle densities (1314 and 280 needels per array) and needle lengths (225, 400 and 600 μm). Three different amounts of ovalbumin (0.5, 5 and 25 μg) were coated onto the tips of the microneedles. For the same array, the skin concentration profile reflected the loading dose. Results showed that amounts of OVA in the epidermis or dermis were similar and independent of the microneedle length used for delivery. The immune response was found to be dose dependent, and mostly independent of depth of delivery, density of microneedles, or area of application (16).

Also in “coat and poke” techniques, there is a trend to use biocompatible and biodegradable materials. Ito *et al.* published a paper in which insulin was put into dextrin microneedles. In this case the drug was not so much coated, but incorporated into the microneedle matrix. The mixture was spread with the aid of a polypropylene tip, and after drying microneedles were obtained. After insertion into the skin, the microneedle dissolves and releases the drug. Insulin was added to dextrin glue and mixed. In an animal study in mice, microneedle and i.v. injection of insulin were compared. Unlike the studies mentioned above, no arrays, but one single microneedle was inserted into the skin. The plasma glucose levels were found to decrease in a dose dependent manner, and compared to the i.v. injections, pharmacological availabilities above 90% were obtained with the microneedles. The skin was shown to completely recover after microneedle injection within 48 hours after administration (17).

3.3. Hollow microneedles systems

When hollow needles are employed, the microneedles are usually attached to a patch containing

some pumping device, being able to pump the drug solution at a controlled rate into the skin. The flow could also be regulated by a sensor connected to the device. The injection of fluids through hollow microneedles into the skin can be blocked by the tissues compressed together as the needle is pushed through the skin, and fluid dynamics can depend on microneedle shape. Sivamani *et al.*used methyl nicotinate as a model drug to test transdermal injection through hollow microneedles in humans, comparing pointed and symmetric microneedles. Arrays consisted of eight evenly spaced microneedles. *In vivo* injections were performed on the volar forearm of healthy volunteers. They showed that the speed at which the fluids could be injected depended on the design of the microneedles. In symmetric needles, the entry zone coincides with its lumen and may be susceptible to clogging and consequently, a higher resistance to fluid flow. In the pointed microneedles, the lumen is offset from its piercing zone, and because of the elliptical structure of its lumen, has a higher area of delivery, resulting in a higher drug injection rate (18). Martanto *et al*. have shown that infusion flow rates can be increased by an order of magnitude by partially retracting microneedles after insertion into the skin. Retraction of the microneedle allows the skin to recoil back toward its original position, relieving skin compaction and resulting in increased local flow conductivity (19,20).

Nordquist *et al.* tested a microneedle-based infusion patch featuring a small electrically controlled drug dispenser to deliver insulin. The needles were organized on 4 × 4 mm chips with 21 hollow needles. Diabetes was induced by an intravenous injection of streptozotocin in adult male Sprague Dawley rats, after which the animals were treated with insulin, administered either subcutaneous or using the microneedle patch. A decrease in blood glucose level was observed for both groups, but with less variation in the microneedle patch compared to the subcutaneous group. This study indicates that a transdermal patch could be an interesting tool for maintaining patients' glycaemic control, improving patient compliance (21). For this type of delivery systems, the whole design has to be miniaturized, including drug reservoirs and pumping systems. In the latter study the fluid was pumped through the microneedles by using an electrically controlled drug dispenser. The electricity is used tho heat up an expandable material. Upon expansion, the matarial puts pressure on the drug reservoir, pushing the fluid through the microneedles. Another pumping device was described by Ma *et al.*(22). They coupled a piezoelectric pump to a hollow microneedle array to deliver insulin (22). Zahn *et al* designed a microneedle array attached to a chip with a MEMS positive displacement micropump. The generation and collapse of thermally generated bubbles, in combination with directional check valves, was used to achieve net pumping of 2 nl/sec (23). In addition Aoyagi *et al.* have recently shown it is also possible to produce biodegradable hollow microneedles with a high aspect ratio, consisting of polylactic acid (PLA). In this case, the microneedles were not developed to deliver drugs, but to take blood plasma samples by capillary force (9).

4. PERSPECTIVE

Many studies have shown the feasibility of using microneedle arrays to deliver a wide variety of drugs transdermally. The increasing knowledge of production processes, natural and supramolecular materials, biocompatibility, coating techniques, injection dynamics and long term effects on skin condition could eventually lead to the commercial production of low cost, safe and convenient to use systems. Several applications are possible, such as the delivery of peptide drugs and vaccination. The development of microsensors in combination with patches with hollow microneedles offers exciting potential for the production of systems which release drugs as the need occurs, for example in the management of diabetes.

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Abbreviations: TEWL: trans epidermal water loss; log *P*; logarithm of partition coefficient in n-octanol/water system; PLGA: poly(lactic-co-glycolic acid); IV: intravenous; MEMS: micro-electro-mechanical systems; BSA: bovine serum albumin; OVA: coated with ovalbumin; PLA: poly(lactic acid).

Key Words: Microneedles arrays, vaccination, transdermal administration, needleshaped microstructures, dextrin microneedles, biodegradable hollow microneedles, injection, review

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