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REVIEW ARTICLE

Polymer microneedles for transdermal drug delivery

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Abstract

A microneedle system has been developed to deliver chemical and biological agents through the stratum corneum, which is the main barrier to drug delivery. Recently, microneedles have been fabricated from various kinds of polymers, including biocompatible polymer, biodegradable polymer, and water-soluble polymer. Polymer microneedles offer the benefits of ease of fabrication, cost-effectiveness, and mass production, as well as controlled drug release using the water solubility and degradation properties of polymer. In this review, the key features of polymer microneedles are discussed, including fabrication, materials, mechanical properties, drug delivery properties, and applications. Polymer microneedles provide a promising method for transdermal drug delivery by utilizing various physical and chemical properties of polymer.

Keywords: Microneedle, polymer, biodegradable, dissolving, transdermal drug delivery, microfabrication

Introduction

A new method of transdermal drug delivery, microneedles, was introduced to overcome the limitations of conventional transdermal drug delivery methods (Kim et al., 2012b). Arrays of microneedles have been created to act as a link between conventional injections and transdermal patches. Microfabrication technology has been implemented to create an array of microneedles for penetrating the stratum corneum without eliciting pain (van der Maaden et al., 2012). Solid silicon microneedles have been demonstrated to increase the permeability of in vitro human skin by three to four orders of magnitude for ingredients ranging in size from a few nm to 50 nm (McAllister et al., 2003; Cleary, 2011).

Microneedles have been made from various materials such as silicon, glass, metal, and polymer (Kim et al., 2012b). Silicon and glass have been attractive options because they are common materials in the microelectronics industry and therefore a great deal is known about their production process. However, silicon and glass are relatively expensive compared to metals and polymers. Furthermore, production of microneedles out of silicon and glass is based on a sophisticated and relatively fragile semiconductor process (Park et al., 2005). Metals are more appropriate material for fabricating microneedles, but they are less attractive because of higher costs compared with polymer microneedles, as well as because of difficulties with mass production. In comparison to silicon, glass, and metal, polymer provides advantages for demanding microneedle applications. Polymer microneedles have the mechanical advantage of improved resistance to shear-induced breakage owing to its viscoelastic property (Ratner et al., 1996). In addition, polymer microneedles can be prepared in a re-usable mold, providing an economic advantage in production (Park et al., 2005). Chemically, biodegradable polymers allow additional functionality of the microneedles themselves. Even if biodegradable polymeric needles break off in the tissue or skin, they degrade in the tissue safely. The combination of these features makes polymer highly suitable for use in the development of microneedles. The combination of pharmaceutical application of

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polymer with microneedle fabrication can provide an effective method for the active and controlled release of drugs transdermally. Microneedles can encapsulate active ingredients by using water soluble polymer and biodegradable polymer. Tips of water-soluble polymer microneedles were developed for rapid delivery and a backing layer was combined with the microneedles to enhance long-term delivery. (Lee et al., 2008), and biodegradable polymers have been used for controlled transdermal drug delivery (Park et al., 2006).

This paper summarizes the fabrication of polymer microneedles and their mechanical properties. Polymer microneedles exploit the drug delivery property of polymer, resulting in unique drug delivery properties. Drug delivery properties of polymer microneedles and their applications will be presented in this manuscript.

Types of polymer microneedles

Polymer microneedles are classified as solid (Type I), drug loaded (Types II, III, IV), and hollow (Type V) (Figure 1). Figure 1(a) shows microneedles are applied on skin and Figure 1(b) demonstrates that microneedles are used for drug delivery through skin. Solid polymer microneedles are prepared from biocompatible polymers, and they are effective in generating holes through the stratum corneum. Because the drug is not encapsulated in solid microneedles, two processes are required to penetrate the skin and apply the drug. This is inconvenient for users and is also susceptible to misuse. On the other hand, solid biodegradable polymer microneedles provide biological safety in case microneedle tips are broken while inserted in the skin. Solid polymers are shown in section A of Figure 2; they are made of biocompatible polymers, poly-lactic acid (Figure 2(a)) (Park et al., 2010), poly-lactic-co-glycolic acid (Figure 2(b)) (Choi et al., 2012a), and poly-methylmethacrylate (Figure 2(c)) (Jin et al., 2009).

Polymer microneedles that encapsulate drugs can be divided into three types based on the type of drug delivery. These are biodegradable polymer microneedle

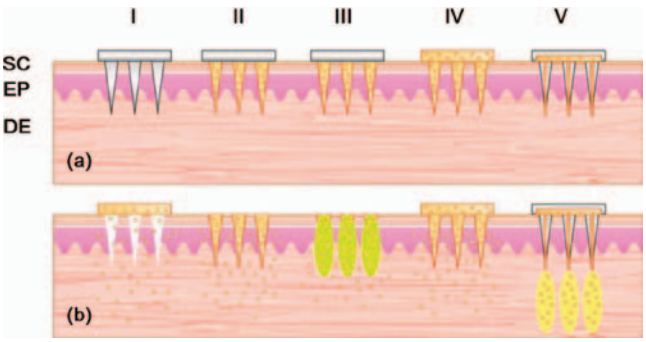

Figure 1. Types of polymer microneedles: microneedles are applied to the skin (SC: stratum corneum, EP: epidermis, DE: dermis), (A) and then utilized for drug delivery (B). (I) solid microneedle, (II) biodegradable polymer microneedle, (III) dissolving microneedle, (IV) dissolving microneedle patch, (V) hollow microneedle.

(Type II), dissolving microneedle (Type III), and dissolving microneedle patch for coherence with the caption of Figure 1. (Type IV). Drugs are encapsulated in biodegradable polymer microneedles for controlled and sustained release after insertion into the skin (Type II). The predetermined release profile of a drug can be obtained by selection of the appropriate biodegradable polymer and the appropriate design. Section B of Figure 2 demonstrates biodegradable microneedles that encapsulate drugs. They are made of biodegradable polymers such as poly-lactic acid, poly-glycolic acid, and their co-polymers, which the FDA has approved for implanting material (Park et al., 2006, Kim et al., 2012a, Park et al., 2007a). Drugs encapsulated in biodegradable polymer microneedles are released by diffusion of the drug through a swollen matrix and hydrolysis of the polymer (Park et al., 2006).

Dissolving microneedles encapsulate model drugs in a water-soluble matrix of microneedles. The drug is dispersed through microneedle tips only for Type III microneedles, and the drug is encapsulated in tips and patches together for Type IV microneedles (Lee et al., 2008). A small dose of drug (only a few hundred micrograms) can be delivered by dissolution of tips of Type III microneedles in skin. A larger drug dose can be delivered using the patch system; however, the patch should remain on the skin for predetermined time. The tips were separated from the base by contact with water in the skin layer and tips remaining in the skin worked as a drug depot for a predetermined time as discussed below (see the section on "Short-term drug delivery"). Section C of Figure 2 shows dissolving microneedles made of poly methylvinylether-co-maleic acid (PVM/MA) Copolymer (Figure 2(g)) (Boehm et al., 2012), poly vinylprrolidone (PVP) (Figure 2(h)) (Ke et al., 2012), and bioglass (Figure 2(i)) (Martin et al., 2012); these encapsulate model drugs. When the drug was encapsulated in a patch in addition to microneedles, a greater drug dose can be delivered through the microneedle channel (Type IV) (Lee et al., 2008). Such a microneedle patch system can overcome the low-dose limit of the dissolving microneedle system, which depends on tip dissolution. By controlling the microneedle patch design, the release property can be controlled over times ranging from a few hours to a few days (Lee et al., 2008).

Hollow microneedles have been used to deliver a drug solution locally (Patel et al., 2011) and systemically (Khumpuang et al., 2007); however, fabrication of hollow polymer microneedle is restricted by the mechanical weakness of the polymer and the simplicity of the micromolding process (Yung et al., 2012). Recently, hollow polymer microneedles have been fabricated out of polymers using advanced injection molding methods (Yung et al., 2012) and X-ray lithography (Khumpuang et al., 2007), and hollow polymer microneedle has been presented as a solution for delivering drugs (Bodhale et al., 2009). Figure 2D demonstrates hollow polymer microneedles made of (j) PMMA (Moon & Lee, 2005), (k) poly-oxymethylene (Yung et al., 2012) and (l) SU-8 (Wang et al., 2009).

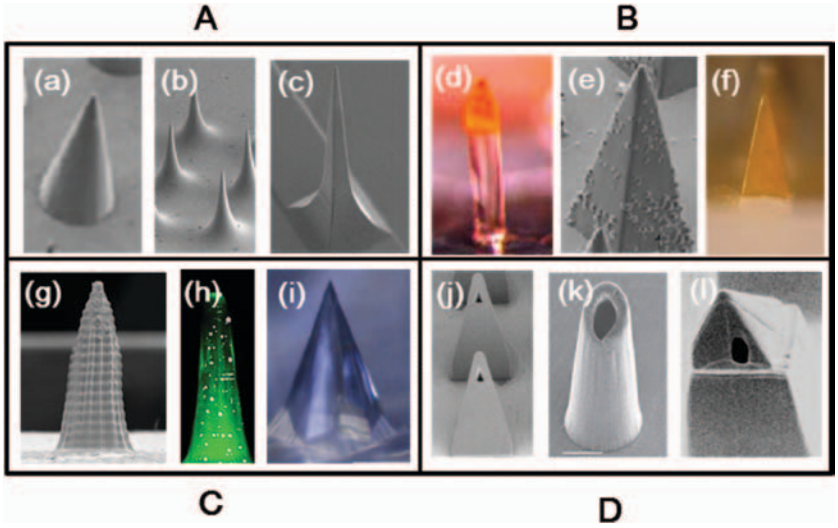

Figure 2. Types of polymer microneedles: (A) solid microneedles (a) (b) (c), (B) biodegradable polymer microneedles (d) (e) (f), (C) dissolving microneedles (g) (h) (i), and (D) hollow microneedles (j) (k) (l).

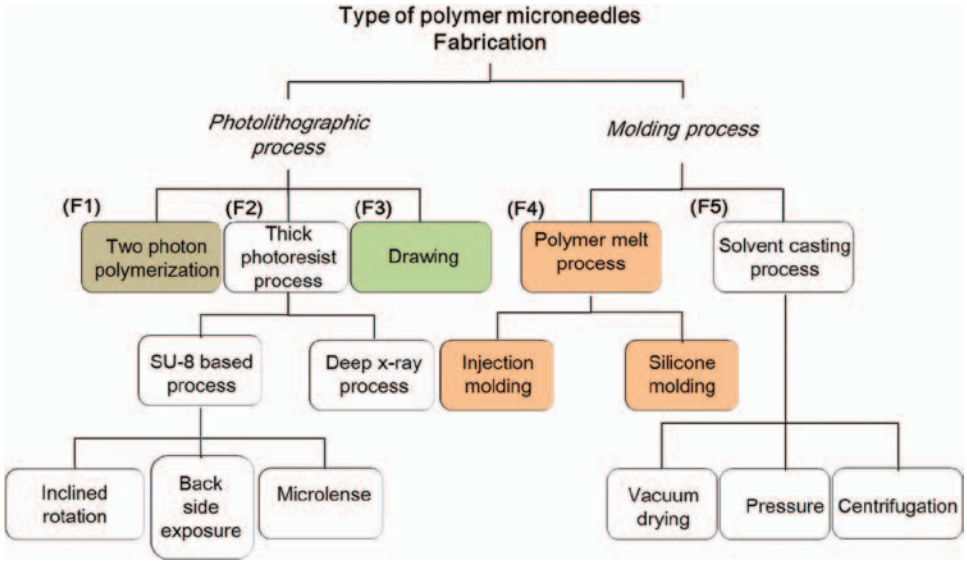

Figure 3. Process of microneedle fabrication.

Materials and fabrication process of polymer microneedles

Polymer microneedles are fabricated mainly by using a photolithographic process and micromolding process. Types of polymer microneedle fabrication process are summarized in Figure 3. The photolithographic process depends on thick photoresist polymer (process F2 in Figure 3), SU-8 and poly-methyl-methacrylate (PMMA), which is used to produce a pattern for high-aspect ratio structure. SU-8 can provide a sophisticated structure by controlling the light path and the focus, resulting in the production of solid tapered microneedles and hollow polymer microneedles (Kim et al., 2004). Exposure on thick SU-8 through a mask defines a glass substrate that creates a tapered column structure because of the light bending induced by the different refractive indexes of SU-8 and glass (Kim et al., 2004). Microlenses are integrated on the glass mask substrate to form a tapered structure in SU-8 by focusing of light in SU-8 and local curing of SU-8 (Park et al., 2007b). Without the additional step for controlling the light path, tapered structures with various heights are fabricated by an inclined rotation method. Inclined exposure is achieved by placing the substrate on a tilting and rotating stage relative to a fixed UV source (Yoon et al., 2006; Choi et al., 2006). The deep x-ray photoresist process uses synchrotron radiation, including high collimation and large absorption length into PMMA, resulting in the ability to fabricate solid and hollow polymer microneedles with high aspect ratio (Khumpuang et al., 2007). The deep x-ray exposure method was used to make solid polymer microneedles out of PMMA, process F2 in Figure 3 (Moon et al., 2005). After the deep x-ray mask and the PMMA sheet were fixed with designed gab, the successive two side deep x-ray

exposures made each side feature of the microneedle shaft by the twice unexposed area to obtain hollow polymer microneedles with high aspect ratio and inside ducts (Moon & Lee, 2005). Convex-shaped polymer microneedles are fabricated from a photo-curable monomer by using two-photon polymerization, process F1 in Figure 3 (Gittard et al., 2009). Two-photon polymerization relies on ultrashort laser pulses that selectively polymerize a negative photosensitive material. Direct two-photon polymerization was also used to form hollow polymer microneedles (Gittard et al., 2010). Drawing lithography with viscoelastic polymer was developed to fabricate microneedles with high aspect ratio, process F3 in Figure 3 (Choi et al., 2012a, Lee et al., 2010, Lee et al., 2011c). Polymer melt is drawn directly from a two-dimensional solid surface using micro-probes without the need for a mask and light irradiation. Solid microneedles made of polymer usually have been used as a master structure for preparation of a mold to fabricate drug-loaded microneedles and hollow microneedles.

Polymer microneedles have been manufactured by using micromolding, which is similar to traditional injection molding. Several molding methods for fabricating microneedles with different polymer substrates have been reported recently, including injection molding using a hard material mold (Yung et al., 2012, Sammoura et al., 2007, Wang & Jeng, 2009a), polymer melt casting using a silicone rubber mold (process F4) (Park et al., 2005, Park et al., 2006, Kuo et al., 2011, Kim et al., 2012a), and solvent casting using a silicone rubber mold (process F5) (Lee et al., 2011a, Lee et al., 2008, Ito et al., 2007a, Ito et al., 2011a, Ito et al., 2007b). Polymer microneedles were replicated by molding polymer melt, including non-biodegradable polymers such as poly-oxymethylene (POM) (Yung et al., 2012) and polycarbonate (PC) (Noh et al., 2010, Jin et al., 2009), dissolving polymer such as maltose (Kolli and Banga, 2008) and galactose (Donnelly et al., 2009), and biodegradable polymers such as poly-lactic acid, poly-glycolic acid, and their co-polymers (Park et al., 2005, Aoyagi et al., 2008, Kim et al., 2012a). Molding polymer melt offers the advantage of low cost for mold preparation, a simple replication process, and high structural accuracy and is therefore suited for microneedle fabrication for rapid prototyping and mass fabrication. However, the high temperature involved in the fabrication process limits the capacity to encapsulate drugs inside the microneedles. To overcome this limitation, an ultrasonic welding method was introduced that minimized protein denaturation while the drug was being encapsulating (Park et al., 2007a, Min et al., 2008).

Recently, polymer microneedles have been fabricated using micromolding based on the solvent casting method, which provides room-temperature fabrication of inexpensive microneedles (Fukushima et al., 2011, Ito et al., 2010a, Ito et al., 2011a, Ito et al., 2010b, Ito et al., 2008a, Ito et al., 2011b, Ito et al., 2008b, Lee et al., 2011a, Lee et al., 2008, Sullivan et al., 2010, Sullivan et al., 2008). An aqueous polymer solution containing a drug was applied on a PDMS mold and dried at room temperature to remove the thermal denaturation. The limitations of the conventional solvent casting method are loss of mechanical strength due to pore formation and partial copying of microneedles due to partial filling of the upper portion of the needle mold. Additional steps such as centrifugation (Lee et al., 2008, Garland et al., 2012a, Donnelly et al., 2009, Garland et al., 2012b), drying under pressure (Ito et al., 2010c), and degassing under reduced pressure (Fukushima et al., 2011) have been developed to obtain polymer microneedles with the proper shape and sufficient mechanical strength. A variety of polymers, including carboxy-methyl-cellulose, fibroin, maltose, dextran, dextrin, poly-vinyl-pyrrolidone, poly-methyl-vinyl-ether-co-maleic acid, sugar glass, sodium chodroitin sulfate, hyaluronic acid, poly-vinyl alcohol, and their combinations, have been used as a dissolving microneedle matrix as shown in Table 1. Multilayered microneedles were also designed and fabricated using the micromolding method to locate the drug only in the tip of the dissolving microneedles. Multilayered dissolving microneedles can encapsulate the drug only in the microneedle tips for immediate release of drug into skin and (Ito et al., 2011a), and different kinds of drug can be encapsulated in each layer of the microneedles for slow drug release over time (Park et al., 2007a). Sharp polymer tips were capped on a metal shaft to offer a quick and convenient administration. Upon insertion, the sharp polymer tips were able to remain embedded within the skin while the metal shafts were removed (Chu & Prausnitz, 2011). Materials used in polymer microneedles and corresponding fabrication process are summarized in Table 1.

Mechanical properties of polymer microneedles

Since polymer has weaker mechanical properties compared with metal, silicon, and glass, polymer microneedles require appropriate design to be inserted into the skin without breaking and bending. Successful insertion can be achieved by using needles with sharp tips, with sufficient mechanical strength, and with sufficient length to overcome skin deformation that occurs before insertion. In this section, the insertion and mechanical behavior of polymer microneedles are discussed.

Insertion of polymer microneedles

Insertion of polymer microneedles into skin has been investigated by the qualitative method using a penetration test into skin (Park et al., 2005) and the quantitative method measuring change in water evaporation from skin (Kalluri & Banga, 2011) and electrical resistance of skin (Lee et al., 2011a). To view microneedle penetration of the skin barrier, the staining of treated skin with dye has been used. Polymeric microneedles are put on the epidermis, pushed in by a predetermined force, and removed. Trypan blue does not stain the stratum corneum, but it will stain the viable epidermis (McAllister

Table 1. Material of polymer microneedle matrix and corresponding fabrication process.

Type of microneedle	Microneedle material	Fabrication method	Reference
Solid	1. SU-8	1. F2, F3, F4	1. Kim et al., 2004, Park et al., 2007b, Yoon et al., 2006, Choi et al., 2006
	2. Poly methyl meth-acrylate (PMMA)	2. F2	2. Moon et al., 2005
	3. Polycarbonate (PC)	3. F4	3. Jin et al., 2009, You et al., 2010
	4. Polyglycolic acid, polylactic acid, polylacticcoglycolic acid	4. F3, F4	4. Wang and Jeng, 2009, Park et al., 2005, Aoyagi et al., 2008, Kim et al., 2011a, Park et al., 2010, Choi et al., 2012
Biodegradable	1. Polyglycolic acid, polylactic acid, polylacticco glycolic acid	1. F4	1. Park et al., 2006, Kim et al., 2011a, Park et al., 2007a
Dissolving	1. Carboxy methyl cellulose	1. F5	1. Lee et al., 2008, Raphael et al., 2010
	2. Fibroin	2. F5	2. You et al., 2011
	3. Maltose	3. F3, F4	3. Kolli and Banga, 2008, Lee et al., 2011, Miyano et al., 2005
	4. Dextrin	4. F5	4. Ito et al., 2006a, Ito et al., 2006b, Ito et al., 2008a
	5. Dextran	5. F5	5. Ito et al., 2008c, Ito et al., 2008a, Fukushima et al., 2011
	6. Polyvinylpyrrolidone	6. F5	6. Sullivan et al., 2008, Sullivan et al., 2010, Chu et al., 2010, Chu and Prausnitz, 2011
	7. poly methylvinylethercoma-leic acid (PMVE/MA)	7. F5	7. Boehm et al., 2012, Garland et al., 2012
	8. Galactose	8. F5	8. Donnelly et al., 2009
	9. Chondroitin sulfate	9. F5	9. Ito et al., 2007, Ito et al., 2008b, Ito et al., 2008a, Fukushima et al., 2010, Ito et al., 2010b, Ito et al., 2010c, Ito et al., 2010a, Fukushima et al., 2011, Ito et al., 2011b
	10. Hyaluronic acid	10. F5	10. Matsuo et al., 2012b, Liu et al., 2012, Matsuo et al., 2012a
	11. Polyethylene glycol	11. F5	11. Park et al., 2007, Takano et al., 2009
	12. Polyvinylalcohol	12. F5	12. Chu et al., 2010, Chu and Prausnitz, 2011, Wendorf et al., 2011
Hollow	1. Polyoxymethylene	1. F4	1. Yung et al., 2012a
	2. Polymethymethacrylate	2. F2, F5	2. Moon and Lee, 2005, Mansoor et al., 2012
	3. Polyethylene glycol dimethacrylate	3. F1	3. Wang et al., 2009

et al., 2003). An optical photomicrograph of an array of blue dots on the skin shows Trypan blue transport through the skin via pathways created when polymeric microneedles were inserted into and then removed from skin. Quantitative measurement was performed by counting the number of blue dots and comparing them with the number of microneedles (Kim et al., 2012a).

The electrical resistance of the stratum corneum is much greater than the more aqueous deep tissues. The stratum corneum provides the largest resistance in the circuit. When the metal-coated-polymer microneedle penetrates the stratum corneum, the measured resistance drops suddenly. The recognition of insertion force is difficult because insertion force is too small to be measured by force-displacement station. The force, displacement, and electrical resistance data are then converted to identify insertion force by the drop in skin resistance. The insertion force is linearly dependent on the interfacial area for a range of 200–5000 μm^2 (Park et al., 2007b). The insertion force of polymer microneedles is a function of the needle tip angle in addition to the cross-sectional tip area of the microneedles (Aoyagi et al., 2008). The interaction between the solid polymer microneedles and the skin was discussed using finite element analysis, and the behavior of microneedle insertion was anticipated based on the mechanical properties of each skin layer (Kuo et al., 2011). The recovery of skin puncture holes was imaged regarding time after solid polymer microneedles were applied across human skin. The hole opening was closing, and after 30 min it was difficult to identify the opening (Park et al., 2010). Trans-epidermal water loss measurement (TEWL) was performed to study recovery of barrier function in solid maltose microneedle treated skin. TEWL values decreased considerably within the first 5 min and slowly reached base value over a period of 4 hr (Kalluri & Banga, 2011). Skin resealing of the holes generated by insertion of dissolving CMC microneedles was monitored by measuring the change in skin electrical impedance (Lee et al., 2011a). Holes in skin resealed quickly after insertion of non-dissolving microneedles as mentioned above; however, impedance of skin treated by dissolving microneedles did not return to pretreatment values over the 24 hr time scale of the study because the holes did not reseal as quickly after the use of dissolving microneedles (Lee et al., 2011a).

Mechanical failure of polymer microneedles

The mechanical behavior of microneedles was investigated by obtaining the force-displacement curve (Kim et al., 2012a, Lee et al., 2008). Upon needle failure, the

force dropped suddenly, and the force applied before dropping was interpreted as failure force. Failure force of polymer microneedles increased with base diameter and Young's modulus of polymer (Park et al., 2005). Failure by buckling can be anticipated by an equation that is a function of Young's modulus, length of microneedle, and diameter of bottom and top surfaces (Park et al., 2007b). Also, the mechanical strength of the microneedles could be weakened by the drug encapsulated in the microneedles because drugs are mechanically weaker than polymer (Park et al., 2006). Previous studies provide the analysis of expected failure force using an elastic buckling model for the specified geometries (Park et al., 2007; Lee et al., 2008; Park et al., 2008). For polymer microneedles with low Young's modulus and low aspect ratio, inelastic stability of intermediate-length and short columns should also be considered as the critical failure mode of tapered microneedles. The ratio of length to equivalent diameter should be considered as the critical factor determining the mechanical failure mode of polymer microneedles (Park & Prausnitz., 2010). Polymer microneedles with a low aspect ratio could provide added mechanical strength for mechanically weak biomaterials like cellulose (Lee et al., 2008). Finite element analysis was carried out to anticipate stress and deformation of microneedles when pressure is applied. ANSYS simulation was used and high stress was generated on the tip of the microneedles (Yung et al., 2012). By analyzing the slope of stress-strain curve, the relative mechanical strength of polymer microneedles could be evaluated, and this method could provide a guide for changes in mechanical strength of different kinds of needle material (Kim et al., 2012a, Lee et al., 2008).

Drug delivery property analysis

Solid (Type I) and hollow microneedles (Type V) are in combination with the external drug reservoir applied after creating microchannels in the skin. Drug delivery strategies with Type I or Type V of microneedles will be more affected by other factors rather than the properties of polymer microneedle matrix, for instance, the transport property of drug (Burton et al., 2011, Chien, 1992), the number or size of microneedles (Park et al., 2010, Badran et al., 2009), and the skin pore resealing (Milewski et al., 2010, Banga et al., 2009).

In addition to the skin insertion with micronized needle structure, drug loaded polymer microneedles (Type II, III, and IV) were designed to serve as drug reservoir themselves to replace the liquid formulation or skip the reconstitution. The materials of drug loaded microneedles are selected to have these two functions (skin insertion and drug reservoir) by considering mechanical and dissolution properties of the matrix. In this review, we confine our discussion to the short-term and the long-term delivery strategies in terms of releasing drugs loaded within polymer microneedles into the skin.

Short-term drug delivery

The first generation of dissolving microneedles was made of sugar molecules with the melting process. Maltose microneedles dissolved in 5 min after insertion into human hand skin (Miyano et al., 2005). Despite the quick dissolving of sugar microneedles due to higher water solubility, high temperature fabrication conditions (Miyano et al., 2005, Lee et al., 2011c) and crystallization after dehydration (Wright et al., 2002, Choi et al., 2012b) may be problematic in encapsulating biomolecules without losing structural integrity. To resolve problems with sugar microneedles, drug-loaded polymer microneedles have been fabricated from various kinds of water-soluble biocompatible polymers, such as carbohydrate-based polymer (Donnelly et al., 2011, Lee et al., 2008, Ito et al., 2006a, Ito et al., 2008a, Fukushima et al., 2010b, Ito et al., 2011a), natural proteins (Lee et al., 2008, You et al., 2011), and synthetic polymers with hydrophilic side groups (Sullivan et al., 2008, Chu et al., 2010, Donnelly et al., 2010, Garland et al., 2012a). These polymer microneedles provide the mechanical strength required for insertion into the skin and the dissolution property for release of the drug.

The higher molecular weight polymer can provide better mechanical properties with a longer polymerization backbone or high crosslinking density; however, it may need to absorb a greater amount of water to be fully expanded and dissolved in the skin (Lee et al., 2008). In contrast to the injection administering a liquid formulation, the release of a drug from polymer microneedles relies on the interstitial fluid in the skin. The release rate of the drug from microneedles can be enhanced by formulating the higher solubility of the microneedle matrix (Lee et al., 2011a) or increasing the surface area of microneedle structures (Raphael et al., 2010). Highly solubilizing polymers may be able to have the rapid swelling with a lesser amount of water or dissociation of the polymer chain network in which the diffusion of the drug will be facilitated (Park & Prausnitz, 2010).

Most water soluble polymer microneedles have demonstrated the pharmacological effect in a time scale of hours to days with the duration of microneedle insertion ranging from minutes to hours, which is longer time than the hypodermic injection but can be reasonable length of treatment depending on the type of application. Three methods were suggested for faster release of the drug from polymer microneedles: (1) fabricating microneedles out of material with higher solubility (2) fabricating smaller microneedles for greater surface area, or (3) loading the drug toward the tip of the microneedles. The mixture of high molecular weight polymer and small molecules such as trehalose (Lee et al., 2011a) or copolymer with two different kinds of monomers (Sullivan et al., 2008, Migalska et al., 2011) was formulated to provide the high strength and high solubilizing property of microneedles for the rapid delivery of biomolecules. As a geometrical approach, the more miniaturized structure of microneedles was demonstrated to facilitate the

dissolution of microneedles by enlarging the surface area with the design of thousands of short projections, in which the smaller microneedles can absorb the interstitial fluid well (Raphael et al., 2010). Another geometrical approach is the localization of active ingredients toward the tip of dissolving microneedles to minimize the loss of drug dose due to the incomplete insertion of microneedles (Chu & Prausnitz, 2011, Fukushima et al., 2011, Ito et al., 2011a). Recently, a new type of sugar dissolving microneedles were made out of a mixture of sucrose and trehalose by using low temperature dehydration methods (Martin et al., 2012) to avoid thermal degradation of drug by melting fabrication method used for the previous sugar microneedles.

In addition to the properties of the soluble polymer matrix, the molecular weight of the target drug and the fabrication process can also affect the delivery strategy. Ito et al. (2010a) demonstrated the effect of different molecular weights on drug absorption, suggesting that the lower bioavailability of the higher-molecular-weight FITC-dextran can be attributed to its decreased diffusion in the skin (Ito et al., 2010a). It was reported that mechanical strength and dissolution properties can be modified by pretreatment of fibroin solution and drug loading (You et al., 2011).

While the interstitial fluid is the key to the quick release of drug from dissolvable polymer microneedles, the rapid delivery can be achieved by hollow microneedles (Yung et al., 2012, Moon et al., 2005, Wang et al., 2009) which does not depend on the limited amount of the skin fluid. After the administered liquid formulation develops the pressure in the skin, the lymphatic vessel in the intradermal layer may control the pressure caused by infusion and provide the faster absorption route to the systemic circulation (Burton et al., 2011).

Long-term drug delivery

The sustained delivery has been pharmaceutically attractive in terms of maintaining the constant range of drug concentration in the body. The sustained delivery with drug loaded microneedles has been attempted by a few different approaches such as lowering the diffusion of drug with additional excipients or less soluble matrix (Park et al., 2006), encapsulating less soluble microparticles in a highly soluble microneedle matrix (Ito et al., 2007a, Donnelly et al., 2010, Kim et al., 2012a), adding the external drug reservoir after the insertion of microneedles (Kolli and Banga, 2008), and utilizing the backing layer of a microneedle patch as an additional drug depot (Lee et al., 2008, Garland et al., 2012a).

Biodegradable polymer microneedles encapsulating calcein were presented to investigate the release of the model drugs from microneedles (Park et al., 2006). PLGA microneedles demonstrated the rapid release of calcein within hours. CMC was added to calcein during encapsulation for reduced diffusion of calcein and PLA microparticles encapsulating calcein was encapsulated within microneedles for slower drug release over weeks.

The sustained release of insulin with a single microneedle was designed by mixing insulin with porous calcium silicate adsorbent and embedding insulin adsorbent particles within chondroitin sulfate matrix for the sustained hypoglycemic effect (Ito et al., 2007a). The plasma glucose level dropped rapidly until 1 h after the administration of a single insulin microneedle and was backed up to the pre-dose level at 3 h after administration, but a microneedle with silicate adsorbed insulin lowered the plasma glucose level slowly until up to 2 h after administration and showed the prolonged hypoglycemic effect until up to 8 h. Kim et al. designed polylactic-co-glycolic acid (PLGA) base microneedles containing hydrogel particles. Fluorescence tagged on the surface of the particles was detected for 3 days after *in vivo* insertion into hairless rats, suggesting that the fast and sustained delivery of a drug is possible by controlling the properties of microparticles and a biodegradable polymer matrix (Kim et al., 2012a).

The additional drug depot can be applied topically to achieve sustained release after the dissolution of the microneedle structure. Kolli et al. demonstrated the possibility of sustained release with the liquid patch applied after the dissolution of maltose microneedles (Kolli & Banga, 2008). Garland et al. (2012a) introduced the combination of dissolving microneedles and electrically assisted delivery (iontophoresis) for using the backing layer as the additional drug depot. While this combination method did not enhance the delivery of small molecular weight drugs, the delivery of proteins (insulin and BSA) was enhanced by more than two-fold order of magnitude. However, sustained release with an additional drug depot outside the skin layer may need to be evaluated further, considering the skin pore resealing process.

Dissolving microneedles with microparticles can be also utilized for the delivery of hydrophobic drugs and sequential co-delivery of hydrophobic and hydrophilic drugs. The hydrophobic model drug, Nile red, has been incorporated into PLGA nanoparticles, which were then encapsulated in a soluble polymer of PMVE/MA (Donnelly et al., 2010). Lipophilic tracers such as Dil and Cy5 were encapsulated in PLGA particles, which were then formulated with a PVP solution mixed with a hydrophilic drug (Ke et al., 2012).

Pharmacokinetics

The pharmacokinetic analysis will aid in designing not only drug loaded polymer microneedles but also the drug delivery strategy to improve therapeutic effect. Several kinds of drug and matrix materials have been reported up to date with pharmacokinetic analysis of drug loaded polymer microneedles. Table 2 summarizes the pharmacokinetics with peak time and bioavailability (or pharmacological effect) presented in studies using dissolving microneedles matrix from 2005 to thus far in 2012. The pharmacokinetic profile of the drug administered with dissolving microneedles will be determined by absorption, distribution, metabolism, and excretion (ADME) in the same way as other administration methods. The

Table 2. Summary of pharmacokinetics studies with dissolving microneedles since 2006.

Matrix (author)	No. of microneedles (dose)	Active drug	Animal	$T_{max\ or\ min^*}$	BA or RBA†	PA or RPA††
Dextrin (Ito et al., 2006a)	1 (1.0 IU/kg)	Insulin	Mouse			93%
Dextrin (Ito et al., 2006b)	1 (50 IU/kg)	Erythropoietin	Mouse	8 h	82.1%	
Chondroitin (Ito et al., 2007a)	1 (2.5 IU/kg)	Insulin and adsorbent insulin	Mouse	0.8 ± 0.1 and 2.1 ± 0.3 h*		
Chondroitin (Ito et al., 2007b)	1 (2300 IU/kg)	Erythropoietin	Rat	18 h		
Chondroitin (Ito et al., 2008b)	1 (1.0 IU/dog)	Insulin	Dog	1.38 ± 0.2 h*		99
Dextran, Chondroitin, and Dextrin (Ito et al., 2008a)	1 (100 IU/kg)	Low Molecular Weight Heparin	Rat	0.8 ± 0.1, 0.8 ± 0.1 and 2.1 ± 0.3 h*		97.7, 81.5, and 102.3%
Chondroitin and Dextran (Ito et al., 2008c)	1 (5000 IU/kg)	Interferon-α	Rat	1.2 ± 0.1 and 3.3 ± 0.3 h	117.8 and 79.7%†	
Chondroitin (Ito et al., 2010a)	1 (5 mg/kg)	10, 20, 40, and 70 kDa FITC-Dextran	Rat	0.67 ± 0.16, 1.67 ± 0.33, 10.25 ± 2.78 and 7.33 ± 2.33 h	99.4, 88.3, 45.7, and 16%	
Chondroitin (Fukushima et al., 2010b)	100 (3.3 and 6.7 IU/dog)	Insulin	Dog	54.0 ± 9.9 and 45.0 ± 6.1 min*	72.1 and 72.4%†	
Chondroitin (Ito et al., 2010c)	100 (1.73 IU for p-tip and 6.08 IU for f-tip)	Insulin	Rat	1.5 ± 0.2 and 1.7 ± 0.2 h*		9.2 ± 1.6 and 30.7 ± 1.8%††
CMC/ Trehalose (Lee et al., 2011a)	100 (164 ug/rat)	Human growth hormone	Rat	0.6 ± 0.2 h	71 ± 17%†	
Chondroitin (Fukushima et al., 2011)	100 (33.6 ug/rat)	Human growth hormone	Rat	15.0 ± 0 min	89.9 ± 10.0%	
PMVE/MA (Migalska et al., 2011)	121 (2.5 mg/rat)	Insulin	Rat	2.67 ± 0.58 h*		
Hyaluronate and dextran (Ito et al., 2011a)	225 (31.6 for h-DM and 24.1 ug/rat for d-DM)	Sumatriptan	Rat	0.13 ± 0.02 and 0.08 ± 0.00 h	100.7 ± 18.8 and 93.6 ± 10.2%	
Chondroitin (Ito et al., 2011b)	100 (29.9 ug/kg)	Leuprolein Acetate	Rat	15.0 ± 0 min	99.2 ± 2.6%†	
Hyaluronate (Katsumi et al., 2012)	190 (0.8 mg/kg)	Alendronate	Rat	0.28 ± 0.11 h	90 ± 14%	
Chondroitin (Ito et al., 2012)	225 (3–100 ug/chip)	Multiple kinds of compounds	Rat	0.1–3.1 h	38–95%	

* In the column, the value with no star means T_{max}. The vaule with star means T_{min}.
† In the column, dagger means RBA and no dagger means BA in the value.
†† In the column, double dagger means RPA and no double dagger value means PA in the value.
BA: Bioavailability, RBA: Relative bioavailability, PA: Pharmacological availability; RPA: Relative availability.

absorption kinetics may be influenced mainly by some parameters such as the total dose loaded within dissolvable microneedles, the dissolution rate of matrix material, and the molecular property of drug or the enzymatic degradation of drug in the skin.

When a higher dose was administered with a microneedle, the outcome was shown as a more enhanced effect such as lower (C_{min}) or higher (C_{max}) peak plasma level, indicating that the pharmacokinetic profile with dissolving microneedles can have dose dependency (Ito et al., 2007b, Ito et al., 2008b, Ito et al., 2008a). In some cases, the dose dependency of pharmacological activity can be exerted with a threshold effect of dosing such that only the higher dose can cause the significant increase of therapeutic effect (Ito et al., 2007b).

Although the available amount of water in vitro is significantly higher than in vivo skin conditions, in vitro release study can provide useful information for choosing the proper material for the therapeutic strategy with dissolving microneedles (Ito et al., 2006b, Lee et al., 2008, Ito et al., 2008c) and assess in vivo absorption in relation with the loss of drug by metabolic processes in the skin (Ito et al., 2011b); however, once dissolving microneedles are completely inserted into the skin without the loss of dose, the higher in vitro dissolution rate of the dissolving microneedle matrix may not be a key consideration to determine pharmacokinetic profile and bioavailability (Ito et al., 2006b, Ito et al., 2008a).

It was reported that insulin delivery into dogs with a single chondroitin sulfate microneedle can be described by the 1-compartment open model with first-order absorption process, and rate constants of both absorption ($7.59 \pm 3.93\ h^{-1}$) and elimination ($1.31 \pm 0.66\ h^{-1}$) are almost the same as the values of subcutaneous injection ($9.72 \pm 5.67\ h^{-1}$ and $1.60 \pm 0.45\ h^{-1}$, respectively) (Fukushima et al., 2010a). If absorption half-life (0.693/absorption rate constant) is shorter than elimination half-life as the most common situation, the decrease of the drug in the body is determined primarily by the disposition, which is the rate-limiting step. Therefore, this finding supports the view that biopharmaceuticals loaded dissolving microneedles may be able to replace the administration of subcutaneous injection and provide a quick administration method of drug by overcoming the skin barrier property, which will be absorption rate-limiting.

Bioavailability can be enhanced by the more complete dissolution of dissolving microneedles. It was demonstrated that the delivery of human growth hormone with CMC-based dissolving microneedles, suggesting that the loss of dose can be minimized by localizing the drug toward the tip of the microneedles or by the deeper insertion of the microneedles (Lee et al., 2011a). Ito et al. also addressed this issue by comparing the effect of partially (p-tip) and fully (f-tip) loaded insulin dissolving microneedles on hypoglycemic activity (Ito et al., 2010d).

It is probable that the absorption of drugs from dissolving microneedles into the systemic circulation is affected by other conditions such as the molecular property of the drug (Ito et al., 2010a), in vivo species differences in skin physiology (Fukushima et al., 2010b), and degradation of drug in the skin (Ito et al., 2011b). Proteins of less than approximately 5 kDa enter blood capillaries easily, but proteins with greater than 20 kDa are less able to traverse the capillary membrane to reach the blood via lymphatic vessels in the skin (Tozer & Rowland, 2006). Ito et al. suggested that hydrophilicity of drugs should be considered in relation to dissolution/release and absorption, indicating that a log *p* value less than 1.0 may be the criterion for selecting a good candidate for developing a transdermal drug delivery system with dissolving microneedles (Ito et al., 2012). It was suggested that the low bioavailability of subcutaneous injection and chondroitin dissolving microneedles may be due to the hydrolytic attack by enzyme in the skin (Ito et al., 2011b).

Applications

The development of transdermal drug delivery with microneedles has gained pharmaceutical interest extensively regarding the delivery of hydrophilic or macromolecular drugs, which has been known as practically impossible with the conventional passive type of transdermal patch system. The areas of transdermal drug delivery have been expanded increasingly with various designs of microneedles. Especially, drug loaded microneedles are dissolvable in the skin, providing attractive merits such as minimally invasive self-administration, localized treatment, and no creation of biohazardous sharp wastes. The applications of dissolving polymer microneedles have applied these advantages to the delivery of cosmetics, vaccines, and metabolism-regulating agents, which are summarized in Table 3.

Microneedle applications have extended the boundaries of cosmetics, such as scar removal and remodeling skin by collagen induction with the better effect than traditionally topical treatment. This area has been approached by stimulating skin cells and proliferating fibroblasts, mainly with solid microneedles (Kim et al., 2011, Fabbrocini et al., 2009) or by applying drugs into the locally created pathway to the epidermal layer after the insertion of solid microneedles (You et al., 2010) or by administering drugs with dissolving microneedles patch (Miyano et al., 2005, Lee et al., 2011c, Ito et al., 2010b). It is likely that this area may have a big size of market soon by combining microneedle technologies with the development of functional biomolecules involved in aging or metabolism of the skin.

The vaccination with dissolving microneedles has been investigated over recent years with the delivery of antigens to immunogenicity cells residing in the skin layer, bringing the immunogenicity comparable to intramuscular injection; influenza virus vaccine (Sullivan et al., 2010, Raphael et al., 2010, Kommareddy et al.,

Table 3. The applications of dissolving polymer microneedles.

	Active Ingredient
Cosmetics	Ascorbic acid (Ito et al., 2010b, Lee et al., 2011c)
Immunologicals	Influenza vaccine (Sullivan et al., 2010, Raphael et al., 2010, Matsuo et al., 2012, Kommareddy et al., 2012)
	Tetanus (Matsuo et al., 2012)
	Diphteria (Matsuo et al., 2012)
	Ovalbumin (Raphael et al., 2010, Matsuo et al., 2012, Naito et al., 2012)
Biopharmaceuticals (peptide, protein, nucleic acids)	Insulin (Ito et al., 2006a, Ito et al., 2007a, Ito et al., 2008b, Fukushima et al., 2010b, Ito et al., 2010d, Migalska et al., 2011)
	Erythropoietin (Ito et al., 2006b, Ito et al., 2007b)
	Interferon-α (Ito et al., 2008c)
	Heparin (Ito et al., 2008a)
	β-galactosidase (Sullivan et al., 2008, Martin et al., 2012)
	Lysozyme (Lee et al., 2008)
	Human growth hormone (Fukushima et al., 2011, Lee et al., 2011a)
	Leuprolide acetate (Ito et al., 2011b)
	Desmopressin (Fukushima et al., 2011)
	siRNA (Gonzalez-Gonzalez et al., 2010)
	P2CMVml-12 (Lee et al., 2011b)
Hydrophilic and small molecular weight drugs	Nicardine hydrochloride (Kolli and Banga, 2008)
	Theophylline (Donnelly et al., 2011, Garland et al., 2012a)
	Sumatriptan (Ito et al., 2011a)
	Alendronate (Katsumi et al., 2012)

2012), ovalbumin (Naito et al., 2012), tetanus, diphtheria, and malaria (Matsuo et al., 2012). In addition to the stimulation of cells involved in the skin immunological defense system, dissolving microneedles can prevent the reuse of biohazardous sharps that have caused the safety issue in global vaccination (Hauri et al., 2004) and improve logistic processes with the potentially enhanced stability of vaccines by formulating them in a solid structure (McNally & Hastedt, 2008).

As the most highlighting aspect of dissolving microneedles system, they can provide a self-administration method without the use of hypodermic needles. This feature will enable patients to have therapy with the simple administration regardless of their location, e.g. work place or vacation and provide less burden for the repetitive treatment of biopharmaceuticals as well as hydrophilic small molecules such as insulin, erythropoietin, growth hormone, leuprolide acetate, desmopressin, interferon, heparin, niacinamide, theophylline, sumatriptan, and alendronate as listed in Table 3. Nucleic acid delivery with dissolving microneedles has recently reported as one of gene delivery methods; however, the efficacy of gene delivery is significantly reduced by the lower cellular uptake, which may need the combination of other technologies, for instance, electroporation to generate pores on the cell surface temporarily (Lee et al., 2011b).

During fabrication, polymer microneedles are exposed to some degree of contamination and therefore they are sterilized. However, most polymeric microstructures are thermally unstable and an additional sterilization process should be considered for polymer microneedles. Recently, ethylene oxide gas and gamma ray radiation have been used for sterilizing microstructures (Ferrara et al., 2007), and these methods also can be utilized for sterilizing microneedles. In the case of formulated microneedles, the needle material and the active drug ingredient remain together in the skin. Thus, the biological safety of formulated microneedles should be evaluated according to the FDA's standards for materials remaining in the skin after insertion. After intradermal delivery, drugs can lose their bioavailability through dermal metabolism (Ando et al., 1997). Therefore, the dermal metabolism of the drug should be studied before preparation of formulated microneedles in order to ensure the correct use of the microneedles. The amount of drug available within the polymer microneedle matrix may also limit drug applications to doses in the microgram range. (Lee et al., 2008).

Only a few solid polymer microneedles are being manufactured commercially, and drug-loaded polymeric microneedles are still under development for commercial use. Several companies are developing formulation-based microneedles, and official information related to their development status is lacking. We list companies that are manufacturing polymer microneedles in Table 4.

Conclusion

Traditional transdermal drug delivery has been limited to small and moderately lipophilic drugs because of the skin barrier. Solid microneedles were designed to create the skin permeation route of hydrophilic macromolecules by mechanically puncturing micron-size holes. Formulated polymer microneedles surpass the previous generation of solid microneedles in terms of safety and mass production. In addition to these advantages, formulated polymer microneedles offer the benefits of manipulating the mechanical properties and the dissolution features of matrix material, which in the future can be adjusted to various delivery strategies for the most effective therapy of biopharmaceutical products.

Microneedle-based formulation have been developed to serve as new, more effective means for transdermal drug delivery and controlled release after insertion. High molecular drugs such as peptides and proteins are suitable candidates for formulation-based microneedles, and controlled release can be achieved by using appropriate polymers. Thus, the stability of model drugs should be studied in regard to fabrication process conditions and the temperature required to avoid loss of bioavailability. Microneedle-based formulations also should be studied and developed to achieve the desired release rate of drugs, both systemically and topically.

Table 4. Companies manufacturing polymer microneedles.

	Company (country)	Type (material)	Application
1	Corium (USA)	Solid and Hollow	Rapid and sustained delivery
2	Elegaphy (JPN)	Dissolving (Saccharide)	Medical or cosmetic
3	ImmuPatch (IRL)	Dissolving	Vaccine delivery
4	Micropoint Technologies (SIN)	Solid	Vaccine delivery and sampling
5	NanoVic (AUS)	Coating on Solid	Biopharmaceuticals transdermal delivery
6	Theraject (USA)	Dissolving (Carboxy-methyl-cellulose based)	Vaccine and protein delivery
7	B2Y (KOR)	Dissolving (Carboxy-methyl-cellulose based	Cosmetics
8	TransDerm (USA)	Dissolving (PVA)	Nucleic acid delivery
9	MITI SYSTEM (KOR)	Solid (Polycarbonate)	Cosmetics
10	CosMED Pharmaceuticals (JPN)	Dissolving (Hyaluronic Acid)	Cosmetics
11	3M (USA)	Solid and Hollow (Polycarbonate)	Cosmetics, medical application

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