Dissolving Microneedles for Transdermal Drug Delivery System

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Abstract. There is a remarkable interest in research on dissolving micromachined needles or dissolving microneedle (DM) for transdermal drug delivery (TDD) because the devices with DMs can deliver drugs without leaving potentially dangerous residues of sharps waste after use. DMs encapsulated medications into microneedles built by water-soluble materials. Both drugs and microneedles can dissolve into the human tissues after the needles insert the skin. This paper reviewed the DM technology, including the materials and pathway for TDD, manufacturing techniques, and facing challenges. The materials and the pathways for TDD are described. Micromachining technology has been employed to manufacture dissolving microneedles including micromolding, lithography, and the droplet-born air blowing. Moreover, their challenges are discussed as well. Finally, the development of DMs has been also prospected.

Keywords: Microneedles; Dissolving needles; BioMEMS; Transdermal drug delivery.

1. Introduction
At present, the injection by exploiting hypodermic needles is a major manner to transport biopharmaceuticals, with over 16 billion cases with injection in the world every year [1]. Nevertheless, since injection with needles can result in bleeding, pain, or needle phobia, the compliant with patients are problematic, let alone the other problems of safety. Therefore, exploring the riskless methods to substitute injection with needles has been pursued by many researchers [2,3]. Most recently, the characteristics of non-invasive and convenient transdermal drug delivery (TDD) to be a prevailing approach to release drugs locally to specific skin microenvironments. Furthermore, TDD can prevent first-pass metabolism and avoid gastrointestinal degradation. Transdermal drug delivery with patches is a substitutional approach for drug delivery due to avoid the tissue trauma and pain resulted from injections, improve patient compliance, and enhance bioavailability [4,5]. As for transdermal drug delivery, safety is important. Usually, a transdermal drug delivery system should be inexpensive and easy to use. Besides, a controlled amount of drugs is also essential to effectively treat an illness or prevent disease. Significantly, a broad range of therapeutics should overspread a wide range of therapeutic agents. The method with a transdermal patch is non-invasive. It is also easy to use and inexpensive. The permeation rate is infinitely increased even though some methods are adopted since the outmost layer of skin, stratum corneum, blocks the permeation of macromolecules. Thanks to the advances in MEMS [6,7], in order to remarkably increase the permeability of skin and enable the transportation of many therapeutics, the microneedle (MN) technology emerged to address the aforementioned problems to pierce the SC [8].
The concept of microneedle used to deliver drugs was dated to 1976 of the presentence of a patent [9]. The first microneedle was fabricated and demonstrated for TDD in the 1990s [8][10]. However, only during the last 20 years, MNs have been intensive studied [8]. It has been proved that microneedles can make most drugs suitable to drug delivery by piercing the obstacle of stratum corneum, the outmost layer of the human skin, thus producing a pathway for the drugs to permeate the dermal tissue below, as shown in Fig.1.

General speaking, according to whether loading drug or not, the MN can be classified into two categories of drug-unloaded and drug-loaded MN, namely, microneedles with no drug loading and microneedles with drug loading. The former include solid and hollow microneedles[11,12]. The latter involves coated [13] and dissolving MN (DM) [14].

![Microneedle-based transdermal drug delivery.](image)

**Figure 1.** Microneedle-based transdermal drug delivery.

### 2. Pathways of TDD by MNs

Up to date, there are four pathways to deliver drugs through microneedle-based techniques by employing (1) solid microneedles: penetrating the skin by solid microneedles followed by a patch at the focal [11]; (2) hollow microneedles: deliver drugs through the channels of microneedles by inserting hollow microneedles into the skin [12,15]. (3) coated microneedles: piecing the microneedles with coated drugs into the skin and then drugs dissolved in the tissue of the skin [13]; and (4) dissolving microneedles: inserting the dissolving needle combined with drugs into the skin for dissolution of drugs [12].

The coated microneedles draw researchers’ attention for transdermal drug delivery. It is easy to be realized for self-administration. Furthermore, coating drugs on microneedles can improve the stability of drugs, especially at room temperature. When using solid microneedles, the needles first penetrate the skin to form pores, and then the patch is applied to deliver drugs through the microchannels resulted from pores. Solid microneedles are just used to make micropores in the skin.

As for hollow MNs, unlike the solid MNs, the microchannels are the hollow space in the MNs comparison to solid MNs.

In order to verify rapid drug delivery, a coated microneedle emerged [13]. The coated microneedles, which are formed through coating the drug on the microneedle surface as a solid film, are used for attractive for self-administration with simple and rapid transport of high molecular weight drugs into the human skin [13]. The drug will release after the microneedles pierce into the skin. The feature of coated MNs is that the coated needle is easy to fabricate. Moreover, the patch with coated needles is convenient to use for sufferers. However, the coated microneedles may involve a safety problem and need handling the disposal of needles to leave sharp, biohazardous waste after use.

Among MNs, a dissolving microneedle (DM) attracted more attention. DMs probably are derived from coated microneedles. The coated microneedle is also a potential hazard to leave the broken needle tips. Compared with coated microneedles, the dissolving microneedles can entirely melt in the tissue of the skin and therefore avoid residues of waste during drug delivery. The materials of dissolving microneedles are water-soluble and biocompatible materials, for example, polymer. Generally, DMs usually have advantageous over the drug-unloaded needles, for example, silicon needles which the silicon microneedles is probably broken during inserting [16]. Moreover, the DM can be built for drug delivery. It is also inexpensive [17]. And what’s more, devices based on DMs are self-administered. It is not necessary for a trained person to handle drug delivery.
3. Fabrication

Although a variety of techniques have been used to produce DMs, most DM fabrication methods demand severe surroundings. Sometimes, the process may even result in the deterioration of drugs. An ideal fabrication approach should enable room-temperature processing and keep away from contact with biological or chemical reagents that can degrade drugs. Besides, the fabrication processes should be simple and no strict limit on manufacturing designs. Moreover, the fabrication of DM should be verified that the processes cannot damage integrity. The materials encapsulated drugs should be biocompatible and mechanically robust. It is important to leave no sharp, biohazardous waste after application. Currently, the most common fabrication method is micromoulding [18], which is made from the production of the mold of MNs and fabrication of MNs from dissolving materials. The other process of fabrication including are also exploited such as photopolymerization, lithography, and droplet-born air blowing techniques.

3.1. Micromoulding

Micromoulding is broadly utilized for making DMs [19], as depicted in Fig.2. It is easy to produce DMs through filling in the mold with a polymer solution and then drying or filling mold in molds with melted polymer and solidifying. After the micromould is accomplished (Fig.2 (a)), the micromould is filled with the concentrated polymer/antigen mixture solution(Fig.2 (b)). The filling is also implemented through employing spray. Following that, the backing solution is added after the centrifugation in order to make the PDMS cavities filled with the melted intermixture(Fig.2 (c)). The final step is peeled off after solidifying the mixture in the mold (Fig.2 (d)).

![Figure 2. The process of dissolving microneedles.](image)

3.2. Photopolymerization

A photopolymerization of the liquid mixture within the dissolving needle mold was developed to fabricate DM at room temperature. The ultraviolet light was employed to polymerize the monomeric vinylpyrrolidone. The polyvinylpyrrolidone(PVP) is water-soluble and physiologically compatible, therefore it is suitable for microneedle fabrication. Moreover, the polymer needed to be strong enough to endure the resisting force during inserting the skin. Meaningfully, the vinyl pyrrolidone monomer was full of molds without a biocompatible solvent due to the liquid being at room temperature. It is suitable to encapsulate thermolabile compounds. PVP may be created by combining vinyl pyrrolidone with azobisisobutyronitrile (AIBN). After that, the compound is poured into the previous mold (PDMS). Then, the microneedle mold was filled with the liquid mixture. Following that, the whole device was exposed by ultraviolet light at room temperature to accomplish photopolymerization. Finally, take the DM array out of the mold.

3.3. Lithography

Lithography is divided into drawing lithography and soft lithography. Drawing Lithography is one of the lithography techniques. This method is to deform the polymer through enlarging to build DM. The polymer is melted to be distributed on a bottom plate (fixed) and lengthened by stretching posts in another moving plate at the upper. Cooling is simultaneously carried out until the temperature is down to the glass transition temperature of the polymer, which the polymer viscosity is gradually increased. Lastly, a solid polymer was produced by the sustaining cooling, therefore, a DM with a suitable
strength was formed. Using this method, only a few polymer wastages were left owing to the polymer drops on the plate. Nevertheless, the suitable glass transition temperature is a strict condition for polymers because only a few of polymers meet this condition. Nevertheless, because the melting temperature of the thermolabile antigens is high and the glass transition temperatures in the process is also high, this method is not suitable for thermolabile antigens. The advantage of this method is no need for 3D molding since the needles can be cured and taken shape very quickly. Drawing lithography utilizes the viscosity of a polymer and the elastic deformation of polymers to build the 3D structure of MNs through stretching deformation.

DMs can be also produced in soft lithography. Firstly, after aligning a polymer to cavities of the mold, they are passed through a heated nip. Then, the mold full of the mixture is set on a water-soluble base. A DM array on the base is obtained after the mold is separated. Sometimes, heated nip can be also substituted by photocuring. This method has advantages such as low expense, good scalability, and short process time. Similarly to drawing lithography, soft lithography is not suitable for thermolabile antigens either, due to high melting and transition temperatures.

The droplet-born air blowing (DAB) method offers fast microneedle manufacture (<10 min) at low-temperature condition (4–25 °C) avoiding drug loss. Firstly, the drops of polymer and drug mixture are distributed on two plates respectively. The upper plate proceeds to the down direction. Consequently, the mixtures at two plates were in touch with one another. Afterward, the two plates are apart to space in about two DM lengths. Finally, the polymer mixtures were solidified and therefore yielding a DM array on both plates.

4. Results and Discussion
Presently, the research on DM technology encounters many obstacles, such as the selection of water-soluble and biocompatible materials, the severe fabrication conditions that restrict many drugs, the finite dose of drug delivery, mechanically robustness, and so on.

The robustness of DM is necessary to piece the outmost layer of the skin without breakage. The mechanical strength of DM is not only depended on the water-soluble materials to build microneedles, but also limited by the specific molecule being delivered.

The further development of fabrication techniques for DMs should focus the requirements including materials with water-suitable property, ability to produce various geometries of MNs, repeated manufacturing capability, the process at low temperature, low expense, short process time and ability of mass production. Generally speaking, the transporting dosage and rate are greatly influenced by the needle array arrangement, the MNs’ materials, and the geometries of the needle. These requirements comply with the need for reproduction and mass manufacture technologies. The future scope for DMs’ technology should be low cost, safety, versatility, reliability, and easy utilization.

The insufficient MNs’ insertion into the skin results from the skin deformation under tension and the weak mechanical strength of water-soluble excipients. The insufficient insertion force also lessens the performance of the system. Moreover, the patch with chemical materials may result in skin allergy; In addition, the adhering is problematic for joint and hairy skin.

5. Conclusion
The DM can furnish significant benefits such as dosage with high-precision, painless drug delivery, and no waste of biohazardous sharp medical waste. DMs’ technology also avoids the potential hazard of the broken tips of needle leaving in the tissue of skin. DMs’ technology for TDD is in the feature with controlled encapsulation and minimally invasive delivery of drugs.

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References
[1] Y.J.F. Hutin, A.M. Hauri and et al, Use of injections in healthcare settings worldwide, liter. Rev. & reg. est., 2000, BMJ 327: 1–5
[2] W. Li, R.N. Terry and et al. Rapidly separable microneedle patch for the sustained release of a contraceptive. Nature Biomedical Engineering, 2019, 3: 220-229.

[3] P.Y. Zhang, C. Dalton, G.A. Jullien. Design and Fabrication of MEMS-based Microneedle Arrays for Medical Applications. Microsystem Technologies 2009, 15(7): 1073 – 1082

[4] M.R. Prausnitz, R. Langer, Transdermal drug delivery, Nature Biotechnology, 2008, 26: 1261–1268

[5] B.W. Barry, Breaching the skin's barrier to drugs, Nat. Biotechnol. 2004, 22 (2): 165–167

[6] S. Gao, Y. Li and P.Y. Zhang, Analysis and Characterization of Compounded CMUTs for Medical Imaging and Therapy, Journal of Imaging Science and Technology, 2019, 63(3): 30402-1-30402-8(8)

[7] S. Gao, Y. Li, P.Y. Zhang, Model of compounded CMUTs for medical imaging and therapy, Basic & Clin. Phar. & tox., 2017, v121: 10-11

[8] P.Y. Zhang and G.A. Jullien, Micromachined needles for microbiological sample and drug delivery system. The 2003 International conference on MEMS, NANO and smart system, Banff, 20-23 July, P247-250

[9] K Lee, H Jung. Drawing lithography for microneedles: A review of fundamentals and biomedical applications. Biomaterials, 2012, 33(30): 7309-7326.

[10] P. Y. Zhang and G.A. Jullien, Microneedle arrays for drug delivery and fluid extraction. The International conference on MEMS, NANO and smart system, Banff, Alberta, Canada, 24-27 July, P392-395, 2005

[11] M. Witting, K. Obst, and et al. Feasibility study for intraepidermal delivery of proteins using a solid microneedle array. International Journal of Pharmaceutics 2015, 486(1–2): 52–58

[12] P.Y. Zhang, C. Dalton, G.A. Jullien. Design and Fabrication of MEMS-based Microneedle Arrays for Medical Applications. Microsystem Technologies 2009, 15(7): 1073 - 1082

[13] L Liang, Y Chen and et al. Optimization of dip-coating methods for the fabrication of coated microneedles for drug delivery, Journal of Drug Delivery Science and Technology 2020 55(2): 101464

[14] Y. Kapoor, M. Milewski, et al. Coated microneedles for transdermal delivery of a potent pharmaceutical peptide. Biomedical Microdevices 2020, 22: 7.

[15] C.Y. Meng, Y.Y. Miao, P.Y. Zhang, Modelling and analysis of drug pathway in tissues with a MEMS-based microneedle array, Basic & Clinical Pharmacology & Toxicology, 2019, v129: 10-11, 2019

[16] K J Lee, J Y Lee and et al. Microneedle drug eluting balloon for enhanced drug delivery to vascular tissue. Journal of Controlled Release, 2020, 321.

[17] B M Lee, C Lee and et al. Dissolving Microneedles for Rapid and Painless Local Anesthesia. Pharmaceutics, 2020, 12(4):366.

[18] T. Evens, O. Malek, et al. A novel method for producing solid polymer microneedles using laser ablated moulds in an injection moulding process. Manufacturing Letters, 2020, 24: 29-32

[19] S.C. Balmert, C. D. Carey and et al. Dissolving undercut microneedle arrays for multicomponent cutaneous vaccination, J. Cont. Rel. 2020,317(1): 336-346