Evolution of transdermal drug delivery devices and novel microneedle technologies: A historical perspective and review

Naveen Joshi[1], Sina Azizi Machekposhti[2], and Roger J Narayan[1,2]
[1]Department of Materials Science and Engineering, North Carolina State University, Raleigh, NC, USA 27695-7907 USA
[2]Joint Department of Biomedical Engineering at University of North Carolina and North Carolina State University, Raleigh, NC, USA 27695-7115 USA

Roger J Narayan
Joint Department of Biomedical Engineering
University of North Carolina and North Carolina State University
Raleigh, NC, USA 27695-7115 USA
Tel: +1 919 696 8488
E: roger_narayan@ncsu.edu; roger_narayan@unc.edu

Abstract

The history of transdermal drug delivery is as old as humankind. Transdermal drug delivery has undergone three generations of development; the third generation has involved the use of medical devices and instruments. This review provides a historical perspective on the primary approaches employed in the three generations of transdermal drug delivery. In addition, we explore some of the recently developed transdermal techniques that are deemed promising in the field of drug delivery. We discuss how advances in these techniques have led to devices for the delivery of a therapeutically effective amount of drug across human skin and highlight the limitations of the first- and second-generation drug delivery tools. As such, a review of the performance of these techniques and the toxicity of the devices used in transdermal drug delivery are considered. In the last section of the review, a discussion of the fabrication and operation of different types of microneedles is presented. The applications of microneedles in the sensing and delivery of various therapeutic agents are described in detail. Furthermore, an overview of the efficacy of microneedles as emerging tools for the controlled release of drugs is presented.

Keywords

3D printing, digital light processing, microneedles, transdermal drug delivery, two-photon polymerization

Introduction

Drug delivery through the skin is a growing focus of pharmaceutical research. The skin is the largest organ in humans, which provides a protective barrier against water loss, injury, and infection (Sabbagh & Kim, 2022). The surface area of the skin in the adult is between 1.5 and 2.0 m^2. The epidermis, dermis, and hypodermis are the three main layers of the skin. The dermis is composed of sweat glands, nerve endings, hair follicles, and lymphatic vessels. It is approximately 3-5 mm thick. The epidermis is the outer layer of human skin that exhibits a thickness of 60-800 μm; the uppermost sub-layer of the epidermis is known as the stratum corneum. The stratum corneum, with a thickness of 10-20 μm, serves as a barrier to water loss and the movement of external materials into the body (Chien, 1991). Fig. 1 shows a cross-sectional schematic of the human skin.

Transdermal drug delivery is being investigated as an alternative to conventional oral drug delivery and intravenous injection methods. It has been common practice for thousands of years to apply substances or plants to the skin; for instance, a wide range of formulations have been prepared for localized treatment. For example, the use of salves, plants, minerals, or animal extract patches was popular in ancient Babylonian and Egyptian medicine around 3000 BC (Geller, 2010; Magner & Kim, 2017; Pastore, Kalia, Horstmann, & Roberts, 2015). Topical therapies were placed on the skin by bandaging and rubbing as described on Sumerian clay tablets (Kramer, 1963). An ochre-rich mixture was liquefied for use as skin protection and decoration in Blombos Cave in South Africa approximately 100,000 years ago (Henshilwood et al., 2011; Pastore et al., 2015). Natural oils (e.g., olive, castor, and sesame oil), animal fats, perfumes (e.g., peppermint, bitter almond, and rosemary), unguents, creams, pomades, rouges, powders were used by ancient people for cosmetic or dermatological purposes (Forbes, 1965). Several hundred drugs were mentioned in the *Papyrus Eber*, which dates to 1550 BC. It has helpful information on treating wounds, blisters, and exudation (Packard, 1927). Transdermal drug delivery approaches were described by well-known individuals such as Galen (AD 129-199) and Ibn Sina (AD 980-1037). Galen, the father of pharmacy, made a cold cream with similar use as current products (Bender & Thom, 1966). Ibn Sina showed

that each topical drug has soft and hard forms. The soft form can penetrate the skin layers; the hard form was applied on top of the skin. Moreover, he suggested that the penetrated portion would reach systematic circulation. As an example, he mixed sulfur and tar and made a plaster-like formulation for treating sciatica (Moghimi, Shafizade, & Kamlinejad, 2011; Pastore et al., 2015). Several new transdermal products have been developed for delivering a greater number of pharmaceutical ingredients. A three-day scopolamine patch for treating motion sickness was the first systemic delivery in 1979 in the United States. Nicotine patches were subsequently approved for use. Nowadays, the number of medicinal patches for transdermal drug delivery is increasing. A new patch was approved every 2.2 years between 1979 and 2002, and this value increased to one new patch every 7.5 months from 2003 to 2007; this number continues to increase (Guy & Hadgraft, 2003; M. R. Prausnitz & Langer, 2008; M. R. Prausnitz, Mitragotri, & Langer, 2004; Wester & Maibach, 1993; Williams, 2003).

Each drug administration route has its own advantages and disadvantages. For example, the oral route is pain-free and convenient; however, many types of drugs are metabolized in the liver before entering the systemic circulation. In contrast, transdermal delivery is often associated with pain-free delivery and a low probability of complications. In addition, transdermal drug delivery provides the controlled release of drugs over an extended period of time (Machekposhti, Soltani, Najafizadeh, Ebrahimi, & Chen, 2017). One of the most important challenges of the transdermal drug delivery method is the limited number of drugs that can be delivered (M. Prausnitz, 2016). Some of the most common advantages and disadvantages of various transdermal drug delivery systems are listed in Table 1.

Transdermal drug delivery systems have been placed in three generations. The first generation considered the delivery of drugs that are able to cross the skin with little enhancement or an absence of enhancement. The second generation aimed to deliver small molecules by increasing the permeability of the skin through the use of driving forces. The third generation aimed to deliver macromolecules and vaccines across the stratum corneum layer using thermal ablation, electroporation, cavitational ultrasound, microdermabrasion, and microneedles (M. R. Prausnitz & Langer, 2008). In this review, we discuss the important approaches

employed in the three generations of transdermal drug delivery. Furthermore, we explore some promising approaches for transdermal delivery. In addition, we consider how microneedles can be manufactured using 3D printing methods.

First generation transdermal drug delivery

Transdermal drug delivery systems were first developed from herbal plants and progressed to the current patch technology. The formulations in this generation, which include ointments, creams, sprays, gels, or patches, must be sufficiently low-molecular-weight, lipophilic, and effective at low doses. Due to these factors, there is a limited number of drugs that can be delivered through the skin. For example, drugs that are lipophilic are capable of crossing the stratum corneum and reaching the capillary bed at a slow rate (M. R. Prausnitz & Langer, 2008).

Second generation transdermal drug delivery

The purpose of the second generation of transdermal drug delivery is to increase skin permeability by temporarily disrupting the function of the stratum corneum in order to allow drugs to cross it. This generation involves the use of different enhancements that do not damage the dermis. Conventional chemical enhancement, iontophoresis, and non-cavitational ultrasound are three approaches associated with this generation (M. R. Prausnitz & Langer, 2008; M. R. Prausnitz et al., 2004; Williams, 2003). Conventional chemical enhancers modulate epidermal lipid biosynthesis, which enhances drug delivery (Tsai et al., 1996). Amphiphilic molecules or solvents and surfactants disrupt the intracellular lipids of the stratum corneum by disorganizing molecular packing or extracting lipids. Conventional chemical enhancers can be used to deliver small molecules; however, these materials have limitations in terms of delivering hydrophilic macromolecules. The other approaches involve adding a cleavable chemical group (e.g., esters or carbonates) to the drug to enhance the lipophilicity of the drug. One advantage of this approach is that it is not associated with skin irritation (Kiptoo, Hamad, Crooks, & Stinchcomb, 2006).

Iontophoresis involves the application of a constant low voltage electric current on the skin that increases the delivery rate of ionized molecules or drugs (Banga, Bose, & Ghosh, 1999); the principle of charge repulsion is the basis of this approach. For example, if there is interest in delivering a positively charged drug, then the positively charged drug needs to be dissolved in the electrolyte with the same polarity(Wang, Thakur, Fan, & Michniak, 2005). The use of electrical energy to increase the penetration of an electrically charged compound is known as iontophoresis (Green, Flanagan, Shroot, & Guy, 1993). The amount of delivered drug can be adjusted by the amount of the current that is applied; this approach may be used for the transdermal delivery of peptides and oligonucleotides (Banga et al., 1999; Green, 1996).

The other member of the second generation of transdermal drug delivery is non-cavitational ultrasound. Fellinger and Schmidt showed that ultrasound was able to facilitate the movement of hydrocortisone ointment across an avascular membrane in 1950 (K. Fellinger, 1954). An ultrasound device was approved by the US Food and Drug Administration in 2004 for local dermal anesthesia with lidocaine (Azagury, Khoury, Enden, & Kost, 2014). Ultrasound pressure waves, which are too high in frequency for the human ear, disrupt the stratum corneum lipid structure and increase the skin permeability for small and lipophilic compounds.

Third generation transdermal drug delivery

This generation of transdermal drug delivery aims to deliver vaccines, proteins, and macromolecules across the stratum corneum layer. This strategy involves enhancing the rate of drug delivery while protecting the deeper layers of the skin from injury. Technologies associated with this generation include electroporation, microdermabrasion, thermal ablation, cavitational ultrasound, and microneedle-based delivery (M. Prausnitz et al., 2008; M. R. Prausnitz & Langer, 2008).

Electroporation is also considered a third generation transdermal drug delivery approach (Pliquett, Langer, & Weaver, 1995; M. R. Prausnitz, Bose, Langer, & Weaver, 1993). Electroporation uses high voltage pulses in a short period of time to disrupt the skin lipid bilayer. This disruption process makes pathways for small molecule drugs, vaccines, peptides, and DNA to be delivered (Denet, Vanbever, & Préat, 2004; Li, Chang,

& Teissie, 2008). Since the stratum corneum has much more electrical resistance than other layers, most of the electric current concentrates in this layer and thus does not affect the deeper layers (Pliquett & Weaver, 2007). After the disruption of the stratum corneum lipid bilayer by the electric current, the electrical resistance of the stratum corneum drops rapidly, which can lead to injury of deeper layers. The closer the probes are, the less risk of injury in the deeper layers (Pliquett & Weaver, 2007). This technology is widely used for animal studies; due to the complexity of this technology, its use in humans is limited (M. R. Prausnitz & Langer, 2008).

Cavitational ultrasound involves the production of cavitational bubbles with exposure to ultrasound energy (Leighton, 2012). The cavitational bubbles can enable targeted effects and enhance transdermal drug delivery (Ogura, Paliwal, & Mitragotri, 2008; M. R. Prausnitz & Langer, 2008). Since cavitational bubbles in the dense stratum corneum cannot grow, they collapse and form shock waves. These shock waves facilitate the movement of the drug across the stratum corneum (Paliwal, Menon, & Mitragotri, 2006; M. R. Prausnitz & Langer, 2008). Park et al. showed that cavitational bubbles improve skin permeability by increasing cavitational activities over the range of frequency higher than 1 MHz (D. Park et al., 2012). In another study, Park et al. demonstrated the delivery of fluorescein isothiocyanate-dextran to a depth of 500 μm via sonophoresis with cavitation (Liao, Ma, Wang, & Yeh, 2016; D. Park, Park, Seo, & Lee, 2014; D. Park et al., 2019).

Thermal ablation generates heat of hundreds of degrees in microseconds to milliseconds; the short heat duration limits the heat from transferring to the tissues below (Bramson et al., 2003; Levin et al., 2005). The high temperature in the stratum corneum vaporizes the aqueous part of the stratum corneum and makes paths for transdermal drug delivery. The temperature generated in the stratum corneum must be higher than the water boiling point for it to be vaporized (J.-H. Park, Lee, Kim, & Prausnitz, 2008). Thermal ablation creates a microscale channel through the stratum corneum, which may be used to deliver drugs or vaccines (Arora, Prausnitz, & Mitragotri, 2008).

Microdermabrasion involves the degradation of the stratum corneum and other skin layers in an effort to increase skin permeability. Previous studies demonstrate that micrometer-scale abrasion results in higher rates of drug delivery (M. R. Prausnitz & Langer, 2008). The microdermabrasion method is able to remove layers of the epidermis beyond the stratum corneum to enhance the drug delivery rate (Andrews, Lee, Choi, & Prausnitz, 2011). Insulin, lidocaine, and 5-fluorouracil have been delivered by microdermabrasion of the skin (Herndon, Gonzalez, Gowrishankar, Anderson, & Weaver, 2004). A vaccine delivery can also be facilitated by microdermabrasion (Glenn et al., 2007).

Microneedles are micrometer-scale needle-shaped structures that can be used to deliver drugs or vaccines through the skin. Microneedles are painless because they have minimal or no interaction with nerve endings in the papillary dermis (Henry, McAllister, Allen, & Prausnitz, 1998). These devices make paths through the epidermis to facilitate transdermal drug or vaccine delivery. Both biodegradable and non-biodegradable types of microneedles have been evaluated. Non-biodegradable microneedles are fabricated from non-biodegradable materials by conventional subtractive or 3D printing (additive manufacturing) techniques. Solid non-biodegradable microneedles have been processed out of several types of materials, including silicon (McAllister et al., 2003), various types of epoxies (Ami, Tachikawa, Takano, & Miki, 2011; Fernández et al., 2009; J.-H. Park, Yoon, Choi, Prausnitz, & Allen, 2007), and polymethylmethacrylate (PMMA) (Moon, Lee, Lee, & Kwon, 2005). Non-biodegradable microneedles can be created with hollow and solid geometries; biodegradable microneedles have been created with solid geometries. Figure 2 contains a schematic that shows all three types of microneedles. Solid microneedles create pores in the skin; drugs can enter deeper layers of the skin via these microneedle-generated pores. When exposed to the aqueous environment of the human skin, the coating carrying the medication in drug-coated microneedles releases. In drug-coated microneedles, the coating carrying the drug is dissolved when it comes in contact with the aqueous environment of the human skin. In non-biodegradable hollow microneedles, drugs delivered via pressure- or diffusion-driven flow. Dissolving microneedles break down on exposure to the

aqueous environment within the skin, releasing both the biodegradable polymer and drug within the skin (Kim, Park, & Prausnitz, 2012).

Non-biodegradable microneedles can be produced in hollow and solid formats. The solid microneedles can be used to make channels in the stratum corneum; a topical solution containing the drug can be applied to the microneedle-perforated skin. Drugs can be used in the form of an ointment, cream, gel, or lotion; the drug-containing formulation will penetrate deeper skin layers through the perforations (Kim et al., 2012). Alternately, the drug can be coated on the microneedle; during skin penetration, the microneedle will carry the drug to deeper layers of the skin (Gill & Prausnitz, 2007). Silicon microneedles have been fabricated via a reactive ion etching; these devices were used to increase the permeability of a model drug, calcein, in human skin (Henry et al., 1998). Metallic microneedles are fabricated via 3D laser ablation (Omatsu et al., 2010), laser cutting (Davis, Martanto, Allen, & Prausnitz, 2005), and wet etching (Matriano et al., 2002). In another study, microneedle patches with 57 microneedles were coated with the photodynamic therapy agent using a micro-precision dip coater. The 5-aminolevulinic acid delivered via the microneedles was shown to reach deeper regions of the skin than via topical application in an in vivo dermal model (Jain, Lee, & Gill, 2016). It should be noted that non-biodegradable microneedles are associated with the generation of hazardous waste.

Hollow microneedles are useful for drug or vaccine delivery by diffusion or pressure-driven flow (Lee et al., 2018). There is no device-related upper limit to the amount of drug that can be delivered using hollow microneedles. Moreover, the drugs used with hollow microneedles can be in liquid form; there is no need to solidify drugs that are distributed in liquid form for use with hollow microneedle devices. This type of microneedle is used in the same manner as conventional hypodermic syringes (Kevin Ita, 2015). Another use of hollow microneedles is the acquisition of interstitial fluid for biosensing by a sensor (Joshi, Riley, Mishra, Azizi Machekposhti, & Narayan, 2022; Miller, Narayan, & Polsky, 2016; Sanjay et al., 2018). Hollow microneedles have the potential to extract a precise volume of interstitial fluid for biosensing applications (Bhatnagar, Dave, & Venuganti, 2017).

Biodegradable microneedles are available in both solid and hollow forms. One technical challenge with biodegradable microneedles involves making devices with sufficient fracture resistance to pierce the stratum corneum without fracture (Narayan, 2014). Polymeric microneedles are usually fabricated using the micromolding technique; water evaporation, ultraviolet light curing, and heat curing are often used to create the solid microneedle device from the liquid precursor. Carboxymethyl cellulose (CMC), Gantrez® AN material (R. D. Boehm et al., 2012), fibroin (You, Chang, Ju, & Pak, 2011), dextrin (Ito, Hagiwara, Saeki, Sugioka, & Takada, 2006), dextran (Fukushima et al., 2011), chitosan (Chen, Ling, Lai, & Pramudityo, 2012), poly methylvinyl ether (PMVE) (McCrudden et al., 2014), polylactic-co-glycolic acid (PLGA) (He, Yang, Zhao, Zhang, & Gao, 2020), and poly glycolic-acid (PGA) (J.-H. Park et al., 2007) are commonly solidified by drying or water evaporation. Polyethylene glycol diacrylate (PEGDA) (Takahashi, Heo, & Shimoyama, 2017) and polylactic acid (PLA) (J.-H. Park, Allen, & Prausnitz, 2005) resins containing a photo-initiator are cured using ultraviolet light. Polyvinylpyrrolidone (PVP) (Machekposhti et al., 2017) is mixed with thermo-initiator that is solidified by heating at 60^{o}C for five hours. Water evaporation during microneedle manufacturing may be accelerated by the use of a vacuum pump or centrifugation (Kim et al., 2012). Heat or ultraviolet light curing methods are faster, but may negatively affect the drug structure. In the fabrication process, drugs be altered through interactions with reactive monomers, photoinitiators, high temperatures, or ultraviolet light (Jung & Jin, 2021; van der Maaden, Jiskoot, & Bouwstra, 2012). Another approach for loading a drug on a biodegradable microneedle involves the use of a coating process; however, the total volume of drug that can be incorporated within a microneedle via a coating process is limited (Bariya, Gohel, Mehta, & Sharma, 2012).

Emerging transdermal drug delivery tools

Advances in transdermal drug delivery technology have made it possible to deliver a therapeutic amount of a drug across human skin. Several device-based transdermal delivery techniques have been demonstrated (Ramadon, McCrudden, Courtenay, & Donnelly, 2022). For example, Quyang et al. explored the efficiency of a triboelectric nanogenerator (TENG) as a miniaturized transdermal device to activate iontophoresis

treatment for an enhancement in drug delivery efficiency [(Ouyang et al., 2019)]. Figure 3 shows the schematic of the drug delivery technology consisting of transdermal patch electrodes, the TENG, and a power management circuit. In another study, Arunprasert et al. described the use of nanostructured lipid carriers-embedded transdermal patches, which were used for the delivery of capsaicin (Arunprasert et al., 2022).

Similarly, the use of microparticles and quantum dot nanostructures is also being explored as tools for transdermal drug delivery. For example, Tadros et al. described the use of STAR particles (star-shaped metallic particles with micron-scale projections designed to penetrate the skin) as a straightforward transdermal technique for the delivery of a wide range of drugs (Tadros et al., 2020). They show that the efficiency of the fluorouracil drug delivered through STAR particles is enhanced, preventing the growth of subcutaneous melanoma and prolonging the life of mice. Roy et al. described the use of a thermoresponsive polymeric composite film made up of carbon quantum dots and cyclodextrin as a non-toxic and fluorescent transdermal drug carrier with improved penetration functionality (Roy et al., 2020).

Microneedles have emerged as attractive transdermal drug delivery devices because of their capability for sustained drug release and sensing. For example, Shukla et al. reported the design of a disposable microneedle device for interstitial fluid (ISF) extraction as well as the monitoring of lactate, glucose, and potassium ions (Shukla, Machekposhti, Joshi, Joshi, & Narayan, 2023). A detailed review on the various types of microneedles and microneedle fabrication methods is given in the subsequent sections.

3D printing of solid microneedles

Inkjet printing: Inkjet printing is an additive manufacturing technique that has been used in the printing of solid microneedles. This technique reproduces images on a substrate by ejecting the ink as droplets to predetermined positions (Singh, Haverinen, Dhagat, & Jabbour, 2010). Inkjet printing is widely explored as a key bioprinting technique because of its low cost, high speed, and high throughput. Based on the process of generating droplets, inkjet printing can be classified as continuous inkjet printing (CIJ) and drop-

on-demand printing (DOD); the DOD inkjet printing approach is primarily used for biomedical and pharmaceutical applications (Azizi Machekposhti, Movahed, & Narayan, 2020). It has been demonstrated that piezoelectric inkjet printing can be used to load gauze with antibacterial and antifungal pharmacologic agents that are difficult to dissolve in aqueous solutions for treating mixed wounds (Azizi Machekposhti et al., 2021). Boehm et al. fabricated biodegradable acid copolymer microneedles via visible light dynamic mask micro-stereolithography-micromolding and subsequent inkjet printing (R. Boehm, Miller, Hayes, Monteiro-Riviere, & Narayan, 2011). Figure 4 shows the SEM images of the as-grown and quantum dot coated-Gantrez® microneedles prepared by the combination of visible light dynamic mask micro-stereolithography-micromolding and subsequent inkjet printing; this study indicated the versatility of this combination approach for fabricating loaded microneedles. By combining inkjet printing with micromolding, they demonstrated the possibility of fabricating solid microneedles with controlled size and composition. Another study used inkjet printing to apply insulin-containing layers to metal microneedles for transdermal delivery (Ross, Scoutaris, Lamprou, Mallinson, & Douroumis, 2015). Surface analysis of the printed layers revealed homogeneous and uniform layers; no defects were noted. They demonstrated rapid insulin release rates from the printed surface, implying inkjet printing is an effective approach for the transdermal delivery of insulin in the solid state. In another study, Uddin et al. used inkjet printing in order to coat metal microneedle arrays with antineoplastic agents for transdermal delivery. They found that inkjet printing performance depends on the applied voltage, nozzle size, and the duration of the pulse (Uddin et al., 2015).

Two-photon polymerization: Two-photon polymerization is an additive manufacturing technique that has been utilized to fabricate hollow microneedles with a variety of geometries. The absorption energy associated with a single photon of ultraviolet (UV) light and the absorption energy associated with two photons of near infrared (NIR) light are shown in Figure 5. It is a technique that enables the fabrication of three-dimensional (3D) structures from computer-aided design models; structures with features below 100 nm can be prepared using this approach (Faraji Rad, Prewett, & Davies, 2021). It is thus possible to fabricate

complex microneedle structures in a straightforward and reliable manner that cannot be achieved by conventional manufacturing methods such as photolithography, etching, and injection molding. Faraji Rad et al. fabricated microneedles via two-photon polymerization; the arrays were successfully penetrated into rabbit ears without fracture (Faraji Rad et al., 2021). Another study used two-photon polymerization and micromolding to create dissolving microneedle arrays containing complex undercut features; the microneedle tips were coated with an adjuvant vaccine component (Faraji Rad et al., 2021). Plamadeala et al. developed pyramidal microneedle arrays that replicated the features of insect anatomy, which allow for the passive transportation of liquid on the microneedle lateral surface (Plamadeala et al., 2020). It should be noted that the slow writing speed and high operational costs limit the large-scale commercial application of two-photon polymerization technique for 3D printing of biomedical devices. Rad et al. suggest that it is feasible to mass-produce low-cost microneedle patches for application in theranostics and immunization at the point of care (Faraji Rad et al., 2021). However, improvements to the throughput of two-photon polymerization may be needed to clinically translate this approach in a cost-effective manner.

Digital Light Processing: Digital light processing is a resin-based 3D printing technique that employs light to cure resin through a projector in a layer-by-layer manner according to a computer model. The use of a projector enables the curing of a full layer each time, allowing for faster print times as compared to other 3D printing techniques (Zhang, Hu, Wang, Tao, & Gou, 2020). Digital light processing is being investigated for the production of hollow microneedles because it can produce high-resolution structures more quickly than traditional stereolithography methods (Economidou, Lamprou, & Douroumis, 2018). Mathew et al. showed that microneedle arrays fabricated via digital light processing could sustain a load up to 300 N (Mathew, Pitzanti, Gomes dos Santos, & Lamprou, 2021). In another study, Yao et al. reported on the fabrication of biocompatible microneedles via a high-precision digital light processing method (Yao et al., 2019). They showed that the stiffness of the microneedles can be controlled by optimizing the printing parameters. Similarly, digital light processing was used for 3D structuring of protein-based microneedles (Shin & Hyun, 2021). This study reported a facile technique to develop a 3D protein structure in an aqueous

solution through digital light processing, which was difficult to fabricate through other 3D printing techniques. Sachan et al. reported on the fabrication of solid microneedle arrays using 3D printing and digital light processing technologies; they demonstrated that the microneedles successfully penetrated human skin (Sachan et al., 2021). Their study indicates that digital light processing may be a feasible approach for the manufacture of polytetrafluoroethylene-based microneedles and other medical devices. Figure 6 shows the images of hollow polymer microneedle arrays manufactured through a digital light processing technique for use in a point-of-care system. The microneedles were used for the extraction of interstitial fluid and the detection of glucose, lactate, and K^+ ions in ex vivo porcine skin [86].

Conclusions

This review paper describes the history of transdermal drug delivery and the development of the field. Three generations of transdermal drug delivery were considered. The developments associated with the three generations of transdermal drug delivery as well as applications of relevant technologies were described. Emergent transdermal drug delivery techniques are discussed with a detailed review of the functionality and methods of fabrication of microneedles. As such, the features of each technique were critically evaluated for different types of microneedles. Material properties and printing resolution are the two key factors that play a vital role in the performance of microneedles. In this regard, 3D printing technology is emerging as an important solution for developing clinically useful microneedles. 3D printing-based prototyping and manufacturing methods enable the versatile production of microneedles with shape complexity and the capability for mass manufacturing. The various techniques described in this review highlight the diverse applications of 3D printing technology in the production and development of microneedles. Due to the benefits of 3D printing technologies, we anticipate that these techniques will be of significant importance for clinical manufacturing of microneedles and other patient-customized drug delivery systems in the near future.

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This review paper has no associated datasets.

This review only cites already published human or animal studies.

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Table 1. Advantages and disadvantages associated with transdermal drug delivery approaches. Reprinted with permission (Sabbagh & Kim, 2022) .

Advantages	**Disadvantages**
Convenience	High cost
Steady infusion	Local irritation
Stable blood levels	Low permeability limits
Self-administration	No rapid drug release
Flexibility of termination	Variation in barrier function
Improved patient compliance	Molecular size restriction

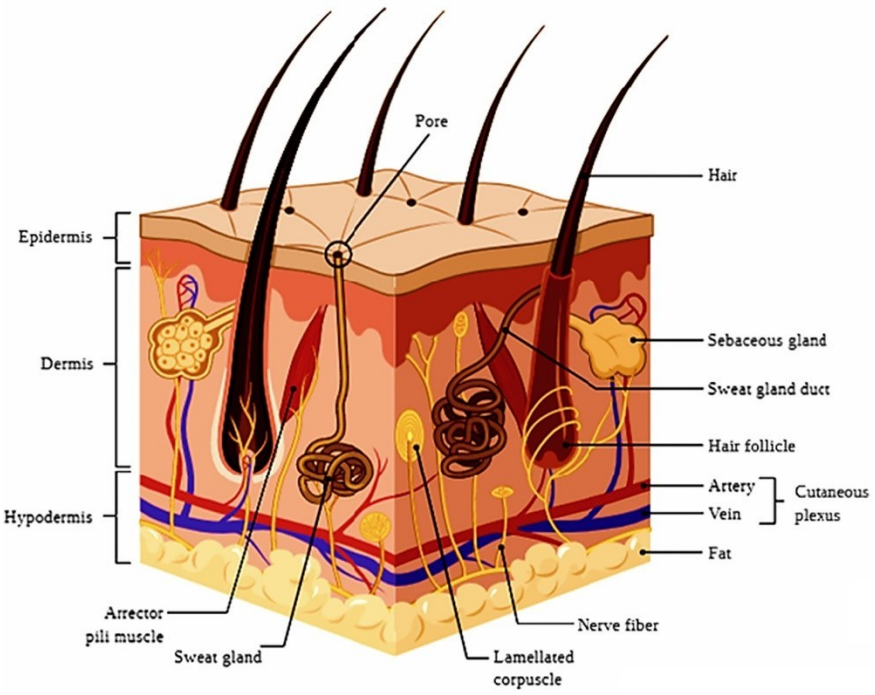

Fig. 1. **Cross-section of human skin.** Histological layers of the skin, including epidermis, dermis, and hypodermis are shown in the figure. Reprinted with permission (Sabbagh & Kim, 2022).

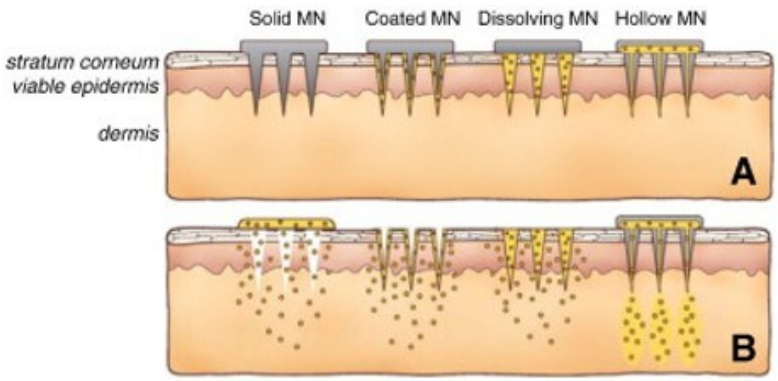

Fig. 2. **Various types and methods of drug delivery to the skin using microneedles.** (A) Microneedles are applied to the skin, and (B) used for drug delivery. Solid microneedles (solid MN) are used as a pretreatment, after which the drug in a topical formulation moves through pores in the skin. After insertion of drug-coated microneedles into the skin, the coating dissolves in the aqueous environment of the skin (coated MN). Drug-loaded microneedles are made of water-soluble or biodegradable materials that encapsulate the drug; the drug is released in the skin upon microneedle dissolution (dissolving MN). Hollow microneedles are used to inject liquid formulations containing the drug into the skin (hollow MN). Reprinted with permission (Kim et al., 2012).

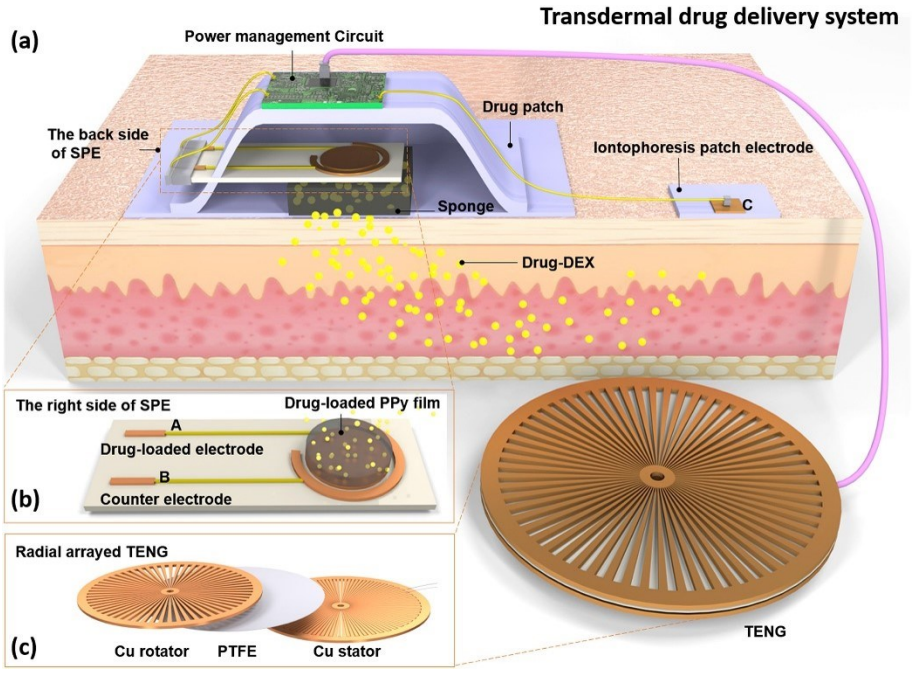

Fig. 3. **Schematic illustration of the self-powered, on-demand transdermal drug delivery system.** The system includes (a) transdermal patches, a triboelectric nanogenerator (TENG), and a power management circuit, (b) screen-printed electrode, showing the mechanism of drug release when the TENG is operated to power electrodes A and B, as well as (c) the radial-arrayed rotary TENG. Reprinted with permission (Ouyang et al., 2019).

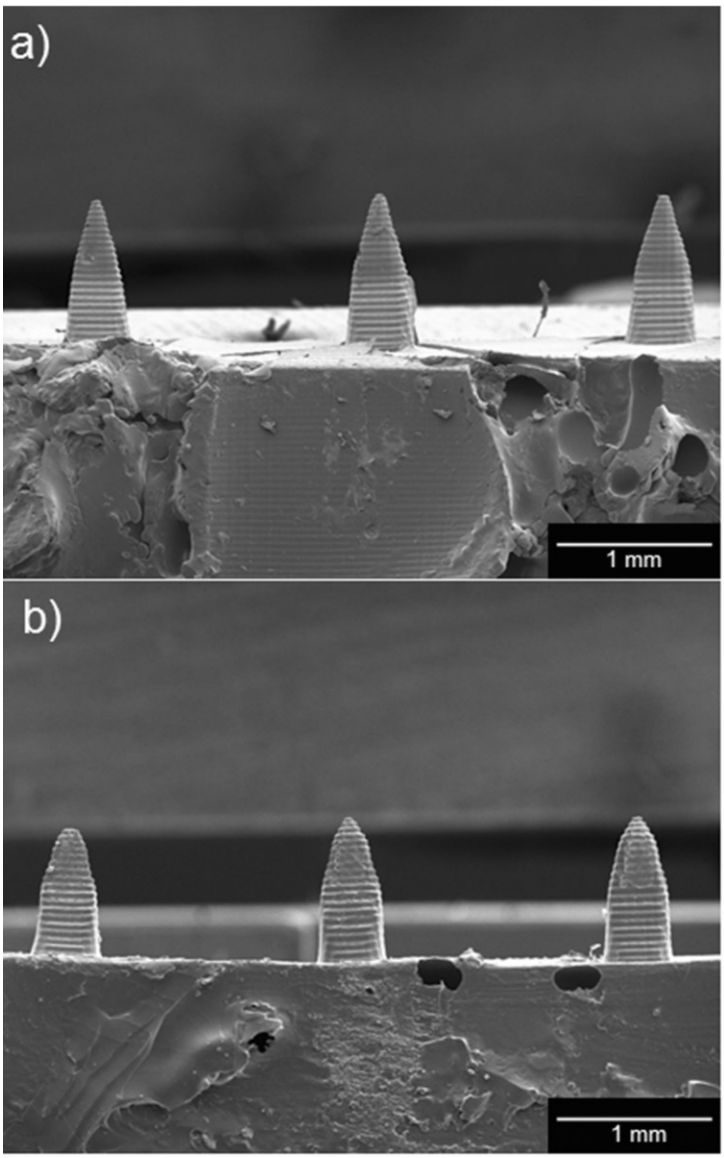

Fig. 4. **Scanning electron micrographs of unmodified and quantum-dot coated Gantrez® microneedles.** The micrographs show (a) unmodified Gantrez® microneedles, and (b) quantum-dot coated Gantrez® microneedles, which were produced using visible light dynamic mask micro-stereolithography-micromolding and piezoelectric inkjet printing. Reprinted with permission (R. Boehm et al., 2011) .

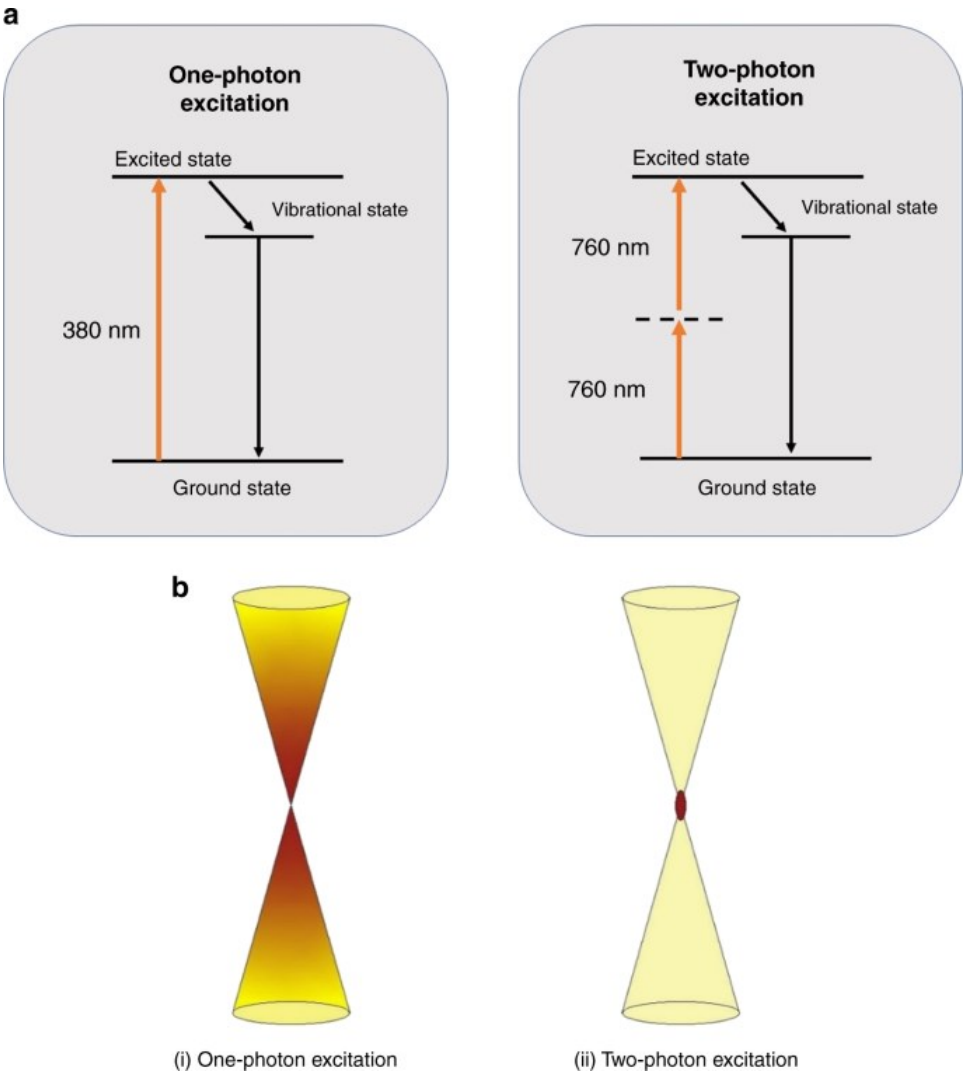

Fig. 5. **A comparison of the interaction of a single photon by ultraviolet (UV) light and the interaction of two photons by near infrared (NIR) light.** (a) Comparison of the absorption energy of a single photon by UV light and two photons by NIR light. (b) Comparison of the excitation volume of (i) one-photon excitation, and (ii) two-photon excitation. In 2-photon polymerization (2PP), regions outside laser focus are less likely to exceed the polymerization threshold of the photoresist. This phenomenon allows the fabrication of complex 3D structures since the proximity effect in two-photon absorption (TPA) is significantly less than that in one-photon absorption (OPA) (Faraji Rad et al., 2021).

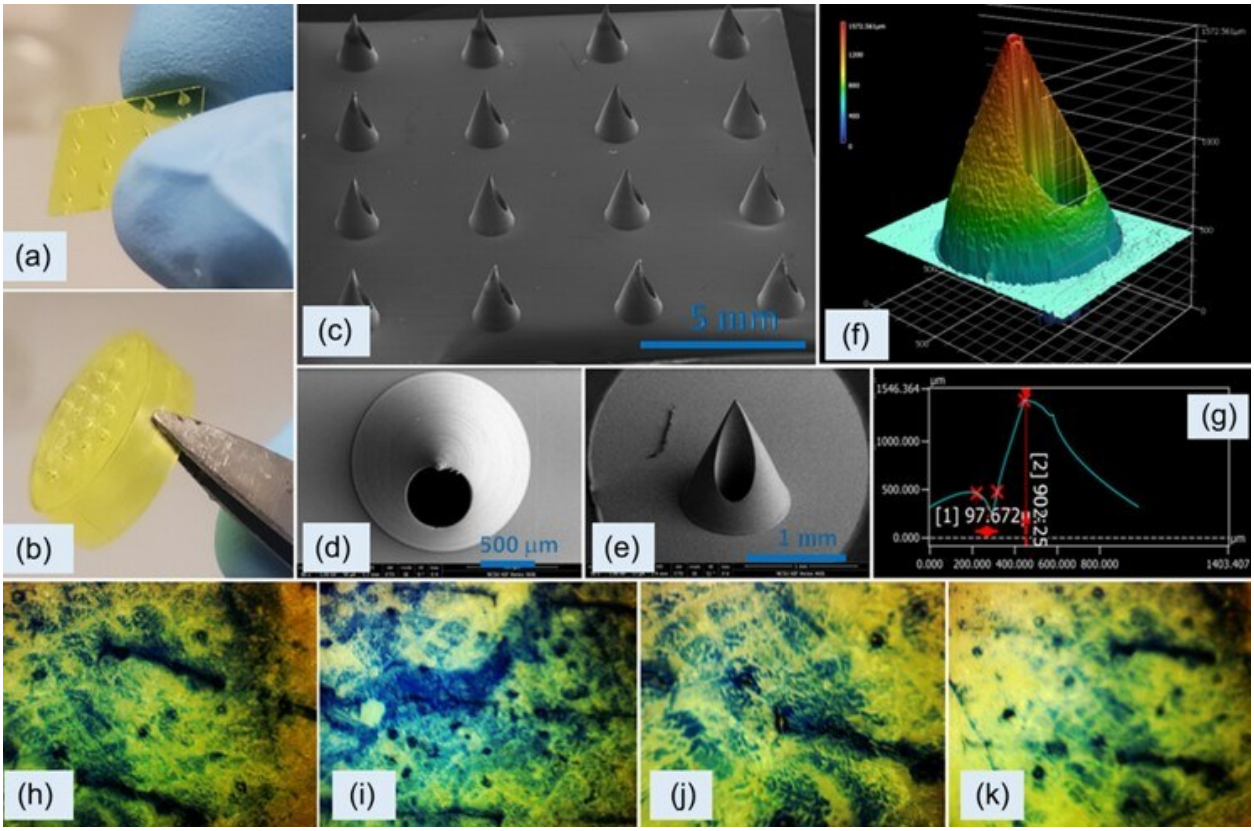

Fig. 6. **The hollow microneedle (MN) array component of a point-of-care system.** Optical images of MN arrays on (a) a square plate and (b) a cap. SEM images of (c) a MN array, (d) a microneedle tip, and (e) a microneedle (oblique view). Keyence laser scanning optical microscopy 3D images of the (f) microneedle, and (g) dimensions of the microneedles as indicated by the plot of the height (y-axis) and width of the needle (x-axis). Optical images of trypan blue-coated punctured porcine skin using MN arrays of height (h) 750 µm. (i) 800 µm, (j) 900 µm, and (k) 950 µm. Trypan blue was applied to the MN array-treated skin for visualization of the MN array-generated pores as shown in Figures 3h-k. The MN arrays were inserted into the skin via manual application. The MN array penetrated the stratum corneum layer of the porcine skin without damage to the MN tips (Shukla et al., 2023) .