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Review article

Polymeric microneedles for controlled transdermal drug delivery

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ABSTRACT

Polymeric microneedle (MN) systems are interesting transdermal drug delivery systems because of their controlled drug delivery, tunable properties, and ease of patient self-administration. They are biocompatible and can easily and painlessly penetrate the stratum corneum, delivering their contents into the dermis where they can be adsorbed into systemic circulation. Polymeric MNs can facilitate appropriate therapeutic dosing by controlling the release kinetics of pre-loaded drugs, targeting specific tissues, or responding to changing physiological conditions. This can be accomplished by modifying the degradation and swelling profiles of the host polymer and the diffusion profiles of the encapsulated drugs. In this review various mechanisms of controlled drug delivery using polymeric MNs, including new strategies, applications, and their future outlook are summarized and evaluated.

1. Introduction

Transdermal drug delivery systems (TDDSs) are a useful alternative drug administration route compared to oral, intramuscular, and intravenous administration. Transdermal delivery avoids the gastrointestinal degradation of certain drugs and avoids first-pass metabolism through the hepatic portal vein system while remaining relatively painless as compared to intramuscular and intravenous injection. Transdermal delivery is non-invasive and can easily be performed by the patient with good compliance [1,2]. TDDSs are promising methods for treating superficial cancers and skin disease, and for the convenient delivery of contraceptive hormones. The transdermal route has been popular for cosmetic and other local therapeutic applications for thousands of years. To date > 20 low molecular weight (≤400 Da) drugs have been approved by the US Food and Drug Administration for transdermal drug delivery [3], contributing to the 32 billion USD global transdermal drug delivery market. Microneedle (MN) technology was introduced in 1966 [4], and became more widely explored for drug delivery applications during the 1990s with contributions from pioneering scientists, such as M.R. Prausnitz [5,6], because it is efficient and suitable for delivering gastric-labile molecules, e.g., proteins, peptides, antibodies, vaccines, RNA, and DNA, in a controlled manner. MNs are micron-sized needles that can painlessly pass through the *stratum corneum* (SC), the main skin barrier that limits the transport of drug molecules, to achieve a therapeutic effect via transdermal delivery of encapsulated drugs. MNs have advantages over the intramuscular and intravenous routes because they can be easily self-administered, have good patient compliance because of their non-invasiveness, and they eliminate hazardous waste sharps [7,8].

Controlled drug delivery systems (CDDSs) deliver therapeutic agents to specific target cells, tissues, or organs in a pre-designed and controllable manner to achieve the desired treatment outcome. For example, because proteins and peptides often have a short half life in serum [9], researchers use hydrogels and nanoparticles to achieve

Abbreviations: APIs, active pharmaceutical ingredients; ARM, artemether; BSA, bovine serum albumin; CDDSs, controlled drug delivery systems; CMC, carboxymethyl cellulose; DAB, droplet-borne air blowing; Dox, doxorubicin; Ex-4, exendin-4; HA, hyaluronic acid; HPC, hydroxypropyl cellulose; HPMC, hydroxypropyl methylcellulose; GOX, glucose oxidase; GRVs, glucose-responsive vesicles; IFN-α, interferon-alpha; MNs, microneedles; NIR, near infrared light; OVA, ovalbumin; PC, polycarbonate; PCL, polycaprolactone; PDMS, polydimethylsiloxane; PEA, polyethylamine; PGA, poly(glycolic acid); PHEMA, poly(2-hydroxyethyl methacrylate); PHEMA-EGDMA, poly(hydroxyethylmethacrylate-co-ethylene glycol dimethacrylate); PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); PmDEGMA, poly (methoxydiethylene glycol methacrylate); PMEMA, poly[(2-N-morpholino)ethyl methacrylate]; PmTEGMA, poly(methoxytriethylene glycol methacrylate); PMVE/MA, poly(methyl vinyl ether-co-maleic acid); PS-b-PAA, polystyrene-block-poly(acrylic acid); PTT, photothermal therapy; PVA, poly(vinyl alcohol); PVP, polyvinylpyrrolidone; rhGH, recombinant human growth hormone; SC, *Stratum corneum*; SCS, sodium chondroitin sulfate; TDDS, transdermal drug delivery systems

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control delivery of these biologics [10,11]. Additionally, the short half life of siRNA can improved by encapsulation in liposomes in combination with doxorubicin (Dox) in an FDA approved formulation [12]. Controlled drug release can be achieved by actively targeting specific sites, modifying drug release kinetics, and/or triggering drug release in tissue-specific physiological environments [13]. Conventional DDSs have major drawbacks, e.g., they are applied systemically and may degrade or become inactivated before reaching their site of action, which may result in an insufficient dose reaching the target site [14]. Conventional TDDSs, e.g., topical creams, foams, gels, lotions, and ointments, may be considered targeted as they can be applied near the desired site of action, but their pharmacological behaviors are not precisely self-controlled because of low skin permeability or inability to penetrate the SC, e.g., by hydrophilic drugs, uncontrolled drug diffusion, and non-specific targeting. Additionally, the delivery efficiency, i.e., the permeation and absorption of active pharmaceutical ingredients (APIs) is often limited, depending on their physicochemical properties and added excipients, and the skin structure and thickness [15]. MN-based controlled TDDS can address these issues because they dramatically improve the efficiency and control of drug delivery [13]. MN-systems can offer precise localization of the drug with reduced dosing frequency, and the ease of self-administration and painlessness improves patient compliance. They can be used to maintain steady drug concentrations in blood, tissues, and specific target sites [16,17]. This technology would be beneficial for young children, elderly people who have difficulty swallowing, or patients suffering from vomiting and nausea.

Many materials, e.g., metal, ceramics, glass, and silicon, have been used in MN fabrication, but they have limited applications because they are not biocompatible and have safety issues [7]. Polymers are the most promising materials for MN fabrication. They may be versatile, biocompatible, readily available, cost-effective, and can have advanced properties, e.g., built-in controlled release mechanisms [18–21]. For example, hyaluronic acid (HA) can selectively bind to the CD44 receptors of cancer cells [22]. Some polymers show redox-responsive behavior that can be used to target specific cells and/or tissues [23–26]. In this critical review, we will discuss controlled transdermal delivery strategies that use polymeric MNs (Scheme 1).

2. Design and fabrication of polymeric MNs

MN design is an important aspect that determines the release of the drug by adjusting several factors, such as the composition of polymeric materials, fabrication methods, and the geometry of the microneedle array, including their base diameter, tip radius, height, aspect ratio, inter-needle distance, needle surface density, and the thickness of the base [27]. Various polymers have been reported to achieve different drug release outcomes; for example, HA and hydroxypropyl cellulose (HPC) are often used for fabrication of instant drug release MNs, whereas poly(lactic-co-glycolic acid) (PLGA) is often used for sustained drug release because of their different intrinstic properties [28]. Moreover, polymers can also be designed to respond to a particular environment or can be modified with some bioactive moieties for a specific target. For example, McCoy et al. fabricated light-responsive hydrogel-forming MNs by crosslinking poly(2-hydroxyethyl methacrylate) (PHEMA) and ethylene glycol dimethacrylate for drug delivery, obtaining sustained drug release over a prolonged period (up to 160 h) in response to light [29]. In addition, other factors, such as skin thickness variation at different body sites, sex, race, variation because of age, and body mass index, can affect the efficacy of MN-based drug delivery [30]. Penetration of polymeric MNs through skin is one of the major challenges influencing the reproducibility of controlled drug release because of the inherent elasticity of skin [27]. Therefore, the physical properties of polymeric MNs, such as heat resistance, stiffness, and mechanical strength, are critical for efficient drug delivery [31]. However, MN skin insertion forces are determined by the polymer composition and MN geometry, such as the MN wall thickness, wall angle, tip radius, length, and inter-needle distance [27]. MNs could be applied either manually or with an applicator so a range of forces should be considered.

2.1. Polymeric MN fabrication techniques

A range of techniques have been developed for polymeric MN fabrication (Table 1), such as micromolding (MM), hot embossing (HE), droplet-borne air blowing (DAB), electro drawing (ED), injection molding (IM), laser micromachining (LMM), drawing lithography (DL), photolithography (PL), investment molding (IM), continuous liquid phase interface production (CLIP), dipping, solvent casting, and X-ray methods. Nevertheless, only a few techniques, i.e., MM, DL, and DAB, are briefly introduced here, as they are the most widely-adopted to fabricate MNs with controlled drug release.

Micromolding is a widely used method for MN fabrication that involves replication of a master structure using molds. The majority of molds are made from polydimethylsiloxane (PDMS) because of its flexibility, excellent thermostability, and reproducibility of the master structure [7]. Moreover, a single master template can produce a large number of PDMS molds. MN fabrication can be accomplished in six steps: fabrication of the master MN template, female micromold preparation, casting of polymer onto female molds, bubble removal, solidification by drying, and removal of MNs from the female molds (Fig. 1). Despite its advantages, micromolding is challenged by its complex multiple-step fabrication process and the loss of drug activity by heat or UV light exposure.

Drawing lithography was adopted to overcome these limitations. In this technique, a key feature is the viscous nature of the polymer in the glass phase to realize 3D microstructure manufacturing (Fig. 2) [33]. Drawing lithography can be characterized by an elastic deformation of polymer materials in glass transitions [45].

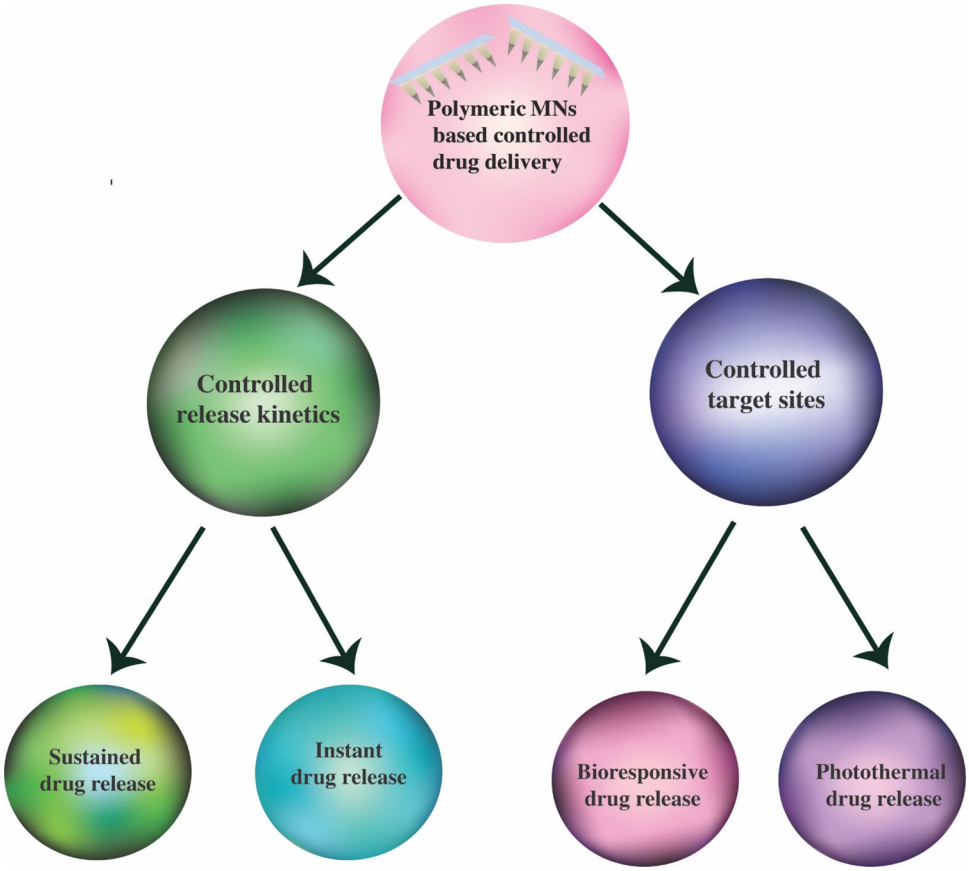
Kim et al. proposed DAB methods to fabricate 3D MNs from polymer droplets through air blowing [46]. The procedure provides fast and mild (4–25 °C) MN fabrication without drug loss. Moreover, drug loading can be controlled by the pressure and droplet dispensing time. Neither heat nor UV radiation is involved in this method. A schematic illustration for dissolving MN fabrication through DAB is shown in Fig. 3. First, the polymer droplets are dispensed on a flat substrate followed by drug-containing droplets. Another surface is applied to the composite droplets, which is then drawn upward to form the MNs, which are fully formed by air blowing and drying. Heat sensitive molecules, such as protein, antibodies, genes, and vaccines, can be delivered by DAB-fabricated MNs Table 4.

To demonstrate how to achieve controlled drug release by formulating the polymer composition and tuning the MN structure, we have provided the fabrication methods for each MN summarized for different controlled release mechanisms and applications (Tables 2,3,5, and 6).

3. Controlled microneedle delivery mechanisms

3.1. Controlled release kinetics

Drug release in polymeric MN systems consists of the transportation of drug molecules from the inner polymeric matrix to its outer surface and their further release into the surrounding tissue [47]. Controlling drug-release kinetics is an important approach to controlled drug delivery. Release kinetics can be manipulated by modifying the polymer or exploiting the intrinsic properties of the drug molecules. Thus, the drug formulation can be modified to achieve specific treatment goals. Both sustained and instant drug delivery have valuable applications and each will be discussed as follows:



Scheme 1. Polymeric microneedle-based controlled drug delivery.

Table 1
Polymeric MN fabrication methods.

Fabrication method	Advantages	Reference
Micromolding	The most widely used, economical, and easily applicable method for different polymeric MNs.	[32]
Drawing lithography	Suitable for MNs with complex 3D structure	[33]
DAB, electrodrawing	Suitable for fabrication of dissolving MNs with a sharp tip from a liquid reservoir; molding free and contact free	[34]
Hot embossing	Suitable for fabrication of 3D MNs with sharp tips and large bases	[35]
Injection molding	Suitable for fabrication of open channel single MN fabrication	[36]
Laser micromachining	This technique allows the fabrication of sharp MNs with tunable height	[37]
Photolithography	MN fabrication without molding and etching	[38,39]
Investment molding	Hollow MN fabrication without post-processing steps	[40]
CLIP	Mold-free and fast MN fabrication techniques	[41]
Solvent casting	Novel techniques for fabrication of out-of-plane MNs by a solvent evaporation process	[42]
Dipping	Suitable for separable dissolving MN fabrication	[43]
X-ray methods	A combination of hot embossing and X-ray exposure; suitable for hollow MN fabrication	[44]

3.1.1. Sustained drug release

The objective of sustained drug delivery is to release a drug at a predetermined rate, maintaining a steady-state concentration for a specific period while minimizing side effects [48]. Sustained drug delivery using MNs can minimize drug administration frequency, decrease cost, and improve patient compliance [49,50]. Reducing administration frequency improves patient compliance through enhanced convenience and minimizing forgotten or missed doses and reduces the risk of infection at the site of administration, especially when compared to intravenous or intramuscular routes.

Hormones and other biomolecules, e.g., peptides and proteins, often require a sustained release for a prolonged time, which is achievable using polymeric MN technology. For example, Chen et al. reported slowly degrading chitosan MNs that yielded sustained transdermal delivery of bovine serum albumin (BSA) for 8 days [51]. The BSA was imaged by fluorescence microscopy at a depth of 300 μm. In addition, Kim et al. fabricated MNs from poly-N-isopropylacrylamide hydrogel microparticles and PLGA that released rhodamine B, a model drug, through the swelling mechanism. After contacting water, the MNs quickly swelled, resulting in a prolonged-release [32].

3.1.2. Sustained-release mechanisms

3.1.2.1. Polymer-based mechanisms. Sustained drug release can be achieved through drug diffusion, MN surface erosion, and/or polymer degradation and swelling. Polymer swelling and degradation are the primary mechanisms in polymer-matrix-based sustained drug delivery; however, the permeability and thickness of the polymer membrane are also significant [52]. Potential candidate polymers for sustained transdermal drug delivery are as follows:

3.1.2.1.1. Biodegradable polymers. Biodegradable polymers have a long history of being used in medicine. In the ancient world, these polymers, i.e., cellulose, e.g., cotton and linen, and keratin, e.g., hair

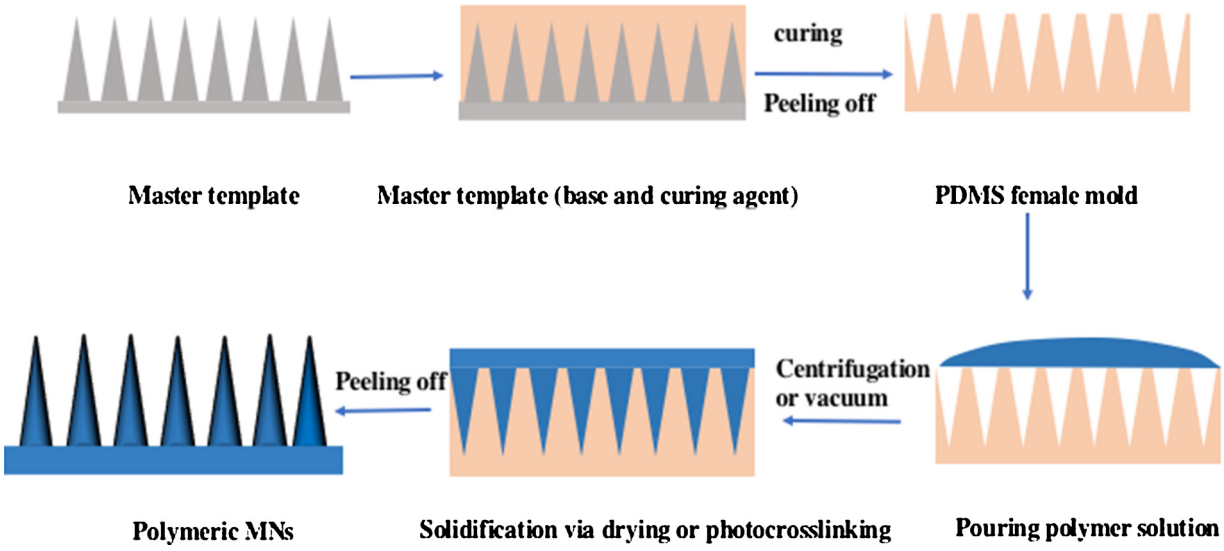


Fig. 1. Schematic illustration of MN fabrication via PDMS micromolding.

and wool, were used for the fabrication of structural materials. MN-based sustained drug delivery can be achieved through controlling the biodegradation rate of multilayer polymeric MNs after embedding in the skin. Biodegradable MNs have been used for extended drug release with high payload [53–55] while decomposing into non-toxic molecules that are eliminated through normal metabolic pathways [56,57]. However, the chemical structure of their monomers, e.g., composition, presence of ionic groups, molecular weight, melting point, and hydrophilicity, influences their breakdown and ultimately their toxicity [58,59]. In addition to the physicochemical properties of the

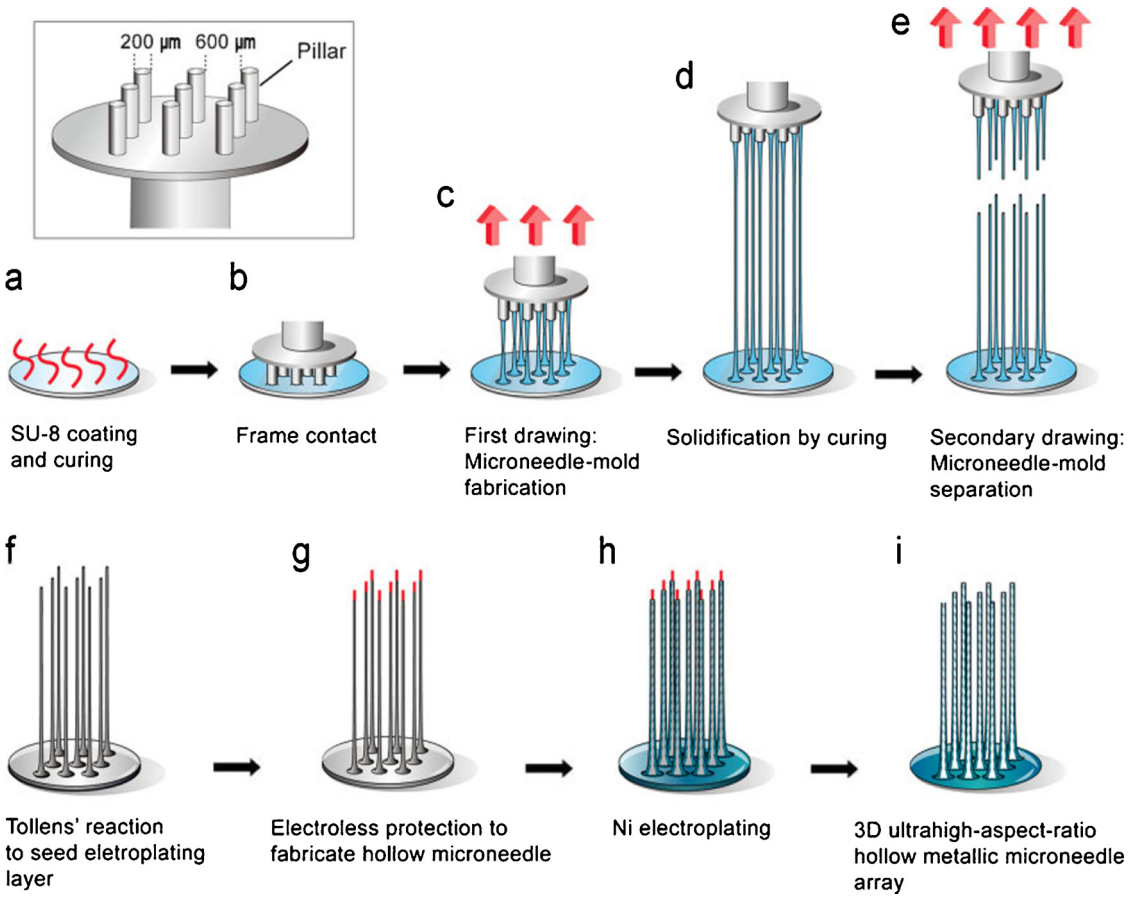


Fig. 2. Schematic of the application of drawing lithography to produce 3D ultrahigh aspect ratio MNs. Stainless steel drills d = 200 μm and l = 3 mm were used pillars. (a) The SU-8 2050 photoresist was spin-coated and cooled on a substrate. (b) The photoresist contacts the pattern pillar and (c) a conical bridge forms between the substrate and pillar as it is drawn away. (d) The micromold is cured and (e) separated from the pillar. Hollow MNs are formed by electroless and electroplating processes (f)–(h) before (i) the photoresist is removed yielding the final product. This figure was reproduced with permission from Ref. [33]. Copyright 2010, Wiley-VCH.

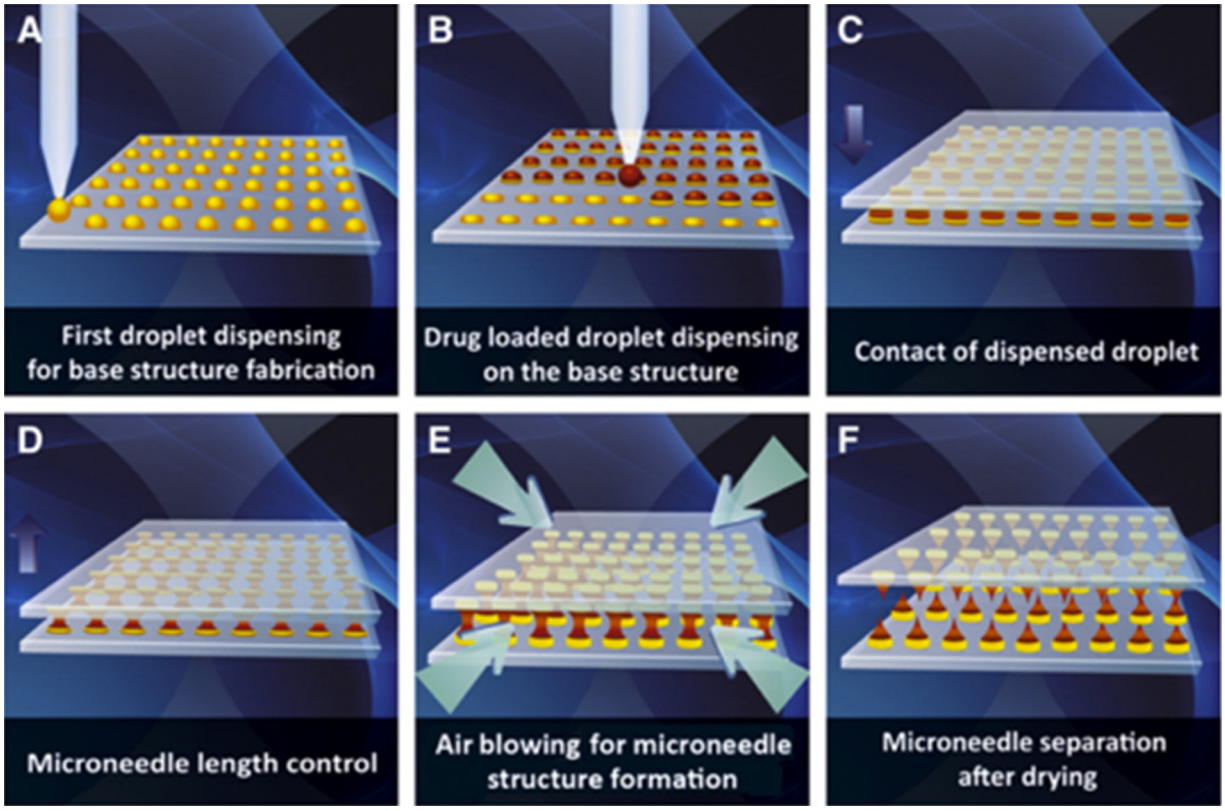


Fig. 3. Droplet-borned air blowing MN fabrication. (A) Biopolymer droplets are dispensed on a flat surface to which (B) drug-loaded droplets are added. (C) A second surface is placed in contact with the droplets and (D) drawn upward to control the microneedle length. (E) Air is blown to form the final microneedle shape and dry the polymers. (F) The plates are separated yielding dissolving MNs on both plates. This figure was reproduced with permission from Ref. [46]. Copyright 2013, Elsevier B.V.

oligomers and polymers in MNs, processing conditions, glass transitions, hydrolysis mechanisms, application sites, and the thickness and length of the MNs significantly affect their drug release behavior [30,60]. Sustained drug release mechanisms are illustrated in Fig. 4.

Biodegradable polymeric MNs do not dissolve in water, but slowly degrade inside skin tissue. Biodegradable polymers used in MN fabrication include poly(lactic acid) (PLA), PLGA, polycarbonate (PC), polystyrene (PS), poly(glycolic acid) (PGA), polycaprolactone (PCL), chitin, chitosan, silk, and combinations thereof [32,51,61–65]. For example, MN patches composed of PLGA can release drugs slowly over several days to months through PLGA degradation [32]. Similarly, chitosan MNs readily pierce the SC and provided sustained release. However, fabricating MNs with good mechanical strength from these materials is still challenging. Biocompatibility and biosafety remain concerns because sometimes these polymers can degrade into toxic

Table 3
Summary of instant drug delivery by polymeric microneedles.

Therapeutics/Drugs	Polymer	Fabrication method	Release time	Reference
Bleomycin	PLA	Micromolding	15 min	[112]
Acyclovir	Gantrez S-97	Micromolding	15 min	[113]
Artemether	HA	Micromolding	120 min	[114]
Ex-4	HA	Micromolding	5 min	[106]
Dihydroergotamine mesylate	PVP	Micromolding	2 min	[115]
rhGH/desmopressin	SCS/HA	Micromolding	15 min	[99]
Meloxicam	PVP	Micromolding	30 min	[118]
Sumatriptan	Dextran/HA	Micromolding	30 min	[119]

Table 2
Summary of sustained drug delivery by polymeric microneedles.

Therapeutics/Drugs	Polymer	Fabrication method	Release time	Reference
Levonorgestrel	PLA/PLGA	Molding and solvent casting	30 d	[80]
Etonogestrel	PVA/HPMC	Micromolding	7 d	[81]
Bovine serum albumin	Chitosan	Solvent casting	8 d	[51]
Rhodamine B	PLGA/poly-N-isopropylacrylamide	Micromolding	3 d	[32]
FITC-dextran	PLGA	Micromolding	7 d	[94]
Antigen ovalbumin	Chitosan	Micromolding	28 d	[93]
Bevacizumab	PVA	Micromolding	7 d	[86]
Doxorubicin	Gelatin methacryloyl	Micromolding	≤1 d	[90]
Ex-4 analogue and peptide E6	Dextra/Sorbitol	Molding and solvent casting	4 d	[91]
Insulin	Silk fibroin	Micromolding	3 d	[95]
Ovalbumin	HA/chitosan	Solvent casting	28 d	[96]
Horseradish peroxidase	Silk fibroin	Micromolding	2 d	[97]

Table 4
Summary of bioresponsive drug delivery biosignals.

Biosignals	Indication	Applications	Reference
pH	Cancer cells have a slightly acidic pH. Insulin can be delivered by pH-sensitive materials. Skin disease can also be treated by pH-sensitive carriers or drugs.	Diabetes and cancer treatment	[120]
Glucose	Glucose levels can be maintained by delivery of glucose-responsive materials. Degradation of glucose can produce starvation therapy in cancer cells.	Diabetes and cancer treatment	[124]
Hypoxia	Hypoxia sensitive polymer for cancer therapy (hyaluronic acid modified with nitroimidazole for hypoxia sensitive insulin delivery)	Cancer, stroke, and diabetes treatment	[125]
Enzyme	Enzyme sensitive polymeric MNs can treat various diseases. Enzyme sensitive therapeutics play key roles in the treatment of several diseases.	Cancer and cardiac treatment	[126]
Temperature	Temperature sensitive polymers can deliver therapeutics at specific temperatures.	Cancer treatment	[111]
Receptor	Biomolecules can bind with specific over-expressed receptors in certain diseases, such as cancer, genetic diseases, and cardiac disorders.	Cancer and genetic disorders	[127]
Mechanical cues	The shape and size of molecules can improve stability and response.	Cancer treatment	[120]

metabolites that produce immunological responses, such as polyacetal polymers and poly(L-lysine) [19,66].

3.1.2.1.2. Swellable polymers. Swellable polymers do not dissolve, rather their polymeric network absorbs large quantity of water while remaining insoluble because of strong chemical or physical crosslinking of individual chains [67]. The resultant release mechanisms are diffusion-controlled and determined by the drug molecules and the swelling and crosslinked structure of the polymer [67]. However, in many cases, the degree of crosslinking determines the swelling properties of the polymer, which can be tuned to influence the drug release rate [68,69]. Polymers that meet the criteria for swellable MN fabrication are PHEMA, polystyrene-block-poly(acrylic acid) (PS-b-PAA), poly(vinyl alcohol) (PVA), poly(methyl vinyl ether-co-maleic acid) (PMVE/MA, Gantrez), and hyaluronic acid acrylate [70–74]. The advantages of swellable MNs are their prolonged stability in the skin and in some cases antimicrobial properties [75]. MN arrays fabricated from Gantrez S-97, PEG, and Na_2CO_3 showed extreme swelling properties, i.e., 1119% swelling within an hour of insertion and 1708% swelling at equilibrium [76].

Crosslinking is often required to prepared swellable polymeric MNs, and usually requires high temperatures, e.g., 90 °C for poly(hydroxyethylmethacrylate-co-ethylene glycol dimethacrylate) (PHEMA-EGDMA) crosslinking, or UV exposure, e.g., methacrylic-HA crosslinking [77]. This can disrupt drug loading and/or affect their biological activities. So, biomolecule-based therapeutics, e.g., proteins, RNA, and other temperature-sensitive drug substances, should be loaded after crosslinking, i.e., after MN fabrication the drug can be attached to the MN base or onto the backing plate, rather than be pre-loaded within the microneedle matrix [73].

Table 6
Microneedle types and photo-absorbers used for the treatment of various diseases using photothermal therapy.

Polymer	Photo absorber	Fabrication method	Disease	Reference
PVP, mesoporous silica NPs	indocyanine green	Solvent casting	Cancer	[182]
PCL	lanthanum hexaboride	Solvent casting	Skin cancer	[183]
PCL	Prussian blue	Micromolding	Diabetes	[184]
HA	PEGylated gold nanorod	Micromolding	Cancer	[185]
PVP	bismuth	Micromolding	Diabetes	[186]

3.1.2.2. Polymeric microneedle drug diffusion kinetics. Diffusion is the main mechanism of mass transport in controlled drug release. The mathematical understanding of diffusion facilitates understanding of the mechanism of controlled release, which can expedite product development. In many cases, the intrinsic properties of the drug can be exploited to release the drug in a controlled manner. From a physiological perspective, drug molecules have to meet many requirements for sustained transdermal drug delivery, e.g., high lipophilicity, low molecular weight and melting point, suitable pKa, and sufficient water solubility between pH 6–7.4. (For a specific example, a delivery rate of 1 mg per day requires a solubility between 0.05–1 mg/mL) [78]. For a reservoir system, where the polymer membrane is surrounding a nearly homogenously distributed drug, the diffusion rate of the drug molecules is modelled by Fick's diffusion law (Eq. 1)

Table 5
Summary of bioresponsive polymeric microneedles.

Therapeutics/ Drugs	Polymer	Fabrication method	Biosensitivity	Reference
Insulin/Gox	MPEG-P(DMAEMA-PBA)	Micromolding	Glucose/Enzyme	[122]
IgG	HA	Micromolding	Receptor	[134]
IFN-α	PVA/SCS	Micromolding	Receptor	[135]
IFN-α	PVA	Micromolding	Receptor	[136]
Insulin/Gox	HA-2-nitroimidazole	Micromolding	Glucose/Enzyme/Hypoxia	[145]
Insulin	silk fibroin-boronate	Micromolding	Enzyme	[146]
STAT3 siRNA	PEA	Micromolding	Protein receptors	[150]
Influenza vaccine	PBAE/ICMV	Dipping	Protein receptors	[169]
OVA	PHEMA	Dipping	pH	[170]
OVA/ TLR agonists imiquimod and monophosphoryl lipid	PLGA	Micromolding	Receptors	[175]
F127/R848/OVA	Pluronic F127/PEG	Micromolding	Receptors	[171]
anti-OVA IgG1 serum antibody	oligo sulfamethazine conjugated poly(β-amino ester urethane)	Solvent casting	pH	[172]
Cisplatin nanoparticles	Cellulose	Micromolding	pH/mechanical cues	[176]

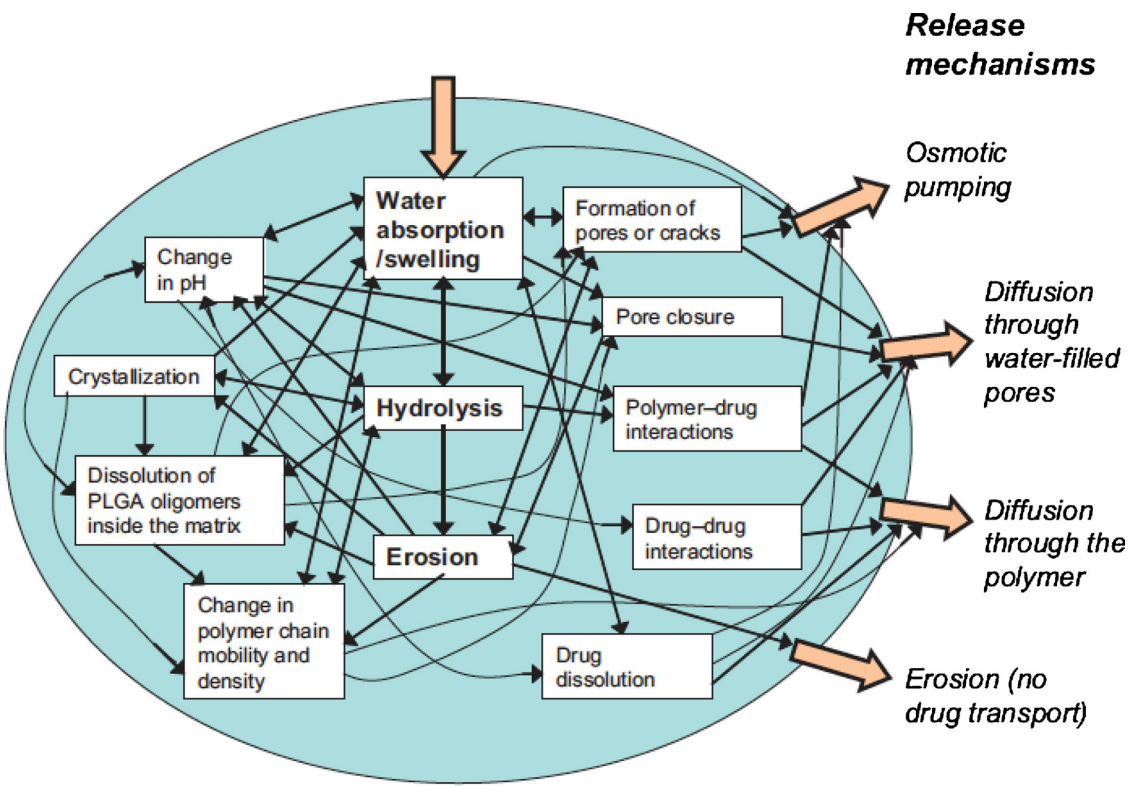


Fig. 4. The physicochemical processes occuring in the degradation of poly(lactic-co-glycolic acid), a biodegradable polymer, that results in drug release. The connections between processes are illustrated with arrows. This figure was reproduced with permission from Ref. [59]. Copyright Elsevier 2011.

$$F = -D\frac{\partial c}{\partial x} \tag{1}$$

Where F is flux per unit surface area, D is the diffusion coefficient, and c is the drug concentration. In polymeric MN systems, where the drug is uniformly dispersed, their unsteady-state diffusion can be described using Fick's second law of diffusion (Eq. 2)

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right) \tag{2}$$

where c is the drug concentration, t is the time, and x, y, and z are the three spatial coordinates.

3.1.2.3. Sustained drug delivery applications. Many drugs have been delivered through MN technology, including biomolecules, e.g., peptides, proteins, hormones, RNA, and DNA, small molecule drugs, and vaccines. MNs are advantageous because they can be incorporated into self-administrable patches while producing the same bio-absorption and bio-availability as hypodermic needles [79]. Biomedical applications of MNs are summarized as follows:

3.1.2.3.1. Hormone therapy. MNs are potent tools for hormone replacement therapy related to contraception. For example, in undeveloped countries, women often have limited access to cost-effective contraception, experience a high failure rate, and low acceptance and incorrect use of contraceptive drugs lead to unplanned pregnancies. Less frequent dosing that can be self-administered can yield more consistent outcomes. Li et al. achieved sustained delivery of the contraceptive hormone levonorgestrel by designing rapidly separable polymeric MN patches from polylactic acid (PLA) and poly(lactic-co-glycolic) acid (PLGA) (Fig. 5). The drug release was controlled by using a drug-free polymer film coating on the MN surfaces, which prevents immediate drug release, and the intrinsically slow diffusion of levonorgestrel. The barrier film was formed by solvent migration into the MN mold, which precipitates or concentrates the PLA or PLGA at the MN mold interface. This MN array was well tolerated and maintained a plasma hormone concentration above the human therapeutic level for one month [80]. Conversely, He et al. fabricated dissolving MNs for the sustained release of etonogestrel. To control its release, the MNs were fabricated with two layers. The first dissolvable layer yielded a burst release after insertion, then the second layer slowly released the drug to maintain a prolonged therapeutic concentration for a week [81]. Overall, MNs are important transdermal hormonal therapeutics that provide several advantages, e.g., sustained drug release, self-administration, and good therapeutic outcomes.

3.1.2.3.2. Small molecule and protein delivery. Most drug molecules having molecular weight < 500 Da can passively penetrate the skin, depending on their chemical properties [82], but might not in sufficient quantities for effective therapy. Therefore, MNs are widely used for enhancing the transdermal delivery of small molecules [83–86].

Lipophilic drugs are potential drug development candidates but, because they need hazardous organic solvents for solubilization, these molecules often fail to reach the pharmaceutical market [87]. Intermolecular forces, e.g., ionic, hydrophobic, and host-guest interactions, between drugs and biodegradable polymers allow for the fabrication of dissolvable biodegradable MNs for effective drug delivery. Dangol et al. reported polymeric dissolving MNs for transdermal delivery of capsaicin to treat rheumatic arthritis. They used a potential platform for solvent-free lipophilic drug delivery, by using a mixture of a hydrophilic polymer, HA, and a more hydrophobic polymer, PVP, to solubilize the lipophilic drug capsaicin and form nanoparticles that were encapsulated in MNs using drawing lithography. Because no hazardous organic solvent was used to solubilize the drug, this process was called a solvent-free fabrication [88]. Additionally, Kearney et al. fabricated hydrogel-forming MNs to deliver donepezil to treat migraines for 24 h, with *in vivo* experiments showing successful sustained drug release [89]. Luo et al. fabricated biodegradable MN patches from gelatin methacryloyl for sustained delivery of the chemotherapeutic, doxorubicin (Dox). The MN patch efficiently penetrated the SC of mouse

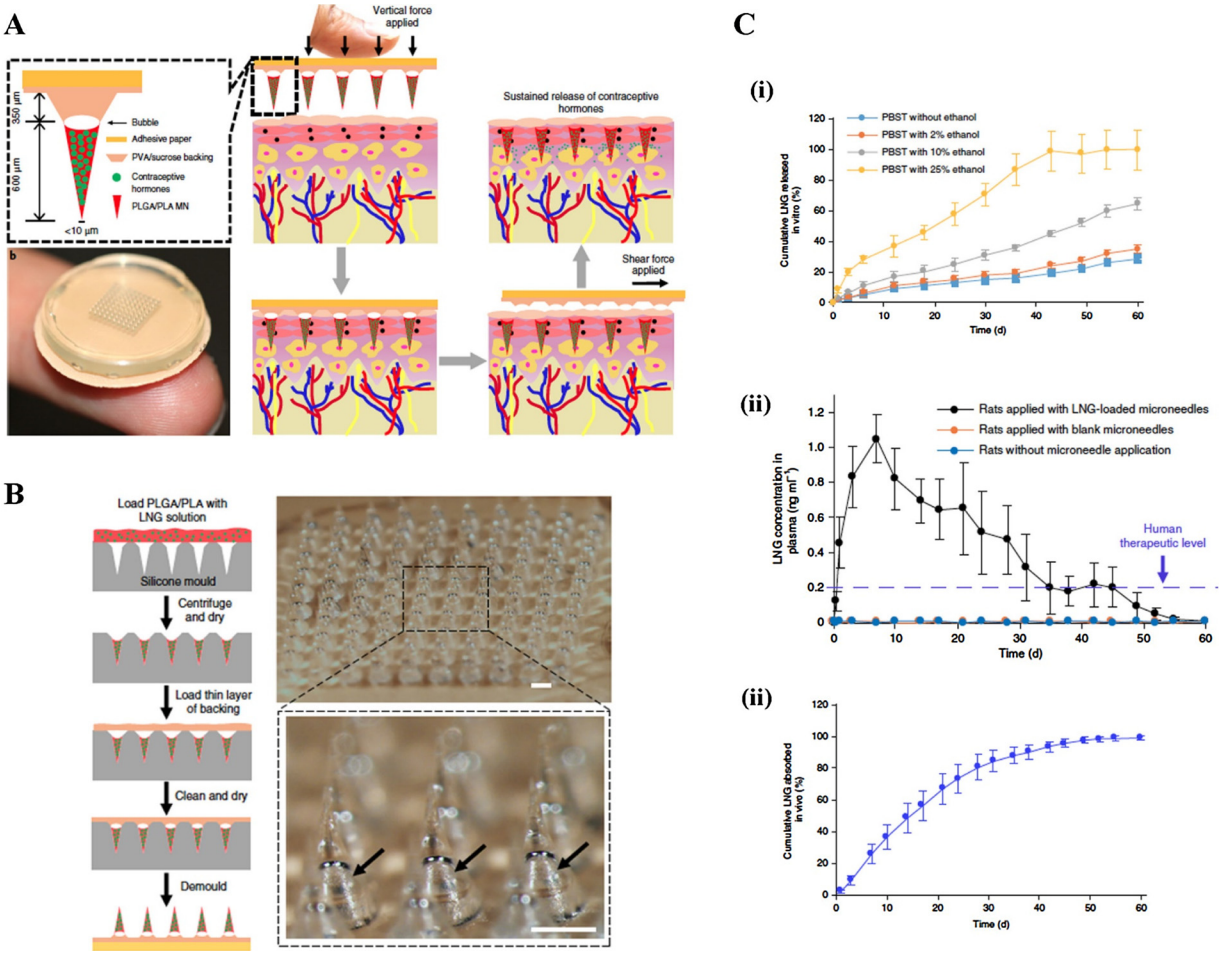


Fig. 5. (A) Schematic representation of rapidly separable microneedle patches and insertion into the skin for sustained release. (B) Schematic of the fabrication process using a mold and bright-field microscopic images of the resultant microneedles. (C) The release of levonorgestrel from rapidly separable microneedle patches *in vitro* in (i) PBS solution, (ii) rat plasma, and (iii) cumulative levonorgestrel absorption *in vivo* after administering loaded microneedles to determine pharmacokinetic modelling. This figure was reproduced with permission from Ref. [80]. Copyright 2017, Nature Publishing Group.

cadaver skin with prolonged drug release [90].

Yang et al. used MN technology to administer peptide E6, a novel analog of Exendin-4 with a serum binding motif on a covalently linked side-chain staple that increased its potency and serum half-life, for sustained glucose tolerance in diabetics of up to 96 h. [91] This MN array was stable for 2 weeks at 25 °C. Additionally, a peptide and vaccine combination has been successfully delivered through MN technology [92]. Other sustained release MN applications include intracorneal drug delivery of antigen ovalbumin for up to 28 days [93,94].

3.1.3. Instant release

In some cases instant drug release is desirable. When instant release MNs penetrate the SC they dissolve and release the encapsulated drug immediately [98]. Instant, or burst, drug release by MNs is an important concept but was often ignored in MN-based controlled drug delivery because it was often considered a negative result when creating long-term controlled release devices. However, in certain conditions, rapid drug delivery is desirable for rapid onset, e.g., analgesia and gene/peptide/protein delivery in tissue repair. For example, Fukushima et al. prepared two-layer dissolving microneedles from sodium chondroitin sulfate (SCS) and dextran for transdermal delivery of recombinant human growth hormone (rhGH) and desmopressin. These MN patches dissolved quickly with maximum drug release within 15 min [99]. The burst release allowed the drug to reach the maximum blood plasma concentration for rapid action. The factors responsible for burst release include polymer surface properties, polymer-drug interactions, and the porous structure of the dry materials [98]. Most dissolvable MN systems release drugs within minutes to hours [100]. Rapidly dissolving polymeric MNs can produce instant drug release at the site of action and are a potent system for wound healing and analgesic drug delivery [101].

3.1.3.1. Polymer-based mechanism. Dissolvable polymers used in MN formulations dissolve completely in the skin after insertion without producing any biohazardous waste [102–104]. Often, water-soluble polysaccharides and similar compounds, e.g., SCS, polyvinylpyrrolidone (PVP), HA, dextran, hydroxypropyl methylcellulose (HPMC), HPC, carboxymethyl cellulose (CMC), and amylopectin, are used in instant release MN formulations [100,105–107]. Polysaccharides are also widely used for dissolvable MNs because of their good biocompatibility, bioactivity, and stability. These MNs can dissolve in the skin within several seconds or minutes depending on their dissolution kinetics, and are thus suitable for the fast delivery of preloaded cargo. The amount of drug released from the polymer with an initial burst, M_t, from MNs can be estimated by (Eq. 3):

$$M_t = \frac{DC_o}{l}\left(t + \frac{l^2}{6D}\right) \quad (3)$$

where D is the diffusion coefficient, C_0 is the drug concentration inside the membrane, t is burst state time, and l is the membrane thickness [98].

Environmentally sensitive materials can achieve triggered release. For example, hydrogel MNs based on anionic and cationic polymers exhibit pH-sensitive swelling and the ability to control the on/off pattern. For example, the cationic polymer PEG-b-poly (β -amino ester) showed 4-times faster drug release in a slightly acidic environment (pH 6.5–7.0) compared to pH 7.4, whereas poly[(2-N-morpholino)ethyl methacrylate] (PMEMA), which has morpholino groups, responds to pH, temperature, and the ionic strength of the medium [108,109]. So, in a suitable pH environment, these polymers exhibit burst drug release.

Additionally, a low critical solution temperature can be used to produce a burst release effect in MNs. Some polymers have high swelling at low temperature and de-swelling when the temperature is raised above the low critical solution temperature. For example, poly(methoxydiethylene glycol methacrylate) (PmDEGMA) and poly(methoxytriethylene glycol methacrylate) (PmTEGMA) showed thermoresponsive drug release [110,111]. Elevated temperature results in burst drug release because drug molecules are squeezed out of the shrinking gels.

3.1.3.2. Drug-based mechanism. The physical and chemical nature of molecules has a significant effect on burst drug release. For example, the small molecular weight drugs that are water-soluble can easily pass through the porous polymer structure even before swelling. The aqueous solubility and partition coefficient of drugs affect the driving force and facilitate rapid release because of the thermodynamic imbalance [98].

3.1.3.3. Instant release microneedle applications. Burst drug release is beneficial to the treatment of various diseases. Drugs that are administered through the intramuscular or intravenous route can be painlessly delivered through MNs. For example, bleomycin, a potent wart treatment, is mostly delivered through intralesional injection. Lee et al. fabricated PLA MNs to make it more patient-friendly. The drug is released under the skin and > 80% of the drug is dissolved within 15 min; it was a suitable method for wart treatment [112]. Similarly, acyclovir is used for the treatment of herpes labialis, but its application is limited by its low skin permeability and poor efficacy. Pamornapathomkul et al. fabricated acyclovir MNs from Gantrez S-97 with sufficient mechanical strength, which dissolved within 15 min, and the resulting skin permeation was ~45 times higher than a commercial cream formulation [113]. Additionally, Qiu et al. fabricated oligo-HA MNs to deliver artemether (ARM). The maximum ARM delivered into the skin was 72% of the initial dose, which was the same dose effect *in vivo* as intramuscular injection [114]. Tas et al. fabricated PVP MN patches containing dihydroergotamine mesylate that dissolved in porcine skin within 2 min with relatively high bioavailability [115]. Another application is the delivery of vitamin K during bleeding [116].

To investigate compliance issues regarding nanomedicine, Kennedy et al. investigated the biodistribution of nanoparticles delivered through dissolving MNs using rhodamine B as a tracker. They detected nanoparticles in the liver, kidney, spleen, and superficial parotid of mice and concluded that NPs can be used for various therapies [117]. Liu et al. encapsulated Exendin-4 (Ex-4) in dissolvable HA MNs through tip coating and found the same efficacy as a subcutaneous injection by hypodermic needles. Most of the drug (90%) dissolved within 5 min and insulin secretion significantly increased after MN insertion [106]. Burst release is useful for specific conditions where instant drug release is required and MNs are a great alternative to reduce pain with several additional qualities for transdermal drug delivery.

3.2. Site-targeted controlled drug delivery

3.2.1. Bioresponsive release

Bioresponsive drug delivery is a precise form of drug delivery that can deliver drugs under specific physiological conditions or bind to specific target sites [120]. The term bioresponsiveness is defined as to generate a biological response upon stimulation by the surrounding environment. Bioresponsive materials are sensitive to certain biological signals or pathological abnormalities and provide precise medication. Bioresponsive MNs can be designed to deliver drugs or therapeutics under certain biochemical conditions, e.g., pH, redox potential, temperature range, or in the presence of specific enzymes, glucose, ions, hypoxia, ATP, or nucleic acids in target sites. When these molecules are exposed to certain biological targets, e.g., receptors, nutrients, enzymes, or whole cells, molecular interactions trigger changes occurring at the molecular level [121].

3.2.2. Bioresponsive release mechanism

Treatment efficacy is directly related to the administration method, which requires advanced materials to achieve precise drug release. Several techniques have been applied to obtain bioresponsive controlled drug delivery through MNs, e.g., coatings, surface functionalization, pH-responsive release, and externally triggered release. Broadly these techniques can be classified into two categories:

3.2.2.1. Physiologically triggered release. Variations in physiological parameters are important indications for distinct types of diseases, e.g., cancer, infections, cardiovascular disease, and autoimmune disorders. These abnormalities provide attractive targets for bioresponsive MN design [120]. Physiological disease parameters, e.g., pH, glucose, hypoxia, temperature, enzymes, receptors, and mechanical cues, are important triggers for effective disease treatment. For example, Zhang et al. synthesized an H_2O_2-labile amphiphilic diblock copolymer. Insulin and glucose oxidase (Gox) were encapsulated inside the copolymer micelles (Fig. 6). The resultant MN patches released insulin with rapid responsiveness under hyperglycemic conditions because the oxidation of glucose by Gox generates H_2O_2 and produces an acidic environment, resulting in insulin release and regulation of blood glucose within the normal range [122].

3.2.2.2. Biologically sensitive-particulates-based release. Physiologically responsive MN fabrication is a popular approach in bioengineering. Surface activation of drug carriers is commonly used in nanomedicine, especially in cancer treatment [123]. Nanocarrier surfaces are activated by a bioresponsive moiety to accumulate the drug in target sites, where MNs are used to deliver the nanomedicine at the site of application.

3.2.3. Bioresponsive release applications

3.2.3.1. Protein and peptide delivery. Proteins have distinct roles varying from enzymatic catalysis to molecular transportation. Protein drugs are used to directly replace dysfunctional endogenous proteins and apply to many cancer treatments, vaccinations, and therapies for genetic disorders [128,129]. The large molecular weight and degradation susceptibility of therapeutic proteins are major impediments for transdermal drug delivery. MN technology can painlessly traverse the SC and directly translocate protein drugs into systemic circulation in a controlled manner [130,131]. Cell permeability as related to molecular size is also critical; small water-soluble peptides < 500 Da are easily delivered through the skin compared to those with larger molecular weights [2,132]. Effective protein delivery has been developed using MN technology, e.g., for desmopressin, erythropoietin, lysozyme, glucagon-like peptide-1, parathyroid hormone, and etanercept [130,133].

Monkare et al. fabricated hyaluronan-based monoclonal IgG-loaded MNs for intradermal drug delivery with protein stability. After dissolving the MNs in PBS > 80% of the protein was recovered without conformation changes. These MNs are dissolved within 10 min of application and hyaluronan and IgG are deposit at a depth of 150–200 μm in the skin [134].

Interferon-alpha (IFN-α) is used for the treatment of chronic viral

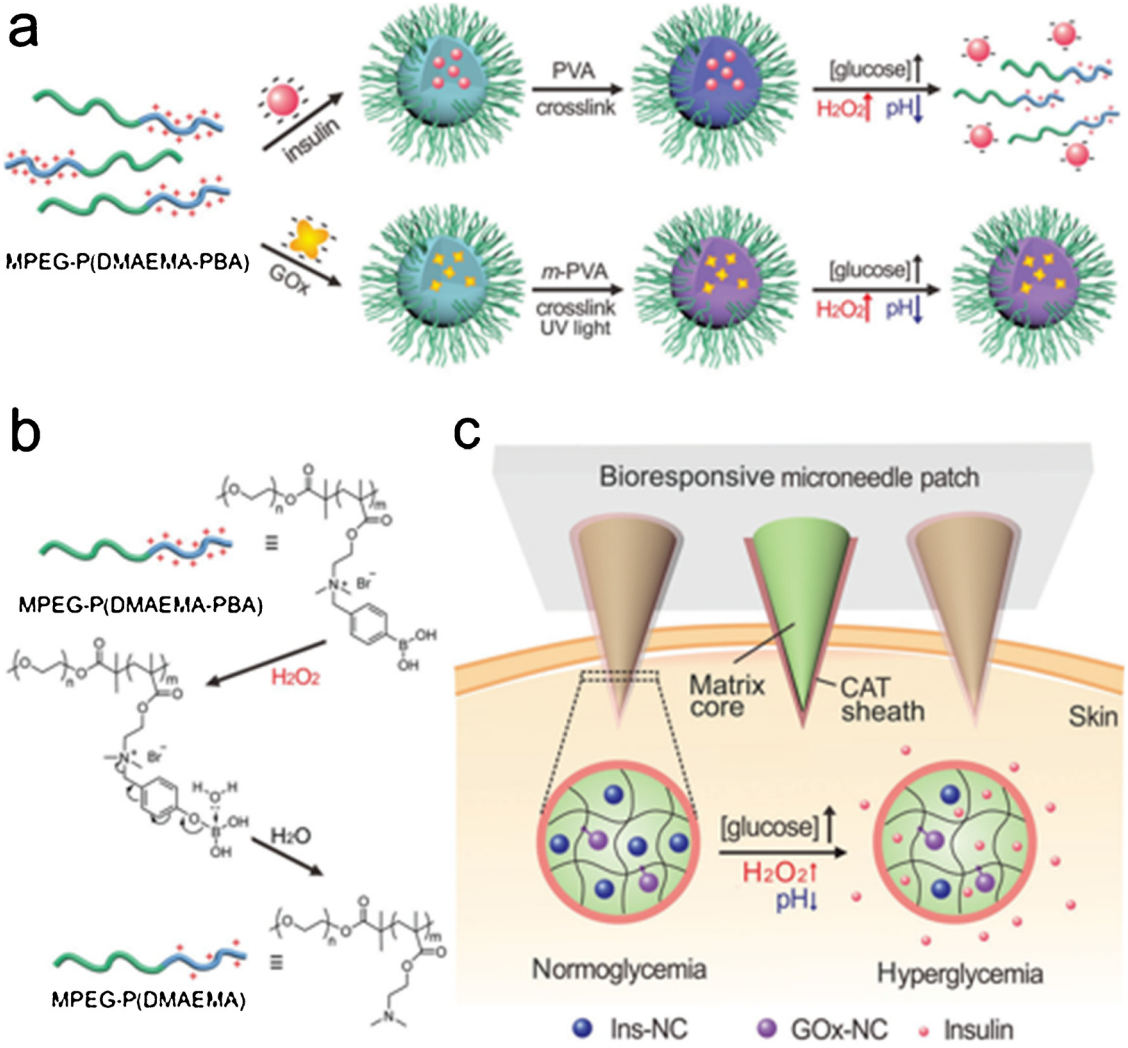


Fig. 6. Schematic of a glucose-responsive insulin delivery system using H_2O_2 and pH cascade-responsive MN arrays. (a) Formation of nanomicelles and the mechanism of glucose-responsive release. (b) Schematic of H_2O_2-triggered charge reduction in the polymer and (c) MN structure for *in vivo* insulin delivery. This figure was reproduced with permission from Ref. [122]. Copyright 2015, Wiley-VCH.

infections and cancer. It is generally administered intramuscularly daily or every other day. Chen et al. encapsulated IFN-α in SCS dissolvable MNs with PVP as a supporting backing layer. These MNs produce a high dose-response compared with intramuscular injection [135]. Similarly, Kusamori et al. coated IFN-α on PVA MNs, which had a similar effect to that of subcutaneous administration [136].

3.2.3.2. Bioresponsive insulin delivery. MNs are an attractive transdermal carrier of insulin [137–140], a life-saving treatment for Type 1 diabetics. Poor absorption and enzymatic degradation of insulin in the GI tract preclude oral administration, necessitating life-long subcutaneous injections. However, the pain, inflammation, and infection associated with this route have negative impacts on quality of life. MNs can deliver insulin painlessly with minimal invasiveness [105,141–144]. Yu et al. reported glucose-responsive insulin delivery devices using a painless MN array containing glucose-responsive vesicles (GRVs) loaded with insulin and glucose oxidase. This device releases insulin under hyperglycemic conditions by triggering vesicle dissociation (Fig. 7). This smart patch effectively regulated the blood glucose level in Type 1 diabetic mouse models [145]. In contrast, Chen et al. fabricated enzyme-free MNs from boronate-containing fibroin semi-interpenetrated by biocompatible silk. Presence of a boronate-hydrogel provides glucose-responsive diffusion control of insulin while the fibroin serves as a matrix-stiffener to ensure skin penetration. This MN array provides long term insulin delivery that is acutely glucose-responsive [146]. Additionally, resin MN patches have been fabricated with 3D printing techniques that can deliver the insulin within 30 min while maintaining its native form [147].

3.2.3.3. Gene delivery. MNs have been used for transdermal gene delivery for genetic and other skin disorders [148,149]. RNA therapy is a potential tool for the treatment of skin conditions, e.g., allergies, hyperpigmentation, psoriasis, and skin cancer that are caused by aberrant gene expression. For example, Pan et al. used dissolvable polyethylamine MNs to deliver STAT3 siRNA for melanoma treatment. An *in vivo* experiment showed the MNs effectively suppressed melanoma development through silencing the STAT3 gene and the inhibition effect was dose-dependent. [150] Similarly, Lara et al. fabricated dissolvable PVA-PMMA MNs to inhibit CD44 gene expression through siRNA. Their *in vivo* study showed that siRNA MNs can be used to treat several skin disorders by receptor inhibition [149].

3.2.3.4. Vaccine delivery. Vaccines are bioformulations that contain a dead disease-causing microorganism or its surface proteins or toxins that provide acquired immunity to a specific disease [151]. MNs have been used to deliver a broad range of vaccines in a controlled manner as they may be painlessly self-administered without skin injury. Moreover,

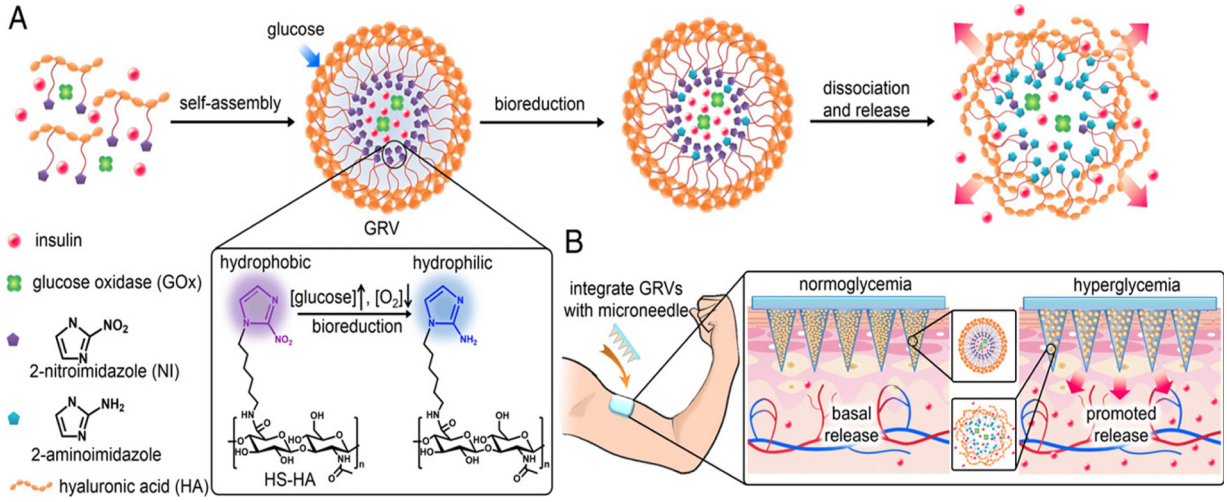


Fig. 7. Schematic of a glucose-responsive insulin delivery system using hypoxia-sensitive vesicles loaded in a MN array. (A) The formation and mechanism of glucose-responsive vesicles (GRV) composed of hypoxia-sensitive hyaluronic acid. (B) GRV-containing MN array for *in vivo* insulin delivery triggered by hyperglycemia to release insulin. This figure was reproduced with permission from Ref. [145]. Copyright 2015, United States National Academy of Sciences.

MNs show superiority over conventional vaccination in terms of vaccine stability, immunogenicity, and dose-sparing ability in humans [152–155]. Skin is an attractive organ for immunization as it contains many epidermal and dermal antigen-presenting cells. Groot et al. administered ovalbumin (OVA)-loaded PLGA nanoparticles with toll-like receptor 3 (TLR3) poly (I:C) agonist using hollow MNs. Their study revealed that PLGA with OVA and poly(I:C) protects against a recombinant strain of the intracellular bacterium *Listeria monocytogens* [156]. Using a different concept, An et al. designed dissolving MNs to deliver an amphiphilic vaccine in lymph nodes. Administration of the vaccine in mice generated a potent cellular and humoral response that was superior to those elicited by transdermal needle-based immunization [157]. Additionally, MNs were successfully used for rubella [158], measles [159,160], influenza [161–164], and other vaccines [165,166]. Prausnitz et al. have done comprehensive work on MN-based vaccination for measles [159,160], rabies [167], and influenza [161,164,168] and concluded that MNs are a potent technology for vaccine delivery. To deliver influenza vaccines, DeMuth et al. fabricated PLGA MN-based stabilized lipid nanocapsules to deliver a model vaccine formulation. These MNs were coated with a multilayer film via layer by layer assembly of cationic poly(β-amino ester) (PBAE) and negatively charged inter-bilayer crosslinked multilamellar lipid vesicles (ICMVs) (Fig. 8). The MNs mediated transcutaneous vaccination with ICMV promoted robust and antigen-specific humoral immune response with a balanced generation of multiple IgG isotypes [169]. Similarly, He et al. designed a layer by layer synthetic pH charged-invertible polymer with faster drug release. They obtained efficient immune activation through MNs in human skin and claimed this system could be potentially a broad application of MN-based vaccination [170].

Despite the potential of DNA-based cancer vaccines, their delivery to antigen-presenting cells to stimulate both humoral and cellular response remains a major challenge. Dissolving MNs are attractive vehicles for immunization because of their superior properties in delivering vaccines through the SC. For immunization against cancer, Kim et al. fabricated dissolving MNs that generated nanomicelles *in situ* upon their dissolution after cutaneous application (Fig. 9). Application of MNs containing tumor model antigen (OVA) and R848 to the skin of

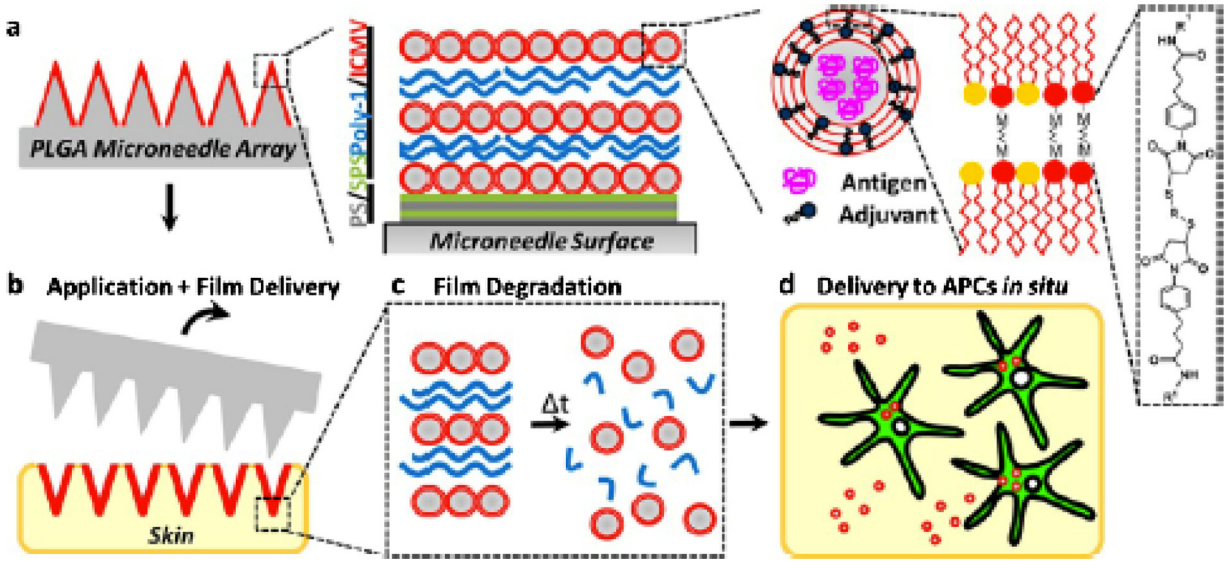


Fig. 8. (a) Schematic of poly-ICMVs multilayers deposited onto PLGA MNs. (b) MNs transfer ICMV coating into the skin as cutaneous deposits at the MN insertion point, (c) hydrolytic degradation of polymer and ICMV release into surrounding tissues, and (d) antigen exposure to initiate adaptive immunity. This figure was reproduced with permission from Ref. [169]. Copyright 2012, American Chemical Society.

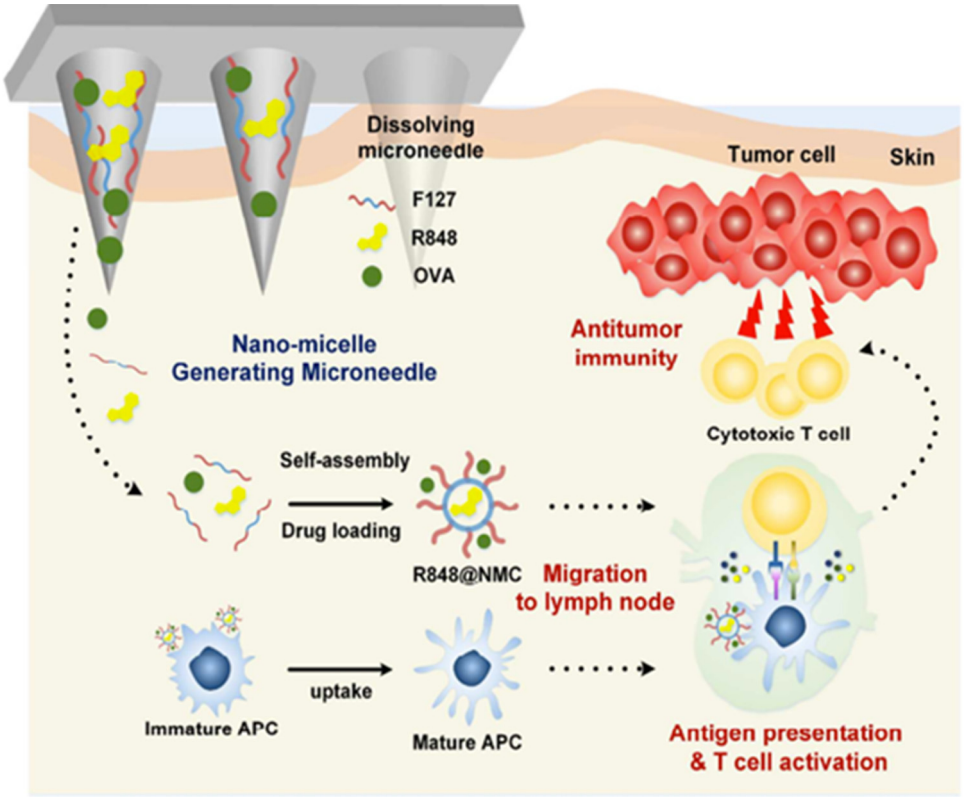


Fig. 9. Schematic illustration of the efficient delivery of hydrophobic immunomodulators and tumor antigens through dissolving MNs for cancer immunotherapy. This figure was reproduced with permission from Ref. [171]. Copyright 2018, American Chemical Society.

EG7-OVA tumor-bearing mice produced antigen-specific humoral and cellular immunity, resulting in significant antitumor activity [171]. Using a different approach for cancer vaccination, Duong et al. fabricated ultra-pH-responsive copolymer-based MNs loaded with a nano-engineered DNA vaccine along with the immunostimulatory adjuvant poly(I:C). This MN system elicits a 3-fold greater frequency of anti-OVA IgG1 serum antibody and 3-fold excess cytotoxicity toward CD8+ T-cells than a soluble DNA vaccine formulation [172]. Other applications including skin allergen immunotherapy [173], and Alzheimer's disease treatment [174] are now well documented. In summary, MNs can be used as bioresponsive drug carriers for various diseases and exploration in this field is required for advanced transdermal drug delivery.

3.3. Photothermal release

The conductive properties of materials can be used for controlled drug delivery. Conductive materials absorb incident photons of a particular wavelength and convert this energy into a local heating effect that can induce a phase transition in a temperature-responsive system. This is known as photothermal therapy (PTT) [177]. The advantages of PTT include high selectivity, minimized side effects, and non-invasiveness [178]. MN systems have been successfully applied for photothermal therapy [179,180].

3.3.1. Photothermal release mechanism

Photothermal controlled drug delivery using MNs has become very attractive. In biological systems, an overheated medium can cause hyperthermia that may cause several deleterious effects, e.g., protein denaturation and aggregation, cytosol evaporation, and cell lysis [181]. This therapy can target specific tissues or disease and relies on an optical absorbing agent (Table 5) for MN fabrication.

3.3.2. Photothermal release applications

Chemotherapy is widely used for cancer treatment, but it is also associated with severe toxic effects on normal cells. To address this problem, Chen et al. developed light-activatable MNs that provide photothermal therapy with a synergistic chemotherapeutic effect (Fig. 10A and B). When the encapsulated drug is exposed to near-infrared (NIR) light, the embedded MN array uniformly heats the target tissue inducing a thermal ablation area before melting at 50 °C with the concurrent release of Dox in a broad area to treat the tumor. This therapy completely eradicated tumors from mice within a week after a single MN application. The photothermal behavior is precisely controlled with the on/off mechanism of a laser [183]. Likewise, Hao et al. combined NIR-responsive PEGylated gold nanorods and Dox in HA MNs for epidermoid cancer therapy (Fig. 10C and D). The photothermal heating can be transferred into the center of the tumor site with the temperature rising to 60 °C within 5 min. Their *in vivo* study showed remarkable antitumor efficacy and all tested mice were cured without recurrence after only one treatment [185]. Additionally, Chen et al. fabricated PCL MNs with silica-coated lanthanum hexaboride as a NIR absorber. The MNs were irradiated with NIR light which caused the MNs to melt, enabling the drug release from the matrix. This MN system exhibited low off-state leakage and good reproducibility with a non-invasive trigger [63]. The advantages that are associated with this therapy are minimal toxic effects to other organs and high selectivity.

4. Conclusion and outlook

MNs are promising for clinical applications because of their substantial advantages over conventional TDDSs and tremendous success in preclinical studies. The international pharmaceutical industry is performing clinical trials on MN-based products, e.g., for the delivery of influenza vaccination, and hormones, such as insulin; however, no MN-based drug delivery products are available in the market yet for the

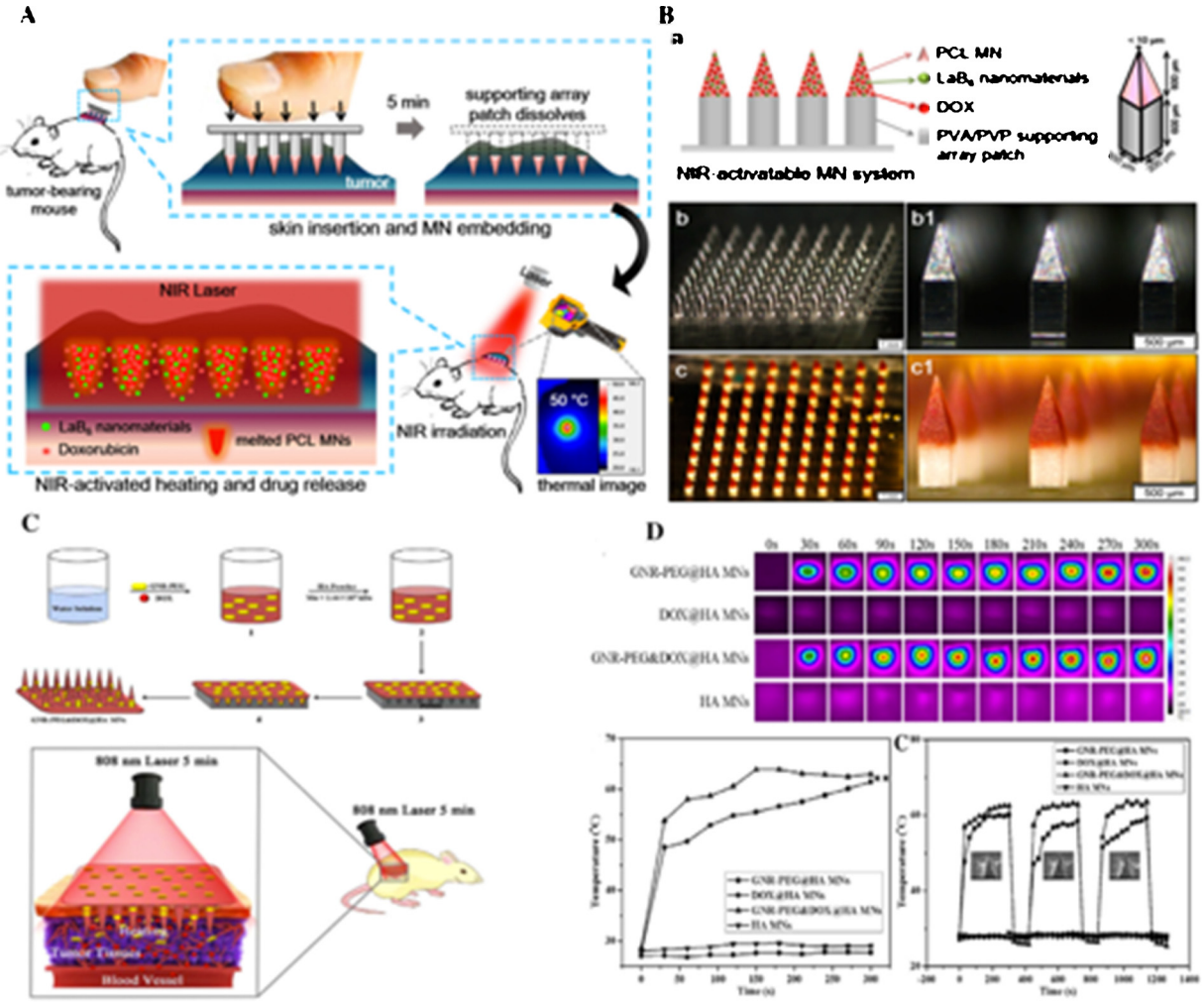


Fig. 10. A) Schematic of the combination of chemo- and photothermal therapy using NIR light activatable MNs. B) Characterization of the MNs system, (a) schematic illustration of MNs system, bright field micrograph of (b and b1) MN master structure and (c and c1) the Dox-loaded PCL MN system. These figures were reproduced with permission from Ref. [183]. Copyright 2016, American Chemical Society. C) Schematic illustration of GNR-PEG@Dox HA-MNs and NIR-responsive MNs treated tumor under an 808 nm NIR laser at 1 W cm^{-2} within 5 min. D) NIR images of MNs within 5 min, the MN heating curve, and MN temperature changes after irradiation with NIR light for 3 cycles with SEM images. These figures were reproduced with permission from Ref. [185]. Copyright 2018, Wiley-VCH.

following reasons: First, specific regulatory guidelines for MN quality control management are required. Particularly, the factors related to human safety and treatment efficacy must be well understood. Second, as a novel TDDS, the pharmacokinetics and pharmacodynamics for each MN type must be studied to ensure their maximal effectiveness with minimal toxicity, which is still the weakness in most published MN-based works, although Prausnitz et al. contributed significant work toward commercialization of MNs by applying placebo MNs for pre-clinical application in human subjects [102]. They were safe and preferred by patients as they are painless and can be self administered. Daddona et al. evaluated the clinical pharmacokinetics/dynamics of parathyroid hormone delivered by transdermal drug-coated MNs for osteoporosis treatment. They found that inter-subject and intra-subject area under curve variability was similar for all dosed patches. Comparable to injection, MNs maintain the therapeutic level for 4–6 h in clinical studies and their therapeutic response was almost the same as injection [187]. Over the last decade, Donnelly et al. have conducted significant exploration in this regard [7,104,188] and demonstrated that MNs are potent, versatile, and safe technologies for small molecules, peptide, nanoparticles, vaccines, and hormone transdermal delivery. Third, large scale manufacturing of MN devices with high precision and uniformity is still a challenge needing further technological innovation. Importantly, fundamental understanding of how the materials composition, geometry, surface properties, and drug encapsulation in MNs affect the pharmacological performance of the drugs must be obtained to establish mathematic models that can guide the MN design, optimize their fabrication, and predict their performance. Additionally, controllable delivery of proteinaceous enzymes and vaccines is a highly important topic; however, there is a lack of comprehensive understanding of MN drug encapsulation, controlled release, intradermal diffusion kinetics, and biomolecule absorption, which may facilitate wide clinical applications of MN-based vaccines.

Briefly, MNs can exploit many triggers to effectively turn drug dosing on and off, or exploit the properties of the polymer network or encapsulated drugs to attain sustained release. In this review, we highlighted different approaches to achieve controlled drug release from MNs, either by controlling the release kinetics or targeting specific sites. In the future, MN technology may address the treatment of superficial cancer and skin disorders, facilitate localized transdermal delivery, vaccine delivery, and the stability enhancement of encapsulated nanoparticles. However, the mechanical strength and safety issues of some polymeric MNs and the delivery of macromolecules are still challenging. Nevertheless, their overall efficiency and ease of patient self-administration result in highly promising clinical applications for polymeric MN TDDS. The current global interest in these devices will fuel the development of future techniques and applications in this field.

Acknowledgements

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