Front. Chem. Sci. Eng. 2020, 14(3): 378–388
https://doi.org/10.1007/s11705-019-1913-1

REVIEW ARTICLE

Enhanced penetration strategies for transdermal delivery

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Abstract Transdermal delivery offers several advantages in drug distribution, including convenience, painless administration, avoidance of first-pass metabolism, and ease of termination. However, the natural protective barriers of the skin, such as the stratum corneum, the topmost layer of skin, limit the systemic absorption of external therapeutics via transdermal delivery. Therefore, extensive application of transdermal delivery in medical treatment has been limited. Over the past few years, many formulation strategies and physical technologies, therefore, have been developed to enhance transdermal delivery. This review summarizes various formulation strategies proposed for transdermal delivery and their application in medical treatment.

Keywords transdermal delivery, stratum corneum, enhanced penetration, therapeutics

1 Introduction

Effective administration of therapeutics that is both patient-friendly and results in potent absorption can greatly enhance the outcomes of skin or internal diseases. In addition to the most extensively used methods, intravenous and oral administration, various strategies to overcome the *in vivo* barriers and achieve optimal pharmacokinetics and pharmacodynamics of drugs have also been developed, including subcutaneous injections and the use of buccal, nasal, or inhalation routes, in order to achieve systemic absorption [1–3]. In conjunction with the development of appropriate formulation strategies, transdermal delivery represents an alternative administration method to oral delivery or intravenous injection [4,5]. Owing to the direct access to the functional site of the skin when using a transdermal approach, dermatological diseases can be effectively treated. In addition, deep tissues or blood diseases can also be treated by transdermal delivery, with the development of therapeutic formulations that overcome the skin barrier and reach systemic circulation [4,5].

Transdermal delivery has a number of advantages compared with conventional administrations [4]. First, it is easy to use and can be self-administered, a patient-friendly delivery method that allows the patient to bypass complicated treatment procedures in the hospital. Second, the delivery of therapeutics by transdermal administration avoids first-pass metabolism, which is common with oral administration and greatly reduces the bioavailability of the therapeutics. Moreover, therapeutics executed by transdermal delivery can be absorbed directly into the systemic circulation after successful permeation of skin barriers, and perform their therapeutic functions with reduced side effects.

The efficient transdermal delivery of hydrophilic and macromolecular drugs is of great importance in clinical treatment. However, successful permeation of the skin barrier by transdermal delivery methods is a bottleneck for extensive translational application owing to the natural protective barriers formed by mammalian skin to ensure protection from the external environment [6]. The main barriers for successful transdermal delivery are rooted in the protective layer structure of the skin. The skin is composed of three major layers: the epidermis, dermis, and hypodermis (Fig. 1) [7]. The topmost layer of the epidermis is stratum corneum, which is the first and most difficult barrier to transdermal delivery. The main component of the stratum corneum, which presents the first robust barrier for the entrance of external substances, is multiple layers of non-living corneocytes with a thickness of approximately 10−20 μm. The stratum corneum meanwhile contains several lipid bilayers, which present another obstacle to the absorption of hydrophilic macromolecules (e.g., protein therapeutics).

Received May 12, 2019; accepted December 4, 2019

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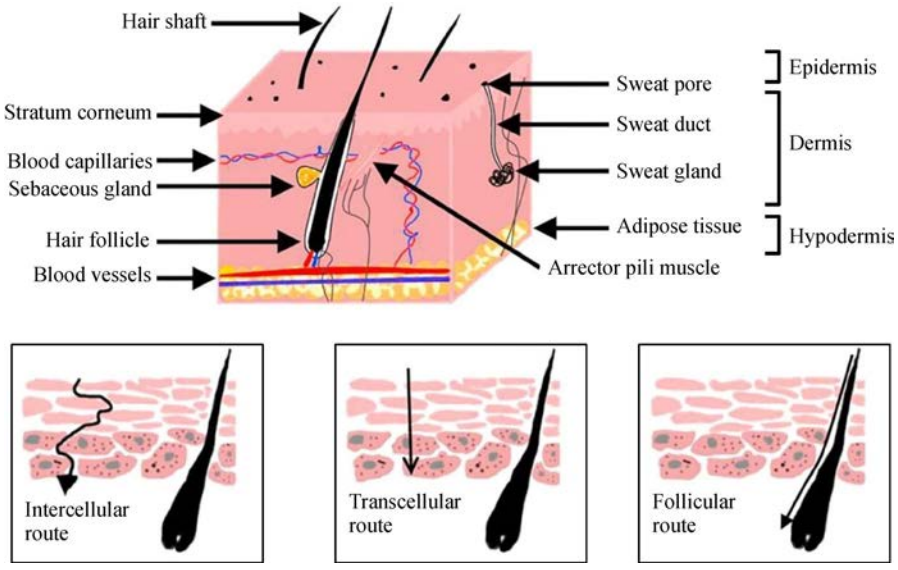

Fig. 1 Schematic representation of the human skin structure and various routes of transdermal penetration [7]. Copyright 2018, Elsevier.

Although these barriers have developed to maintain a stable physical state through isolation from the external environment, they can also block the functional therapeutics for various diseases. Underneath the stratum corneum is the avascular epidermis with a thickness of approximately 50–100 μm; the therapeutics must also transport through this layer to arrive the dermis, which contains the abundance of capillaries for systemic drug absorption.

2 Transdermal delivery

Transdermal delivery, a non-parenteral and non-invasive delivery route, has major advantages compared with conventional oral administration or intravenous injection, including painless self-administration, avoidance of first-pass metabolism, and sustained release. Many methodologies for enhanced transdermal delivery, such as chemical engineering and formulation technologies, have been targeted to develop and expand the application of these treatments. The main target for transdermal delivery is to overcome these barriers from the stratum corneum [8]. Thus far, only few drugs have been successfully administered by transdermal delivery [4], as skin barriers allow the passage of foreign molecules up to a few hundred Daltons. The reality is that most therapeutic drugs are much larger than a hundred Daltons, not to mention the rapid development of protein therapeutics above 5 kDa [9]. To address the bottleneck of transdermal penetration, many formulation strategies, as well as chemical enhancers, iontophoresis, electroporation, microneedles, and noncavitational ultrasound [4], are currently being exploited for the enhanced penetration of drugs to improve therapeutic outcomes (Fig. 2). This review has predominantly summarized the formulation-related technologies for transdermal delivery and their application in *in vitro* investigations or *in vivo* treatments.

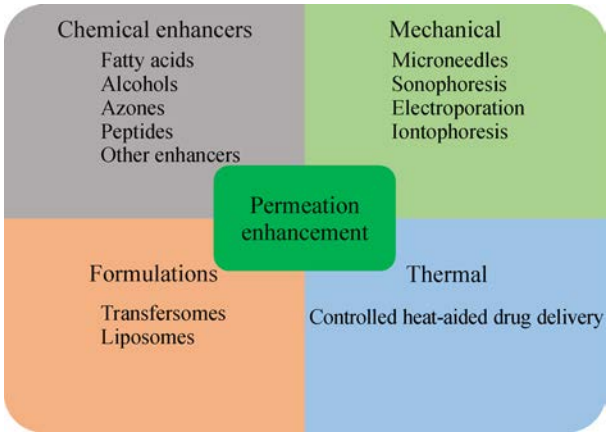

Fig. 2 Transdermal penetration enhancement strategies.

3 Chemical penetration enhancers

Although chemical enhancers have been studied extensively for facilitating transdermal drug penetration, over many decades, and are well reviewed in other related literature [10–12], it is necessary to mention them here owing to their great importance and convenience for translational application. The exact theory behind the function of chemical enhancers is complicated, and several mechanisms have been proposed. According to the lipid-protein-partitioning theory, chemical enhancers function by one or more major mechanisms, including (i) disruption of the corneocyte envelope; (ii) interaction with protein junctions, for example, fatty acids or peptides directed

against tight junction molecules for transdermal delivery [13]; (iii) alteration of the partition coefficient between the stratum corneum components and the lipid bilayers in the diffusion pathway [10,11,14]. More than 300 chemicals have been studied as transdermal penetration enhancers [15]. Here, we have briefly highlighted several mainstream chemical enhancers; for a more in-depth review of other chemical enhancers, the readers are directed to related literature [10,16].

3.1 Fatty acids

Fatty acids such as oleic acid, stearic acid, isopropyl palmitate, and ethyl oleate function as inactive penetration ingredients in a number of products approved by the US Food and Drug Administration [17,18]. The penetration effect of fatty acids has been shown to be dependent on their structure, such as the length of the alkyl chain and the degree of saturation [19]. Aungst et al. studied a series of fatty acids as chemical enhancers for naloxone transdermal penetration and investigated their activity-structure relationships [20,21]. The carbon chain length and structure of fatty acids imposed significant influence on the penetration effectiveness. The maximum enhancement effect was observed for saturated fatty acids with a alkyl chain length from 10 to 14 carbon atoms. Although an increase occurred with chain lengths beyond 14 carbons, a decrease penetration effect was obtained. Ibrahim and Li investigated fatty acids (lauric acid, myristic acid, and capric acid) as chemical enhancers for the controlled release of triprolidone [17]. Unsaturated fatty acids conferred a higher penetration effect than the same carbon chain with a saturated structure, owing to the stronger disruption of the lipid layer of the skin. Therefore, owing to its unsaturated state and carbon chain structure, oleic acid has been well studied as a penetration enhancer, which increases the diffusion coefficient of the skin due to its enhanced interaction with the lipid layer of the skin [20–22].

3.2 Alcohols

Alcohols are commonly used as penetration enhancers to improve the transdermal delivery of drugs. Short-chain alcohols such as ethanol and isopropyl alcohols or long-chain alcohols such as fatty alcohols (1-butanol, 1-propanol, 1-octanol, and decanol), have been used in dermal and transdermal products [23]. Among these, ethanol and isopropyl alcohols are generally employed as penetration enhancers as well as functional co-solvents in many transdermal and topical commercial formulations — for example, in the marketed product Estraderm™ [24,25]. Various mechanisms for the penetration activity of alcohols have been proposed, including extraction of lipids and proteins from the stratum corneum at high concentrations (75% v/v), increasing the partition coefficient in the stratum corneum of the drugs, improving drug solubility, and altering the thermodynamics of the drugs [18,26]. Liu et al. investigated the impact of isopropyl myristate and isopropanol on the permeation efficiency of estradiol in human skin. The uptake of isopropanol showed linear positive correlation with the solubility of estradiol in the stratum corneum [27], which could be explained by the increase in the lipid fluidity of drugs facilitated by alcohols via disturbance of the intercellular lipid bilayer structure. Watkinson et al. studied the permeation effect of ibuprofen when dissolved in ethanol or ethanol-water mixtures [28]. It was reported that the penetration of ibuprofen increased with ethanol:water ratio; that is, a higher content of ethanol increased the solubility of ibuprofen. However, at an ethanol content above 75%, ethanol could be easily evaporated, which decreased the penetration of ibuprofen. Given that most drugs are hydrophobic [29], the concentration of ethanol should be well balanced when designing an ethanol-based enhancer formulation. Although the solubility of drugs can be enhanced when a higher ratio of ethanol is used, it may also increase the evaporation rate of the solvent. It should also be noted that long chain alcohols with unsaturated or saturated structures function through complicated mechanisms generated from the synergistic effect of alcohols, carbon chains, double bonds, or multiple double bonds [30,31]. A parabolic relationship was observed between the carbon numbers of saturated fatty alcohols and penetration efficiency to human skin: saturated fatty alcohols with 10 carbon atoms yielded the maximum transdermal delivery of melatonin. The increased penetration of human skin was observed when the unsaturation increased from one to two double bonds, but decreased penetration with three double bonds.

3.3 Azone

Azone was investigated widely as the first penetration enhancer in the 1980s and 1990s [26]. The structure of azone comprises a polar head (seven-membered ring) group attached to a C12 chain. It is an effective enhancer and has very low toxicity with mild skin irritancy [32]. The penetration mechanism of azone is still unclear; some hypotheses has been proposed that combine many factors, such as interaction with the lipid bilayer of skin and enhanced flux leading to an increase in drug diffusion [32–34]. Jampilek et al. suggested that the azone could disrupt the intact structure of lipid bilayer of stratum corneum by injecting the long carbon chains of azone into the hydrophobic domain [32,35]. Hadgraft et al. considered that the polar group of azone could interact with ceramides that are abundant in the skin, thereby increasing penetration ability [36].

In addition to fatty acids, alcohols, and azone, a diverse range of other penetration enhancers, such as surfactants, amides, sulfoxides, and phospholipids, were also investigated for the transdermal delivery for different drugs

[18,26]. They also functioned through various mechanisms according to their chemical structures or functional groups, such as enhancing the penetration of the drug into and through the skin, remodeling the dispersion coefficient of the drugs between skin and formulations.

3.4 Peptides

Cell-penetrating peptides (CPPs) have been investigated widely for intracellular delivery or crossing blood brain barriers (BBBs) owing to their distinctive transduction functions [37,38]. To extend the application of CPPs, the transdermal delivery of therapeutics with penetrating peptides has emerged as an attractive and promising topic. In the past few decades, peptides, such as INF7 (an influenza hemagglutinin derived peptide) [39,40], TAT (derived from the transactivator of transcription of human immunodeficiency virus) [41–43], polyarginine [44–46], meganin [47], penetratin [48], TD-1(transdermal peptide) [9], and SPACE-peptide (skin penetrating and cell entering peptide) [49], have been studied as penetrating functional units for transdermal delivery of therapeutics including small-molecule drugs, siRNA, or proteins. For example, the PD-1 peptide could carry siRNA through the skin and silence a target gene [50]. Candan et al. investigated the efficiency of the transdermal delivery of hydroquinone meditated by a polyarginine peptide [51]. Although the detailed penetration mechanisms of CPPs are still unclear, the efficient transdermal delivery of these peptides may be beneficial for the treatment of superficial skin diseases. Here, we have mainly focused on the protein transdermal delivery facilitated by peptides.

Gautam et al. tested a new human protein-derived arginine-rich peptide, IMT-P8 (Institute of Microbial Technology-Peptide 8, peptide sequence, RRWRRWNRF-NRRRCR) for the transduction of peptides or proteins [52]. They first verified that IMT-P8 could deliver different sizes of molecules, such as FITC (fluorescein isothiocyanate), KLA peptides (apoptosis-inducing peptide), and green fluorescent protein (GFP), into various human cell lines. As the results showed that IMT-P8 could transport KLA and GFP across the membrane of the human tumor cells, they then investigated if this IMT-P8 peptide was also suitable for transdermal penetration. For this purpose, GFP, TAT-GFP and IMT-P8-GFP were applied topically on shaved skin of mice, and fluorescence imaging of GFP was performed by confocal microscopy. Mice treated with TAT-GFP and IMT-P8-GFP both showed significant transdermal delivery, as revealed by green fluorescence from attached GFP; however, the fluorescence intensity of the mice treated with IMT-P8-GFP was much higher than that treated with TAT-GFP, as determine from quantification of the data from two-dimensional surface plots (Fig. 3). The following detailed experiments showed that TAT-GFP and IMT-P8-GFP tended to accumulate in epidermis, hair follicles, and deeper layers of skin.

In the past few years, a series of cyclopeptides was developed as delivery vector of proteins and other biomacromolecules to enhance *in vivo* pharmacokinetics [49,53]. Chang et al. designed a series of cationic cyclopeptides based on the amino acid sequence of the TD-1 (ACSSSPSKHCG) peptide [54]. The structure-function relationship of multiple peptides based on TD-1 was studied in reasonable detail. They used these peptides as insulin vectors and evaluated the blood glucose concentration after cutaneous administration, and reported

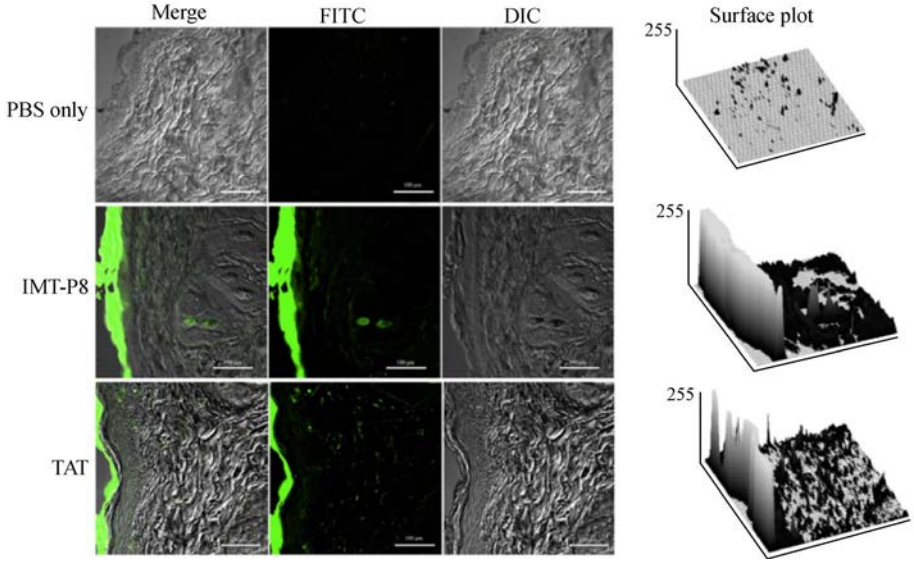

Fig. 3 Penetration ability of IMT-P8 and TAT in a mice model (The intensity and thickness of the fluorescence signal from IMT-P8-modified GFP was higher than that of TAT-modified GFP and the PBS control group, demonstrating the strong penetration ability of IMT-P8 in mice skin) [52]. Copyright 2016, Nature Publishing Group.

that the cyclic structure of the peptide was important for the transdermal penetration. Although both TD-34 and TD-1 resulted in effective percutaneous absorption of insulin by dynamically loosening the tight junction of epithelium tissue in follicles, TD-34 bis-substituted lysine at N-5 and N-6, showed the most efficient decreased in the level of the blood glucose, which was reduced to only 26% of the initial value in diabetic rats.

4 Transfersomes

In the past few years, the function of transfersomes as topical drug delivery agents for enhanced transdermal penetration has garnered an impressive amount of attention. Transfersomes are ultra-flexible elastic lipid nanostructures consisting of phospholipids and an edge activator (Fig. 4), usually a single chain surfactant with a high radius of curvature that can both destabilize the bilayers of the vector and improve deformability of the lipid bilayers [55–57]. The elastic characteristic of transfersomes endows them flexibility to squeeze through the intercellular spaces of stratum corneum and then access the systemic circulation; thus, they represent good formulation candidates for therapeutics for transdermal delivery [58–60].

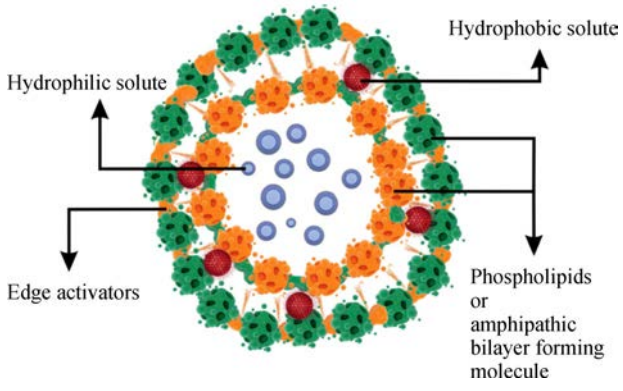

Fig. 4 Schematic diagram to depict the structure of transfersomes [61]. Copyright 2017, Taylor & Francis Group.

Wang et al. recently designed mixed monoterpenes (limonene-citral mixture) edge-activated PEGylated transfersomes (MMPTs) synthesized by an ethanol injection process [62]. The optimized transfersomes were used for loading simonenine, a pure alkaloid extracted from the stem of *Sinomenium acutum* (SIN), which has been frequently used in clinic to treat rheumatoid arthritis [63–65]. The permeation/deposition characteristics of MMPTs were related with the content of edge activator terpenes and DSPE-PEG 2000. It was reported that the steady state concentrations of SIN from the optimized MMPTs released in the skin were 8.7- and 8.2-fold higher than those from the control liposomes respectively, as revealed by the *in vivo* cutaneous pharmacokinetic study. The optimized transfersomes modified with terpenes and DSPE-PEG 2000 exhibited excellent percutaneous permeation properties. Pentoxifylline (PTX) is a dimethyl xanthine derivative used for the treatment of intermittent claudication and chronic occlusive arterial diseases [66]. PTX is usually administered via the oral route and undergoes first-pass metabolism, which results in low *in vivo* bioavailability (20%) and a short half-life (0.4−0.8 h) [67–69]. To improve the therapeutic efficiency of PTX, Al Shuwaili et al. synthesized a series of transfersomes loaded with PTX, and realized efficient sustained release of PTX that avoided first-pass metabolism and improved PTX therapeutic activity after subcutaneous administration [57]. Transfersomes can also be a good vector for the delivery of therapeutics for the treatment of skin cancers such as basal cell carcinoma and melanoma [70].

Furthermore, the design of transfersomes can be personalized by the use of different edge activators to load both small and large therapeutics. The edge activators are able to adapt to external stress by squeezing themselves through the intercellular spaces of stratum corneum, subsequently conferring increased transdermal flux of the therapeutic modules.

5 Liposomes

Since liposomes were first introduced in 1964 [71], they have been extensively investigated as parenteral carriers for various components including imaging agents [72,73], small-molecule drugs [74–76], and proteins [77–79]. Liposomes can also be designed with transdermal penetration ability. Dermal liposome formulations have been exploited for the cosmetic industry since 1987; currently, over than 100 liposome and niosome cosmetic products have been commercialized [80].

Formulations that facilitate the rapid penetration of nonsteroidal anti-inflammatory drugs into deeper skin tissues would benefit the treatment of peripheral pain and inflammation diseases derived from musculoskeletal injuries and disorders. Sacha et al. tested the transdermal penetration ability of three commercialized diclofenac products by using an *ex vivo* skin model: liposomal gel formulation of diclofenac sodium (1%, Ratiopharm GmbH) and emulsion gel formulation of diclofenac sodium (1.16% and 2.32%, Novartis Consumer Health GmbH) [81]. They used the receptor compartment fluid to collect the portion crossing the skin and analyzed the transdermal penetration of diclofenac by high performance liquid chromatography. They concluded that the transdermal permeability coefficient for the liposome formulations was the highest, at $(69.3\pm14.4)\times10^{-8}$ cm·s^{-1}, compared with $(34.9\pm9.1)\times10^{-8}$ cm·s^{-1} and $(47.1\pm9.5)\times10^{-8}$ cm·s^{-1} for the emulsion gel 1.16% and emulsion gel 2.32%, respectively. This demonstrated the advantages

liposomal formulations for transdermal delivery. Yang et al. encapsulated an X-shaped oligodeoxynucleotides complex (XL-DNA) into liposomes (Lipo) fabricated from 1,2-dioleoyl-sn-glycero-3-phosphocholine,1,2-dioleoyl-sn-glycero-3-phospho-(1'-rac-glycerol) and cholesterol [82]. XL-DNA has an immunostimulatory function and can activate toll-like receptor 9 in dendritic cells to treat immune diseases such as atopic dermatitis. It was reported that Lipo-XL-DNA was efficiently delivered into the epidermis and dermis in a mice model and led to effective therapeutic outcomes for atopic dermatitis symptoms.

Environment-sensitive formulations confer the carriers with "intelligent" characteristics able to release the functional payloads when triggered by the target sites, thus simultaneously improving the specificity of the drugs and reducing the side effects to other healthy tissues. Yamazaki et al. synthesized novel functional liposomes modified with methacrylate-based copolymers poly(MD-*co*-MAA-*co*-LT)s [83] that were equipped with pH- and temperature-responsive characteristics generated from the carboxyl and oligo (ethylene glycol) groups anchored in the polymers. They demonstrated that the polymer-modified liposomes loaded with the imaging agent calcein exhibited strong skin penetration triggered by a synergistic effect of acidic pH and temperature (Fig. 5). The fluorescence signals of calcein diffused into the underlayers of skin, corresponding to stratum granulosum and stratum spinosum. They concluded that a proportion of the liposomes penetrated into the stratum basale and were taken up by melanocytes.

6 Microneedles

Over the past few years, microneedles (MN)-mediated carriers with biomacromolecular and small molecular drugs have attracted much interest from researchers [84–86]. MNs consist of a needle-like micro convex array-based positioned on a baseplate; the piercing properties of MNs confer them with inherent transdermal delivery ability [87–90]. MNs are loaded with therapeutics by a variety of strategies, including spray coating [91,92], dip coating [93–95], and inkjet printing [95,96]. MNs penetrate the stratum corneum by forming micro-channels through minimally invasive physical interaction; thus, the payloads encapsulated in the cavity of MNs can access the dermal environment located in the deeper layers of the skin.

To improve the penetration efficiency of hydrophobic

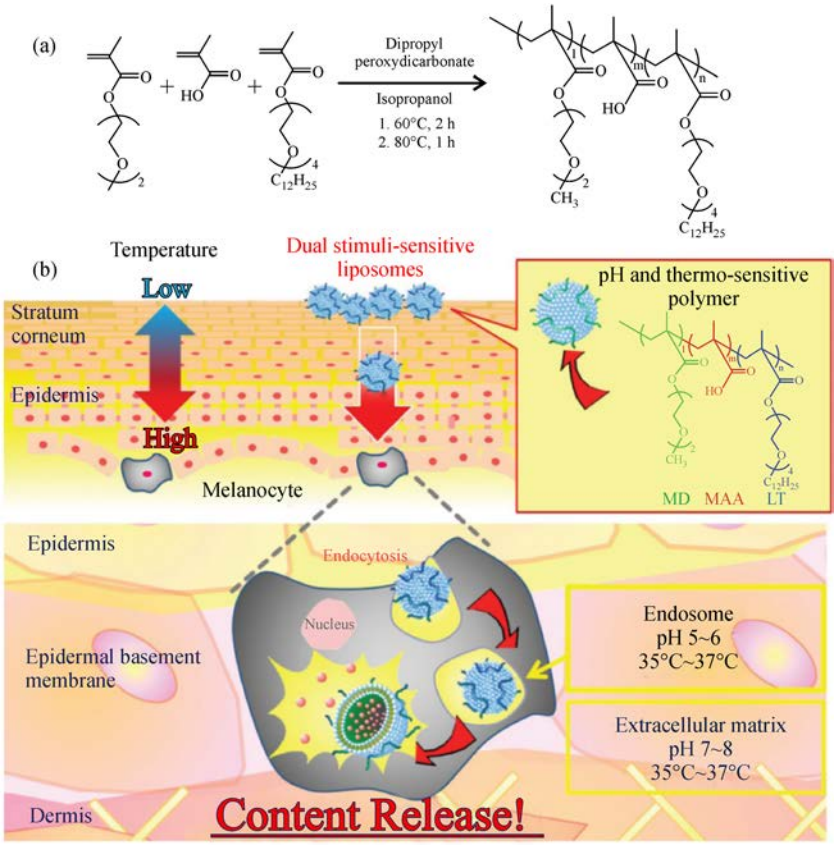

Fig. 5 Transdermal delivery of liposomes. (a) Synthesis of copolymers poly(MD-MAA-LT)s; (b) pH-Sensitive and temperature-sensitive polymer-modified dual-responsive liposomes used in a transdermal drug carrier system that is triggered by both the temperature of the epidermis and an acidic pH environment at the endosome interior [83]. Copyright 2017, RSC.

drugs, Yao et al. designed soluble MNs by the incorporation of chitosan and beta-sodium glycerophosphate (*β*-GP): first, they assembled the hydrophobic levonorgestrel (LNG) into the molecules of hydroxypropyl beta cyclodextrin (HP-*β*-CD) to form LNG-HP-*β*-CD inclusion compounds, and then the compounds were loaded into the soluble MNs [97]. It was reported that the LNG encapsulated in MNs showed similar pharmacokinetic behaviors through subcutaneous injection as those of oral administration. Wang et al. prepared soluble polymer MNs fabricated with *N*,*N*'-methylenebis (acrylamide), cross-linked hyaluronic acid, and photoinitiator by *in situ* polymerization following exposure to UV light. Acid-sensitive dextran nanoparticles (NPs) that encapsulated aPD1 and catalase (CAT) to improve hypoxia, and glucose oxidase (GO_x) to convert blood glucose to gluconic acid, were then loaded into the cavity of the polymer MNs [98]. When the MNs loaded with therapeutic proteins were intratumorally administered into mice with melanoma, MN-patched mice displayed effective immune therapy through the release of aPD1, which was triggered by a synergistic effect from CAT to assist glucose oxidation by the generation of O_2, GO_x to convert blood glucose to gluconic acid in the presence of O_2, and then by self-dissociation of NPs triggered by the tumor acidic microenvironment.

The rapid fabrication of MNs with tightly, controllable design parameters is a bottleneck for their widespread application. Johnson et al. reported a method to fabricate MN patches with a range of compositions and geometries by the additive manufacturing technique of continuous liquid interface production (CLIP) [99]. They then used model proteins such as bovine serum albumin (BSA), ovalbumin, and lysozyme for dip coating into CLIP MNs by controllable spatial deposition [100] (Fig. 6). The proteins within encapsulated within CLIP MNs could release both in solution and upon insertion into a porcine skin, while maintaining their bioactivities after release from the MNs. To investigate the *in vivo* behavior of the protein-encapsulated MNs, MNs coated with AlexaFluor 680-BSA (AF680-BSA) were applied to the back of BALB/c mice and compared to the application of AF680-BSA alone via subcutaneous injection as a control group. The mice subcutaneously injected with AF680-BSA alone had a rapid decrease in fluorescent signal, with 14% signal remaining at the 6 h post-treatment and 4% at the 72 h post-treatment, suggesting rapid release of the protein. In contrast, the AlexaFluor 680-BSA-loaded MN-treated mice had 79% fluorescence signal remaining at 6 h and 19% at 72 h post-treatment, which demonstrated the sustained release of the protein with retained activity from the MNs. This would be of great benefit for the vaccine administration, as the sustained antigen release can potentially stimulate a prolonged immune response and enhance the immune efficiency [101,102].

In short, transfersomes, liposomes, and MNs offer promising drug formulation strategies for dermal and transdermal administration and are well worth of development in the future. However, their success for marketed application is far from what we have expected for some immature technologies. For instance, it is of great importance to develop the uniform quality of transfer-

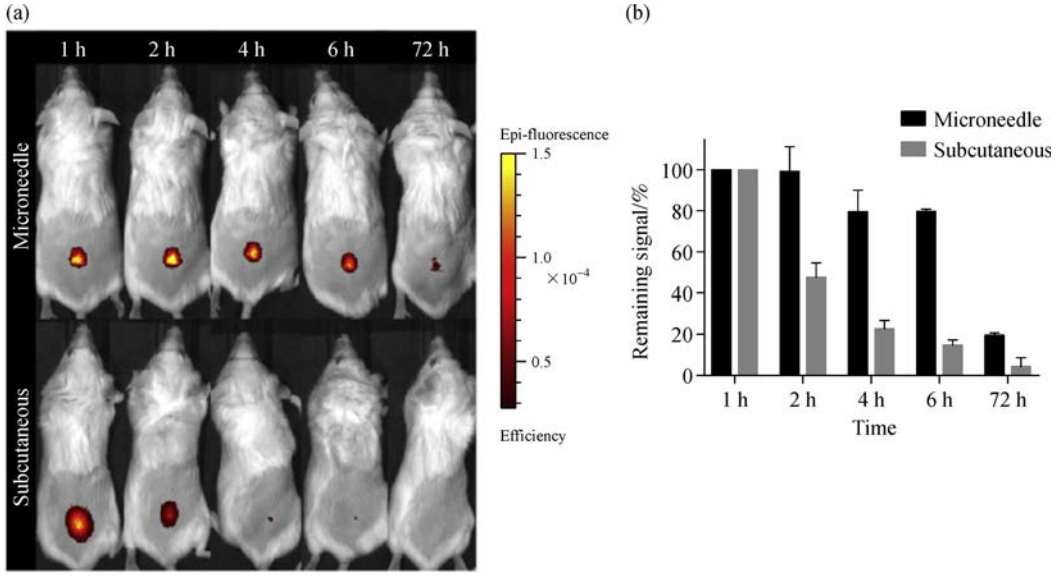

Fig. 6 Transdermal delivery of labeled BSA with microneedles. (a) Fluorescence imaging of mice using IVIS (PerkinElmer) at time points 1, 2, 4, 6 and 72 h post-treatment with AF680-BSA-coated microneedles (top) and subcutaneous AF680-BSA injection (bottom); (b) Quantization of fluorescent signal remaining at administration site during 1−72 h post-treatment, percent remaining signal calculated as compared to signal present at 1 h post-treatment [100]. Copyright 2018, Elsevier.

somes, liposomes or MNs when preparing for the related formulations in industrial production.

7 Conclusions and outlook

Transdermal drug delivery is a promising administration route compared with intravenous injection that is accompanied by inconvenience and pain, to the oral route with low bioavailability of therapeutics, and the limited controlled-release drugs of both. Moreover, transdermal delivery also suggests potential application in the skin tissue engineering, such as bacterial inhibition, cartilage, and dermal applications [103–105]. However, the intact stratum corneum provides inherent barriers to the penetration of both exogenous small-molecule and macromolecular drugs. The development of both novel chemical formulations and smart physical devices has been a tactic to improve the transdermal delivery efficiency in a controllable pattern. In this review, we have examined various skin penetration strategies that mediate transdermal delivery, including chemical formulations, such as chemical enhancers, peptides, transfersomes, and liposomes, as well as combinatorial technology, such as microneedles. These strategies all possess their own advantages or disadvantage; for example, chemical enhancers offer flexibility, compatibility for incorporation into inexpensive and simple formulations, convenience of use, ease of industrial manufacture. These advantages make chemical enhancers a universal strategy for transdermal drug delivery. However, there are also disadvantages to chemical enhancers, including skin irritation, and they not suitable for the delivery of macromolecules. Although peptides perform efficient transdermal delivery, the industrial production of peptides is very expensive. In the meantime, the quality control procedures required to adequately prepare transfersomes, liposomes, and microneeedles are of great importance in their translational application. In addition, most of the current transdermal delivery has focused on a single strategy mentioned from those discussed; the combination of formulation technologies with these transdermal delivery methods may integrate their advantages and mitigate their disadvantages, most likely leading to efficient and low-cost transdermal penetration formulations.

Acknowledgements Xiaowen Liu acknowledges support by the startup funding from Jinan University and the Fundamental Research Funds for the Central Universities (No. 11618337), the National Natural Science Foundation of China (Grant No. 81903546).

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