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Functional nano-systems for transdermal drug delivery and skin therapy

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Transdermal drug delivery is one of the least intrusive and patient-friendly ways for therapeutic agent administration. Recently, functional nano-systems have been demonstrated as one of the most promising strategies to treat skin diseases by improving drug penetration across the skin barrier and achieving therapeutically effective drug concentrations in the target cutaneous tissues. Here, a brief review of functional nano-systems for promoting transdermal drug delivery is presented. The fundamentals of transdermal delivery, including skin biology and penetration routes, are introduced. The characteristics of functional nano-systems for facilitating transdermal drug delivery are elucidated. Moreover, the fabrication of various types of functional transdermal nano-systems is systematically presented. Multiple techniques for evaluating the transdermal capacities of nano-systems are illustrated. Finally, the advances in the applications of functional transdermal nano-systems for treating different skin diseases are summarized.

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1. Introduction

Transdermal drug delivery is one of the least intrusive and patient-friendly ways for therapeutic agent administration. It can not only boost medication bioavailability by concentrating drug molecules in a particular skin region, but also limit the possibility of unforeseen adverse effects.[1–3] Therefore, transdermal drug delivery is an appealing option for oral administration and an alternative to hypodermic injection. In the 1970s, the Food and Drug Administration (FDA) first authorized the transdermal patch to administer scopolamine for the treatment of motion sickness.[4] Since then, various physical and chemical strategies of transdermal drug delivery systems (TDDs) have been developed with significant progress achieved. Physical methods include epidermal erosion, skin puncture devices using probes, high-frequency oscillating needle bundles, microneedle arrays, and high-velocity dry powder jets, whereas chemical methods include the use of penetration enhancers and prodrugs.[5] However, physical methods and chemical methods possess their own drawbacks. Physical methods such as iontophoresis may lead to pain, a burning sensation, blister formation, and skin necrosis with increasing current strength or if applied for a longer period.[6] Slight itching, irritation, and a burning sensation have been reported with sonophoresis.[7] Microneedles may cause skin irritation or allergy in sensitive skin. Topical formulations such as pastes, creams, gels, oils and ointments[8,9] have been developed with significant progress achieved but have poor permeation through the stratum corneum (SC) and require a high dose and repeated applications in a day, which may cause severe side effects like skin rashes and itching that lead to poor patient compliance for long term therapy.[10] Moreover, the application of pro-drugs is another chemical technique to conquer the barrier function of the skin. The main disadvantage of this approach is that the pro-moiety is basically a redundant coarse stone, which, when released, may result in adverse effects.[7] Thus, it is highly desired to develop new types of TDDs, improve drug penetration across the skin barrier and achieve therapeutically effective drug concentrations in the target cutaneous tissues.

Ever since the term "nanoparticles" was known to the scientific world from the 1970s, functional nano-systems have attracted great scientific interest and have always been the research hotspot in the dynamic interdisciplinary branch of science.[11–13] Functional nano-systems typically have diameters ranging from 10 to 1000 nm in at least one dimension and are composed of different biocompatible materials, including

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natural or synthetic polymers and lipids.[14] Due to their distinct characteristics, including small size and large specific surface area, high encapsulation capacity of both hydrophilic and lipophilic drugs and applicability for multiple administration routes, functional nano-systems can be used as superior drug delivery platforms, which can regulate the release rate, change the biodistribution and improve the bioavailability of the delivered drugs. As a result, functional nano-systems provide new concepts and opportunities for developing new TDDs. Recently, functional nano-systems have been attracted a great deal of interest for transdermal drug delivery, and plenty of research and significant achievements have been made. Various functional nano-systems, such as nanogels, polymeric nanoparticles, metallic nanoparticles, dendrimers, micelles, lipid nanoparticles and quantum dot nanocarriers, have been demonstrated to be an effective strategy to overcome the skin barrier, while causing no tissue harm and promoting transdermal drug delivery (Fig. 1).[15–20] Therefore, a comprehensive depiction of the whole scene on functional nano-systems for transdermal drug delivery, from fundamentals to evaluations and various advanced applications, is desired.

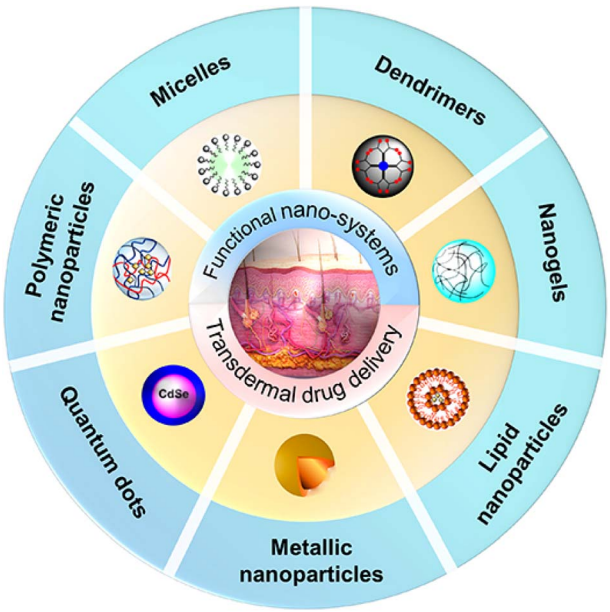

Fig. 1 Schematic illustration of representative functional nano-systems for promoting transdermal drug delivery, including liposomes, quantum dots, hybrid NPs, dendrimers, micelles, ionic liquid-based NPs and polymeric nanogels. Adapted from ref. 19. Copyright 2016 John Wiley & Sons Ltd. Adapted from ref. 20. Copyright 2019 MDPI.

In this review, we highlight the recent progress on functional nano-systems for promoting transdermal drug delivery. First, the fundamentals of transdermal delivery, including skin biology and penetration routes, are introduced. Then, the characteristics of functional nano-systems for facilitating transdermal drug delivery are elucidated. Moreover, the fabrication of various types of functional transdermal nano-systems are systematically presented. Besides, multiple techniques for evaluating the transdermal capacities of nano-systems are illustrated. Finally, the advances in applications of functional transdermal nano-systems for treating different skin diseases are summarized. We present an overview of functional nano-systems for transdermal drug delivery covering from basic fundamentals to progress made for advanced therapeutic applications in recent years.

2. Fundamentals of transdermal delivery

2.1 Skin biology

As the biggest organ of the human body with simple accessibility, the skin is a prospective option for medication administration. Thus, it been extensively examined, and its biological structure is well understood.[21] The skin structure can be

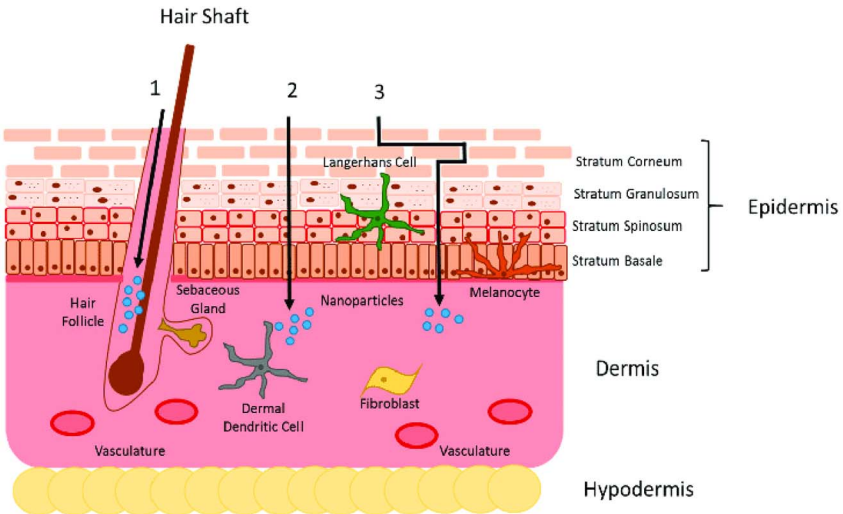

Fig. 2 The skin biological structure and three distinct pathways: (A) transcellular, (B) intercellular and (C) appendageal routes. Adapted from ref. 26. Copyright 2016 licensee MDPI.

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categorized into three layers epidermis, dermis, and subcutaneous "fat" tissue (Fig. 2). The epidermis comprises two main layers: stratum corneum (SC), the viable epidermis (VE). The SC, with a thickness of 10–20 μm, consists of dead, flattened, keratin-rich cells (keratinocytes) and an intercellular lamellar lipid bilayer, which acts as the outer layer of the skin. The lipid layer primarily consists of ceramides (50%), cholesterol (25%), and other free fatty acids, and is estimated to be <100 nm wide, limiting passive diffusion to small, lipophilic molecules.[21] The SC is characterized as having a 'brick-and-mortar' structure due to the long, flat, tile-like form of the corneocytes[22] and responsible for the most of the skin's barrier function.[23–26] The keratinocytes underlying the SC make up the VE, which is approximately 100–150 μm thick. These cells continually proliferate, pushing older cells to the surface where they undergo keratinization and programmed cell death, resulting in the formation of the SC.[27] Keratinocytes can produce cytokines and chemokines to boost immune activity at the site of infection.[28] Patrolling dendritic cells may be recruited as a result of this signaling.

The dermis, which is ~1200 μm thick, is on top of the skin's middle layer. It is made up of connective tissue like collagen, elastin, fibronectin, and glycosaminoglycan matrix, and it is dotted with blood and lymphatic vessels, nerve endings, hair follicles, sebaceous glands, and sweat glands.[21,29] The hair follicles and sweat ducts form a direct connecting path from the dermis to the skin surface, bypassing the stratum corneum and henceforth involved in providing the appendageal route of skin permeation.[29]

The superficial fascia, or the loose connective and adipose tissue beneath the dermis that connects and supports the skin and muscle, is known as the subcutaneous "fat" tissue. It is composed of cells that contain large quantities of fat, making the cytoplasm lipoidal in character.[30] The collagen between the fat cells provides the linkage of the epidermis and the dermis with the underlying structures of the skin.

2.2 Skin penetration routes

In accordance with the skin biological structure, the process of transdermal delivery can occur *via* three distinct pathways: (A) intercellular route, (B) transcellular route, and (C) appendageal route (Fig. 2). The intercellular route has been identified as the primary pathway, in which the penetrating nanocarriers cross the intercellular lipids by diffusion between the cells.[31] The size as well as the mechanical characteristics of the nanocarriers must be considered for this pathway since they must be flexible.[17] Rigid nanocarriers, like metal NPs, have been reported to have a limited ability to enter the SC *via* the intercellular pathway. It has been proposed that their lack of flexibility impedes their diffusion between cells.[32] In contrast, highly flexible polymer-based nanocarriers have been shown to be able to penetrate into the SC. The transcellular route is the most direct and fast pathway for the nanocarriers to permeate the skin; however, this pathway is challenging as NPs must overcome both the lipophilic (cell membrane and the lipid matrix) and lipophobic barriers (inside the cells) within the skin cells.[33] Functional nanocarriers with a high degree of amphiphilicity may be suitable options for overcoming such barriers. The follicular pathway is the most commonly postulated method for highly rigid nanocarriers to penetrate the skin. This approach addresses the administration of medications directly through hair follicles and glandular ducts. However, this route is severely constrained since hair follicles and glandular ducts account for just 0.1 and 0.01% of the entire skin surface area, respectively.[34] Meanwhile, there is sufficient evidence that the size of the applied nanocarriers has an important impact on the penetration depth and selective targeting of certain compartments inside the hair follicle.[35] Toll *et al.* showed that the penetration depth in terminal hair follicles increases when smaller NPs are used.[36] Similarly, Alvarez Roman *et al.* demonstrated with animal models that ~20 nm NPs penetrate deeper than polystyrene ~200 nm particles.[37] Furthermore, the accumulation of nanocarriers within the hair follicle canal can benefit from their depot activity, allowing for continuous drug release over time. Thus, a constant drug level in tissue could be achieved opening the way for transdermal delivery of active compounds to specific targets within the hair follicle.[38,39] Taken together, each of the penetration routes represents a chance for nano-systems to overcome the skin barrier and the properties of the functional nano-systems must be fine-tuned to meet the requirements of the selected routes.

3. Characteristics of functional nano-systems for facilitating transdermal drug delivery

Functional nano-systems with the capacity to cross the skin offer an attractive option to facilitate transdermal drug delivery. It is worth noting that due to the unique physicochemical features of nano-systems, such as nanoscale effect, form, stiffness, thermo-responsiveness, surface charge, and pH-responsiveness, that can all impact skin penetration and interact with biological components to improve the transdermal capacity, the efficacy of nano-systems is more from their capacity to cross the skin, rather than acting as a skin surface depot. The representative characteristics of functional nano-systems that contribute to the facilitation of the transdermal drug delivery are discussed in detail in the following sections.

3.1 Nanometer effects

Among all the characteristics, the intrinsic nanometer effects are no doubt the most important factor. Specifically, the nanometer effects refer to the phenomenon that nanocarriers have size-dependent penetration capacities across the epidermal barriers.[40–42] For example, the penetration of differently sized citrate-coated gold nanoparticles, with diameters of 15, 102, and 198 nm, were investigated, respectively. Smaller NPs can permeate deeper into the skin (fibrous layer and adipose tissues), whereas larger NPs gather mostly in the epidermis and dermis.[40] Moreover, the reduction in the size of nanocarriers and the relative increase in the surface area of the nanocarriers may improve the function of bioactive

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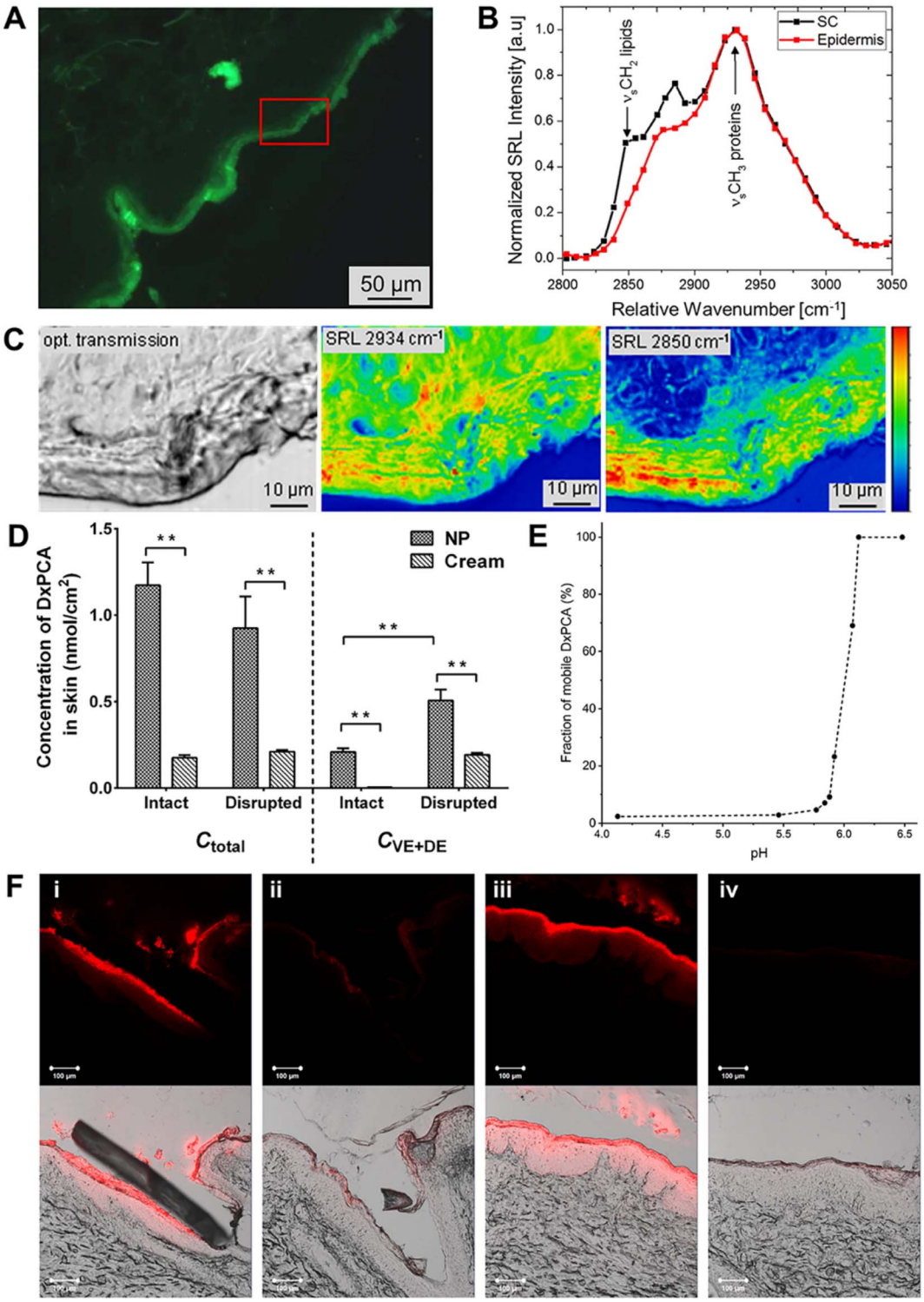

Fig. 3 Illustration of Stimulated Raman-Loss (SRL) images of the skin distribution of proteins and lipids by treating with tNG, and pH-sensitive Eudragit® L 100 NPs for transdermal delivery. (A) Fluorescence microscopy image of the skin region for SRL (red frame). (B) SRL spectra of the SC and viable epidermis and (C) optical transmission image (left); distributions of proteins (middle) and lipids (right). (D) Differential permeation of DxPCA from NPs and cream in intact and barrier-disrupted porcine ear skin. (E) Release efficiency of DxPCA from NP dispersion calculated from simulated EPR spectra under different pH conditions. (F) Confocal laser scanning microscopy (CLSM) images of the hair follicles (HFs) (i and ii) and glabrous skin (iii and iv) of the intact skin after the application of Nile red (NR) loaded in NPs (i and iii) and cream (ii and iv). (A–C) Adapted from ref. 47. Copyright 2016 Elsevier. (D and E) Adapted from ref. 53. Copyright 2019 Elsevier.

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compounds; when the size is reduced, the ability of functional nano-systems to interact with biological membranes is also enhanced, promoting their biological activity.[43] Moreover, Wiraja *et al.* demonstrated framework nucleic acids (FNAs) with distinct shapes and sizes for topical applications. Skin histology reveals size-dependent penetration, with FNAs ≤75 nm effectively reaching the dermis layer. 17 nm-tetrahedral FNAs show the greatest penetration to 350 μm from the skin periphery.[44]

3.2 Hydrating effects

Apart from having a nano-meter effect, functional nano-systems show the hydration effect that can promote skin hydration and be useful in transdermal delivery applications. Generally, the skin hydration can promote the transdermal transport of both hydrophilic and hydrophobic drugs, while hydrophobic compounds can hardly penetrate and cause skin irritation in some situations.[45,46] Thermo-responsive nano-systems, such as nanogels (NGs) and nano-capsules, have been demonstrated to induce skin hydration by releasing water in response to temperature change, which enhances the penetration of hydrophilic compounds, ranging from dyes to proteins.[47] For instance, Giulbudagian *et al.* reported the unique properties of thermos-responsive nanogels (tNGs) acting as penetration enhancers to increase skin hydration.[47] Three types of tNGs were synthesized by employing dendritic polyglycerol as a multifunctional crosslinker and poly(*N*-isopropylacrylamide) (PNIPAM), p(GME-*co*-EGE) and p(di(ethylene glycol) methyl ether methacrylate-*co*-oligo ethylene glycol methacrylate) p(DEGMA-*co*-OEGMA475) as three kinds of thermo-responsive polymers. These NGs were covalently tagged with indodicarbocyanine (IDCC) and loaded with fluorescein to study both the penetration of tNGs and the penetration of released fluorescein. The results showed that skin samples treated with NGs were swollen and the SC exhibited a disruption in the structure of its proteins and lipids as opposed to untreated skin samples (Fig. 3A–C). Furthermore, after adhering to the skin surface, lipid-based nanocarriers can alter skin moisturizing keratin and modify the structure of both SC lipids and keratin. Both keratin hydration and structural alterations to the lipids and keratin can weaken the SC's barrier function, allowing the medication to penetrate deeper into the skin.[43]

3.3 pH-Responsiveness

Together with temperature, pH is one of the important stimulus-response mechanisms that has been widely applied to trigger drug release from nano-systems. Healthy skin is known to have an acidic surface with a pH range of 4.1 to 5.8. As the skin layers change, the pH of the deeper skin layers and hair follicles shifts to a near-neutral environment.[48] In addition, skin illnesses (inflammations and epidermal lesions) can alter pH levels.[49] Due to these pH changes in different skin layers and environments, pH-responsive nano-systems can exhibit physicochemical changes in various skin layers or diseased areas, which facilitate the transdermal drug delivery.[50] Eudragits and chitosan (CS) are two pH-responsive polymers that have been used in therapeutics.[51,52] For instance, Dong *et al.* designed pH-responsive NPs based on Eudragit L100 and loaded with spin-labeled dexamethasone (DxPCA). When pH was above 6, NPs showed higher skin permeation than commercial cream in both intact and barrier disrupted skin (Fig. 3D–F).[53] Moreover, CS is a common natural pH-responsive polymer whose responsiveness arises from its amino groups, which undergoes protonation in an acidic environment, leading to repulsion of the positively charged groups followed by swelling. Sahu *et al.* developed a CS nanogel loaded with 5-fluorouracil (5-FU) to act against melanoma and demonstrated the triggered release of 5-FU in a slightly acidic microenvironment, resulting in selective drug accumulation at the melanoma site.[52]

3.4 Electrostatic charges

The surface charge can affect functional nano-system permeation and penetration on skin.[54] Specifically, the surface of cells presents a negative charge mainly caused by sulfated proteoglycan molecules, which are responsible for cell proliferation, migration and movement.[55] Thus the electrostatic interactions between the cell membrane and nano-systems can be achieved when nano-systems present a positive charge and therefore promote the transdermal permeation.[41,56] Meantime, the negatively charged nano-systems also show high cellular uptake due to a non-specific process of nano-system adsorption on the cell membrane and to the formation of clusters of nano-systems.[49] The adsorption of negatively charged NPs to positively charged sites occurs *via* electrostatic interaction neutralization and membrane bending, or cellular uptake *via* endocytosis.[55] There is no change of the permeation of neutral nano-systems across the endothelial cell monolayer.[55]

4. Fabrication of functional transdermal nano-systems

With the above-mentioned characteristics, functional nano-systems hold great feasibility to improve transdermal delivery while lowering the undesirable side.[57–59] In the following section, functional nano-systems including polymeric nanocarriers (polymeric NPs, polymeric micelles, and dendrimers), lipid-based NPs (solid lipid NPs and nanostructured lipid carriers), vesicular nanocarriers (liposomes, niosomes, transfersomes, and ethosomes), and inorganic NPs (metallic NPs, metallic oxide NPs, silica NPs, and quantum dots) are discussed. To offer a whole scene of the functional nano-systems for transdermal drug delivery, we have elaborately summarized their detailed information including the compositions and fabrication methods in Table 1 and Table 2 shows the advantages and disadvantages of these developed functional nano-systems.

4.1 Lipid carriers

Various types of lipid-based nano-systems, such as solid lipid NPs (SLNs), nanostructured lipid carriers (NLCs), and vesicular nanocarriers, are developed for transdermal drug delivery. They can alter SC barrier integrity by disrupting lipid bilayers, as well as increasing epidermal distribution of drug molecules and hair follicle targeting of lipid nanocarriers.

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Table 1 Summary of the composition and fabrication methods of functional nano-systems

Nano-systems	Composition	Characterization	Fabrication methods	Reference
SLNs	Solid lipids, surfactants, co-surfactants	Shape: spherical Size: 50–1000 nm Drug: amphotericin B	Thin film hydration; hand shaking; reverse-phase evaporation; sonication; ether injection; pro-niosome method; freeze and thaw; dehydration; rehydration; bubble method; solvent injection-homogenization technique; microfluidics	60–66
NLCs	Solid lipids, liquid lipids (oils), surfactants	Shape: spherical Size: 120.9–185.2 nm Drug: simvastatin	High pressure homogenization (hot/cold); ultrasonication (probe/bath); solvent evaporation; solvent emulsification diffusion; microemulsion; supercritical fluid; spray drying; hot-melt extrusion (HME) methods	29, 60, 67–76
Liposomes	Cholesterol, phospholipids	Shape: spherical Size: 25–5000 nm Drug: diflucortolone valerate	Reverse-phase evaporation; membrane extrusion; thin film hydration; sonication (probe/bath); ethanol injection; ether injection; freeze-thaw; micro-emulsification; microfluidics; heating methods	77–92
Ethosomes	Ethanol, phospholipids	Shape: spherical Drug: lipophilic or hydrophilic drugs	Thin film hydration; vortex/sonication; ethanol injection; hot and cold methods	25, 55, 93, 94
Transfersomes	Phospholipids, surfactant/edge activators, alcohol buffering agent	Shape: spherical Size: 90–140 nm Drug: meloxicam	Thin film hydration	95–101
Niosomes	Cholesterol, nonionic surfactant	Shape: spherical Size: 100 to 2000 nm	Cold and hot method	55, 102–113
ISAsomes	Inverse bicontinuous (Q2) and discontinuous hexagonal (H2) phases	Shape: nonlamellar Size: 100–200 nm Drug: progesterone	High-energy emulsification methods, microfluidization, high-pressure homogenization	114–120
Polymeric NPs	Natural/synthesis polymers	Shape: spherical Size: 10 to 1000 nm Drug: donepezil hydrochloride	Emulsification/solvent diffusion; salting; nanoprecipitation; polymerization; dialysis; solvent evaporation; supercritical fluidization	55, 123–131
Polymeric micelles	Polymers preferably, polyethylene glycol, aqueous solution, ligands (target molecules)	Shape: spherical Size: 113.0 ± 34.0 nm, 498.7 ± 35.4 nm Drug: curcumin	Chemical conjugation; physical entrapment through dialysis; emulsification; poly-ionic complexation	23, 25, 79, 132–137
Dendrimers	Core molecule, surface units, monomers	Shape: spherical Size: 20 nm	Divergent; convergent method	60, 139–145
Metallic NPs	Metal atom, ligands	Shape: rod, spherical, triangular, spherical Size: 2–100 nm	Microfluidics	79, 109, 125, 148–166
Metallic oxide NPs	Metal oxide	Shape: non-spherical Size: <100 nm	Green synthesis methods	34, 168, 169
QDs	Metalloid crystalline core, surface groups/ polymer/peptide ligand/ antibody	Shape: spherical Size: 20 nm	Oxidative cleavage, hydrothermal/solvothermal, microwave/ultrasonic-assisted, electrochemical, pulsed laser ablation, chemical vapor deposition, electron beam irradiation, controllable synthesis, carbonization	54, 173, 174
Silica NPs	Silica	Shape: spherical Size: 0.05–2 nm	A system chemical method	41, 79, 170–172

4.1.1 Lipid carriers

4.1.1.1 SLNs. The SLNs made of physiological and biodegradable lipids are widely employed transdermal nanocarriers.[60,61] At room temperature, these lipids can create a solid lipophilic matrix into which hydrophilic or lipophilic drug molecules can be incorporated. Structurally, they are spherical and have an estimated mean particle size in the range of 50–1000 nm, with a narrow particle size distribution around the mean particle size.[61] Various techniques, including hot and cold homogenization, solvent emulsification, evaporation, microemulsion, W/O/W double emulsion method, and microfluidics, are applied to fabricate SLNs.[62–65] As shown in Fig. 4A and B, SLNs can be fabricated in a microchannel system by the liquid flow-focusing and gas displacing method (LFGDM). The size of the fabricated NPs can be tuned approximately in the range of 100–220 nm and 80–210 nm, respectively (Fig. 4C).

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Table 2 Advantages and disadvantages of nano-systems for transdermal drug delivery

Nano-systems	Advantage	Disadvantage	Reference
SLNs	Feasibility in incorporation of lipophilic and hydrophilic drugs, producing on a large industrial scale, good biocompatibility and biodegradability	No deeper penetration for SLNs, drug expulsion during storage cause by lipid polymorphism for SLNs, and risk of gelation for SLNs	60–66
NLCs	Better drug loading capacity, high permeation (NLCs: 86.35%, marketed formulation: 69.41%), prevention of drug expulsion during storage, better stability	No deeper penetration	29, 60, 67–76
Liposomes	Encapsulation of amphiphilic drugs, low toxicity and biocompatibility (erythema and eschar formation value 0–1), improves localized delivery	Require special storage conditions, higher production cost, poor permeation to the viable epidermis and dermis, poor physicochemical characteristics for long-term stability (storage at 4–6 °C, in a refrigerator and adjustment of the pH of the dispersions to pH values close to neutral)	77–92
Niosomes, transfersomes, ethosomes	Incorporation of both lipophilic and hydrophilic drugs, higher encapsulation efficiency, simple and inexpensive to manufacture compared with liposomes, the ability of intact transport across the SC due to their soft and malleable characteristics, enhanced penetration and permeation (niosomes: up to a depth of 120 nm)	Skin irritation and toxicity (erythema and eschar formation value 0∼1) due to chemical excipients	25, 55, 93–113
ISAsomes	Better drug loading capacity, high permeation (NLCs: $48.57 \times 10^{-2} \pm 0.7$ μg cm^{-2})	Unknown toxicity and coalescence	114–120
Polymeric NPs	Targeted to a specific site, higher stability than lipid-based ones, tunable chemical and physical properties, existence of pH, enzymatic, hydrolysis, *etc.*, sensitive properties when preferred appropriate polymers	Mass production is difficult, unknown toxicity, and coalescence	55, 123–131
Polymeric micelles	Acts as penetration enhancers, increased solubility of highly lipophilic drugs, protecting drug from environmental conditions	Useful only for lipophilic drugs, low drug-loading capacity, dependent on critical micellar concentration	23, 25, 79, 132–137
Dendrimers	Multifunctional surface modification, target specific drug delivery	Not suitable for hydrophilic drugs, higher cost, toxicological (hemolysis rates >5%)	60, 139–145
Metallic NPs	Potential therapeutic and diagnostic tools, stability against oxidation, *in vivo* degradation, biocompatibility, bioavailability of entrapped drug targeted action, targeted drug action	Scaling up process is difficult, the use of toxic NPs	79, 109, 125, 148–166
Metallic oxide NPs	Biocompatibility, stability, and targeted action, potential therapeutic and diagnostic tools	Exhibited phototoxicity and cellular membrane damage	34, 168, 169
QDs	Biocompatibility, cellular targeting enhanced specificity, deliver a wide range of bioactive (430–720 nm), imaging tool	Toxicity of heavy metals	54, 173, 174
Silica NPs	Biocompatibility, surface functionalization	Potential toxicity of NPs	41, 79, 170–172

Furthermore, due to small particle size and hence a larger surface area, these NPs make intimate contact with the superficial junction of corneocyte clusters and channels of the SC.[60] This is especially crucial for improving drug accumulation and local drug depot development, which may be utilized for regulated drug administration over time. SLNs also have a specific occlusive characteristic, which may enhance the penetration of drugs through the SC by reducing trans-epidermal water loss. Therefore, SLNs are being extensively researched for therapeutic efficacy *via* the skin delivery route. Butani *et al.* designed topical amphotericin B-loaded SLNs to improve the therapeutic antifungal activity. The result demonstrated higher drug accumulation in the upper layers of the skin and minimize the diffusion of the drug from the dermis layer into the systemic circulation.[66] The smallest particle sizes are observed for SLN dispersions with a low lipid content (up to 5%). Both the low concentration of the dispersed lipid and the low viscosity offer challenges for the subsequent dermal administration. In most cases, the incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation that can be administered to the skin. Besides, cycles of ultrasonication may later the size and stability of the dispersion. This is why

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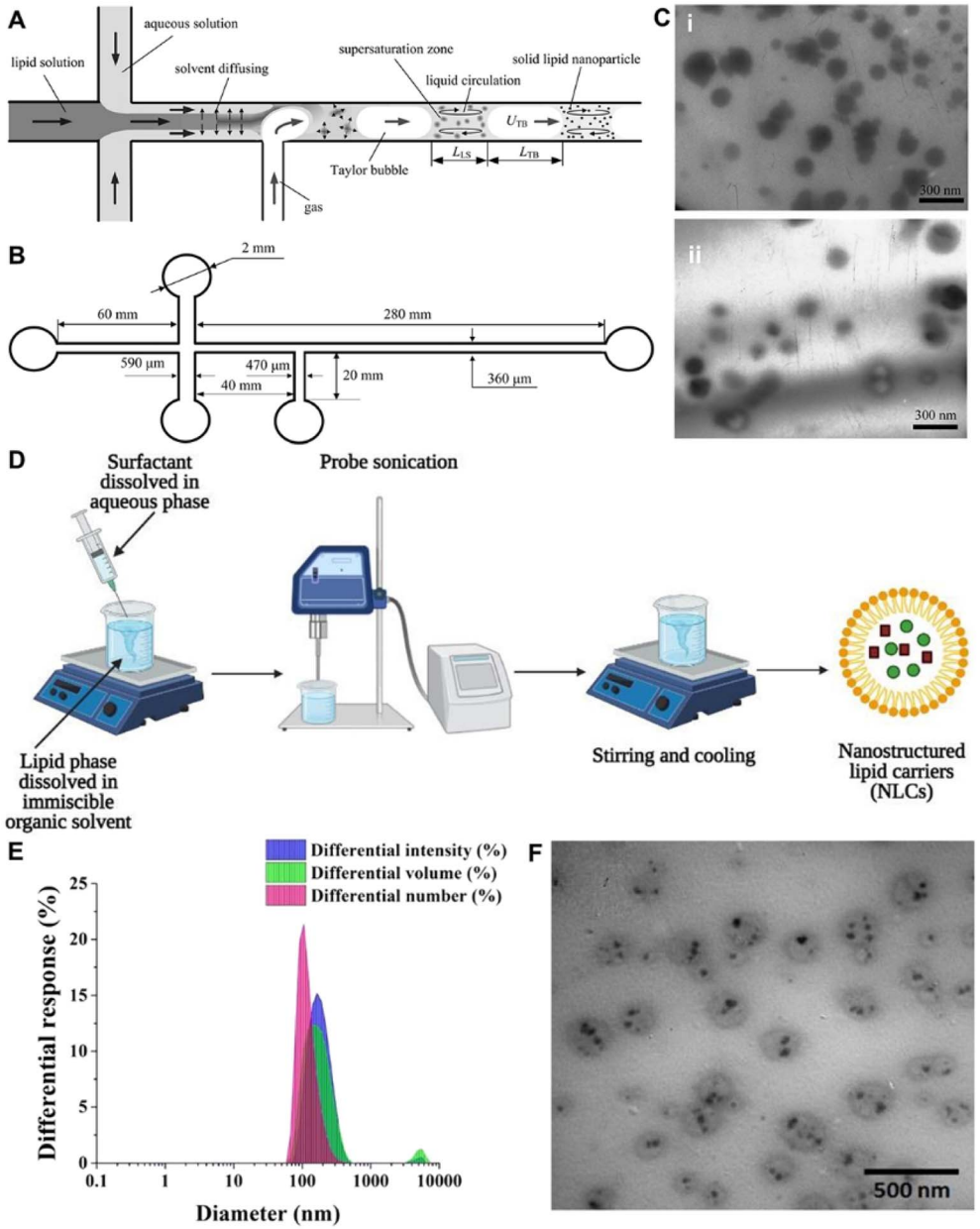

Fig. 4 Preparation and characterization of SLNs and NLCs. (A and B) The preparation of SLNs by LFGDM by microfluidics. (C) Transmission electron microscopy (TEM) photographs of the fabricated SLNs. (D) Schematics of the preparation of NLCs *via* the emulsification-solvent evaporation technique. (E) Histograms showing the intensity-, volume-, and number-averaged hydrodynamic diameter distributions of simvastatin-loaded NLCs. (F) TEM image of simvastatin-loaded NLCs showing spherical or elliptical vesicles with smooth surfaces. (A–C) Adapted from ref. 64. Copyright 2009 Elsevier. (D) Adapted from ref. 71. Copyright 2021 Elsevier. (E and F) Adapted from ref. 72. Copyright 2021 Elsevier.

sometimes scale-up of SLNs fails even though perfect initial lab results are achieved.

4.1.1.2 NLCs. NLCs, as a new improved generation of lipid NPs, are presently being explored extensively.[60] NLCs are produced by combining at least one liquid lipid (oil) with one or more solid lipids to form nano-capsules, where the liquid lipid phase can be embedded in a solid matrix or localized on the surface of solid particles (Fig. 4F).[67,68] High-pressure homogenization,[69] melt-emulsification,[70] emulsification-solvent evaporation (Fig. 4D),[71,72] ultra-sonication,[73] solvent-diffusion,[73] and spray drying techniques[74] are used in the fabrication of NLCs. The normal weight ratio of solid lipid to liquid lipid ranges from 70 : 30 to 90 : 10.[29] Therefore, several types of NLCs are obtained based on the technique of manufacturing and the content of the lipid blend. Moreover, using dynamic light scattering (DLS) and transmission electron microscopy (TEM), the characterized information of nano-systems based on the intensity, volume, number, and morphology can be obtained (Fig. 4E and F). The intensity-, volume- and number-averaged hydrodynamic diameters of NLCs are 185.2, 175.9 and 120.9 nm, respectively. NLCs

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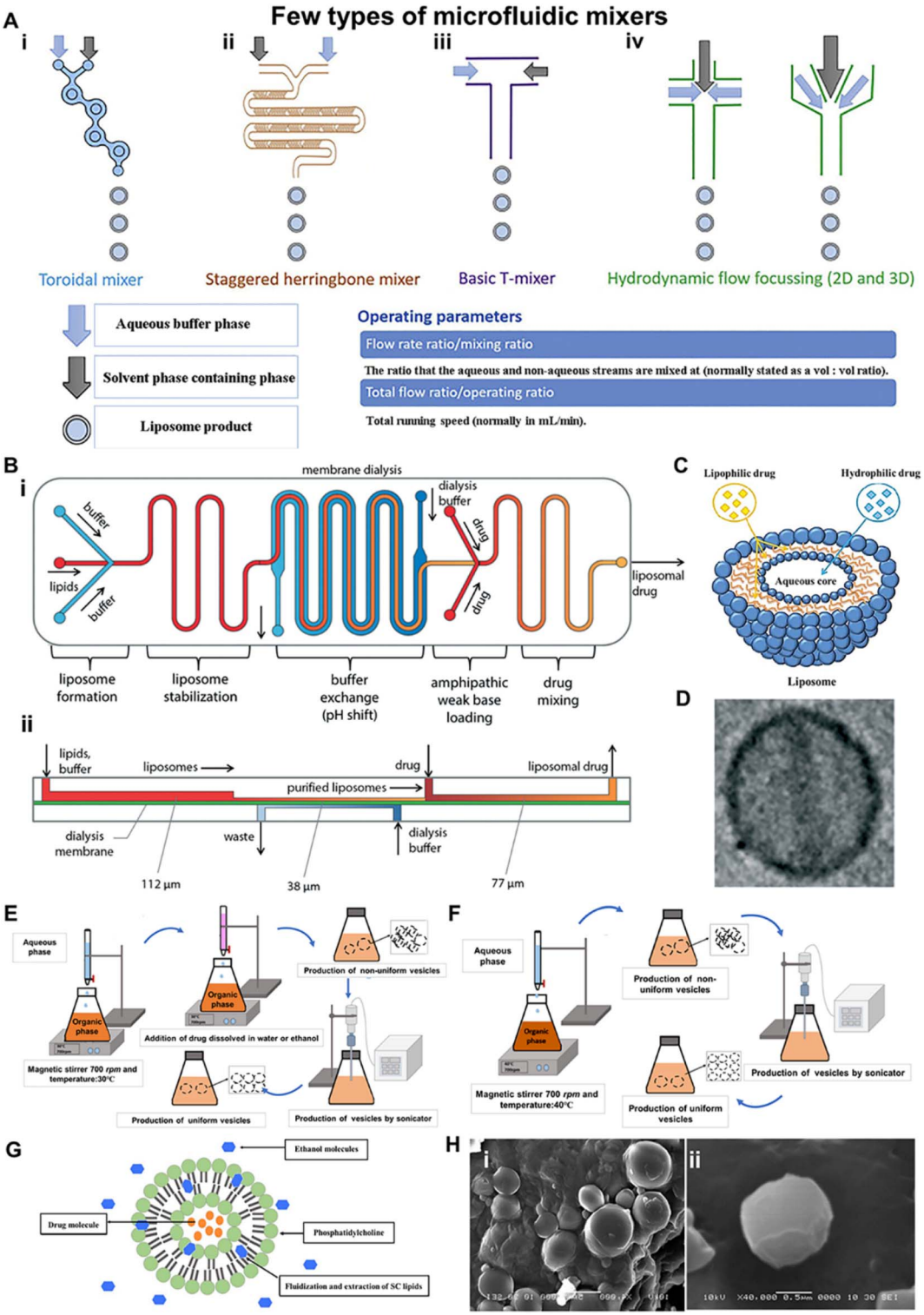

Fig. 5 Preparation and characterization of liposomes and ethosomes for transdermal drug delivery. (A) Various design types of micromixer cartridges for producing liposomes. (i) A toroidal mixer with planar geometry employing centrifugal forces to encourage uniform mixing. (ii) The staggered herringbone micromixer with embossed chevrons. (iii) A basic T-mixer with two inlets where fluids are forced into a T junction and (iv) hydrodynamic flow focusing with three inlets where a central stream of solvent is focused by aqueous fluid streams either in 2D or 3D. (B) Rapid single-step preparation of liposomes using microfluidics. (i) Schematic of the fully integrated microfluidic device for remote loading of liposomal therapeutic nanomedicines in-line with liposome synthesis. (ii) Cross-sectional view of the microfluidic system, revealing the differing channel heights supporting each process step. (C) Schematics of the liposome structure and lipophilic or hydrophilic drug entrapment models. (D) A TEM image of a liposome with a size of 225.5 nm ± 44.8 nm. (E) Preparation of ethosomes by the cold method. (F) Preparation of an ethosome by the hot method. (G) Diagram of the ethosome and ethanol fluidization of SC lipids of skin. (H) Scanning electron microscope (SEM) image of ETC5 ethosmal suspension (i) × 4000 and (ii) × 40 000. (A) Adapted from ref. 83. Copyright 2020 Elsevier. (B and D) Adapted from ref. 84. Copyright 2014 The Royal Society of Chemistry. (C) Adapted from ref. 80. Copyright 2012 American Scientific Publishers. (E and F) Adapted from ref. 85. Copyright 2018 Bentham Science Publishers. (G) Adapted from ref. 105. Copyright 2013 Informa UK Ltd.

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have a spherical shape. Since, NLCs are smaller in size, they have better surface contact with the SC and consequently increase the number of active compounds penetrated through the skin. Moreover, nano-sized particles may closely attach to the skin surface, allowing for more regulated medication administration. Furthermore, since NLCs provide higher drug loading than SLNs, they can achieve a high drug concentration gradient on the skin surface to facilitate drug permeation.[75,76] NLCs have been successfully utilized to deliver drugs *via* topical routes for improving drug permeation, skin hydration, controlled drug release, and drug stability. NLCs have a remarkably wide range of properties which make them useful for TDDs and have been well investigated to reduce the toxic side effects of the drugs and increase the efficacy of the treatment. However, because of the unpredictable gelation tendency and inherent low incorporation rates resulting from the crystalline structure of the solid lipid, the total number of commercialized NLC products on the market is still limited, which deserves further efforts in advancing the transformation of scientific research.

4.1.2 Vesicular nanocarriers

4.1.2.1 Liposomes. Liposomal systems have been demonstrated as one of the promising vesicular nanocarriers in terms of bypassing the epidermal barrier.[77] Liposomes are lipid-based microscopic vesicles composed of one or more lipid bilayers arranged in a concentric fashion that enclose the same number of aqueous compartments as biological membranes. Liposomes are generally spherical in form and range in size from 25 to 5000 nm.[78] Due to this unique structural composition, hydrophilic drugs can be loaded in the aqueous core while hydrophobic drugs can be loaded in the lipid bilayer (Fig. 5C).[79,80] Thin-film hydration,[81] reversed-phase evaporation,[82] microfluidic methods (Fig. 5A–D),[80,83,84] and solvent injection techniques[85] are most commonly used conventional liposome preparation techniques. For instance, different types of micromixer cartridges are adopted to facilitate the fabrication of liposomes (Fig. 5A). Particularly, the toroidal mixer with planar geometry and the staggered herringbone micromixer with embossed chevrons employ centrifugal forces to encourage uniform mixing. In addition, the basic T-mixer has two entrances where the liquid is forced into the T-junction and subsequently produces liposomes. Moreover, a rapid single-step preparation method of liposomes using microfluidics is also developed (Fig. 5B). Several theories have been advanced regarding the mechanism of skin delivery *via* liposomes. Some of the prominent theories include intact vesicular skin penetration,[86,87] adsorption effect,[87] and the penetration of liposomes through the trans-appendageal route.[69,88] However, some researchers have recently suggested that the permeation enhancement effect of liposomes is due to the interaction of liposomes with the skin lipid causing partial fluidization of the skin lipid and consequently delivering the drug to the deeper skin layers (below the SC layer).[89–92] Although liposomes facilitate the delivery of drugs to target specific areas of the skin, their therapeutic effects would be overestimated if the toxicity is not considered seriously. Studies showed these liposomes could induce toxic effects like inflammation, myelosuppression, proliferation, and carcinogenesis. Therefore, to further demonstrate the potential of liposomes in transdermal drug delivery, a comprehensive assessment about the potential toxicity of liposomes is necessary.

4.1.2.2 Niosomes. Niosomes are non-ionic surfactant vesicular systems with size from 100 to 2000 nm.[25] The surfactants used for forming niosomes are biodegradable, biocompatible, and non-immunogenic. Niosomes have higher encapsulation efficiency, improved chemical stability, enhanced penetration, and lower cost compared with liposomes.[25] Another advantage is the straightforward approach for producing niosomes on big scale niosomes as versatile carrier systems can be administered through various routes, including transdermal delivery.[93,94] Examples of transdermal drug delivery using niosomes are minoxidil and ellagic acid. Niosomes have been reported to enhance the residence time of these drugs in the SC and epidermis, while decreasing the systemic absorption of the drug and improving the penetration of the trapped substances across the skin.[55] Although there are multiple advantages of the niosomal delivery system, stability is still an important issue since the drug may be hydrolyzed with the aqueous suspension of niosomes. Moreover, the problem of drug leakage from the entrapment site and aggregate formation of niosome may also occur. These all need to be considered when developing a niosomal delivery system for skin treatment.

4.1.2.3 Transfersomes. Transfersomes are another vesicular system firstly designed in 1992 by Cevc *et al.*[95] These transfersomes have at least one inner aqueous compartment that is surrounded by a lipid bilayer with appropriately tailored properties. Morphologically, transfersomes resemble lipid vesicles, liposomes, but functionally, they are sufficiently deformable to penetrate pores much smaller than their own size.[96] Moreover, they are metastable, making the vesicle membrane ultraflexible and highly deformable. Due to their deformable characteristics, transfersomes can penetrate sufficiently through skin pores.[97] Cevc *et al.* proposed that hydrophilic elastic vesicles squeezed into the narrow intercellular paths, causing the intercellular pathways to widen by 20–30 nm.[98] The deformable transfersomes were then moved into skin layers through skin microchannels along the transdermal hydration gradient. After that, the transfersomes distributed between corneocytes *via* intercellular pathways and were found in the subcutaneous tissue.[98,99] Despite the fact that the transfersomes' shape and volume adaptation changed transiently the size did not change after crossing the barriers.[98] Therefore, the transfersomes are proposed as superior nanocarriers over the conventional lipid vesicles for the enhancement of drug permeation and vesicle–skin interactions.[98,100] Furthermore, Duangjit *et al.* established that meloxicam-loaded transfersomes penetrated the skin by disrupting and fluidizing the SC lipids (acting as penetration enhancers).[101] It is worth noting that the use of transfersomes is limited because oxidative degradation makes its predisposition. In addition, the formulation process of transfersomes is expensive without easily accessible.

4.1.2.4 Ethosomes. Ethosomes are lipid vesicular systems embodying ethanol in relatively high concentrations for superior permeability.[102] They are primarily made up of

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phospholipids, ethanol, and water (Fig. 5G).[103] Structurally, ethosomal are composed of a phospholipid bilayer and an aqueous inner core that contains the entrapped active ingredient.[104] Ethosomes can be prepared by two conventional methods including a hot method and cold method (Fig. 5E and F).[103,105,106] The nano-systems were nearly uniform and of spherical shape as shown in Fig. 5H. Due to the high ethanol concentration, their soft and malleable properties allow them to cross the skin or membrane barrier and affect the degree of transdermal penetration.[107] These ethosomal systems, unlike liposomes and transfersomes, can encapsulate either lipophilic or hydrophilic drugs and deliver them into systemic circulation under both occlusive[108,109] and non-occlusive conditions.[55] In addition, the size of ethosomes is smaller than that of a liposome when prepared under the same conditions, due to the high alcohol content. This reduction in size is due to ethanol imparting a net negative charge to the vesicle surface. Ethosomes have been shown to exhibit high encapsulation efficiency for a wide variety of molecules including lipophilic drugs due to the multi-layered vesicles and the presence of ethanol, which allows for better solubility of many drugs.[110,111] Phospholipids and high concentration of ethanol in the ethosomes have created a synergistic mechanism for drug penetration into deeper layers of the skin in transdermal drug delivery.[112] Ethanol increases the lipid fluidity of the ethosomal and skin lipid bilayers while decreasing the density of the highly ordered lipids of the SC. The soft flexible ethosome perturbed intercellular lipid layers of the SC penetrate into the deeper skin layers. After the ethosomes fuse with the lipid contents of the SC, the drug diffuses into deeper skin layers or systemic circulation.[113] It is important to assess the skin tolerability and safety of topical ethosomes on intact as well as wounded, infected and damaged skin by *in vitro* and *in vivo* experiments. Besides, the phospholipid contents of ethosomes are prone to hydrolysis and trigger oxidation, which would lead to stability problems for ethosomes, and therefore an evaluation of the long-term stability of ethosomal systems is required.

4.1.2.5 ISAsomes. Internally self-assembled somes or particles (ISAsomes) are non-lamellar structured lipid NPs, including cubosomes and hexosomes.[114] ISAsomes are nano-self-assemblies, sharing common features with SLNs. Meanwhile, ISAsomes envelope internally non-lamellar liquid crystalline phases (inverse bicontinuous (Q2) and discontinuous hexagonal (H2) phases). They appear inside the kinetically stabilized dispersed particles. Non-lamellar liquid crystalline nanoparticles have typically sizes in the range of 100–200 nm.[114,115] These nanosystems are typically formed in the presence of an efficient stabilizer by applying high-energy emulsification methods that include ultrasonication, microfluidization, and high-pressure homogenization.[116–118] ISAsomes have unique lyotropic liquid crystalline nano-structural features, making them attractive as nanocarriers for transdermal drug delivery systems.[119] They are able to encapsulate active ingredients, to interact with the skin strata after cutaneous administration and to release their content in a controlled fashion. Mohyeldin *et al.* reported the result that four progesterone-loaded nanocarriers, cubosomes, nanoliposomes, nanoemulsions and nanomicelles, to enhance progesterone penetration *via* the human abdominal skin.[120] All nanocarriers exhibited higher transdermal flux relative to free progesterone in *ex vivo* skin permeation. Compared with other nanocarriers, cubosomes revealed a higher skin penetration with a transdermal steady flux of $48.57 \times 10^{-2} \pm 0.7$ μg cm^{-2} h^{-1}. Al-Zuhairy *et al.* developed a novel hexosome by mixing lipid-forming liquid crystals (LCs) with petrolatum, to allow for more medication penetration through the skin. In an *in vitro* skin permeation study, the mixture formulations dramatically enhanced drug skin concentrations compared to the white petrolatum.[121] These results showed that ISAsomes will bring about enormous opportunities in transdermal drug delivery.

4.2 Polymeric nanocarriers

In recent years, an increasing number of polymeric nanocarriers for transdermal delivery have been developed.[122] Nanocarriers fabricated from biodegradable polymers have the potential to overcome limitations associated with other lipid systems, such as lower drug loading and phase stability issues. Moreover, sustained and controlled release of the drug as well as specific targeting could be achieved over the physicochemical characters of these polymeric nanocarriers.[123]

4.2.1 Polymeric NPs. Polymeric NPs range in size from 10 to 1000 nm and are made of biocompatible and low immunogenicity polymers. Drugs can be dissolved, entrapped, encapsulated, or attached in the polymeric matrix.[55,124] The preparation of polymeric NPs can be achieved by nanoprecipitation (also called the solvent displacement method),[125] various types of emulsification/solvent evaporation,[65] and the salting out method.[65] For instance, Karnik *et al.* synthesized poly(lactide-*co*-glycolide)-*b*-poly(ethylene glycol) (PLGA-PEG) NPs on a microfluidic platform by nanoprecipitation for a variety of biomedical applications (Fig. 6A and B).[125] The prepared spherical nano-systems with diameters typically in the range of 10–50 nm were observed by using TEM (Fig. 6C). Biodegradable polymeric materials like gelatin, CS, albumin, hyaluronic acid (HA), and polylactic acid (PLA) are frequently used.[126] One of the most widely investigated natural polymers is CS. The mucoadhesive property and availability of functional groups on the CS molecules permit the conjugation of ligands to promote site-specific targeted action.[127] Besides, some of the other benefits of this polymer are biocompatibility, biodegradability, and maximal drug loading capacity.[128]Although CS has many enticing properties, its low stability limits its usage in pharmaceutical products.[129] Some researchers have reported the use of more stable anionic polymers as well as the use of cross-linking agents combined with CS to address this difficulty. The prepared NPs have good stability and skin permeation. For example, Takeuchi *et al.* explored donepezil hydrochloride (DP)-loaded poly(lactic-*co*-glycolic acid) (PLGA)-CS core–shell NPs to treat osteoporosis.[130] Compared to a DP solution, core–shell NPs improved both skin accumulation and delivery of DP into hair follicles. Moreover, synthetic polymers are also applied to form NPs. Compared to natural biodegradable polymers, the biodegradation process of synthetic

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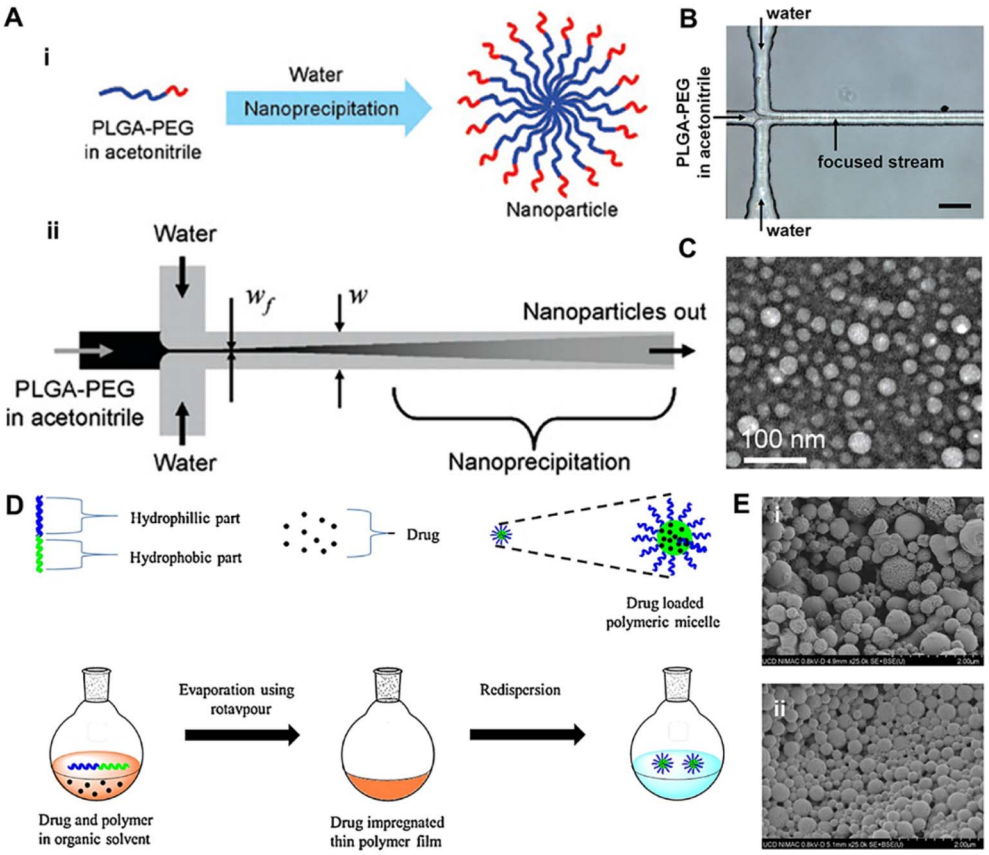

Fig. 6 The synthesis and representation of polymeric nanoparticles and polymeric micelles. (A) The synthesis of polymeric nanoparticles using nanoprecipitation in a microfluidic device. (i) Nanoprecipitation of PLGA-PEG copolymers. (ii) The process of mixing can be carried out in a microfluidic device using hydrodynamic flow focusing, where the polymer stream is focused into a thin stream between two water streams with higher flow rates. Rapid mixing and nanoprecipitation occur due to the diffusion of the solvent out of the focused stream and diffusion of water into the focused stream. (B) A microfluidic device for hydrodynamic flow focusing of polymeric nanoparticles in water. Scale bar 50 μm. (C) TEM image of nanoparticles synthesized by nanoprecipitation of PLGA15K-PEG3.4K by hydrodynamic flow focusing showing a spherical PLGA core–PEG corona structure of the nanoparticles. (D) Solvent evaporation method/solution casting method. (E) Scanning electron microscopy images of polymeric micelles, (i) PLGA-Dex10 and (ii) PLGA-Dex10-curc. (A–C) Adapted from ref. 125. Copyright 2008 American Chemical Society. (D) Adapted from ref. 135. Copyright 2019 Elsevier. (E) Adapted from ref. 139. Copyright 2021, Springer Nature.

polymers is significantly different, taking several weeks to a few years by enzymolysis or chemical and physical cues. For example, hydrophobic PLGA NPs with high skin permeability can be degraded *in vivo* by scission of ester linkages to produce glycolic acid and lactic acid in several weeks.[131] Moreover, most of the polymeric NPs are generally water-soluble. They can present a surface modification (PEGylation) to achieve a selective accumulation.[132] However, the limitations like one particular process or technique is not suitable for the encapsulation of all drugs, post-preparative steps, such as purification and preservation, incomplete or discontinuous films, and inadequate stability of certain active components still remain to be solved. Despite these technological challenges, nanoparticles have been showing great promise for the development of TDDs.

4.2.2 Polymeric micelles. Polymeric micelles for transdermal delivery have gained great attention in recent years.[133] To reduce surface-free energy in an aqueous medium, these micelles can self-assemble from amphiphilic block copolymers at/above specific polymer concentration (critical micelle concentration) forming a hydrophobic core and a hydrophilic shell.[79] The hydrophobic core contributes to both drug solubility and the depot effect, whereas the hydrophilic shell contributes to stabilization.[25,134] Moreover, micellar forms such as worm-like, dislike, or sheet are generated dependent on the number of copolymer blocks and their arrangement in the dispersion.[23] The polymeric micelles can be generated by using a variety of processes, including the solvent evaporation method (solution casting method) (Fig. 6D), self-assembly method, and solid dispersion method.[135–137] Moreover, as an important assay method, SEM can be used to evaluate the morphology of nanosystems. For instance, the results showed that the curcumin-functionalized PLGA-dextran micelles (PLGA-Dex10-curc) have much larger hydrodynamic diameters (498.7 ± 35.4 nm) in contrast with PLGA-dextran (PLGA-Dex10) (113.0 ± 34.0 nm). Meantime, the micelles also seem to have a rougher surface (Fig. 6E). This biocompatible, extremely stable colloidal system with enhanced drug solubilization and localized drug release to the targeted region keeps the polymeric micelles more intact

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under dermatological conditions, mainly psoriasis, burns, and acne. Polymeric micelles also have the other superiorities of polymeric nanocarriers such as tunable chemical and physical properties.[25] However, they have some limitations including the dependence of critical micelle concentrations and low drug-loading capacity.[25,138] Polymeric micelles are one of the most promising types of nano-systems for transdermal drug delivery. At present, numerous micelle-based formulations are being developed and are at various stages of clinical trials. We may expect the wide utilization of these nano-systems in practical applications in the near future.

4.2.3 Dendrimers. Dendrimers are unimolecular, monodisperse, synthetic polymers (generally <15 nm) having symmetrically placed branching units that can from a spherical shape (Fig. 7B).[140] These nanocarriers are made up of three parts, a core, internal dendritic branches, and peripheral surface that is functionalized with a land layered structure.[141] Conventionally, dendrimers can be synthesized by convergent synthesis and divergent synthesis (Fig. 7A).[142–144] For instance, PAMAM-G7 NPs have a spherical shape with a mean diameter size of 20 nm (Fig. 7C). Meanwhile, they also display a multi-layered-like structure, which has smaller spherical substructures. Dendrimers gained significant attention as polymeric skin permeation enhancers that can increase drug transport through the skin.[142,145,146] Dendrimers promote drug penetration by increasing drug solubility and enhancing partitioning and diffusion of the drug molecules into the skin.[60] The size and surface properties of dendrimers are critical for their dermal applications. The properties of dendrimers or dendrimer–cargo complexes can be modified as needed to enhance or inhibit their dermal penetration, as needed.[142] However, there are still issues that need to be addressed before such systems can be translated to the clinic trials. For example, while the oligomeric and dendritic systems are attractive for clinical applications due to their well-defined structures, the syntheses of these molecules require tedious steps and therefore will be complex and costly for scaling up. In addition, the steric hindrance at the dendrimer periphery has thus far limited the molecules to relatively low generations, in turn limiting the degree of amplification that can be achieved.

4.3 Inorganic NPs

4.3.1 Metallic NPs. Metallic NPs possess specially designed structures in which drugs are encapsulated, and surface functionalized physicochemical properties such as higher surface-to-volume ratios, improved ionic conductivity, and aid in crossing barriers to target sites.[150,151] These NPs may be generated using chemical synthesis techniques.[79,149,152] Moreover, microfluidic technology has been used to facilitate the controllable production of metallic NPs (Fig. 7D and F). Silver or gold NPs are the most commonly employed metallic NPs in the skin delivery industry.[153,154]

Gold NPs (AuNPs) have been widely explored as promising candidates for transdermal therapeutic applications.[155] AuNPs are available in a variety of colors based on their size (between 3 and 120 nm), the oscillations of conduction band electrons at appropriate wavelengths, form, and amount of aggregation. These colors include orange, blue, red, and yellow.[156] The size and surface characteristics of AuNPs appear to have an important impact on intracellular uptake and cytotoxicity.[157] These carriers can be produced using a variety of technologies, such as microfluidic method,[158] and the use of a green chemistry route.[159] For instance, anisotropic AuNPs can be fabricated in a Y-shaped channel. AuNPs with irregular shapes and polydispersity were obtained in the reaction channel due to

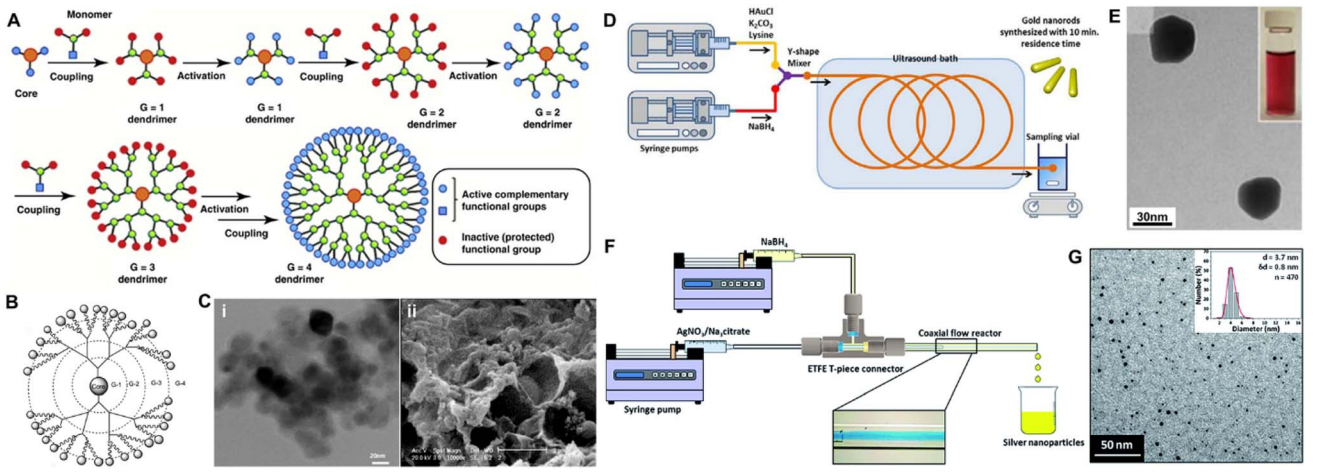

Fig. 7 The synthesis and characterization of dendrimer and metallic NPs for transdermal delivery. (A) Process of forming a dendrimer using the divergent growth method. (B) Conceptional scheme of the PAMAM-G4 dendrimer. (C) Microscopic images of the dendrimer. (i) TEM image of PAMAM-G7; scale bar: 20 nm (ii) SEM image of PAMAM-G7; scale bar: 2 μm. (D) Microfluidic-mediated gold nanorod synthesis. (E) TEM image of gold nanostructures obtained. (F) Schematic of the coaxial flow reactor setup. Inset shows flow visualization of laminar flow inside the coaxial flow reactor with blue dye flowing through the inner tube and water flowing through the outer tube. (G) TEM image and size distributions of the prepared silver nanoparticles. (A) Adapted from ref. 143. Copyright 2016 Elsevier. (B) Adapted from ref. 141. Copyright 2018, MDPI. (C) Adapted from ref. 144. Copyright 2017, BMC Infectious Diseases. (D) Adapted from ref. 147. Copyright 2019 SAGE Publishing. (E) Adapted from ref. 148. Copyright 2012 The Royal Society of Chemistry. (F and G) Adapted from ref. 149. Copyright 2015 The Royal Society of Chemistry.

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adjustment of the concentration of shape modulating agents (Fig. 7E). They can be coupled with peptides/proteins, nucleic acid (NA) moieties, small drug molecules through either chemical conjugation (thiol derivative bonds and streptavidin linker), or physical interactions (charge and hydrophobic interactions).[126] Over the past decade or so, AuNPs have increasingly been utilized in TDDs besides the conventional systemic administration. Recent research has shown that topically administered AuNPs may pass the skin barrier and reach the epidermis and even the dermis layer.[160] Correspondingly, various skin-related applications have been proposed. Researchers loaded vascular endothelial growth factor (VEGF) onto negatively charged AuNPs through ionic interaction for skin penetration, stimulating angiogenesis in the dermis layer as verified through α-SMA immunostaining and vessel density.[161,162] Likewise, AuNPs received significant attention as transdermal nanocarriers for NA moieties (siRNAs and antisense oligonucleotides), enabling facile and effective gene therapy. In diabetic mice, Randeria *et al.* demonstrated that ganglioside-monosialic acid 3 synthases (GM3S) targeted spherical nucleic acid (SNA) modulated keratinocyte migration, proliferation, and insulin-like growth factor-1 (IGF1) receptor activity to promote wound healing (Fig. 8A–C).[111] Apart from therapeutic applications, the surface plasmon resonance phenomena of AuNPs makes it ideal for diagnostic applications as well (through fluorescence dequenching of molecular probes upon interaction with the target moiety). Using this technique, known as Nano-Flare of Au-based SNAs, small chemicals and mRNA targets, either extracellular or intracellular, can be used as sensors.[163,164] Combining SNA skin penetration ability with its mRNA sensing Nano-Flare configuration, Yeo *et al.* investigated its utilization to monitor connective tissue growth factor (CTGF) mRNA expression of skin fibroblasts, for facile, biopsy-free detection of abnormal scarring (Fig. 8D).[165] Besides, CTGF Nano-Flare reported specifically the presence of abnormal fibroblasts on the rabbit and modified *ex vivo* human skin (Fig. 8E).[165] Apart from AuNPs, silver NPs (AgNPs) have emerged as attractive metallic NPs for transdermal therapeutic purposes. AgNPs are particulate dispersions or solid particles with diameters ranging from 1 to 100 nm.[166,167] Synthesized AgNPs include spherical, truncated, and triangular with different diameters (2–100 nm) and a higher surface to volume ratio. These NPs are promising candidates for the treatment of bacterial infections due to their potent and broad-spectrum antibacterial properties.[168] Although green synthesis of AgNPs is favorable compared to conventional chemical and physical procedures, its simplicity, cost, and time consumption should also be considered. Synthesis procedures using mediated fungus, bacteria, and other organisms are difficult since they involve the isolation and growth of the strains, which are intricate operations requiring several complicated steps. Also, these procedures are problematic in terms of maintaining the culture medium as well as the physical and chemical conditions. Plant extracts have recently been considered because of their ease of extraction, abundant availability, and their potential to eliminate the above-mentioned complicated procedures of cell culture maintenance.

4.3.2 Metallic oxide NPs. Metal oxide NPs have gained popularity in the diagnosis and treatment of dermatologic illnesses, as well as in cosmetics, due to their broad spectrum of biological activity and unique physicochemical features.[169,170] TiO_2 and ZnO NPs are two of the most often utilized metallic oxide NPs. TiO_2 NPs and ZnO NPs contributed well in dermatological situations due to their strong photostability and capacity to absorb UV radiation with wavelengths less than 365 and 380 nm, respectively.[35] However, the absorption of UV radiation by metallic oxides gives rise to reactive oxygen species (ROS) that exhibited phototoxicity and cellular membrane

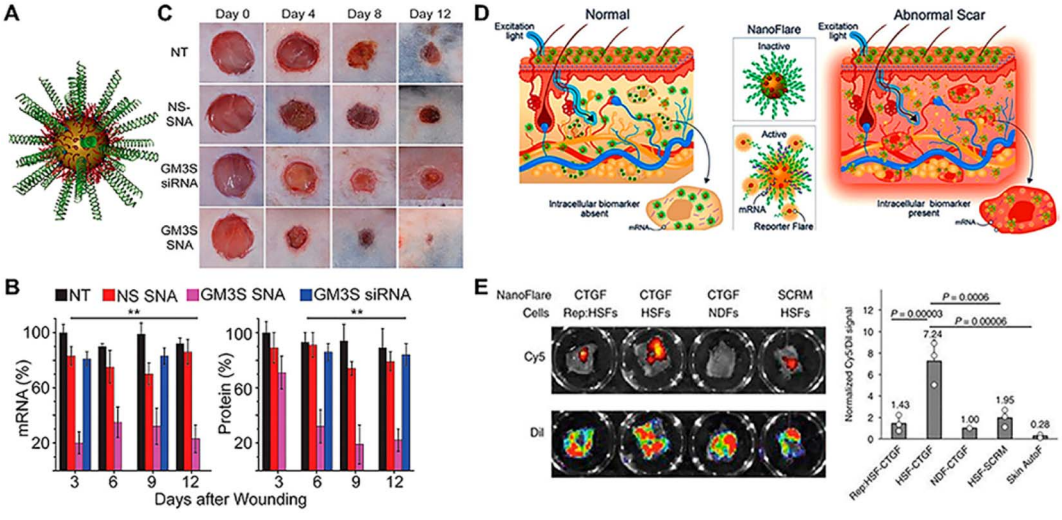

Fig. 8 Topically applied Au-based SNAs for wound healing and early scar diagnosis. (A) Schematic of Au-SNA carrying GM3S siRNA and ethylene glycol (GM3S SNAs). (B) Efficacy of GM3S SNAs in down-regulating cutaneous GM3S mRNA and protein levels in an obese mice model. (C) GM3S SNAs prevent the delayed wound healing in the obese mouse. (D) Early, facile detection of abnormal scarring through topical application of SNA Nanoflare. (E) SNA Nanoflare targeting connective tissue growth factor (CTGF) mRNA revealed the presence of HSFs in *ex vivo* skin, relative to NDFs or drug-treated HSFs. Adapted from ref. 126. Copyright 2021 American Chemical Society.

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damage in human keratinocytes which has limited their application.[35] Metals such as Ag and Au are favored in the creation of NPs to overcome the aforementioned restrictions. These NPs form a rigid functionalized surface structure with drug entrapment inside the core. They are made in a variety of sizes with customizable surface properties. Besides, the mechanisms of toxicity of metallic oxide NPs still remain largely uncharted. Metal oxide NPs exhibit varying degrees of toxicity, which are noticed less in their bulk counterparts. Before being applied in clinic applications, an evaluation and assessment of the risks and adverse effects are required.

4.3.3 Silica NPs. Silica NPs, which have a large surface area, well-defined size, customizable pore dimensions, high loading/encapsulation of desirable therapeutic molecules, and stimuli-responsivity, are another type of viable nanocarrier.[79] The drugs can be loaded in the pores or on the surface of silica NPs, shielding from enzymes and other compounds in the environment. A sequence of chemical processes was used to create silica NPs with sizes ranging from 0.05 to 2 nm.[171,172] Various skin-related uses of silica NPs have been widely investigated. Rancan *et al.* confirmed the influence of size and surface charge on the penetration capabilities of silica NPs in human skin explants pretreated with cyanoacrylate skin surface stripping (CSSS).[41] The size of silica NPs is a crucial factor of translocation across the SC. Hirai and colleagues demonstrated skin penetration and cellular localization of well-dispersed amorphous nano-silica particles with a diameter of 70 nm using TEM. The results suggested that silica NPs can pass the epidermal barrier and are transferred to the lymph nodes after three days of topical treatment on mice *in vivo*.[173] Before the realization of the use of silica NPs in clinical applications, several major challenges should be overcome, including improvement of drug loading, enhancing incorporation efficiency, spatial and temporal control of drug release, and highly efficient targeting of disease sites. A thorough understanding of the toxicity profile is not only a scientific concern but also a prerequisite for the clinical application of silica NPs. Nevertheless, by integrating silica NPs with other systems such as polymers and small molecule materials, it is expected that more strategic and scale-up production of "intelligent" and composite nano-reagents will be achieved.

4.3.4 Quantum dots (QDs). QDs are nanoscale crystals constructed from semiconductor materials with a core, shell, and coated surfaces. The quantum effect of light absorption or emission is caused by the presence of semiconductors in the core (CdSe), and fluorescence effects and photostability are the functions of the shell (ZnS).[54,79] Thus QDs have fluorescence features that allow them to be tracked inside the skin. Since Cd was discovered inside the liver and kidney after skin exposure, Tang *et al.* demonstrated QDs can penetrate and permeate through rat skin, while raising concerns about QD's toxicity.[174] Wang *et al.* demonstrated that QDs can enter the skin, especially when it is injured or prepared with UVB rays, and Cd can diffuse into internal organs.[175] For further development of QDs, researchers need to find commercially available and effective methods to fabricate various QDs. Multiple devices and applications can benefit from QDs because of their special optical and electrical properties. Promising strategies have been provided by elaborate designs of micro-structures and device structures for practical applications and future research. However, the research on QDs is still in its early stage compared to graphene. There is still a long way to go for extensive practical applications, and there is also a wide space of exploration for researchers.

5. Evaluating the transdermal capacities of nano-systems

In the past, the transdermal passage of nanoparticles, or the capacity of nanoparticles to promote the passage of drugs to the systemic circulation, is a rather controversial field.[176] However, the evaluation of the enhanced transdermal drug delivery facilitated by functional nano-systems has been addressed using a variety of microscopic, spectroscopic, and structural methods. Label-based or label-free instrumental approaches can be used to characterize the characteristics of functional nano-systems and their penetration into the skin. Diffusion cell method, TEM/SEM, cryo-electron microscopy (Cryo-EM), soft X-ray spectromicroscopy, Raman microscopy, atomic force microscopy (AFM), surface enhanced Raman scattering (SERS), and Fourier transformed infrared (FTIR) and infrared (IR) microscopy are label-free methods. Meanwhile fluorescence spectroscopy (intensity-based, spectrally-resolved, time-resolved, and raster scanning-based correlation techniques), single-molecule fluorescence microscopy, and electron paramagnetic resonance (EPR) techniques are examples of label-based techniques. The sensitivity, specificity (information content), geographical resolution, and technological requirements of these approaches differ. This paragraph will provide an outline of the various techniques for evaluating the transdermal capacities of nano-systems.

5.1 Label-free technique

5.1.1 Diffusion cell method. The diffusion cell method is the gold standard in the evaluation of TDDs, which can provide numbers of quantifiable data to support the capacity of NPs to cross the epidermal layer.[177,178] For example, Özcan *et al.* designed lecithin–chitosan NPs to investigate the topical delivery of quercetin. In an *in vitro* percutaneous study, compared with the quercetin solution, NPs could significantly enhance the cumulative amounts of quercetin in the dermis and epidermis within 12 hours of application ($P < 0.05$), and the amounts of quercetin in the epidermis and dermis were 9.00 ± 0.40 μg and 3.31 ± 0.51 μg, respectively, which were 1.45 and 1.32 times those of the control formulation. *In vivo*, quercetin extracted from the epidermis and dermis was analyzed by HPLC at every sampling point. For the nanoparticles, the amounts of quercetin in the epidermis and dermis were 8.4 ± 1.53 μg and 2.21 ± 0.01 μg, respectively, which were 2.3 and 1.2 times those of the control formulation. The permeation behavior of quercetin *in vivo* was similar to that *in vitro* ($P < 0.05$). Özcan *et al.* synthesized diflucortolone valerate (DFV) loaded lecithin/chitosan NPs to evaluate if the *in vitro* accumulation of

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clobetasol-17-propionate would improve the efficacy *in vivo*.[179] It produced a significantly higher amount of DFV in the SC + epidermis and dermis in comparison with the tested dosage forms ($P < 0.05$). The results indicated that these nanoparticles showed 6.33- and 5.79-fold higher retention compared with commercial cream for DFV in SC + epidermis and dermis, respectively.

5.1.2 TEM/SEM and AFM. TEM, CryoEM, and SEM are routinely used to evaluate the shape and surface morphology of NPs, and also be utilized to investigate nanoparticle localization in skin tissue.[122] TEM is sensitive to electron-dense spots in the material and offers good pictures of skin slices (human skin and murine skin), particularly for metallic or silica NPs with ultrastructural spatial resolution down to 0.1 nm.[32,180] SEM, which employs a raster scan of an electron beam over a surface, in conjunction with an X-ray microanalyzer that is sensitive in the excited volume element, enables simultaneous viewing and elemental analysis of the specimen.[32]

5.1.3 AFM. AFM "touches" the surface of the sample with a mechanical probe to characterize its morphology and record its mechanical properties.[181] AFM provides information on height differences in the nm range. AFM has recently become an important tool for studying the micro/nanoscale properties of skin and nanosystems. For example, clusters of dispersed NPs (particle dimension: 37.5 nm width at half height) in the dermal collagen network were visualized in human skin cryosections using this technique.[182] In addition, AFM can provide insights into the electrical properties of nanoscale data, leading to a better understanding of the mechanisms of how nanosystems interact with and influence skin electrical properties. This is because the change of charge is proportional to the contact surface potential. When the surface electric potential changes, the charge will change accordingly.

5.1.4 X-ray spectromicroscopy. X-ray microscopy is a potent label-free technology that uses the resonant excitation of the target samples (polymers or drugs) in the soft and hard X-ray regimes.[183] For example, the medication dexamethasone's *ex vivo* penetration profile in human skin can be achieved by using X-ray microscopic scanning of skin sections.[184] The absorption of the drug (here at the oxygen K-edge at 530.6 eV) can be selectively measured and visualized in the image. The concentrations of dexamethasone as low as 1–2 μg cm^{-2} were detected in human skin.[184]

5.1.5 Vibrational spectroscopy and microscopy including IR, FTIR, Raman, and surface enhanced Raman scattering (SERS). The vibrational states of molecular bonds can be reveled *via* the absorption in the infrared spectral region. Accordingly, information on molecular composition and structural organization of lipid lamellar phases becomes available. *In vivo* studies of nanocarrier penetration and drug release were carried by collecting various layers of the SC using the tape stripping technique. Combining FTIR[185] and FTIR photoacoustic spectroscopy, the quantitative distribution patterns in the human SC can be obtained.[186] Furthermore, FTIR measurements on isolated SC sheets can provide direct information on skin hydration, protein, and lipid composition as well as secondary protein structures.[187] The lateral organization and conformational ordering of the lipids in the sample can be observed *via* the methylene scissoring and stretching modes.[188] However, because of the significant IR absorption of water *in vivo* IR spectroscopy investigations are only sensitive to the epidermis. Since Raman-active bonds can vary their polarizability when excited with a certain frequency of light, Raman spectroscopy can enable selectivity to specific bonds. While the intensity of the Raman peak is directly proportional to the concentration of the respective molecule, non-invasive detection and quantification of Raman-active compounds in the skin are feasible *in vivo*.[189,190] When employing Raman microspectroscopy, this label-free technology also delivers pictures and direct visualization (resolution down to ~1 μm), together with chemical analysis, and it may be utilized for *in vivo* applications on human skin.[191–193] For *in vivo* confocal Raman studies, water profiles, SC thickness, and penetration profiles of hydrophilic compounds with a depth resolution of 5 μm were described.[191] By deconvolution with the known model spectra, the penetration profiles of Raman-active nanoparticles may be derived from the overlapping Raman spectra of the NPs and the skin compounds, such as cholesterol, ceramide, keratin, urea, water, and other skin compounds.[193] Moreover, SERS is a sophisticated label-free imaging technique based on molecular vibrational spectroscopy with resolutions down to the submicrometer region, that have been applied for the detection of nanoparticles and drugs in the skin (porcine skin and murine skin).[193,194]

5.2 Label-based techniques

5.2.1 Fluorescence spectroscopy. Fluorescence spectroscopy can be used to track skin penetration *in vivo* by exciting fluorophores connected to the nanocarrier (normally in the UV to near IR spectral range).[195,196] Endogenous fluorophores (porphyrins, nicotinamide adenine dinucleotide (NADH), collagen, and elastin), fluoresce pharmaceuticals, and exogenous fluorophores are examples of these fluorophores. For example, the transport capacity of zinc(II) phthalocyanine (ZnPc)-loaded small NPs in the skin has been investigated using fluorescence spectroscopy (Fig. 9A–C). The distribution of ZnPc-NPs/(2-hydroxypropyl)-β-cyclodextrin (HPβCD) in different skin layers can be observed (Fig. 9C). Besides using fluorescence intensity or the emission wavelength as a readout, fluorescence lifetime and time-resolved anisotropy can be employed. Fluorescence lifetime is highly sensitive to the environment and therefore allows, among others, sensing of polarity, pH, calcium concentration, or biomolecular interaction. The analysis of time-resolved anisotropy provides insights into the molecular dynamics of the nanocarrier.[197,198]

5.2.2 Single molecule microscopy. Studying fluorescent molecules in the skin at the single-molecule level is challenging. To circumvent this, single fluorescently labeled NPs are studied using multiphoton microscopy.[199] Recently, a single particle tracking based approach was developed using *ex vivo* skin combined with tape stripping to visualize and determine the diffusion constants and spatial confinements of diffusion (penetration pathways) of a model drug in the SC with

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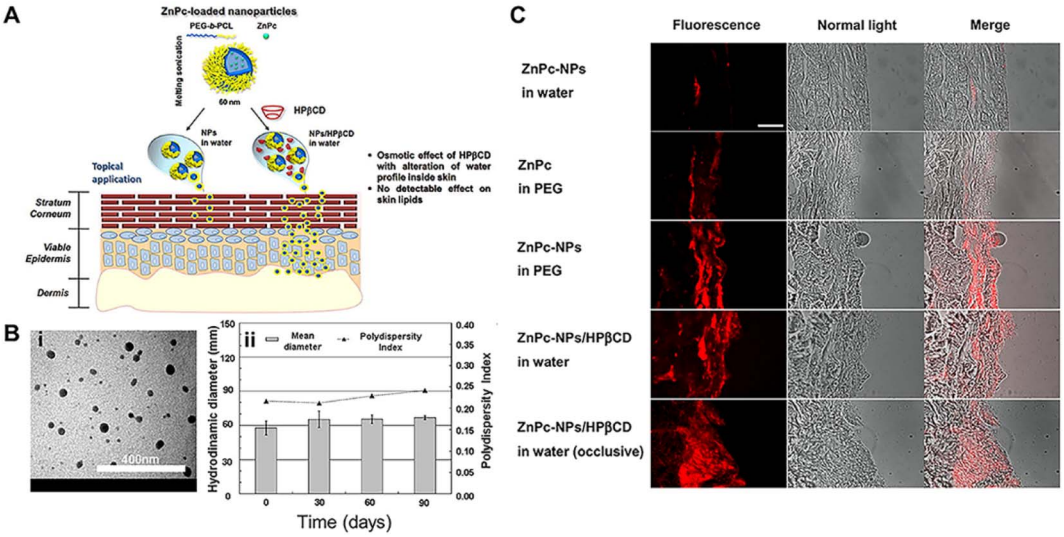

Fig. 9 Preparation and evaluation of polymer NPs through the skin. (A) Poly(ethylene glycol)-poly (ε-caprolactone)-amphiphilic diblock copolymer (PEG-*b*-PCL) NPs coupled with (2-hydroxypropyl)-β-cyclodextrin (HPβCD) NPs as a novel vehicle for the transdermal delivery of highly lipophilic compounds. (B) The evaluation and characterization of NPs. (i) TEM image of ZnPc-NPs (0.2% theoretical loading) and (ii) colloidal properties of freeze dried ZnPc-NPs/HPβCD stored in the dark at 4 °C after dispersion in water. (C) Fluorescence images of skin sections after 24 h of permeation experiment. ZnPc red fluorescence can be observed. Merged pictures were obtained by superimposing brightfield and fluorescence images of the same area. Scale bar: 500 μm. Adapted from ref. 196. Copyright 2015 Elsevier.

nanometer resolution at a depth of about 2–4 μm.[200] This technique may also be used to apply nanocarriers and pharmaceuticals to the skin *in vivo*.

5.2.3 EPR spectroscopy. EPR spectroscopy can detect unpaired electrons in paramagnetic molecules and can be subsequently utilized to investigate the *ex vivo* and *in vivo* penetration of hyperbranched nano-transporters or nanostructured lipid carriers in porcine skin using spin-labeled molecules as cargo.[201] The change of the EPR signal within the skin is used to track the penetration. In addition, free radicals are spontaneously produced in organisms as they are essential for various metabolic processes. ROS, containing one or two unpaired electrons, may be overproduced under stress situations (nanoparticle uptake). Therefore, cytotoxicity and antioxidant status may be measured using EPR spectroscopy.[202]

6. Applications of transdermal functional nano-systems for treating skin diseases

As a novel strategy, functional nano-systems have improved the penetration of drugs across the SC, and enhanced target-specific transdermal drug delivery.[92] The use of nano-systems in various skin diseases, such as infectious skin diseases and wound healing, skin inflammation, and skin cancer (atopic dermatitis and psoriasis), has resulted in better therapy.

6.1 Skin infection and wound healing

The skin, as the body's defensive barrier, is vulnerable to external micro-organism infection such as bacterial and fungal infection.

Fungi like Candida, Aspergillus, and Tinea can invade and colonize the dead tissue of the SC, leading to red, scaly, and itchy skin. Fungal infections can be superficial or invasive. Nano-systems have been found to be beneficial in the treatment of fungal skin diseases like tinea versicolor. Recently, novel SLNs were developed to release the antifungal agent Fluconazole (FLZ) for the treatment of Pityriasis Versicolor (PV), a type of fungal infection caused by Malassezia species in the SC.[203] Two formulations of FLZ-SLN topical gels were explored, with release capacities of 50 and 80% of the encapsulated drug, respectively. A randomized controlled clinical trial (RCT) on 30 well-diagnosed PV patients was performed and the results were compared with the commercialized product Candistan®. The trial lasted 4 weeks, and the FLZ-SLNs were administered twice a day to the afflicted region. The results showed that by employing FLZ-SLNs, the cure rate for fungal infection can be increased to 99% after full therapy. While Candistan® could only eliminate 80% of the whole fungal infection (Fig. 10A–D).

Bacterial species such as *Staphylococcus aureus* (*S. aureus*) and streptococcus pyogenes can infiltrate either the intact skin (Impetigo and Cellulitis) or wound skin.[204] Various functional nano-systems have been developed for topical drug delivery to the skin against bacterial infections. Salatin *et al.* designed a novel nano-platform that incorporates polymeric NPs in thermosensitive hydrogels, which offer distinct advantages such as improved tissue localization, minimized burst release, and controlled drug release.[205] The results of the extensive *ex vivo* and *in vivo* experiments revealed the possible utility of the cephalexin nanohydrogel for transdermal drug delivery. Besides, the discovery of nanocarriers brings about new concepts for wound healing, since metal NPs or polymeric NPs might be coupled with dressing materials by means of coating or other methods. They have been intensively explored to serve

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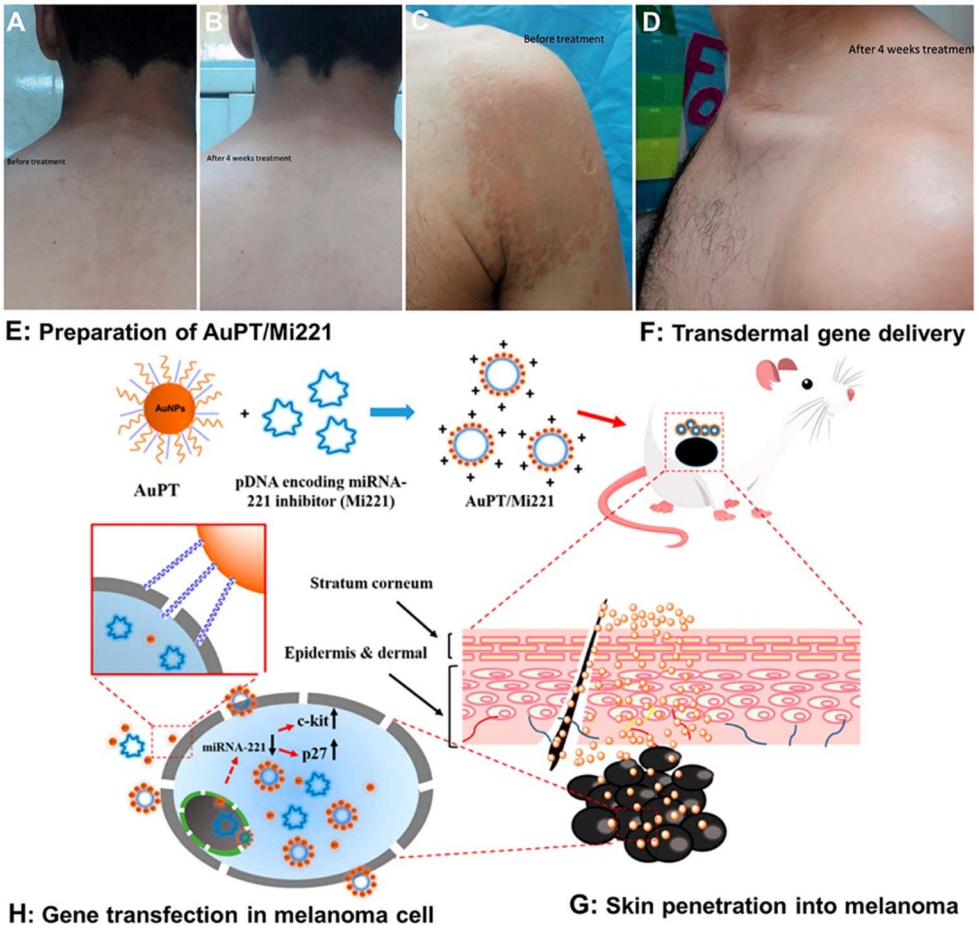

Fig. 10 Illustration of the application of nano-systems in skin infection and skin cancer. (A) Before treatment, (B) after 4 weeks of treatment, (C) before treatment, and (D) after 4 weeks of treatment using FLZ-SLNs. The AuPT NP mediated skin cutaneous melanoma treatment consists of four different steps, including (E) preparation of AuPT/Mi221 nanocomplexes. (F) Topical application of AuPT/Mi221 and the skin penetration of AuPT/Mi221. (G) Skin penetration into melanoma, and (H) gene transfection of AuPT/Mi221 in melanoma cells for tumor therapy. (A–D) Adapted from ref. 203. Copyright 2017 Taylor & Francis Group. (E–H) Adapted from ref. 227. Copyright 2017 American Chemical Society.

as antimicrobial compounds or to supply endogenous molecules and bioactive compounds to promote the healing process as well as protecting the wound sites from infections. For instance, a CS-Au@2-mercapto-1-methylimidazole (MMT)/gelatin wound dressing was developed to treat multiple antibiotic-resistant bacteria related wound infections. In the study, CS and MMT capped AuNPs showed a synergistic effect and skin was close to full recovery after 16 days of treatment for a rabbit dorsal wound model.[206] Moreover, a functional nano-system can overcome existing drug resistance mechanisms, including decreased uptake and increased efflux of the drug from the microbial cell, biofilm formation, and intracellular bacteria.[207] Liu *et al.* developed surface-adaptive, pH-responsive mixed-shell polymeric micelles (MSPMs), which penetrate and accumulate in a staphylococcal biofilm to kill bacteria over the depth of the biofilm.[208] As demonstrated for fluorescent Nile red loaded micelles using confocal-laser-scanning-microscopy, MSPMs could be demonstrated to penetrate and accumulate in a biofilm compared with single-shell-polymeric-micelles. The two-dimensional nano-system with atomical thickness and exceptional properties has demonstrated great promise as a therapeutic target for bacterial wound infection.[209,210] For example, Zheng *et al.* designed a hybrid thermo-sensitive hydrogel (Cip-Ti3C2 TSG) by incorporating Cip-Ti3C2 nanocomposites into the network structure of Cip-loaded hydrogels to effectively trap and kill bacteria. *In vitro* antibacterial results showed that the CIP-Ti3C2 nanocomposites achieved high-efficiency sterilization (>99.99999%) (7.03 log 10) for the inhibition of methicillin-resistant *Staphylococcus aureus* (MRSA) by combining photothermal therapy with chemotherapy. In an MRSA-induced murine skin infection model, the hybrid hydrogel simultaneously achieved high-efficiency sterilization and long-term inhibition effects, avoiding the rebound of bacteria after photothermal therapy.[211]

6.2 Skin inflammation

The most prevalent relapsing and chronic inflammatory skin disorders in the world are atopic dermatitis (AD) and psoriasis.[212] Many causes, including impaired skin barrier function,

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Table 3 The application of functional nano-systems for transdermal drug delivery and treatment of skin diseases

Skin disease	Nano-system	Composition	Therapeutic effects
Fungal infection	SLNs	Lipids, poloxamer 407, cremophor RH 40	The developed FLZ-SLN topical gels have a superior significant fast therapeutic index in the treatment of PV over commercially available Candistan® cream[192]
Bacterial infection	Nano-hydrogel	CS, cephalexin, pluronic®F-127	The promising data obtained from the comprehensive *ex vivo* and *in vivo* tests demonstrated the potential use of the cephalexin nano-hydrogel for topical drug delivery[194]
	AuNPs	CS, 2-mercapto-1-methylimidazole	The *in vivo* rabbit wound healing model revealed that the CS-Au@MMT/gelatin dressing possesses significant antibacterial potential against methicillin-resistant *S. aureus*-associated wound infection[195]
	Polymeric micelles	Poly(ethylene glycol), poly(β-amino ester)	Killing bacteria in their biofilm mode of growth, bypassing biofilm recalcitrance to antimicrobial penetration[197]
	Two-dimensional functional nanomaterials	Ti3C2 MXene	Provides an example of efficient MXene-based antimicrobials to treat localized bacterial infections such as methicillin-resistant *Staphylococcus aureus* (MRSA)-induced skin abscess[200]
Atopic dermatitis	Liposomes	Betamethasone valerate, diflucortolone valerate	TEWL and erythema measurement results showed that liposomes might be an effective and safe carrier for corticosteroids in skin disease treatment[202]
	NLCs	Liquid lipids (oils)	The anti-inflammatory activity of NLC gel showed a rapid onset of action, as well as a prolonged duration of action as compared with the marketed gel[203]
	SLNs	Cyclosporin-A, trehalose monooleate	SLNs based on trehalose monooleate were fabricated using the microemulsion technology and utilized to administer cyclosporin-A, which can reduce systemic side effects and increased the amount of the cyclosporin-A level in the SC and dermis compared to the control[206]
Psoriasis	Polymeric NPs	Polymers (E100), surfactants (PVA)	*In vivo* results showed that psoriasis was induced in the mice model and successfully treated, which was also confirmed by H & E staining[203]
	Ethosomes	Pluronic®F-127, anthralin	Anthralin ethosomes could serve as a potential treatment of psoriasis[218]
	Liposome	Lecithin, cholesterol, triptolide	The combination of TP-LHP and microneedle technology could provide a safe and efficient administration method of triptolide for treating RA[221]
Skin cancer	AuNPs	Plasmid DNA, twin-arginine translocation peptide	Penetrating peptide conjugated cationic gold nanoparticles offer a promising vehicle for both the skin penetration and transfection of pDNAs, possessing great potential in topical gene therapy[227]
	Polymeric NPs	Poly (lactic-*co*-glycolide), apigenin	Therapeutic efficacy of NAp can be enhanced by PLGA nanoparticle formulations to have better ameliorative potential in combating skin melanoma[228]
	Transfersomes	Cell-penetrating-peptide, paclitaxel	The PTX-CTs were shown to effectively slow the tumor growth in combination with the systemic chemotherapy using taxol, the commercial PTX formulation on a xenograft B10F16 melanoma mouse model[229]

microbial colonization, diet, and other irritants, can trigger the inflammation.

AD is typically triggered during childhood with severe eczematous lesions. Corticosteroids and calcineurin inhibitors are considered as the gold standard to treat AD, and functional nano-systems can improve their transdermal penetration. For instance, with the aid of the hydrating effect, liposomes show efficient therapy of atopic dermatitis on the SC. Eroğlu *et al.* investigated betamethasone valerate (BMV) and diflucortolone valerate (DFV)-loaded liposomes and incorporated into CS gel. The developed liposome/NP gel formulation inhibited atopic dermatitis on paw in rats more effectively than commercial creams.[213] Similarly, Asad *et al.* explored nano-systems for NLC-based gel to treat AD. The anti-inflammatory activity of NLC gel showed a rapid onset of action, as well as a prolonged duration of action as compared with a marketed gel.[214]

Psoriasis is a recurrent, chronic inflammatory condition marked by red heavily scaled plaques.[215] A broad range of

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treatments involving systemic therapy, topical therapy, and phototherapy are conducted. However, these techniques can only alleviate the disease process and the therapeutic effects are limits. Therefore, to get enhanced treatment benefit, nano-systems are applied to work against psoriasis.[216] For instance, SLNs based on trehalose monooleate were fabricated using a microemulsion technology and utilized to administer cyclosporin-A, which can reduce systemic side effects and increased the amount of the cyclosporin-A level in the SC and dermis compared to the control, and therefore promote the therapeutic effects.[217] In a more recent study, Fathalla *et al.* prepared various liposomal and ethosomal preparations loaded with anthralin to enhance efficacy against psoriasis. The clinical efficacy and safety of liposomal and ethosomal Pluronic®F-127 gels were evaluated in patients having psoriasis (**https://clinicaltrials.gov/**identifier is NCT03348462). Safety was assessed by recording various adverse events. The results showed, at the baseline, that the patients had a median Psoriasis Area and Severity Index (PASI) of 3.4 for liposomes and 3.6 for ethosomes without a significant difference. After treatment, the mean PASI change was −68.66% and −81.84% for liposomes and ethosomes, respectively, with a significant difference in favor of ethosomes. No adverse effects were detected in both groups. Study findings suggest that anthralin ethosomes could serve as a potential treatment of psoriasis.[218] In order to better promote the percutaneous absorption of a drug or make the drug arduous to diffuse into the skin by passive diffusion, hybrid systems such as nanoparticles and hydrogels, nanoparticles and microneedles gained favorable progress in enhancing the efficacy of nanomedicines.[43,219,220] Moreover, Asad MI *et al.* developed a pH-sensitive polymeric NP loaded hydrogel to act against psoriasis. Compared with a free methotrexate (MTX) hydrogel and marketed cream, a significant decrease in the Psoriatic Area and Severity Index (PASI) score was observed from day 10 from the group of mice treated with the MTX-NP loaded hydrogel. An improvement in the normalcy of mice skin was observed.[214] Chen *et al.* evaluated the effect of a triptolide-loaded liposome hydrogel patch (TP-LHP) combined with a microneedle array in percutaneous penetration and pharmacokinetics and pharmacodynamics.[221] The pharmacokinetic results showed that TP-LHP assisted by microneedles yields plasma drug levels in line with the one-compartment open model. The results of the pharmacodynamic study indicated that TP-LHP can reduce the degree of joint swelling and inhibit the utterances of fetal liver kinase-1, hypoxia-inducible factor-1α in the synovium, and fetal liver tyrosine kinase-4.

6.3 Skin cancer

The three most common kinds of skin cancer are basal cell carcinoma, squamous cell carcinoma (SCC), and melanoma.[126] Despite the fact that SCC is the most frequent skin cancer, malignant melanoma is the leading cause of mortality. Located in the bottom layer of the epidermis, melanoma has high metastasis and lethality.[222] Chemotherapy, radiotherapy, or immunotherapy is currently used to treat melanoma; however these treatments face drawbacks like tumor reoccurrence and toxic side effects.[223,224] Thus, functional nano-systems can act as an alternative for treating skin cancer.[225] Usually, a functional nano-system after intravenous injection circulates throughout the body and accumulates in the tumor passively through an enhanced permeation and retention (EPR) effect.[226] However, with TDDs, in comparison with the passive targeting method, there is a possibility for more targeted drug delivery to cells and tissues. For example, Niu *et al.* developed a cell-penetrating peptide and cationic poly(ethyleneimine) conjugated gold nanoparticle (AuPT) loaded pDNA system (AuPT/Mi221) to inhibit the encoding of miRNA-221. As an efficient carrier of pDNAs, AuPT improved the transfection efficiency and reversed the progression of melanoma (Fig. 10E–H).[227] Moreover, Das *et al.* designed apigenin (Ap) (a dietary flavonoid) loaded in poly (lactic-*co*-glycolide) nanoparticles (NAp) as the therapeutic agent of skin melanoma, in which nano-apigenin targeted nuclear DNA and promoted the accumulation of ROS.[228] Jiang *et al.* designed a paintable oligopeptide hydrogel with paclitaxel (PTX)-encapsulated cell-penetrating-peptide (CPP)-modified transfersomes (PTX-CTs) to enhance transdermal PTX delivery for topical melanoma treatment.[229] Comparted with the PTX-CT solution, PTX-CTs/Gel can be painted as a patch on the skin above the melanoma with a prolonged retention time. Due to the superior deformability of the transfersomes, the PTX-CTs are able to efficiently extrude through the gaps in the SC into the epidermis where the melanoma cells are located, further enhancing the skin permeation. The PTX-CTs were shown to effectively slow the tumor growth in combination with the systemic chemotherapy using taxol, the commercial PTX formulation on the xenograft B10F16 melanoma mouse model (Table 3).

7. Conclusion

Transdermal drug delivery is one of the least intrusive and patient-friendly ways for therapeutic agent administration. It can not only boost medication bioavailability by concentrating drug molecules in a particular skin region, but also limit the possibility of unforeseen adverse effects. Various formulations of TDDs have been developed, while their application is still limited due to the low drug distribution efficiency through the skin, which is mainly caused by the inherent skin barrier function. Recently, functional nano-systems as one of the most promising strategies to treating skin diseases have attracted a great deal of interest with significant progress achieved.

8. Outlook

The skin layer is the intrinsic barrier to impede the delivery of nanosystems into the deep skin tissue. Novel functional nano-systems open new perspectives for promoting transdermal drug delivery and treating skin diseases. Although significant achievements have been obtained, there is still a wide space of exploration for researchers.[230–233] Here in this section, we offered a comprehensive outlook of formulation strategies point-by-point to further highlight the future directions of

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nanotechnology-based on skin therapy, including: (1) developing novel nano-systems with more sophisticated structures and shapes; (2) expanding the scope of materials used for developing novel nano-systems; (3) developing novel nano-systems with minimized toxicity effects; (4) executing more deeper and comprehensive investigation over the specific skin penetration mechanism for different nano-systems.

8.1 Developing novel nano-systems with more sophisticated structures and shapes

Available reports focus on size-dependent skin penetration of NPs, mainly through follicular pathways. However, advancements in developing different structured nano-systems have facilitated their applications in transdermal delivery.[234] For instance, Tak *et al.* demonstrated that the skin penetrating capabilities of AgNPs show shape-dependence.[234] Franz diffusion cell system was used *in vitro* to study the skin penetrating capabilities of AgNPs with different shapes. The amount of silver permeated through skin to the receptor cell at different time intervals was measured using inductively coupled plasma-mass spectrometry (ICP-MS). AgNPs showed shape-dependent permeation through skin. After 12 h the amount of silver penetrated from rod-shaped nanoparticles (RNPs), spherical nanoparticles (SNPs) and triangular nanoparticles (TNPs) through the unit area of skin was 1.82, 1.17 and 0.52 μg cm^{-2}. An *in vivo* study using SKH-1 hairless mice showed varying skin penetration rates of differently shaped AgNPs in plasma-mass spectrometry (ICP-MS) analysis, when systemic circulating blood samples were analyzed after five days of treatment. RNPs showed the highest concentration in blood of 108.57 ± 5.43 ng mL^{-1}, whereas the concentration of silver permeated from SNPs and TNPs in blood was 50.00 ± 2.50 ng mL^{-1} and 39.29 ± 1.96 ng mL^{-1}, respectively. The consideration of the shape dependency of nanosystems in skin penetration capabilities could help develop an ideal topical agent with the highest efficacy and low systemic toxicity.

8.2 Expanding the scope of materials used for developing novel nano-systems

As the basic skeleton unit of nanocarriers, materials are one of the sources of unique functions of nanosystems.[18,206,235] At present, nature provides us with a variety of materials, from metal to non-metal, and from organic to inorganic. For the reasonable choice of materials, it can make our designed work of art stand out. Drug resistant bacteria are a headache in the medical field. At present, researchers combine antibacterial materials with antibiotics/non-antibiotics to achieve dual antibacterial effects.[236,237] For example, the interaction between the positive charge in the chitosan molecule and the negative charge in the microbial cell membrane leads to the leakage of bacterial proteins and other cell components, resulting in the antibacterial effect. The combination of the two will greatly improve the antibacterial effect.[237,238] Chemical excipients such as ethanol and glutaraldehyde are often used in the formula, which may cause skin irritation, allergic reaction and dermatitis, and are widely criticized. Therefore, materials with good biocompatibility have attracted more attention. For example, Zhang *et al.* developed a new TDDS for the treatment of hypertension using atenolol (ATE) based on poly (acrylic acid) (PAA)-decorated three-dimensional (3D) flower-like MoS_2 nanoparticles (PAA-MoS_2 NPs) that respond to NIR laser irradiation. The skin irritation assay of PAA-MoS_2 was performed by using a rabbit model. *In vivo* skin erythema index indicates that PAA-MoS_2 can be applied safely in clinics without causing irritation.[239]

8.3 Developing novel nano-systems with minimized toxicity effects

At present, most investigations of functional transdermal nano-systems are at the pre-clinical stage and far from being applied in clinical trials, which leaves large space and deserves more deep and systematic studies. For instance, since nanomaterials display active interactions with the skin barrier, the assessment of nano-systems' toxicity is very important. However, most research focuses on *in vitro* toxicity using the coculture system of human fibroblasts and keratinocytes. The methylthiazoltetrazole (MTT) test is commonly used to determine the toxicity of curcumin-Cs NPs when incubated with HaCaT keratinocytes.[240] Biodegradable self-assembling gelatin/epigallocatechin gallate (EGCG) nanoparticles (GE NPs) were demonstrated for good biocompatibility. In this study, cell viability assays indicated that 10 μg mL^{-1} concentrations of EGCG or GE were non-toxic to human dermal fibroblast (WS1) cells.[241] Moreover, Au-NPs with 5 nm at a concentration up to 200 mM were shown to be safe to keratinocytes, since materials with cell viability more than 80% are often considered as biocompatible.[242] While cell-based *in vitro* research is important to determining the toxicity toward specific cells or tissues, *in vivo* experiments are essential to test their systemic toxicity for the organs and the whole body. Besides, chemical excipients such as ethanol are used in the formulation of nano-systems, which could cause skin irritation, an allergic reaction, and dermatitis. Therefore, the toxicity effects of nano-systems need to be evaluated by using rabbit and rat models. For example, the skin irritation assay of triptolide (TPL) loaded NPs was performed by using a rat model. The result showed that TPL-NPs can be applied safely in clinics without inducing irritation.[243]

8.4 Executing more in-depth and comprehensive investigation over the specific skin penetration mechanism for different nano-systems

The specific skin penetration mechanism for each type of nano-system deserves more in-depth and comprehensive investigation. Currently, the transdermal mechanism for some types of nano-systems has been revealed, but for most of the types, their specific mechanism remains unclear. The diffusion cell method is the gold standard in the evaluation of TDDs, which is the most commonly used.[177,178] Patlolla *et al.* demonstrated size-dependent penetration by using TEM, with AuNPs (15 nm) effectively reaching a deeper region of the skin layer whereas larger particles were observed mainly in the epidermis and dermis. Moreover, one solution would be to label nano-systems

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with fluorescent dyes, which can be used to monitor the penetration process with the help of confocal imaging. For instance, the inclusion of the transactivating transcriptional activator (TAT) peptide on the surface of NPs enables better binding to the SC through its positively charged groups, enhancing NP occlusion and facilitating passage into the SC.[244] Furthermore, while skin penetration of nano-systems can be achieved, the precise control over the penetration depth still needs investigation. The physicochemical properties of nano-systems and their composition may influence their penetration depth. For example, the different sizes of AuNPs are used to target different areas in the skin.[40] In addition, when there is an incomplete formation of nanocarriers, it could lead to coalescence. Therefore, the composition and physicochemical properties of nano-systems should be elaborately modified in accordance with their specific therapeutic application.

Abbreviations

FDA	Food and Drug Administration
TDDs	transdermal drug delivery systems
NPs	nanoparticles
CNTs	carbon nanotubes
SC	stratum corneum
NGs	nanogels
tNGs	thermos-responsive nanogels
PNIPAM	poly(*N*-isopropylacrylamide)
IDCC	indodicarbocyanine
SRL	Stimulated Raman-Loss
CS	chitosan
DxPCA	spin-labeled dexamethasone
5-FU	5-fluorouracil
CLSM	Confocal laser scanning microscopic
HFs	hair follicles
NR	Nile red
SLNs	solid lipid NPs
NLCs	nanostructured lipid carriers
HA	hyaluronic acid
PLA	polylactic acid
PLGA	poly(lactic-*co*-glycolic acid)
AuNPs	Gold NPs
NA	nucleic acid
VEGF	vascular endothelial growth factor
SNA	spherical nucleic acid
IGF1	insulin-like growth factor-1
GM3S	ganglioside-monosialic acid 3 synthases
CTGF	connective tissue growth factor
AgNPs	silver NPs
ROS	reactive oxygen species
TEM	transmission electron microscopy
QDs	quantum dots
CSSS	cyanoacrylate skin surface stripping
SEM	scanning electron microscope
Cryo-EM	cryo-electron microscopy
AFM	atomic force microscopy
SERS	surface enhanced Raman scattering
FTIR	Fourier transformed infrared
IR	infrared
EPR	electron paramagnetic resonance
AD	atopic dermatitis
FLZ	Fluconazole
PV	Pityriasis Versicolor
RCT	randomized controlled clinical trial
S. aureus	*Staphylococcus aureus*
BMV	betamethasone valerate
DFV	diflucortolone valerate
SCC	squamous cell carcinoma
AuPT	gold nanoparticle
AuPT/Mi221	gold nanoparticle loaded pDNA system
Ap	apigenin
Nap	a dietary flavonoid loaded in poly (lactic-*co*-glycolide) nanoparticles
PASI	Psoriatic Area and Severity Index
DLS	dynamic light scattering
LFGDM	liquid flow-focusing and gas displacing method
PLGA-PEG	poly(lactide-*co*-glycolide)-*b*-poly(ethylene glycol)
PLGA-Dex10	poly(D, L-lactide-*co*-glycolide)-dextran
PLGA-Dex10-curc	curcumin-functionalized PLGA-dextran micelles
PAMAM-G7	poly (amidoamine)
NADH	nicotinamide adenine dinucleotide
HPbCD	(2-hydroxypropyl)-β-cyclodextrin
MMT	mercapto-1-methylimidazole
MTX	methotrexate
MTT	methyl thiazolyl tetrazolium
TAT	transactivating transcriptional activator
VE	viable epidermis
FNAs	framework nucleic acids
HPLC	High Performance Liquid Chromatography
MSPM	mixed-shell polymeric micelles
MRSA	methicillin-resistant *Staphylococcus aureus*
PASI	Psoriasis Area and Severity Index
MTX	methotrexate
TP-LHP	triptolide-loaded liposome hydrogel patch
EPR	enhanced permeation and retention
PTX	paclitaxel
CPP	cell-penetrating-peptide
PTX-CTs	paclitaxel (PTX)-encapsulated cell-penetrating-peptide (CPP)-modified transfersomes
EGCG	epigallocatechin gallate
GE NPs	gelatin/epigallocatechin gallate (EGCG) nanoparticles
WS1	human dermal fibroblast
TPL	triptolide
ATE	atenolol
PAA	poly (acrylic acid)
3D	three-dimensional
ICP-MS	plasma-mass spectrometry
RNPs	rod-shaped nanoparticles
SNPs	spherical nanoparticles
TNPs	triangular nanoparticles
ICP-MS	plasma-mass spectrometry
LC	liquid crystals
ISAsomes	Internally self-assembled somes or particles

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Conflicts of interest

There are no conflicts of interest to declare.

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