

Review

Recent Advances in Nanomaterials for Dermal and Transdermal Applications

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Abstract: The stratum corneum, the most superficial layer of the skin, protects the body against environmental hazards and presents a highly selective barrier for the passage of drugs and cosmetic products deeper into the skin and across the skin. Nanomaterials can effectively increase the permeation of active molecules across the stratum corneum and enable their penetration into deeper skin layers, often by interacting with the skin and creating the distinct sites with elevated local concentration, acting as reservoirs. The flux of the molecules from these reservoirs can be either limited to the underlying skin layers (for topical drug and cosmeceutical delivery) or extended across all the sublayers of the epidermis to the blood vessels of the dermis (for transdermal delivery). The type of the nanocarrier and the physicochemical nature of the active substance are among the factors that determine the final skin permeation pattern and the stability of the penetrant in the cutaneous environment. The most widely employed types of nanomaterials for dermal and transdermal applications include solid lipid nanoparticles, nanovesicular carriers, microemulsions, nanoemulsions, and polymeric nanoparticles. The recent advances in the area of nanomaterial-assisted dermal and transdermal delivery are highlighted in this review.



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Keywords: dermal delivery; transdermal delivery; permeation; cosmeceuticals; skin care; lipid nanocarriers; nanoemulsion; microemulsion; nanospheres; nanocapsules; transfersome; ethosome; liposome

1. Introduction

The skin plays a vital role in protecting the human body, functioning both as an effective permeability barrier against the penetration of exogenous molecules, pathogens, and irritants, and as a protective multilayer shield against dehydration, temperature fluctuations, ultraviolet radiation, and other environmental hazards [1–4]. This barrier function is attributed primarily to the *stratum corneum* (SC), the outermost layer of the epidermis, constructed of a dense network of keratin in a form of flattened corneocytes surrounded by a lipid matrix, which consists of ceramides, free fatty acids, and cholesterol [5–7]. This dense network effectively blocks molecular permeation into the deeper layers (strata) of the skin and across the skin [8].

Despite this permeability challenge, the skin is considered to be an attractive organ for local (topical, dermal) and systemic (transdermal) delivery of active substances. Being the largest organ in the human body, the skin offers a vast, painless, and accessible interface for the administration of pharmaceuticals and cosmeceuticals [9]. Topical administration of pharmaceuticals that treat skin disorders has the ability to target the disease site without a significant risk of systemic absorption and systemic side effects [9]. Topical application of cosmeceuticals allows to rejuvenate, moisturize, nourish, smoothen, and protect the skin. Transdermal delivery, in which the drug reaches the bloodstream after being absorbed through the skin, also offers several key advantages, such as avoidance of gastrointestinal side effects, escaping hepatic first-pass metabolism, and minimizing the fluctuations in plasma drug concentrations [9].

Various delivery routes have different requirements for the depth of active substance penetration. The transdermal route typically requires drugs to pass all sublayers of the epidermis (the SC and the sublayers of the viable epidermis) to reach the microcirculation of the dermis. To achieve a local activity in the skin many active substances need to be transported at least across the SC [8]. There is a plethora of factors that can impact the effectiveness of the SC barrier function. Area of application, contact time, degree of skin hydration, subject age, skin pre-treatment, physicochemical properties of the penetrant, and its concentration are among the most influential parameters that govern the spontaneous permeation through SC [10].

The majority of molecules cross the SC via three main pathways [6,11,12]. The main pathway is the intercellular route through the lipid matrix located between the corneocytes. This pathway allows small hydrophobic molecules (typically with a molecular weight below 500 Da) to permeate through tight lipid junctions between the cells in a tortuous route (Figure 1a) [13,14].

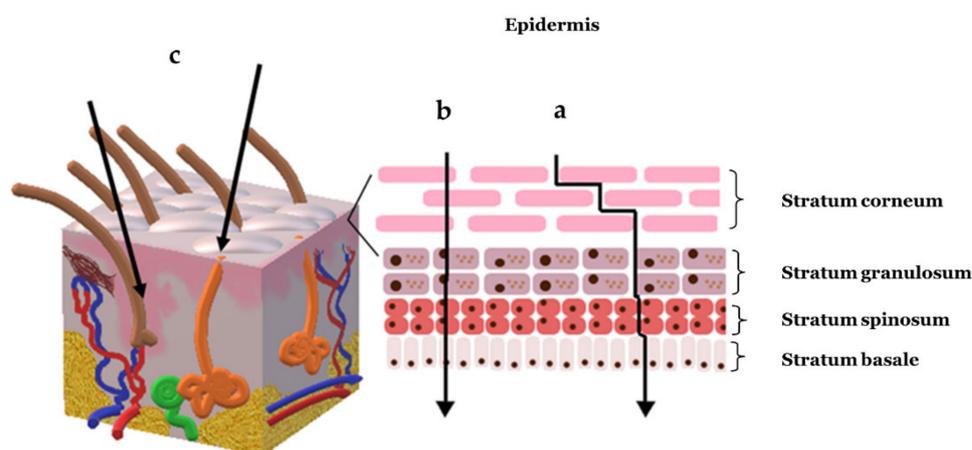


Figure 1. Skin layer structure and penetration routes: (a) intercellular (b) transcellular (c) transappendageal pathways.

Other pathways include the transcellular route, in which the penetrants pass through the corneocyte cells themselves (Figure 1b), and the transappendageal route, in which the molecules take advantage of skin appendages to penetrate (Figure 1c). The transcellular pathway enables the penetration of small hydrophilic or moderately lipophilic molecules ($\log p = 1-3$) through the keratinized corneocytes, but limits the permeability of highly lipophilic compounds. The permeation by the transappendageal pathway takes place through hair follicles, sebaceous glands and sweat ducts, which together comprise only about 0.1% of the total skin surface area (Figure 1c) but can uniquely allow the passage of atypical penetrants. Hair follicles, for example, can serve as the penetration site for large hydrophilic molecules, whose permeation through the skin is extremely challenging in general. It is noteworthy, however, that the presence of sebum, an oily material produced by the sebaceous glands, in the hair follicles may impede this permeation process [15–17].

For certain molecules, the passage by these pathways is extremely slow, which makes it challenging to attain an effective level of an active substance in the deeper skin layers or deliver substantial amounts into the bloodstream [18]. In addition, the existence of an excessive skin metabolism has been reported, and, although it is considered to be less significant than the hepatic first-pass effect, it may cause some degradation of an active substance [19,20].

Therefore, a lot of effort is being invested in the development of cutaneous nanoparticulate delivery systems that can deliver active substances of a variety of molecular weights and lipophilicity into and across the skin, protect them from skin metabolism, and supply a sustained release of drugs and cosmeceuticals from the SC, boosting their effective concentration in deeper skin strata and in the bloodstream [18].

Some nanoparticulate structures have a sufficient flexibility to deform and penetrate through the untreated SC along with their active cargo [21]. These particles often use either appendage or intercellular routes for penetration [21]; and a plausible explanation for the driving force behind such permeability of particles larger than skin openings is the hydration gradient-driven transport [22]. Other nanoparticulate structures fail to passively penetrate on their own, but enable an efficient permeation of their active cargo at higher concentrations due to the specific interactions with the skin, for instance, the occlusive effect that is formed as a result of surface coverage [21].

The most prevalent types of nanocarriers being investigated for the cutaneous delivery of drugs and cosmeceuticals are: solid lipid nanoparticles [23–25], nanovesicular carriers [26–28], microemulsions [29,30], nanoemulsions [30], and polymeric nanoparticles [31–33]. It is noteworthy, that many of the investigated formulations comprising these nanomaterials are intended for topical treatment rather than for systemic administration through the skin. This may be owing to the fact that for the development of an effective transdermal formulation it is necessary not only to successfully transport drugs across several skin layers but also to employ an appropriate animal model for evaluation of systemic distribution, which may be challenging in some research settings. Nevertheless, several novel transdermal formulations are reported for almost every type of the aforementioned nanocarriers. The applications of these nanocarriers in topical and transdermal deliveries since 2015 are highlighted in this review.

2. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles (SLN) are nanometric colloidal carriers composed of solid lipid core with the entrapped active substance and stabilized by surface-active agents [34–36]. SLN were designed in the 1990s and exhibit some unique properties, such as intrinsic protection of active substance against degradation, excellent toxicity profile, high loading capacity, biodegradability, chemical versatility, scalability and the ability to undergo sterilization [23,25,36–41]. Furthermore, the interaction between the lipid core of the SLN and the waxy lipids in the SC leads to a significant permeation enhancement of the encapsulated material into the skin [42].

SLN are composed of a highly ordered solid lipid core matrix, stabilized by surfactants (Figure 2). Lipophilic active substances can be solubilized and incorporated into the lipid core, which is solid at room temperature and is liquid at hyperthermic temperatures (above 40 °C) [38]. This nature enables the SLN to act as an effective controlled release delivery system, which protects the encapsulated drugs from the external environment and enhances long-term stability [38,43].

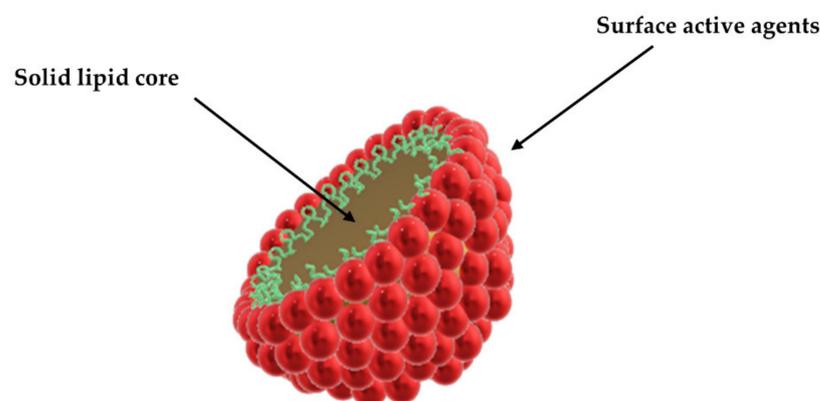


Figure 2. Solid lipid nanoparticles (SLN).

A second generation of the lipid nanoparticles called nanostructured lipid carriers (NLC), is composed of a blend of solid lipids and liquid lipids in the core in the ratio of 7:3 to 9:1 [44], which makes the lipid matrix core less ordered and decreases the melting point

to prevent recrystallization of solid lipids (Figure 3) [36,38]. NLC are considered to be a modified version of the SLN, having the same unique properties with more versatile core composition, which leads to a higher drug loading capacity, greater stability and the ability to work at lower temperatures. Notably, the NLC are still solid at body temperature [45].

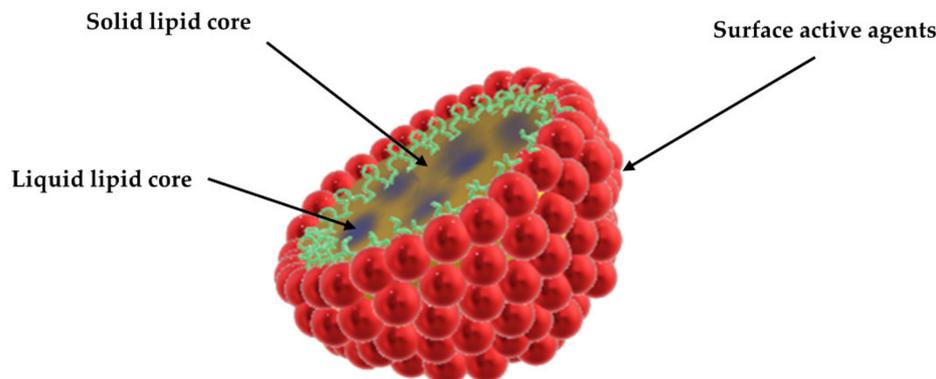


Figure 3. Nanostructured lipid carriers (NLC).

There are myriad of methods to form SLN and NLC, while the main technique used today is high-pressure homogenization. This technique is divided into a hot homogenization, in which the lipids are processed above their melting point, and to a cold homogenization, which is carried out at low temperatures and is suitable for hydrophilic and temperature-sensitive substances [37,46]. Other methods include sonication/ultra-sonication [47,48], membrane contactor technique [39,45], phase inversion [49], solvent injection [50], emulsification [50,51], the microemulsion method [39,52], and others.

In cutaneous applications, SLN and NLC create a thin hydrophobic monolayer upon contact with the skin. This monolayer has a marked occlusive effect; it provides molecular retention, facilitates active substance penetration, and prevents water loss from the skin [53]. When topically applied, the nanoparticles interact with the sebum and skin lipids, and can alter the natural organization of the corneocytes. This interaction releases the encapsulated molecules and may enhance their penetration to deeper epidermis and dermis layers, depending on their lipophilicity [42,54]. Hence, SLN and NLC are extensively employed in cutaneous delivery systems. Several selected works demonstrating the most recent advances involving SLN and NLC for dermatological treatments are detailed herein.

2.1. Topical Delivery with SLN and NLC

2.1.1. Antifungal activity

Butani et al. developed a stable SLN system containing amphotericin B for enhancing antifungal activity, with an average size of 111 nm, negative zeta potential, and drug loading of 94% [55]. The SLN were prepared by solvent diffusion method and showed at least twice higher drug permeation and about 60% higher drug accumulation in the skin compared with the conventional gel in ex vivo hairless rat skin [55]. El-Housiny et al. formed fluconazole-containing SLN by modified hot homogenization method and ultrasonication using different concentrations of solid lipids [56]. The mean particle size was between 292 and 500 nm, the particles were spherical and negatively charged. The SLN showed a controlled release of the drug in vitro and a significantly higher cure rate of *pityriasis versicolor* compared with the commercial cream Candistan[®] 1% in clinical trials [56]. Carbone et al. designed NLC containing Mediterranean essential oils and clotrimazole for the treatment of candidiasis [57]. Stable NLC were prepared by a hot homogenization method and had an average size of below 100 nm with a broad size distribution. In vitro studies demonstrated a prolonged release of clotrimazole, without an initial burst effect, and the enhancement of the antifungal activity of clotrimazole [57].

2.1.2. Anti-inflammatory Activity

Pivetta et al. designed thymol-loaded NLC for the local treatment of inflammatory skin diseases [58]. The NLC were prepared using a sonication method and had an average size of 108 nm, negative zeta potential, and entrapment efficiency of 89%. They were incorporated into a gel and showed anti-inflammatory activity in two different skin inflammation mouse models, and improved healing in an imiquimod-induced psoriasis mouse model [58]. Gad et al. encapsulated chamomile oil in SLN for the treatment of wounds [59]. The formulation contained stearic acid and chamomile oil (7:3 respectively) and was prepared by the hot homogenization method. Resulted nanoparticles were irregular in shape, had an average size of around 540 nm, and were strongly negatively charged. Topical application in rats with wounds showed wound reduction, collagen deposition, and other biomarkers of wound healing acceleration [59].

2.1.3. Antioxidant Activity

Shrotriya et al. developed resveratrol loaded SLN for the treatment of irritant contact dermatitis, which is a chronic skin disease with severe eczematous injuries [60]. The SLN were formed by the hot ultrasonication method, had spherical shapes and an average size of below 100 nm. The nanoparticles were negatively charged and had a resveratrol entrapment efficiency of 86-89%. They were incorporated into carbopol gel and showed increased antioxidant activity compared with resveratrol-containing plain gel, and 3.5 times higher ex vivo retention of resveratrol in human skin [60]. Okonogi and Riangjanapatee prepared NLC loaded with three different concentrations of lycopene by a hot high-pressure homogenization [61]. The particles had sizes of 150-170 nm with narrow size distributions. The in vitro release study showed a fast release in the first 6 h with retardation in the next 18 h for all samples. It was found that the NLC with the highest concentration of lycopene had the slowest release rate, the most significant occlusion effect on the skin, and the highest antioxidant activity [61].

2.1.4. Anti-acne Activity

Kelidari et al. designed SLN of spironolactone for the treatment of acne [62]. Drug-loaded SLN were prepared by a modified emulsion/solvent evaporation method followed by ultrasonication. It was found that with the increase in the ratio of surfactant to drug-lipid concentration, the particle size of SLN decreased and the smaller particles showed a narrower size distribution. The in vitro dissolution study showed a faster drug release from the SLN at the initial stage followed by a sustained release pattern. The ex vivo skin permeation study in rat skin revealed a significantly higher percutaneous absorption of spironolactone from SLN compared with the free drug, and a higher amount of the drug retained in the skin [62]. Ghatge et al. formed NLC for the delivery of tretinoin, which has both an anti-aging and anti-acne potential [63]. The NLCs were prepared by hot melt microemulsion and hot melt probe sonication methods. The size of the NLC prepared by the microemulsion technique was greater compared to those prepared by the sonication method. Tretinoin-loaded NLC in carbopol gel showed a sustained release pattern. The in vivo skin irritation test in rats showed no irritation or erythema after the application of the gel-incorporated NLC for seven days, whereas a commercial tretinoin gel showed irritation and slight erythema within only three days of application due to a significant skin irritation effect of tretinoin [63]. Malik and Kaur, developed azelaic acid-loaded NLC, prepared by melt emulsification and ultra-sonication method [64]. These stable, spherical nanoparticles with a mean size of around 50 nm had high drug entrapment efficiencies (>80%). They were incorporated into aloe-vera-based carbopol hydrogels and demonstrated a deeper skin penetration and prolonged retention abilities compared with the commercially available product (Aziderm 10%). The NLC were well tolerated with no signs of irritation, edema, redness, or dryness. The in vivo anti-acne activity was checked in *Cutibacterium acnes* inoculated mice ear models and showed a higher anti-inflammatory

effect of NLC incorporated into a gel compared with the plain drug suspended in the gel [64].

2.2. Transdermal Delivery with SLN and NLC

Lin and Duh prepared lansoprazole-loaded NLC for transdermal delivery to treat elevated gastrointestinal acidity [65]. Drug-loaded NLC were prepared by the hot emulsification method. They contained a cationic lipid and were stabilized by an anionic surfactant. The NLC had particle sizes between 90 and 210 nm and were strongly negatively charged. The NLC were incorporated into hydrogels and administered transdermally to rats. The systemic absorption and pharmacokinetics studies showed a much slower elimination rate of the drug after transdermal administration compared to the intravenous injection and revealed that lansoprazole systemic concentration remained high for 24 h after the transdermal administration, although the maximum drug concentration (C_{max}) and the area under the concentration-time curve (AUC) were significantly compromised in comparison with intravenous injection. It was concluded that the drug was not absorbed through the skin at once but rather accumulated in the skin and continuously penetrated into the bloodstream to maintain a constant concentration over time. There was no skin irritation observed after the transdermal application [65]. Alam et al. formed NLC loaded with an anti-hyperglycemic agent, pioglitazone, by hot homogenization followed by ultrasonication [66]. The average particle size ranged from 81 to 182 nm, the drug loading was between 6% and 13% and the transdermal flux was between 30 and 50 $\mu\text{g}/\text{cm}^2/\text{h}$. The pharmacokinetics of the transdermal NLC-based formulation in vivo was compared to this of the commercial oral tablet of pioglitazone. It was found that the absorption of the drug from the transdermal formulation was much slower and lasted over an extended period of time in comparison with the oral tablet. Overall, the extent of systemic absorption of the drug from the transdermal formulation was significantly higher than that from the oral tablet, which could be attributed to the avoidance of the extensive first-pass effect. Also, the transdermal formulation demonstrated a longer antidiabetic effect compared with the commercial oral tablet [66]. Additional recent works involving SLN and NLC in dermal drug delivery are summarized in Table 1.

Table 1. Recent studies on dermal/transdermal drug delivery systems comprising NCL and SLN.

Type of Lipid Nanoparticle	Drug/Active Material	Purpose	Reference
SLN	Doxorubicin	Development of doxorubicin-loaded cationic lipid nanoparticles for cancer therapy	[67]
SLN	Sesamol	Formulation of solid lipid nanoparticles containing sesamol for treatment of skin cancer	[68]
SLN	Benzocaine	Formulation of benzocaine loaded solid lipid nanoparticles for local anesthetic activity	[69]
SLN + NLC	Human recombinant epidermal growth factor	Development of lipid nanoparticle-based dressings for topical treatment of chronic wounds	[70]
SLN	Adapalene	Development of topical adapalene loaded solid lipid nanoparticle in the gel for anti-acne treatments	[71]
SLN	Amphotericin B	Design of topical amphotericin B solid lipid nanoparticles for antifungal treatment	[55]
SLN	Peptide LL37 and serpin A1	Development of nanoparticles encapsulated with peptide LL37 and serpin A1 for wound healing	[72]
SLN	Doxorubicin	Preparing of doxorubicin-loaded solid lipid nanoparticles for the treatment of skin cancer	[73]

Table 1. Cont.

Type of Lipid Nanoparticle	Drug/Active Material	Purpose	Reference
SLN	Paclitaxel	Formulation of solid lipid nanoparticles containing paclitaxel for the treatment of skin cancer	[74]
SLN	Flutamide	Design of flutamide loaded solid lipid nanoparticles as a potential tool for the treatment of androgenic alopecia	[75]
SLN	Triamcinolone acetonide	Fabrication of triamcinolone acetonide loaded solid lipid nanoparticles for topical treatment of psoriasis	[76]
SLN	Aceclofenac	Preparation of aceclofenac in hydrogel-based solid lipid nanoparticles for non-steroidal anti-inflammatory treatments	[77]
NLC	Tretinoin	Formulation of nanostructured lipid carriers for the topical delivery of tretinoin for anti-aging and anti-acne treatments	[63]
NLC	Peptide LL37	Formulation of peptide LL37 loaded nanostructured lipid carriers for the topical treatment of chronic wounds	[78]
NLC	Adapalene and vitamin C	Fabrication of adapalene and vitamin C loaded nanostructured lipid carriers for acne treatment	[79]
NLC	Antimicrobial peptide nisin Z	Preparation of antimicrobial peptide nisin Z with conventional antibiotics loaded nanostructured lipid carriers to enhance antimicrobial activity	[80]
SLN + NLC	Lidocaine and prilocaine	Design and evaluation of lidocaine- and prilocaine-co-loaded nanostructured lipid carriers and solid lipid nanoparticles for anesthetic analgesic therapy	[81]
SLN	Resveratrol	Preparation of resveratrol loaded solid lipid nanoparticle engrossed gel for chemically induced irritant contact dermatitis	[60]
SLN	Piperine	Formulation of piperine loaded solid lipid nanoparticles for treatment of rheumatoid arthritis	[82]
SLN + NLC	Propolis by-product	Preparation of nanostructured lipid systems containing propolis by-product for wound healing	[83]
SLN	Piroxicam	Formulation of piroxicam loaded solid lipid nanoparticle for anti-inflammatory activity	[84]
SLN + NLC	Minoxidil	Development of minoxidil loaded nanostructured lipid carriers and solid lipid nanoparticles for alopecia topical treatment	[85]
SLN	Resveratrol, vitamin E, and epigallocatechin gallate	Development and evaluation of solid lipid nanoparticles containing resveratrol, vitamin E, and epigallocatechin gallate for antioxidant benefits	[85]
SLN	Silybin	Development of silybin loaded solid lipid nanoparticle enriched gel for irritant contact dermatitis	[86]
SLN	Fluconazole	Formulation of fluconazole loaded solid lipid nanoparticles topical gel for the treatment of pityriasis versicolor	[56]

Table 1. Cont.

Type of Lipid Nanoparticle	Drug/Active Material	Purpose	Reference
SLN	Itraconazole	Development of solid lipid nanoparticles containing itraconazole with a layer of azole dimethyldioctadecylammonium bromide for skin cancer treatments	[87]
NLC	Thymol	Development of nanostructured lipid carriers for topical delivery of thymol for anti-inflammatory activity	[58]
NLC	Lidocaine	Development of lidocaine loaded nanostructured lipid carriers for topical anesthesia	[88]
NLC	Mometasone furoate	Formulation of nanostructured lipid carrier-based hydrogel of mometasone furoate for the treatment of psoriasis	[89]
SLN	Metformin	Development of metformin loaded solid lipid nanoparticles for anti-inflammatory treatments	[90]
SLN	Ibuprofen	Formulation of topical ibuprofen loaded solid lipid nanoparticle gel for anti-inflammatory treatment	[91]
NLC	Donepezil	Preparation of nanostructured lipid carriers containing donepezil for transdermal delivery for Alzheimer's disease treatment	[92]
NLC	Voriconazole	Development and evaluation of voriconazole loaded nanostructured lipid carriers for antifungal applications	[93]
SLN	Idebenone ester with polyglutamic acid	Formulation of solid lipid nanoparticles containing idebenone ester with pyroglutamic acid for antioxidant activity and enhancing hydrating effects	[94]
SLN	Chamomile oil	Formulation of chamomile oil loaded solid lipid nanoparticles to enhance wound healing	[59]
SLN	Tazarotene	Development and optimization of tazarotene loaded solid lipid nanoparticles for the treatment of psoriasis	[95]
NLC	Rosemary essential oil	Encapsulation of rosemary essential oil into nanostructured lipid carriers for wound healing	[96]
NLC	Clotrimazole	Preparation of clotrimazole loaded Mediterranean essential oils nanostructured lipid carriers for the treatment of candida skin infections	[57]
NLC	Dithranol	Formulation of dithranol loaded nanostructured lipid carrier-based gel for the treatment of psoriasis	[97]
NLC	Peppermint essential oil	Encapsulation of peppermint essential oil in nanostructured lipid carriers for wound healing	[98]
NLC	Triptolide	Development of triptolide loaded nanostructured lipid carriers for transdermal delivery to treat rheumatoid arthritis	[99]
SLN	(+)-Limonene 1,2-Epoxyde-	Preparation of (+)-limonene 1,2-epoxyde loaded solid lipid nanoparticles for anti-cancer activity	[100]
SLN	Miconazole nitrate	Formulation of miconazole nitrate loaded lipid-based nanocarrier for antifungal activity	[101]

Table 1. Cont.

Type of Lipid Nanoparticle	Drug/Active Material	Purpose	Reference
SLN	Sumatriptan	Preparation of sumatriptan loaded solid lipid nanoparticles for transdermal delivery to treat migraine	[102]
SLN + NLC	Ropinirole	Development of ropinirole loaded lipid nanoparticles embedded in hydrogel for Parkinson's disease treatment	[103]
SLN + NLC	Capsaicin	Formulation of capsaicin loaded lipid nanoparticles to treat pain with reduced skin irritation	[104]
NLC	Azelaic acid	Preparation of azelaic acid loaded nanostructured lipid carriers for the treatment of acne vulgaris	[64]
NLC	Apremilast	Formulation of nanostructured lipid carriers for topical delivery of apremilast for psoriasis treatments	[105]
NLC	Itraconazole	Development of topical lipid nanoparticles containing itraconazole for treatment of fungal infections	[106]
NLC	Halobetasol propionate	Formulation of nanostructured lipid carriers loaded with halobetasol propionate for anti-inflammatory treatment	[107]
NLC	Tacrolimus and tumor necrosis factor α siRNA	Design of nanostructured lipid carrier co-delivering tacrolimus and tumor necrosis factor α siRNA for the treatment of psoriasis	[108]
NLC	Clobetasol propionate	Preparation of nanostructured lipid carrier-based controlled release topical gel of clobetasol propionate for eczema treatment	[109]
SLN	Adapalene	Formulation of adapalene loaded solid lipid nanoparticles for anti-acne therapy	[110]
SLN	Retinoic acid	Development of solid lipid nanoparticles loaded with retinoic acid and lauric acid for acne vulgaris topical treatments	[111]
SLN	Isotretinoin and α -tocopherol	Formulation of isotretinoin and α -tocopherol acetate loaded solid lipid nanoparticles in the topical gel for anti-acne activity	[112]
NLC	Spironolactone	Design of spironolactone loaded nanostructured lipid carrier-based gel for effective treatment of mild and moderate acne vulgaris	[113]
NLC	Diflucortolone valerate	Formulation of diflucortolone valerate loaded nanostructured lipid carrier to be used as anti-inflammatory sunscreen	[114]
SLN	Aconitine	Formulation of aconitine loaded solid lipid nanoparticles for transdermal delivery for the analgesic purpose	[115]
SLN	Avanafil	Formulation of avanafil loaded solid lipid nanoparticles for transdermal delivery to treat erectile dysfunction	[116]
SLN	Colchicine	Fabrication of colchicine loaded solid lipid nanoparticles for transdermal delivery for anti-gout treatment	[117]

Table 1. Cont.

Type of Lipid Nanoparticle	Drug/Active Material	Purpose	Reference
SLN	Curcumin	Formulation of curcumin loaded solid lipid nanoparticles for transdermal delivery for antioxidant, anti-inflammatory, and anti-tumor purposes	[118]
SLN	Ivermectin	Development of ivermectin loaded solid lipid nanoparticles for transdermal delivery for anti-inflammatory treatment	[119]
NLC	Bupivacaine	Design of hyaluronic acid-modified nanostructured lipid carriers containing bupivacaine for local anesthetic activity	[120]
NLC	Diclofenac	Preparation of diclofenac loaded nanostructured lipid carriers for transdermal drug delivery for anti-inflammatory treatment	[121]
NLC	Donepezil	Preparation of donepezil loaded nanostructured lipid carriers for transdermal drug delivery for cholinesterase inhibition	[92]
NLC	Lansoprazole	Design of lansoprazole loaded nanostructured lipid carriers for transdermal drug delivery for stomach infection treatment	[65]
NLC	Pioglitazone	Design of pioglitazone loaded nanostructured lipid carriers for transdermal drug delivery as an anti-hyperglycemic agent	[66]
NLC	Rivastigmine	Development of rivastigmine loaded nanostructured lipid carriers for transdermal drug delivery for treatment of dementia	[122]
NLC	Ropivacaine	Formulation of ropivacaine loaded nanostructured lipid carriers for transdermal drug delivery as an anesthetic agent	[123]
SLN	Curcumin	Formulation of ceramide palmitic acid complex-based, curcumin containing solid lipid nanoparticles for transdermal delivery for the anti-inflammatory purpose	[124]
NLC	Tadalafil	Formulation of tadalafil loaded nanostructured lipid carriers for transdermal delivery for erectile dysfunction treatment	[125]
NLC	Methotrexate	Preparation of methotrexate loaded nanostructured lipid carriers for transdermal drug delivery for treatment of rheumatoid arthritis	[126]
NLC	Aceclofenac	Preparation of aceclofenac loaded nanostructured lipid carriers for transdermal drug delivery for anti-inflammatory treatment	[127]

3. Nanovesicular Carriers

Conventional liposomes are considered to be the first generation of nanovesicular carriers. These are sphere-shaped vesicles comprising one or more phospholipid bilayers that enclose an inner aqueous core (Figure 4). Their size can range from 20 nm to several micrometers and they can have a single phospholipid bilayer (unilamellar vesicles) or multiple bilayers (multilamellar vesicles). Unilamellar vesicles are further classified into two categories: (1) small unilamellar vesicles with sizes in the range of 20–100 nm, and (2) large unilamellar vesicles, which are larger than 100 nm [128]. In multilamellar

liposomes, vesicles have an onion structure of concentric phospholipid spheres separated by layers of water [128].

Several methods exist for liposome preparation, including thin-film hydration, reverse phase evaporation, and microfluidic mixing [129]. In certain conditions, a spontaneous liposome formation can also occur [130]. The process that is employed to generate the liposomes will impact their size and lamellarity [129]. The physicochemical nature of the drug to be entrapped in the liposomes also plays a crucial role in the selection of their preparation method. Thus, the preparation methods of drug-loaded liposomes are classified into: (1) passive loading- methods in which liposomes are formed concurrently with drug loading, and (2) active loading-methods in which the liposomes that contain a transmembrane gradient, i.e., different aqueous phases inside and outside the liposomes, are first generated, and then the drug is loaded [129]. In general, passive loading can be employed either for hydrophilic compounds, which are distributed homogeneously in the aqueous phase prior to liposome formation, or for lipophilic drugs, which are retained inside the lipid bilayer. In active loading, an amphipathic drug is dissolved in the exterior aqueous phase after liposome formation and permeates across the phospholipid bilayer(s), followed by interactions with a trapping agent in the core of the liposome to retain it there [129].

In 1980 Mezei and Gulasekharan reported the first generation of liposomes as possible drug delivery systems for topical administration [131]. Ever since, liposomes are widely used as dermal drug carriers [132,133]. The main component of liposomes is typically phospholipids, whereas cholesterol is often added to enhance the stability of liposomal bilayers by filling the gaps caused by imperfect packing [134]. Many theories are proposed for the mechanism of liposome skin penetration, such as penetration through transappendageal route, adsorption effect, intact vesicle penetration, and interaction of the membrane with SC lipids that results in its partial fluidization [135]. Notably, liposomal vesicles with sizes above 600 nm are typically unable to penetrate to the deep skin layers, whereas liposomes smaller than 300 nm can potentially reach deeper epidermal and dermal strata [136].

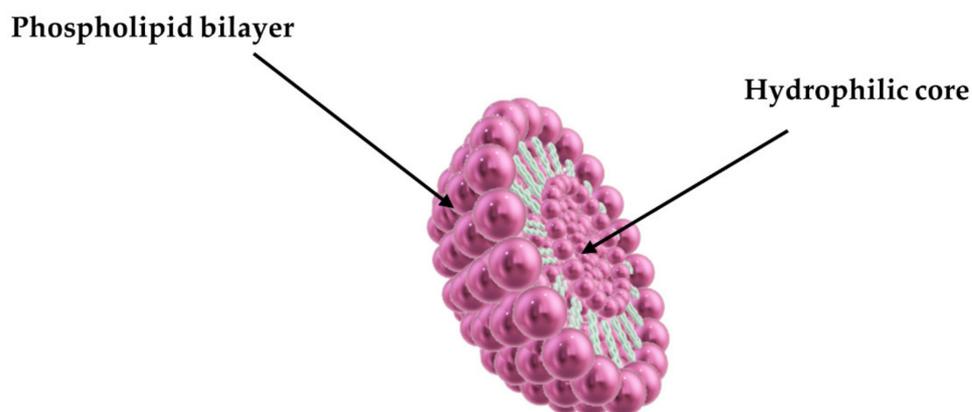


Figure 4. Schematic illustration of a conventional liposome.

The second generation of nanovesicular carriers was developed by Cevc et al. in 1992. These vesicles are called transfersomes, and they are modified liposomes that have an average diameter of under 300 nm and contain an edge activator. The edge activator is a bilayer softening component, such as a surface active agent that makes transfersomes up to 8 times more flexible than the conventional liposomes (Figure 5) [137–140].

Examples of edge activators are dipotassium glycyrrhizinate, sodium cholate, sorbitan esters, and polysorbates [141]. The ability of transfersomes to squeeze themselves through tiny openings, 5 to 10 times smaller than the vesicle diameter, and their multiple advantages over the conventional liposomes for cutaneous delivery have been extensively discussed [142–144]. Yet, to further improve the permeation abilities, in 1996 Touitou designed the ethosomes [145]. These vesicular systems contain a high concentration of

ethanol ranging from 20 to 45 wt%, which leads to the formation of fluid bilayers in their structure [140]. In fact, they are characterized by bilayers from wall to wall and, unlike liposomes or transfersomes, do not contain a core. It is also noteworthy that in contrast to liposomes, these vesicles cannot be separated from the liquid phase and the whole system is used following its preparation. Ethosomes provide a permeation enhancement effect that can occur in both occluded and nonoccluded skin conditions and results in drug penetration up to 200 μm depth (Figure 5) [145–149].

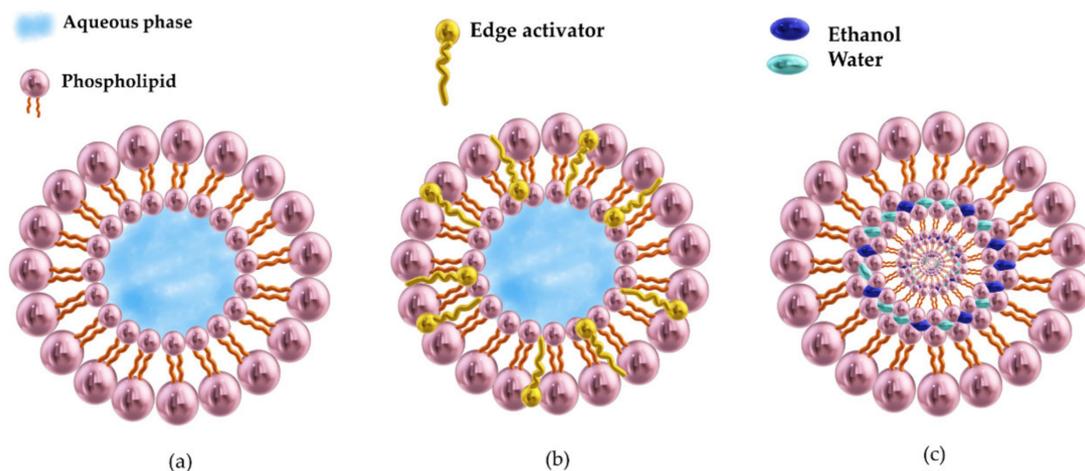


Figure 5. Membrane structure of (a) conventional liposome, (b) transfersome (with edge activators), (c) ethosome (with ethanol and water between the bilayers).

It was also found that increasing ethanol content in ethosomes leads to a decrease of their average size. However, there is a critical concentration of ethanol that may cause a destabilization due to phospholipid bilayers interdigitation [148]. Multiple studies showed the effectiveness of ethosomes for dermal drug delivery in occlusive and nonocclusive applications [141,150,151], and demonstrated their excellent ability to enhance the cutaneous permeation of drugs, including highly lipophilic and highly hydrophilic active compounds [147,152–154].

A schematic illustration of the penetration mechanisms of the nanovesicular carriers is shown in Figure 6.

Another type of the nanovesicular carrier widely used for dermal drug delivery is called niosomes [155]. These vesicles are based on nonionic surfactants and cholesterol or its derivatives and are considered to be more stable and less expensive than liposomes [135]. The type of surfactants and lipids determine the shape of the niosome, which can be ellipsoid, discoid, or polyhedral [156]. Several methods can be employed to prepare niosomes, such as high-pressure homogenization, extrusion, or sonication, and they all can yield an average particle size between 50 and 200 nm. However, as the size of these vesicles gets smaller, the drug loading and stability deteriorate. This problem can be potentially overcome by the addition of a stabilizer [135]. Niosomes can enhance skin permeation by distortion of SC intercellular lipids and subsequent fusion with the SC, which causes a high thermodynamic activity gradient of the active compound at the vesicle-SC interface [135].

Additional nanovesicular carriers that are being increasingly explored for dermal delivery in recent years are cubosomes, hexosomes, aquasomes, colloidosomes, sphingosomes, and ufasomes [157,158]. Cubosomes are composed of bicontinuous cubic liquid crystalline phase with two nonintersecting hydrophilic areas separated by a lipid bilayer (Figure 7) [157–159]. Their preparation typically requires the usage of high-energy dispersion techniques [157,160,161]. Similarly, hexosomes are composed of hexagonal liquid crystalline phases dispersed in a continuous aqueous medium [162]. Both cubosomes and hexosomes exhibit excellent stability, increased drug loading, and the ability to incorporate hydrophilic, hydrophobic, and amphiphilic drugs (Figure 7). These vesicles are extensively

investigated for dermal and transdermal drug deliveries [158,163,164]. For example, it was recently shown that incorporating bile salt edge activators in hexosomes can greatly enhance their skin penetration properties, favoring accumulation in deep skin layers and transdermal permeation [165].

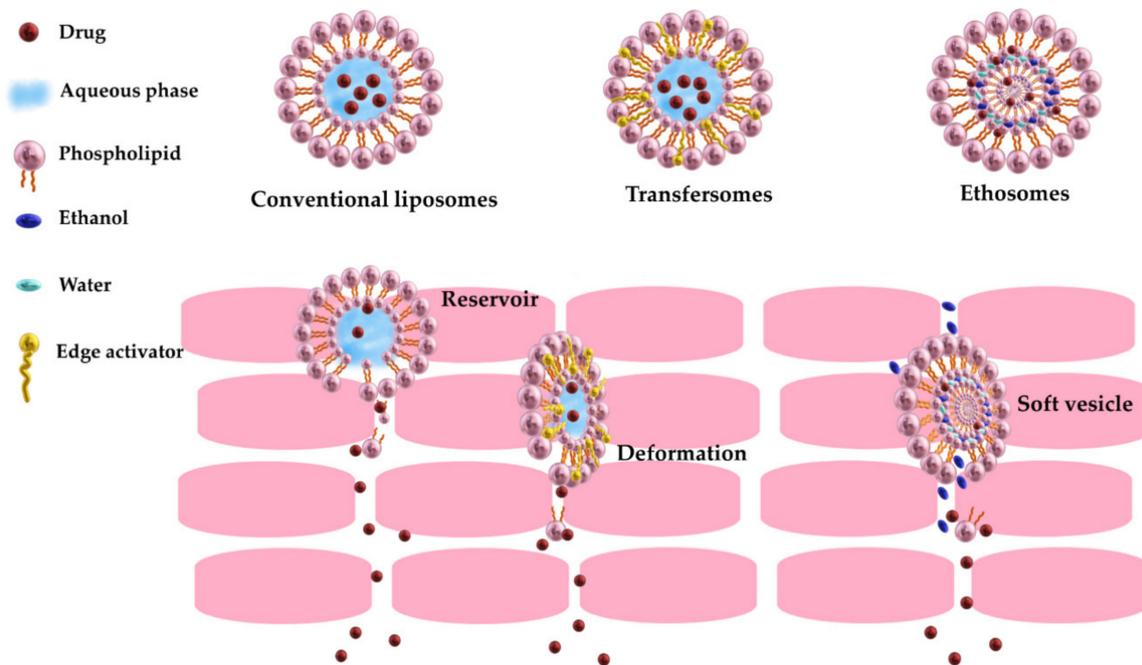


Figure 6. Schematic illustration of the penetration mechanism of conventional liposomes, transfersomes, and ethosomes.

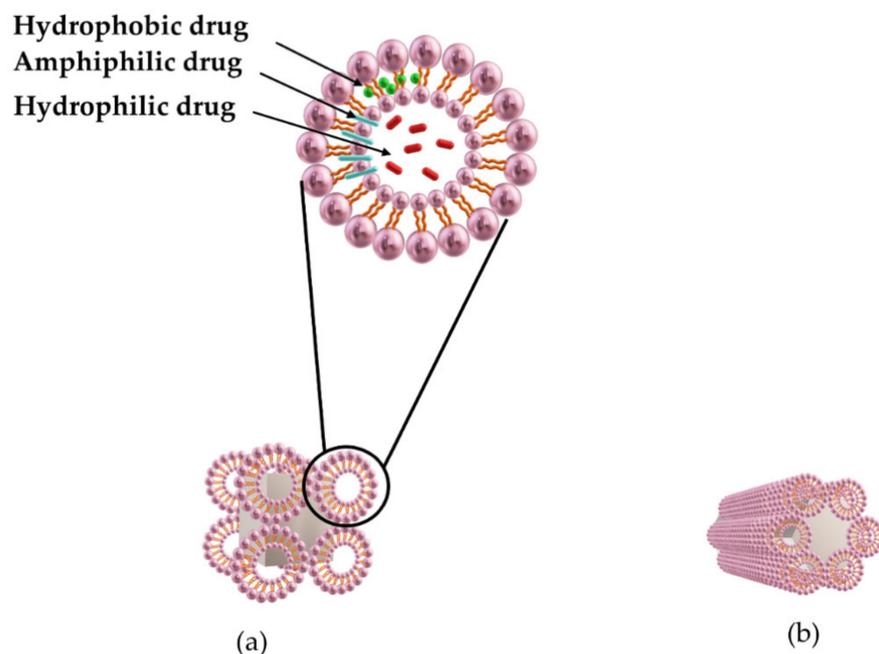


Figure 7. Schematic illustration of (a) cubosome; (b) hexosome.

Aquasomes are self-assembled nanovesicles composed of three layers: A solid nanocrystalline core, an oligomeric shell, and a layer of a bioactive substance absorbed onto the shell [157]. The techniques used for the fabrication of the core are colloidal precipitation, sonication, plasma condensation, and inverted magnetron sputtering. These nanovesicles enable a high drug loading and are capable of protecting fragile drug molecules from

degradation [166]. Colloidosomes are hollow shell microcapsules composed of coagulated particles. These structures are typically employed to encapsulate sensitive bioactive molecules [157]. They can be prepared by self-assembly of colloidal particles at the water-oil interface in water-in-oil emulsions [157,167]. Sphingosomes are comprised of sphingolipids such as sphingosine, ceramide, sphingomyelin, or glycosphingolipid, and are concentric, bilayered nanovesicles with typically an acidic pH inside [168]. The resultant systems can be unilamellar, multilamellar, oligolamellar, or multivesicular. Their preparation methods include mechanical dispersion, film hydration, solvent injection, sonication, reverse phase evaporation, freeze–thaw, and microfluidization. Their unique structure leads to the enhanced drug loading efficiency, low susceptibility to degradation, and long circulation time in vivo [168,169]. Ufasomes are composed of closed lipid bilayers derived from unsaturated fatty acids and ionic surfactants [157,170,171]. Compared to the conventional liposomes, ufasomes are more stable, and have a higher entrapment and drug loading efficiency, but are more prone to oxidation [157,172].

Selected works on employing nanovesicular carriers in dermal drug delivery are highlighted below.

3.1. Topical Delivery with Nanovesicular Carriers

3.1.1. Anticarcinogenic Activity

Cosco et al., report on the formation of ultradeformable liposomes for combined delivery of resveratrol- and 5-fluorouracil [173]. These vesicles contained phospholipid and sodium cholate and were investigated for the treatment of non-melanoma skin cancers. The percutaneous permeation through the human SC and viable epidermis membranes increased 8.3-fold for resveratrol and 6.2-fold for 5-fluorouracil when delivered by these ultradeformable liposomes compared with the free drugs. This effect may be attributed to the intact penetration and the accumulation of the vesicles in the deeper skin strata, which generates a cutaneous depot from which resveratrol and 5-fluorouracil are gradually released. The co-encapsulation of the drugs improved their anti-cancer activity on skin cancer cells as compared to both the free drugs and the individually entrapped agents [173]. Jiang et al., developed cell-penetrating peptide-modified paclitaxel containing transfersomes consisting of a phospholipid, Polysorbate 80, and sodium deoxycholate [174]. An oligopeptide hydrogel containing these transfersomes was painted as a patch over subcutaneous melanoma in mice and prolonged the retention time of the drug in the skin while enhancing the anti-cancer effect of co-administrated Taxol [174]. Cristiano et al. evaluated ethosomes and transfersomes vesicular carriers for the percutaneous delivery of sulforaphane, a natural compound that exhibits a significant antiproliferative activity, but has very poor percutaneous permeation [175]. Resultant ethosomes and transfersomes contained phospholipid and either ethanol or sodium cholate, had mean sizes below 400 nm and a low size polydispersity index. The stability studies demonstrated that ethosomes containing 40% (*w/v*) of ethanol were the most suitable carriers for the percutaneous delivery of sulforaphane. The *in vitro* studies with these vesicles showed an increased permeation of the active substance through the human SC and epidermis membranes, and the vesicles had an enhanced anti-cancer activity compared with free sulforaphane in a melanoma cell line [175].

3.1.2. Antipsoriatic Activity

Abdelbary and AbouGhaly designed topical methotrexate-loaded niosomes for the management of psoriasis [176]. Psoriasis, a skin disorder characterized by impaired epidermal differentiation, is commonly treated by systemic methotrexate, an effective cytotoxic drug, but with numerous side effects, which are minimized by the local administration. The niosomes were prepared by thin-film hydration technique, and comprised a surfactant (Span 60) and cholesterol (optimal composition was 2:1 ratio). They displayed spherical morphology and had a mean particle size of around 1.4 μm with a high drug encapsulation

efficiency (79%). The *in vivo* skin deposition study in rats showed the increased drug deposition in the skin from niosomal formulation compared with the free drug solution.

3.1.3. Local Anesthetic Activity

Babaie et al. prepared lidocaine loaded-nanometric ethosomes (nanoethosomes) for penetration into deep strata of the skin [177]. The particle size of the optimized formulation was around 100 nm and the ethosomes had strongly negative zeta potential. Surprisingly, it was found that increasing the concentration of ethanol from 10% to 40% resulted in the production of ethosomes with 4-times larger particle size. It was assumed that elevating ethanol percentage disrupted the vesicle membrane and subsequently increased the vesicle size. The *in vivo* penetration studies in rat skin showed that nanoethosomes could enhance model dye penetration through the SC into the lower layers of the epidermis, while the same dye in the hydroethanolic solution remained mostly in the SC.

3.1.4. Antifungal Activity

Perez et al. prepared ultradeformable liposomes containing amphotericin B for the treatment of cutaneous fungal infections and leishmaniasis [178]. The effects of different edge activators, phospholipid and drug concentration, and phospholipid to edge activator ratio on liposomal deformability, as well as on the drug liposomal content, were tested. Liposomes comprising Tween 80 as an edge activator had maximal deformability and the highest drug/phospholipid ratio. They had an average vesicle diameter of around 110 nm and almost neutral zeta potential. Amphotericin B was encapsulated in their bilayer at 75% encapsulation efficiency. Drug-loaded liposomes were more toxic to fungal strains than to mammalian cells. The accumulation of amphotericin B in the excised human skin was tested after 1 h of non-occlusive incubation and was found to be 40 times higher from the ultradeformable liposomes than from the commercial liposomal preparation, AmBisome®.

3.1.5. Anti-vitiligo Activity

Garg et al. developed nanosized ethosome-based hydrogel formulations of methoxsalen for enhanced topical delivery and effective treatment of vitiligo [179]. The optimized ethosomal formulation contained approximately 28% of ethanol and had a mean vesicle diameter of 280 nm. These ethosomes were subsequently incorporated into carbopol gel and showed a significant skin permeation through rat skin, with accumulation in epidermal and dermal layers. Also, the developed formulation caused reduced skin phototoxicity and erythema compared with the conventional cream.

3.1.6. Antibiotic Activity

In 2005 Godin et al. developed ethosomal system as a new approach for dermal delivery of antibiotics to enhance their permeation through the SC to the deeper skin layers, as well as the penetration through bacterial membrane/cell wall [180,181]. Recently, Zahid et al., formulated ethosomes containing clindamycin phosphate by using a cold method [182]. The resulted system comprised spherical vesicles with an average size of 110 nm and showed high clindamycin entrapment efficiency of around 82%. Then, the optimized formulation was incorporated into carbopol gel and demonstrated an excellent *in vitro* drug release, which followed zero-order kinetics [182].

3.1.7. Antiviral Activity

Acyclovir has been extensively investigated for topical treatment of viral infections since the introduction of this synthetic acyclic nucleoside analog more than four decades ago [183]. In 1999, Horwitz et al. developed an ethosomal carrier system for acyclovir, which improved its clinical efficacy compared with commercial Zovirax® cream in a clinical study [184]. Recently, Shukla et al. developed an ethosomal gel system of acyclovir, in which the ethosomes were prepared by the cold method [185]. The ethosomes in the optimized system had a mean vesicle size of around 330 nm, 80% drug entrapment, and

zeta potential of -21 mV. The system showed in vitro drug release of 82% over 8 h with a zero-order release profile [185].

3.1.8. Anti-acne Activity

The two major processes involved in acne vulgaris (known as acne) pathophysiology are (1) proliferation of *propionibacterium acnes* bacteria in pilosebaceous units of the skin, and (2) local inflammation [186]. Topical anti-acne agents typically cause adverse effects such as burning, scaling, photosensitivity, erythema, flare-up, and bacterial resistance [187]. In 2008 Touitou et al. designed an ethosomal system containing clindamycin phosphate and salicylic acid gel for the efficient delivery of these drugs to pilosebaceous units as well as for enhanced topical tolerability [186]. In a recent work Apriani et al. developed azelaic acid ethosome-based cream against *propionibacterium acnes* [188]. Azelaic acid exhibits an anti-acne effect by inhibiting thioredoxin reductase enzyme of *propionibacterium acnes*, and must penetrate through the stratum corneum to the sebaceous tissue and into the cytoplasm of the bacteria in order to act, and therefore benefits from incorporation in ethosomes. The ethosomes were prepared by the thin-layer hydration method and had a particle size of below 200 nm. The ethosomal cream demonstrated a superior antibactericidal activity compared with the marketed cream Zelface® [188].

3.2. Transdermal Delivery with Nanovesicular Carriers

In 2003, Lodzki et al. proposed ethosomal carriers as an efficient system for enhancing the transdermal delivery of cannabidiol for anti-inflammatory treatments [189]. Later on, Shumilov et al. developed two ethosomal systems for transdermal delivery of ibuprofen and buspirone [4,190]. In a recent work, Shuwaili et al. designed transfersomal system for transdermal delivery of pentoxifylline, a xanthine derivative indicated in chronic occlusive arterial diseases [191]. Pentoxifylline has low oral bioavailability and a short half-life; and thus, it is a good candidate for transdermal delivery. The transfersomes comprised sodium cholate and nonionic surfactants as edge activators, exhibited drug entrapment efficiency of 75 %, vesicles elasticity of $145 \text{ mg s}^{-1} \text{ cm}^{-2}$, zeta potential of -35 mV, average vesicle diameter of 700 nm, and permeation flux of $56 \text{ } \mu\text{g}/\text{cm}^2/\text{h}$. They enhanced drug permeation through the excised rat skin by up to 9-fold compared with pentoxifylline solution. Results of the in vivo pharmacokinetic study in healthy human volunteers showed that transfersomal formulation increased the amount of the drug absorbed into the circulation over time and maintained higher plasma levels comparing with the commercial oral SR tablets (Trental™ 400 mg), which could be attributed to the avoidance of the first-pass effect [191]. Qumbar et al. formed transdermal lacidipine-loaded niosomes for the management of hypertension [192]. Niosomes were prepared by the thin-film hydration technique and had an average size of around 700 nm, and a flux value of $38.43 \text{ } \mu\text{g}/\text{cm}^2/\text{h}$ for the optimized niosome-containing gel. The blood pressure decrease caused by the transdermal niosomal gel was compared to the decrease caused by oral lacidipine suspension and was found to produce a more gradual effect, controlling the blood pressure up to 48 h [192].

Additional works demonstrating employment of nanovesicular carriers in dermal drug delivery are summarised in Table 2.

Table 2. Recent studies on dermal/transdermal drug delivery systems comprising nanovesicular carriers.

Type of Lipid-Based Nanoparticle	Drug/Active Material	Purpose	Reference
Niosomes	Methotrexate	Design of topical methotrexate loaded niosomes for management of psoriasis	[176]
Niosomes	Resveratrol	Formulation of resveratrol loaded niosomes for skin cancer and psoriasis treatment	[193]

Table 2. Cont.

Type of Lipid-Based Nanoparticle	Drug/Active Material	Purpose	Reference
Niosomes	Benzoyl peroxide	Development of benzoyl peroxide loaded niosomes for anti-acne treatment	[194]
Niosomes	Benzoyl peroxide and tretinoin	Design of niosome gel containing benzoyl peroxide and tretinoin for anti-acne activity	[195]
Transfersomes + ethosomes	Ginsenoside Rh1	Formulation of transfersomes and ethosomes containing ginsenoside Rh1 from red ginseng for treatment of tumors, inflammation, diabetes, stress, and acquired immunodeficiency syndrome	[196]
Transfersomes	Capsaicin	Formulation of capsaicin loaded transfersomes for anti-inflammatory treatment	[197]
Transfersomes	Indocyanine green	Preparation of indocyanine green loaded transfersomes for acne vulgaris	[198]
Ethosomes	Lidocaine	Development of lidocaine loaded ethosomes for topical delivery of anesthetics	[177]
Ethosomes	5-Fluorouracil	Development of ethosomes containing 5-fluorouracil as a novel therapy for laryngotracheal stenosis	[199]
Conventional liposomes	Licorice	Formulation of licorice loaded liposomes for treatments of oxidative stress injuries	[200]
Transfersomes	5-Fluorouracil	Design of 5-fluorouracil loaded transfersomes for skin cancer treatments	[201]
Transfersomes	Resveratrol and 5-fluorouracil	Preparation of transfersomes containing resveratrol for skin cancer treatments	[173]
Niosomes	Diacerein	Formulation of niosomes for topical diacerein delivery for treatment of psoriasis	[202]
Transfersomes	Amphotericin B	Development of amphotericin B loaded transfersomes for antifungal and antileishmanial treatments	[178]
Conventional liposomes	Quercetin and resveratrol	Formulation of quercetin and resveratrol loaded liposomes for treatment of inflammatory/oxidative response associated with skin cancer	[203]
Transfersomes	siRNA	Development of transfersomes containing siRNA to deliver to the human basal epidermis for melanoma therapy	[204]
Transfersomes	RNAi	Formulation of transfersomes containing RNAi for psoriasis treatments	[205]
Niosomes	Moxifloxacin	Design of chitosan gel embedded moxifloxacin niosomes for burn infection treatment	[206]

Table 2. Cont.

Type of Lipid-Based Nanoparticle	Drug/Active Material	Purpose	Reference
Niosomes	Zingiber cassumunar roxburgh	Formulation of niosomes containing zingiber cassumunar roxburgh for anti-inflammatory activity	[207]
Transfersomes	Asenapine	Preparation of nano transfersomes containing asenapine maleate for transdermal delivery for treatment of schizophrenia and bipolar disorder	[208]
Transfersomes	Ketoprofen	Development of ketoprofen loaded transfersomes for treatment of muscle soreness following exercise	[209]
Ethosomes	Methoxsalen	Formulation of ethosomes containing methoxsalen for topical delivery against vitiligo	[179]
Ethosomes	Griseofulvin	Design of griseofulvin loaded ethosomes for antifungal treatments	[210]
Ethosomes	Aceclofenac	Formulation of ethosomes containing aceclofenac for treatment of pain and inflammation	[211]
Ethosomes	Cryptotanshinone	Formulation of cryptotanshinone loaded ethosomes for anti-acne treatments	[212]
Niosomes	Pregabalin	Preparation of pregabalin loaded niosomes as anti-inflammatory treatments	[213]
Niosomes	8-Methoxypsoralen	Development of niosomes containing 8-methoxypsoralen for photochemotherapeutic treatments	[214]
Niosomes	Acyclovir	Preparation of acyclovir loaded niosomes for treatments of herpes	[215]
Niosomes	Inositol hexaphosphate	Formulation of inositol hexaphosphate loaded niosomes as an antiangiogenic agent	[216]
Transfersomes	Indocyanine	Formulation of indocyanine loaded transfersomes for the treatment of basal cell carcinoma	[217]
Transfersomes	Clindamycin	Formulation of development of clindamycin loaded transfersomes for the treatment of acne	[218]
Ethosomes	Phenylethyl resorcinol	Design of phenylethyl resorcinol loaded ethosomes for skin lightening applications	[219]
Niosomes	Melatonin	Preparation of melatonin loaded niosomes to induce daytime sleep in children	[220]
Transfersomes	Paclitaxel	Development of transfersomes containing paclitaxel and modified by a cell-penetrating-peptide embedded in oligopeptide hydrogel for topical treatment of melanoma	[174]
Transfersomes	Sodium stibogluconate	Formulation of sodium stibogluconate loaded transfersomes for treatment of leishmaniasis	[221]

Table 2. Cont.

Type of Lipid-Based Nanoparticle	Drug/Active Material	Purpose	Reference
Niosomes	Natamycin	Formulation of natamycin loaded niosomes for treatment of fungal keratitis	[222]
Niosomes	Celastrol	Preparation of celastrol loaded niosomes for treatment of psoriasis	[223]
Niosomes	Artemisone, clofazimine and decoquinatone	Preparation of artemisone, clofazimine, and decoquinatone encapsulated in niosomes for mycobacterium tuberculosis	[224]
Niosomes	Pregabalin	Development of pregabalin loaded niosomes for fibromyalgia treatment	[213]
Transfersomes	Lidocaine	Development of lidocaine loaded transfersomes for local anesthetic activity	[225]
Ethosomes	Curcumin	Formulation of ethosomes containing curcumin for anti-inflammatory treatment	[226]
Ethosomes	Epigallocatechin-3-gallate	Formulation of epigallocatechin-3-gallate loaded ethosomes for treatment of skin cancer	[227]
Ethosomes	Thymoquinone	Formulation of topical thymoquinone loaded ethosomes for treatment of acne	[228]
Transfersomes	Sulforaphane	Preparation of transfersomes containing sulforaphane for treatment of skin cancer	[175]
Transfersomes	Miltefosine polyphenol	Formulation of miltefosine polyphenol loaded transfersomes for topical treatment of cutaneous leishmaniasis	[229]
Ethosomes	Harmine	Formulation of harmine loaded ethosomes for transdermal delivery for anti-inflammatory treatment	[230]
Ethosomes	Vismodegib	Preparation of ethosomes containing vismodegib for the treatment of basal cell carcinoma	[231]
Ethosomes	Clobetasol propionate	Formulation and evaluation of ethosomes of clobetasol propionate for eczema treatment	[232]
Liposomes	Tretinoin	Formulation of tretinoin loaded liposomal formulations for the treatment of acne	[233]
Liposomes	Benzoyl peroxide	Encapsulation of benzoyl peroxide and chloramphenicol in liposomes for anti-acne treatments	[234]
Liposomes	Clindamycin	Formulation of clindamycin loaded liposomal gel for effective treatment of acne	[235]
Liposomes	Benzoyl peroxide and adapalene	Development of benzoyl peroxide and adapalene loaded modified liposomal gel for improved acne therapy	[236]
Ethosomes	Tretinoin	Formulation and evaluation of gel containing tretinoin loaded ethosomes for anti-acne treatments	[237]

Table 2. Cont.

Type of Lipid-Based Nanoparticle	Drug/Active Material	Purpose	Reference
Ethosomes	Azelaic acid	Formulation of azelaic acid loaded ethosomes for anti-acne treatments	[188]
Niosomes	Roxithromycin	Development of roxithromycin solid-state loaded niosomes for acne therapy	[238]
Transfersome	N-acetylcysteine	Formulation of n-acetylcysteine loaded transfersomes for antioxidant activity in anti-aging cream	[239]
Liposomes	Oxaprozin	Formulation of oxaprozin loaded liposomes for transdermal delivery for anti-inflammatory activity	[240]
Niosomes	Ursolic acid	Formulation of ursolic acid loaded niosomes for transdermal delivery for anti-arthritic activity	[241]
Transfersomes	pentoxifylline	Formulation of pentoxifylline loaded transfersomes for transdermal delivery for treatment of chronic occlusive arterial diseases	[191]
Niosomes	Lacidipine	Formulation of lacidipine loaded niosomes for transdermal delivery for anti-hypertensive activity	[192]
Niosomes	Pumpkin seed oil	Formulation of pumpkin seed oil loaded niosomes for many applications such as cardiovascular health boost, treatment of benign prostatic hyperplasia, reduction of hair loss, and as an antioxidant agent	[242]
Niosomes	Celecoxib	Formulation of celecoxib loaded niosomes for transdermal delivery for anti-inflammatory activity	[243]
Transfersomes	Risperidone	Formulation of risperidone loaded transfersomes for transdermal delivery for antipsychotic treatment	[244]
Transfersomes	Ondansetron	Formulation of risperidone loaded transfersomes for transdermal delivery for management of chemotherapy/ radiotherapy-induced nausea and vomiting	[245]
Transfersomes	Recombinant human epidermal growth factor	Formulation of recombinant human epidermal growth factor loaded transfersomal emulgel for anti-aging purposes	[246]
Cubosomes	antimicrobial peptide (AMP) LL-37	Formulation of cubosomes for topical delivery of the antimicrobial peptide (AMP) LL-37 for treatment of skin infections caused by bacteria	[247]
Cubosomes	Miconazole	Formulation of miconazole nitrate-based cubosome hydrogels for antifungal treatments	[248]
Cubosomes	silver sulfadiazine (SSD) and Aloe vera	Formulation of cubosomes loaded with silver sulfadiazine and aloe vera for topical treatment of infected burns	[249]

Table 2. Cont.

Type of Lipid-Based Nanoparticle	Drug/Active Material	Purpose	Reference
Cubosomes	Erythromycin	Formulation of erythromycin loaded cubosomes for treatments of acne	[250]
Cubosomes	Tretinoin	Formulation of tretinoin loaded cubosomes for treatments of acne	[251]
Cubosomes	Fluconazole	Formulation of fluconazole loaded cubosomes for antifungal treatments	[252]
Hexosomes, cubosomes	Ketoconazole	Formulation of ketoconazole loaded hexosomes for antifungal treatments	[253,254]
Hexosomes, cubosomes	Catechin	Formulation of catechin loaded cubosomes and hexosomes for antioxidant applications	[165]
Ufasomes	Minoxidil	Formulation of minoxidil loaded ufasomes for hair loss treatments	[255]
Cubosomes and hexosomes	Corcin	Formulation of corcin loaded cubosomes and hexosomes for antioxidant applications	[256]
Cubosomes	Dapsone	Formulation of dapsone loaded cubosomes for antibiotic activity	[257]
Cubosomes	Etodolac	Formulation of etodolac loaded cubosomes for topical pain relief	[258]
Cubosomes	Capsaicin	Formulation of capsaicin loaded cubosomes for treatments of psoriasis, pruritus, apocrine chromhidrosis, and contact allergy	[259]
Cubosomes	Paclitaxel	Formulation of paclitaxel loaded cubosomes against skin cancer	[260]
Cubosomes	Methotrexate	Formulation of methotrexate loaded cubosomes for topical treatment of rheumatoid arthritis	[261]
Cubosomes	Paeonol	Formulation of paeonol loaded cubosomes for anti-inflammation treatments	[262]
Cubosomes	Lornoxicam	Formulation of lornoxicam loaded cubosomes for anti-inflammation treatments	[263]
Cubosomes	Resveratrol	Formulation of resveratrol loaded cubosomes for anti-aging and anti-cancer treatments	[264,265]
Cubosomes	Progesterone	Formulation of progesterone loaded cubosomes for topical use to balance and neutralize the effects of excess estrogen	[266]
Cubosomes	Ketoprofen	Formulation of ketoprofen loaded cubosomes for treatments of arthritis	[267]
Cubosomes	Curcumin	Formulation of curcumin loaded cubosomes for antibacterial activities	[268]
Cubosomes	Alpha lipoic acid	Formulation of alpha-lipoic acid loaded cubosomes for anti-aging	[269]

4. Microemulsions and Nanoemulsions

Microemulsions and nanoemulsions are nanometric dispersive systems of two immiscible liquid phases that offer several advantages over the traditional topical drug delivery formulations due to their capacity to penetrate to deeper skin strata [270]. There is evidence that they are able to disrupt the structural order of the SC lipids, which leads to the loss of the barrier properties of the skin [271]. Both systems are low viscosity colloidal dispersions, but despite the apparent similarities between them, they are classified as completely different formulations [272,273]. Microemulsions are thermodynamically stable and they form spontaneously when the precise amounts of immiscible liquids (typically oil and water) and surface active agents are mixed together at the specific conditions of pressure and temperature [274,275]. Co-surfactants, such as short alkyl chain alcohols, are typically required for the spontaneous formation of microemulsions. No high-shear forces are needed to be applied to form this isotropic and visually transparent system, in which the droplet size is usually below 100 nm [276–278]. By modifying the ratio between the components of the microemulsion or the chemical nature of the surfactants, various structural types of microemulsions can be formed. Three main structural types of these systems are: (1) oil-in-water (O/W) microemulsion, in which nanometric droplets of oil (organic phase) are distributed throughout the aqueous phase, (2) water-in-oil (W/O) microemulsion, in which nanometric aqueous droplets are dispersed in the continuous organic phase, and (3) bicontinuous microemulsion, in which organic and aqueous phases form interdispersed nanometric domains [279,280]. Figure 8 illustrates the first two structural types of microemulsions. Nanoemulsions, on the other hand, can reach the droplet size of 250 nm and their appearance may vary between milky, translucent, and transparent depending on the droplet size [273]. These systems are kinetically stable owing to the presence of the surface active agents on the oil-water interface (typically at lower concentrations than in microemulsions), but there is no thermodynamic stability, and therefore droplet size should be assessed periodically for stability evaluation. External energy has to be typically applied in the process of nanoemulsion formation to bring the droplet size to the nanoscale [281,282].

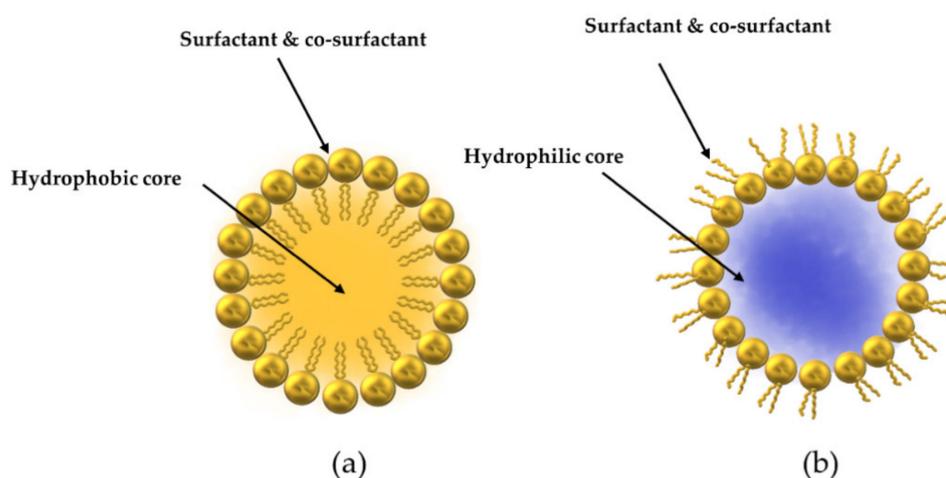


Figure 8. Schematic illustration of (a) O/W microemulsion system, (b) W/O microemulsion system.

Two major categories of preparation methods are employed to form nanoemulsions. The first category is high-energy emulsification methods, such as high-pressure homogenization, microfluidization, jet dispersing, and ultrasonication. The second category is low energy emulsification methods, which use only the physicochemical properties of the system, such as phase inversion, spontaneous emulsification, and solvent displacement [283]. Several recent works on cutaneous drug delivery with formulations based on nanoemulsions and microemulsions are detailed herein.

4.1. Topical Delivery with Microemulsions and Nanoemulsions

4.1.1. Anti-inflammatory Activity

Alvarado et al. designed two nanoemulsion systems for dermal administration of natural or synthetic mixtures of pentacyclic triterpenes, which exhibit anti-inflammatory activity [284]. The average droplet size of the optimized nanoemulsions ranged between 140 and 590 nm. Larger than typical droplet size was attributed to the high molar mass of the loaded compounds. Natural and synthetic triterpene-containing formulations showed slightly different permeation profiles, whereas synthetic mixture permeated faster. The overall amount of triterpenes retained in the skin was higher than the amount of compounds permeated through the skin for both formulations, indicating the suitability of the nanoemulsion systems for the local topical delivery. The nanoemulsion with the natural triterpene mixture demonstrated greater anti-inflammatory ability in the mouse ear inflammation model than the one with the synthetic mixture, probably due to the slower permeation through the skin of the former [284]. Goindi et al. report on an ionic liquid-in-water microemulsion formulation that can solubilize etodolac, a poorly water-soluble anti-inflammatory drug [285]. The average droplet size of this microemulsion was 32 nm, and it had almost neutral zeta potential. The ex vivo permeation studies showed a better permeation profile of drug-loaded ionic liquid-in-water microemulsion over the oil-in-water microemulsion and a solution of etodolac in oil, probably owing to the better drug solubilization and penetration enhancing effect of the ionic liquid. Anti-arthritic and anti-inflammatory activities evaluated in vivo in different rodent models revealed that the ionic liquid-based microemulsion is more effective in controlling inflammation than the oily solution, the oil-based microemulsion and the marketed formulation of etodolac (Proxym gel[®]) [285].

4.1.2. Local Anesthetic Activity

Negi et al. prepared nanoemulsions for the enhanced percutaneous absorption of lidocaine and prilocaine [286]. Nanoemulsions were prepared using a high-shear mixing followed by the high-pressure homogenization, had droplet size of around 100 nm and almost neutral zeta potential. The permeation rates and permeability coefficient values of the drugs from the optimized nanoemulsion systems were significantly higher than those from the marketed cream. The nanoemulsions were further incorporated into carbopol hydrogel, which decreased the skin permeability of the drugs, because of the higher vehicle viscosity. The nanoemulsions and the nanoemulsion gel formulations had a significantly stronger anesthetic effect in vivo compared with the marketed formulation at the same concentrations of the drugs; a quicker onset of action, and a prolonged duration of anesthetic effect as compared to the marketed formulation.

4.1.3. Antifungal Activity

Coneac et al. developed microemulsion-loaded hydrogels for the topical delivery of fluconazole [287]. Microemulsions were stabilized by nonionic surfactants, and had average droplet sizes between 4 and 5 nm, while the drug molecules were mainly located at the oil-water interface. The optimized microemulsions were incorporated in carbopol gels and showed higher flux values and higher release rate in vitro in comparison with a conventional hydrogel. These optimized microemulsion-loaded hydrogels also exhibited similar or slightly higher in vitro antifungal activity against *candida albicans* as compared to that of the conventional hydrogel and Nizoral[®] cream, respectively.

4.1.4. Antioxidant Activity

Lv et al. employed essential oil-based microemulsions to improve the solubility, pH stability, photostability, and skin permeation of quercetin for topical application [288]. The droplet size of the resultant microemulsions depended on the surfactant mix/ essential oil ratio but was under 100 nm for all measured ratios. In this study, the self-microemulsifying drug delivery systems (SMEDDs) were first prepared and then formed microemulsions

when diluted 20 times by deionized water. The droplet size of the selected microemulsions was below 20 nm. The solubility of quercetin was superior in the SMEDDs compared with the pure oil, and it was significantly higher in the microemulsions compared with water. In addition, the microemulsions protected quercetin to a certain extent from degradation in alkaline environment and under UV radiation. Also, the *in vitro* skin permeation study on rat skin revealed that the essential oil-based microemulsions could enhance the permeation capacity of quercetin by 2.5–3 times compared with the aqueous solution.

4.1.5. Antipsoriatic Activity

Kaur et al. reported on the development and optimization of clobetasol propionate- and calcipotriol- loaded nanoemulsion gel for the topical treatment of psoriasis [289]. Nanoemulsions were formed by the spontaneous emulsification method. Carbopol 980 was used as a gelling agent to achieve the final drug concentration of 0.05% wt and 0.005% wt respectively for clobetasol propionate and calcipotriol. Keratinocyte cell lines showed higher uptake of the drugs from the nanoemulsion, and the penetration of both drugs from the nanoemulsion and gel formulations into the skin (SC and viable layers) was increased. Nanoemulsion-containing gel also demonstrated a significantly higher anti-psoriatic activity in the imiquimod-induced psoriasis model in mice compared with the free drugs and a marketed formulation [289]. Rajitha et al. prepared methotrexate loaded nanoemulsion based on chaulmoogra oil [290]. Self emulsification method was employed and the resultant nanoemulsion had an average droplet size of around 35 nm, was strongly negatively charged, and had skin-compatible acidity levels. The *ex vivo* skin permeation using porcine skin indicated the enhanced permeation and retention of the drug in the deep skin layers when compared with methotrexate solution. The *in vivo* anti-psoriatic studies were done in the imiquimod psoriatic mice model and revealed the superior anti-psoriatic efficacy and the effective drug retention in the skin [290].

4.1.6. Anticarcinogenic Activity

Pham et al. developed a scalable, low-energy nano-emulsification approach for optimized incorporation of Tocomin[®], tocotrienols-rich palm oil possessing anti-cancer activity, for adjunctive therapy of skin carcinomas [291]. Tocomin[®]- loaded nanoemulsions were obtained by different preparation methods. The hybrid nano-emulsification technique of single-phase inversion temperature homogenization cycle followed by a reduced ultrasonication produced stable Tocomin[®]-loaded nanoemulsion. This system demonstrated a superior cytotoxic profile against two human cutaneous carcinoma cell models compared with Tocomin[®]-in propyleneglycol admixture.

4.2. Transdermal Delivery with Microemulsions and Nanoemulsions

Wang et al. developed ionic liquid-in-water microemulsion for transdermal delivery of the hydrophilic hemostatic agent, dencichine [292]. The microemulsion had an average droplet size of 48 nm, a negative zeta potential of -15 mV, and it enhanced the *in vitro* skin permeation of dencichine approximately 10-fold compared with the drug solution in water. The pharmacodynamic evaluation performed in rats *in vivo* indicated a significant hemostatic activity after the application of dencichine loaded microemulsion. In [292] El-Leithy et al. investigated nanoemulsions for transdermal delivery of indomethacin [293]. Most of the evaluated systems had average droplet sizes between 40 and 131 nm and showed flux values between 5.79 and 55.81 mg/cm²/h. Pharmacokinetics studies in rats *in vivo* demonstrated that nanoemulsion formulae and the commercial indomethacin topical gel containing alcohol (Farcomethacin[®]) resulted in similar levels of indomethacin in plasma. This was attributed to the permeation enhancement effect of alcohol [293].

Table 3 summarizes additional advances in cutaneous drug delivery systems based on nanoemulsions and microemulsions.

Table 3. Recent studies on dermal/transdermal drug delivery systems comprising nanoemulsions and microemulsions.

Type of Emulsion System (Microemulsion/Nanoemulsion)	Drug/Active Material	Purpose	Reference
Nanoemulsion	Oleanolic and ursolic acid	Design a nanoemulsion system containing oleanolic and ursolic acid of dermal controlled release for anti-inflammatory activity	[284]
Nanoemulsion	Lidocaine and prilocaine	Design of lidocaine and prilocaine loaded nanoemulsion for enhanced percutaneous absorption for local anesthetics	[286]
Nanoemulsion	Ferulic acid	Design of ferulic acid loaded nanoemulsion against UVA mediated oxidative stress	[294]
Nanoemulsion	Curcumin	Formulation of curcumin loaded nanoemulsion for effect in inflammatory arthritis disorders	[295]
Nanoemulsion	Indomethacin	Development of indomethacin loaded nanoemulsion for transdermal delivery for increasing plasma levels	[293]
Microemulsion	Etodolac	Development of an ionic liquid-in water microemulsion containing etodolac for anti-inflammatory treatments	[285]
Microemulsion	Fluconazole	Design of fluconazole loaded microemulsion for antifungal activities	[287]
Microemulsion	Itraconazole	Formulation of microemulsion containing itraconazole for antifungal efficacy against a standardized tinea pedis infection	[296]
Microemulsion	Pseudolaric acid B	Formulation of pseudolaric acid B loaded microemulsion for antifungal activity against azole-resistant candida species	[297]
Microemulsion	Fusidic acid	Development of fusidic acid loaded biocompatible microemulsion for eradicating methicillin-sensitive staphylococcus aureus bacterial infections	[298]
Microemulsion	Bleomycin, cisplatin and ifosfamide	Formulation of microemulsion containing bleomycin, cisplatin, and ifosfamide for anti-tumor activities	[299]
Microemulsion	Diethylenetriaminepentaacetic acid calcium trisodium salt hydrate	Development of diethylenetriaminepentaacetic acid calcium trisodium salt hydrate loaded microemulsion for decorporation applications	[300]
Microemulsion	Resveratrol	Design of microemulsion containing resveratrol to protect skin against UV-induced damage	[301]
Nanoemulsion	Amphotericin B	Design of amphotericin B loaded nanoemulsions for antifungal treatments	[302]

Table 3. Cont.

Type of Emulsion System (Microemulsion/Nanoemulsion)	Drug/Active Material	Purpose	Reference
Nanoemulsion	Benzyl benzoate	Formulation of benzyl benzoate loaded nanoemulsion for treatment of scabies	[303]
Nanoemulsion	Ketoconazole	Preparation of ketoconazole loaded nanoemulsion converted into nanoemulgel for effective management of onychomycosis	[304]
Nanoemulsion	Triterpenoids isolated from ganoderma lucidum	Formulation of triterpenoids loaded nanoemulsion for frostbite treatment	[305]
Nanoemulsion	Isotretinoin	Design of isotretinoin loaded nanoemulsion for acne treatments	[306]
Nanoemulsion	Tocotrienol	Formulation of nanoemulsions containing tocotrienol for topical delivery against skin carcinomas	[291]
Microemulsion	Tazarotene	Formulation of tazarotene loaded microemulsion for treatments of psoriasis	[307]
Microemulsion	Pentoxifylline	Developing of microemulsion containing pentoxifylline for anti-inflammatory activity	[308]
Microemulsion	Methotrexate	Preparation of methotrexate loaded microemulsion for psoriasis treatments	[309]
Microemulsion	Ibuprofen	Formulation of ibuprofen loaded microemulsion for anti-inflammatory activity	[310]
Microemulsion	Sertaconazole	Development of sertaconazole loaded microemulsion for antifungal treatments against candida albicans	[311]
Microemulsion	Imiquimod	Development of microemulsion containing imiquimod for the treatment of neoplastic skin diseases	[312]
Nanoemulsion	Clobetasol propionate and calcipotriol	Formulation of nanoemulsions containing clobetasol propionate and calcipotriol for treatments of psoriasis	[289]
Nanoemulsion	Cyclosporine	Preparation of cyclosporine loaded nanoemulsions for psoriasis treatments	[313]
Nanoemulsion	Psoralen	Preparation of psoralen loaded nanoemulsion for psoriasis and vitiligo treatments	[314]
Nanoemulsion	Phenytoin	Design of nanoemulsion containing phenytoin for topical wound healing	[315]
Nanoemulsion	Zinc phthalocyanine	Development of zinc phthalocyanine loaded nanoemulsion for use in photodynamic therapy for leishmaniasis	[316]
Nanoemulsion	Phenylethyl resorcinol	Formulation of phenylethyl resorcinol loaded nanoemulsion for skin lightening	[317]

Table 3. Cont.

Type of Emulsion System (Microemulsion/Nanoemulsion)	Drug/Active Material	Purpose	Reference
Microemulsion	Retinoid	Formulation of retinoid loaded microemulsion for psoriasis treatments	[318]
Microemulsion	Tacrolimus	Preparation of tacrolimus loaded microemulsion for anti-psoriatic activity	[317]
Microemulsion	Quercetin	Preparation of microemulsion containing quercetin as a powerful antioxidant	[288]
Microemulsion	Clotrimazole	Formulation of microemulsion coated with chitosan and containing clotrimazole for antifungal activity	[319]
Microemulsion	Griseofulvin	Development of griseofulvin loaded microemulsions for antifungal treatments	[320]
Nanoemulsion	Coenzyme Q10	Formulation of coenzyme Q10 loaded nanoemulsion as an antioxidant agent	[321]
Nanoemulsion	8-Methoxypsoralen	Formulation of 8-methoxypsoralen loaded nanoemulsions for treatments in vitiligo and psoriasis	[322]
Nanoemulsion	Adapalene and tea tree oil	Preparation of nanoemulsion containing tea tree oil and adapalene for antibacterial activity against propionibacterium acnes	[323]
Nanoemulsion	Rosmarinic acid	Development of rosmarinic acid loaded nanoemulsions for antioxidant activity	[324]
Nanoemulsion	Hydroxyethylcellulose	Preparation of nanoemulsions containing hydroxyethylcellulose for anti-herpes treatment	[325]
Nanoemulsion	Heparinoid	Development of heparinoid loaded nanoemulsion for the treatment of superficial thrombophlebitis	[326]
Microemulsion	Diclofenac sodium	Formulation of diclofenac sodium loaded microemulsion for anti-inflammatory activity	[327]
Microemulsion	20(S)-protopanaxadiol	Development of 20(S)-protopanaxadiol loaded microemulsion for anti-aging activity	[328]
Microemulsion	Tetrapeptide PKEK	Preparation of microemulsion containing tetrapeptide PKEK for reducing UVB induced effects	[329]
Microemulsion	Astilbin	Preparation of astilbin loaded microemulsions for anti-inflammatory activity	[330]
Nanoemulsion	Capsaicin	Formulation of nanoemulsion containing capsaicin for anti-inflammatory effects	[331]

Table 3. Cont.

Type of Emulsion System (Microemulsion/Nanoemulsion)	Drug/Active Material	Purpose	Reference
Nanoemulsion	Chaulmoogra oil-based methotrexate	Formulation of chaulmoogra oil-based methotrexate loaded nanoemulsion for the treatment of psoriasis	[290]
Nanoemulsion	Thymol	Preparation of thymol loaded nanoemulsion for anti-acne vulgaris treatments	[332]
Nanoemulsion	Daidzein, genistein, and glycitein (from a soybean isoflavone)	Formulation of daidzein, genistein, and glycitein loaded nanoemulsion for antioxidant activity	[333]
Nanoemulsion	Mangiferin	Formulation of mangiferin loaded nanoemulsions for anti-inflammatory treatments	[334]
Nanoemulsion	Clove oil	Development of nanoemulsion containing clove oil for activities against candida	[335]
Nanoemulsion	Pomegranate seed oil	Development of pomegranate seed oil loaded nanoemulsions for photo-protective purposes	[336]
Microemulsion	3,5,4'-Trimethoxy-trans-stilbene	Preparation of 3,5,4'-trimethoxy-trans-stilbene loaded microemulsion for treatment of osteoarthritis	[337]
Microemulsion	Betamethasone dipropionate	Development of betamethasone dipropionate loaded microemulsion for anti-inflammatory effects	[337]
Microemulsion	Histidine capped silver nanoparticles	Formulation of microemulsions containing histidine capped silver nanoparticles for treatments of burn wound infections	[338]
Microemulsion	Resveratrol	Design of microemulsions containing resveratrol for chemoprevention of skin cancer	[339]
Microemulsion	5-Fluorouracil	Formulation of microemulsions containing 5-fluorouracil for skin cancer treatments	[340]
Microemulsion	Benzophenone-rich extract	Preparation of benzophenone-rich extract loaded microemulsion for antifungal treatments	[341]
Microemulsion	Retinyl palmitate	Development of microemulsion containing retinyl palmitate for treatments of skin disorders such as acne, aging, and psoriasis	[342]
Microemulsion	Pioglitazone	Preparation of microemulsion containing pioglitazone for anti-inflammatory treatments	[343]
Nanoemulsion	Cyclosporine	Formulation of cyclosporine loaded nanoemulsion for treatments of psoriasis	[344]

Table 3. Cont.

Type of Emulsion System (Microemulsion/Nanoemulsion)	Drug/Active Material	Purpose	Reference
Nanoemulsion	Ivermectin	Development of nanoemulsions containing ivermectin to treat different types of parasite infestations	[345]
Nanoemulsion	Vitamin A+E	Formulation of vitamin E and A loaded nanoemulsion for the treatment of acute skin inflammation	[346]
Nanoemulsion	Phloretin	Design of phloretin loaded nanoemulsion for treatment of vaginitis	[347]
Nanoemulsion	Retinyl palmitate and dead seawater	Preparation of retinyl palmitate and dead sea water loaded nanoemulsions for topical anti-photoaging and anti-inflammatory treatments	[348]
Nanoemulsion	Triptolide	Development of triptolide nanoemulsion gels for percutaneous administration for treatment of eczema	[349]
Microemulsion	Triamcinolone	Formulation of microemulsion containing triamcinolone for transdermal delivery for eczema treatments	[350]
Microemulsion	Nicotinamide	Formulation of microemulsion based gel of nicotinamide for acne and cellulite treatments	[351]
Nanoemulsion	Tretinoin	Preparation of nanoemulsion system for topical delivery of tretinoin for effective anti-acne activity	[352]
Microemulsion	Indian penny wort, walnut, and turmeric	Formulation and clinical evaluation of topical dosage microemulsion of indian penny wort, walnut, and turmeric for eczema treatments	[353]
Nanoemulsion	Curcumin	Formulation of curcumin loaded nanoemulsion for transdermal delivery for anti-inflammatory treatments	[354]
Nanoemulsion	Foeniculum vulgare mill. essential oil	Formulation of foeniculum vulgare mill. essential oil loaded nanoemulsion for transdermal delivery for antioxidant and antidiabetic activities	[355]
Microemulsion	Dencichine	Formulation of dencichine loaded microemulsion for transdermal delivery for hemorrhage treatments	[292]
Microemulsion	Methyl dihydrojasmonate	Formulation of methyl dihydrojasmonate loaded microemulsion for transdermal delivery for anti-tumor activity	[356]
Microemulsion	Boswellia carterii oleo-gum-resin	Preparation of boswellia carterii oleo-gum resin loaded microemulsion for the treatment of inflammatory dermatological diseases, such as acne and eczema	[357]

5. Polymeric Nanoparticles

Polymeric nanoparticles are widely employed in many areas of drug delivery [358–368], while in dermal applications they typically prolong the residence time of active materials in the SC and other upper layers of the skin. These particles localize in the follicular openings in a time- and size-dependent manner and can efficiently liberate their active cargo there, enhancing skin distribution and permeability of the active material [369]. Depending on their inner structure and the content, polymeric nanoparticles may be further classified as nanospheres or nanocapsules [370]. Polymeric nanospheres are typically composed of a solid polymeric matrix, while polymeric nanocapsules contain a liquid/solid core coated with a polymeric shell or just a polymeric shell filled with a drug [371,372]. These morphology variations of polymeric nanoparticles lead to different entrapment mechanisms, while drugs can be either encapsulated in nanocapsules or dispersed in the polymeric matrix of nanospheres (Figure 9) [372–374].

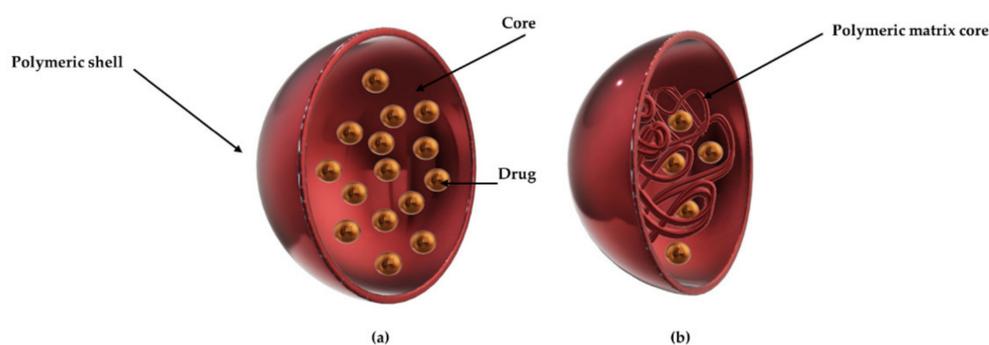


Figure 9. Schematic illustration of (a) nanocapsules, (b) nanospheres.

Due to their outer solid structure, polymeric nanoparticles may provide additional advantages in cutaneous application besides prolonging the residence time of the active material in the skin. Thus, they can control the rate and the extent of drug release and also protect drugs from degradation upon exposure to the external environment on the skin surface [375,376]. Various types of polymers, natural and synthetic, biodegradable and nonbiodegradable, can be employed to prepare polymeric nanoparticles [377]. These polymers include chitosan, alginate, gelatin (natural), aliphatic polyesters, poly(ϵ -caprolactone), poly(lactide-co-glycolide) (biodegradable), and polyacrylates, poly (methyl methacrylate) (nonbiodegradable) [378,379]. Different methods are being employed to produce polymeric nanoparticles. These methods use two main strategies: (1) in situ polymerization, (2) precipitation of pre-formed polymers [371,372,380,381]. In many preparation techniques an organic solvent is required to dissolve the polymer and the active substance, and it can be subsequently removed to avoid toxicity [382].

Some recent works that describe employing polymeric nanoparticles in dermal drug delivery systems are highlighted below.

5.1. Topical Delivery with Polymeric Nanoparticles

5.1.1. Anti-inflammatory Activity

Mathes et al. investigated three types of polymeric nanocarriers (nanospheres, nanocapsules, and lipid-core nanocapsules) with average sizes between 100 and 260 nm and slightly negative zeta potential for the delivery of potent glucocorticoid, clobetasol propionate, to treat inflammatory-based scalp diseases by a sustained release of the drug into hair follicles [383]. The three types of nanoparticles were prepared by the nanoprecipitation-solvent evaporation technique using poly(ϵ -caprolactone) and showed a successful encapsulation of clobetasol propionate. They all demonstrated sustained-release characteristics, reduced permeation across the skin, and achieved a differential accumulation in hair follicles, while nanocapsules had the highest follicular recovery. This could be because of the more flexible

core-shell structure of nanocapsules compared with the rigid matrix of nanospheres, and the reduced stiffness of the former compared with the lipid-core nanocapsules.

5.1.2. Antiviral Activity

Donalisio et al., developed acyclovir loaded chitosan nanospheres for the topical treatment of herpes simplex virus [384]. Chitosan nanospheres were prepared from W/O nanoemulsion and had an average size of about 200 nm, with a strongly positive zeta potential (~+40 mV). The loading capacity of the drug was around 8.5% with an encapsulation efficiency of about 87%. The in vitro permeation study showed the enhancement of acyclovir permeation through the skin when delivered by the chitosan nanosphere gel compared with a commercial cream formulation. The acyclovir-loaded chitosan nanospheres also showed higher antiviral activity compared to that of the free drug against both the HSV-1 and the HSV-2 virus strains.

5.1.3. Alopecia Treatment

Roque et al., employed poly(lactic-co-glycolic acid) nanoparticles for topical delivery of finasteride, a potent anti-alpecia agent [385]. Finasteride has a beneficial effect on hair regrowth; however, it may cause severe side effects when taken orally. The polymeric nanoparticles were prepared by a modified emulsification/solvent diffusion method and had an average size of 300 nm, which is suitable for the delivery into hair follicles, and very slightly negative zeta potential. High encapsulation efficiency was achieved for hydrophilic finasteride (~80%), which suggested a possible interaction between poly(lactic-co-glycolic acid) and the drug. Scanning electron microscope images showed that the nanoparticles had a spherical shape and a smooth surface. In vitro release studies in physiological conditions indicated that the nanoparticles led to a prolonged release of finasteride for 3 h. Safety testing of the excipients using human volunteers indicated that the formulation excipients were compatible with the skin.

Additional recent works on employing polymeric nanoparticles in dermal drug delivery systems are summarized in Table 4.

Table 4. Recent studies on dermal drug delivery systems comprising polymeric nanocapsules/ nanospheres/ microspheres.

Type of Polymeric Nanosystem (Nanoparticles/Spheres/Capsuls)	Drug/Active Material	Purpose	Reference
Nanoparticles	Curcumin	Formulation of curcumin encapsulated nanoparticles based on silica/polyethylene glycol/ chitosan as antimicrobial and wound healing agent	[386]
Nanoparticles	Selenium nanoparticles	Preparation of selenium nanoparticles stabilized by chitosan for antioxidant activity	[387]
Nanoparticles	Curcumin	Formulation of curcumin loaded polylactic-co-glycolic acid nanoparticles in hydrogel for anti-psoriatic treatments	[388]
Nanoparticles	7,3',4'-Trihydroxyisoflavone	Design of acid-responsive polymeric nanoparticles based on polyvinyl alcohol for 7,3',4'-trihydroxyisoflavone topical administration as antioxidant and melanin inhibitor	[389]
Nanoparticles	Porphyrin	Development of hydrogels containing porphyrin loaded nanoparticles based on polylactic-co-glycolic acid for topical photodynamic applications	[390]

Table 4. Cont.

Type of Polymeric Nanosystem (Nanoparticles/Spheres/Capsuls)	Drug/Active Material	Purpose	Reference
Nanoparticles	Finasteride	Design of finasteride loaded nanoparticles based on polylactic-co-glycolic acid for the potential treatment of alopecia	[385]
Nanoparticles	Corticosteroids	Development of corticosteroids loaded nanoparticles based on eudragit RS for controlled delivery in corneal epithelium treatments.	[391]
Nanoparticles	Betamethasone	Formulation of polymeric nanoparticles based on poly- ϵ -caprolactone as the polymeric core modified with fatty acids encapsulating betamethasone for inflammation treatment	[392]
Nanoparticles	Betamethasone	Formulation of betamethasone loaded nanoparticles based on chitosan and modified with hyaluronic acid for anti-atopic dermatitis efficacy	[393]
Nanoparticles	Dexamethasone	Formulation of dexamethasone loaded pH-sensitive polymeric nanoparticles based on different types of eudragit, hydroxypropyl methylcellulose phthalate and cellulose acetate phthalate for anti-inflammatory activity	[394]
Nanoparticles	Fluorescent marker	Preparation of polylactic acid nanoparticles as anti-inflammatory drug vehicle	[395]
Nanoparticles	Elvitegravir	Preparation of polylactic acid hyperbranched polyglycerols nanoparticles loaded with the antiretroviral elvitegravir against viral sexually transmitted diseases such as human immunodeficiency virus (HIV)	[396]
Nanocapsules	Acetazolamide	Design of novel polymeric nanoparticles based on polyethylcellulose and eudragit RS100 for ophthalmic administration of acetazolamide	[397]
Nanoparticles	Benzocaine	Formulation of benzocaine loaded poly- ϵ -caprolactone nanoparticles incorporated into poloxamer 407 based hydrogel for topical pain relief	[398]
Nanocapsules	Imatinib mesylate	Formulation of layer-by-layer polyethylene imine branched and polystyrenesulfonate coated gold nanoparticles for topical delivery of imatinib mesylate to treat melanoma	[384]

Table 4. Cont.

Type of Polymeric Nanosystem (Nanoparticles/Spheres/Capsuls)	Drug/Active Material	Purpose	Reference
Nanocapsules	Imiquimod	Formulation of chitosan as a cationic coating or gel vehicle for polymeric nanocapsules containing imiquimod for enhancing the penetration in vaginal tissue	[399]
Nanocapsules	α -tocopherol	Design of α -tocopherol loaded chitosan oleate nanoemulsion for wound healing treatments	[400]
Nanocapsules	Silibinin	Preparation of hydrogel containing silibinin and pomegranate oil loaded nanocapsules based on polyethylcellulose exhibiting anti-inflammatory effects on skin damage UVB radiation	[401]
Nanocapsules	Neutrophil elastase inhibitor	Preparation of starch nanocapsules containing a novel neutrophil elastase inhibitor with an improved pharmaceutical performance for psoriasis treatments	[402]
Nanocapsules	Ebselen	Development of topical delivery of ebselen encapsulated in biopolymeric nanocapsules based on alginate for antifungal activity	[403]
Nanocapsules	Tea tree oil	Design of nanoemulsions of tea tree oil and nanocapsules based on polycaprolactone which provide anti-edematogenic effect and improved skin wound healing	[404]
Nanocapsules	Triptolide	Formulation of chloramphenicol and essential oil loaded poly(ϵ -caprolactone)-pluronic nanocapsules for MRSA candida co-infected chronic burn wound treatments	[405]
Nanocapsules	Phenytoin	Preparation of chitosan nanocapsules containing phenytoin for wound healing activity	[406]
Nanocapsules	Cyclosporin	Formulation of solvent-free protamine nanocapsules as carriers for cyclosporin for anti-inflammatory activity	[407]
Nanocapsules	Dexamethasone	Formulation of cationic polymeric nanocapsules based on eudragit RS 100 for delivery of dexamethasone for the treatment of inflammatory and allergic skin disorders	[408]
Nanocapsules	Essential oil of <i>R. officinalis</i> and <i>L. dentata</i>	Preparation of <i>rosmarinus officinalis</i> L. and <i>lavandula dentata</i> essential oils encapsulated in polymeric nanocapsules based on eudragit EPO for antioxidant applications	[409]

Table 4. Cont.

Type of Polymeric Nanosystem (Nanoparticles/Spheres/Capsuls)	Drug/Active Material	Purpose	Reference
Nanocapsules	Latanoprost	Latanoprost loaded polymeric nanocapsules based on poly- ϵ -caprolactone for effective topical treatment of alopecia.	[410]
Nanocapsules	5-Fluorouracil	Preparation of topical formulations containing aptamer-functionalized nanocapsules based on chitosan and polyvinylpyrrolidone-alt-itaconic anhydride poly copolymer for encapsulation of 5-fluorouracil for skin cancer therapy	[411]
Nanocapsules	Clobetasol	Formulation of nanocapsules based on poly- ϵ -caprolactone for optimizing the balance between interfollicular permeation and follicular uptake of topically applied clobetasol for anti-inflammatory scalp diseases	[383]
Nanospheres	Vitamin D3	Formulation of polymeric nanospheres based on tryospheres (copolymers with hydrophobic blocks of oligomers of desaminotyrosyl tyrosine esters and diacids and hydrophilic blocks of poly(ethylene glycol)) encapsulating vitamin D3 for treatment of several skin disorders including psoriasis	[412]
Nanospheres	Acyclovir	Development of acyclovir loaded chitosan nanospheres for topical treatment of herpes virus infections	[413]
Nanocapsules	Itraconazole	Development of itraconazole loaded nanocapsules based on polycaprolactone	[414]
Nanocapsules	Cyclosporine	Formulation of topical nanocapsules based on polylactic-co-glycolic acid encapsulating cyclosporine for atopic dermatitis treatment	[415]
Nanospheres	Erianin	Development of erianin loaded dendritic mesoporous silica nanospheres with pro-apoptotic effects and enhanced topical delivery for psoriasis treatments	[416]
Nanospheres	Rapamycin	Formulation of rapamycin loaded nanospheres based on polylactic-co-glycolic acid for anti-glioma treatment	[417]
Nanospheres	Hyperforin	Development of hyperforin loaded nanospheres based on acetylated dextran for anti-inflammatory activity	[418]
Nanocapsules	Amphotericin B	Formulation of nanocapsules based on poly- ϵ -caprolactone encapsulating amphotericin B for antifungal treatments	[419]

Table 4. Cont.

Type of Polymeric Nanosystem (Nanoparticles/Spheres/Capsuls)	Drug/Active Material	Purpose	Reference
Nanocapsules	Ciprofloxacin	Formulation of nanocapsules based on polylactic-co-glycolic acid-containing ciprofloxacin for antibiotic treatments	[420]
Nanocapsules	Curcumin	Development of curcumin loaded polylactic-co-glycolic acid-based nanocapsules for enhanced solubility and antibacterial activity	[421]
Nanocapsules	Curcumin	Formulation of curcumin loaded nanocapsules based on polyethylene glycol-polypropylene glycol-polyethylene glycol for anti-cancer activity	[422]
Nanocapsules	Paclitaxel	Development of paclitaxel loaded nanocapsules based on polylactic-co-glycolic acid-polyethylene glycol for cancer therapy	[423]
Nanocapsules	Cymbopogon martini Roxburgh (Palmarosa oil)	Development of cymbopogon martini roxburgh (palmarosa oil) loaded nanocapsules based on polycaprolactone for antioxidant/antimicrobial activity	[424]
Nanocapsules	Thymus vulgaris L. (Thyme oil) Roxburgh (Palmarosa oil)	Formulation of thymus vulgaris L. loaded nanocapsules based on eudragit L100-55 for antioxidant activity	[425]
Nanocapsules	Citrus bergamia Risso. (Bergamot oil) and Citrus sinensis L. (Orange oil)	Formulation of citrus bergamia risso. and citrus sinensis L. loaded nanocapsules based on eudragit L100-55 for antimicrobial activity	[426]
Nanoparticles	Adapalene	Development and characterization of adapalene containing polymeric nanoparticles based on tryospheres for topical acne therapy	[427]
Nanospheres	Adapalene	Formulation of adapalene loaded biodegradable nanospheres based on poly(ϵ -caprolactone) for topical treatment of acne	[428]
Micro-nanocapsules	Retinyl palmitate	Development of micro/nanocapsules based on pectin polymer containing retinyl palmitate for anti-aging activity	[429]
Nanocapsules	Flufenamic acid	Development of flufenamic acid loaded nanocapsules based on polylactic-co-glycolic acid for anti-inflammatory treatments	[430]

6. Nanomaterials in Cosmetics and Skincare

Although skincare has been in practice since the time of Ancient Egypt 6000 years ago [431] only recently the Food and Drug Administration (FDA) officially described cosmetics as “articles intended to be applied to the human body or any part thereof for

cleansing, beautifying, promoting attractiveness, or altering the appearance” [384]. The FDA does not have the legal duty to approve skincare products before they are released to the market, however, these products must be safe for consumers and properly labelled [432]. The term “cosmeceutical” was coined to describe a cosmetic product comprising ingredients of potential bioactivity. Because of the aforementioned ability of nanomaterials to concentrate the active ingredients in the upper layers of the skin and increase their permeation, the performance-enhancing potential of nanometric formulations in cosmeceuticals is evident. However, due to the fact that the FDA is not involved in the testing or approving of these nanoformulations, there are substantial concerns among consumers pertaining to their safety. The most frequently raised concern is the risk of systemic absorption of nanoparticles from cosmetic products, for example of mineral nanoparticles from sunscreen creams. Various studies have extensively looked into this possibility and showed that mineral nanoparticles do not penetrate deeper than the epidermis. For instance, Lekki et al. have investigated the ability of titanium oxide nanoparticles with an average size of 20 nm to penetrate the skin, and it was found that the nanoparticles were present only in the 3–5 uppermost layers of the SC and in the hair follicles [433]. Similarly Menzel et al. investigated skin permeation of titanium oxide nanoparticles with an average size between 45 nm and 150 nm and found that the majority of the particles were retained on the skin surface and in the SC, with some penetration into the *stratum granulosum*, but with no presence in the *stratum spinosum* [434].

Despite these aforementioned concerns, a significant amount of research is being invested into the development of new cosmetic nanometric delivery systems for improved performance. In fact, all of the nanoparticle types discussed in the previous sections of this review are being widely investigated for applications in cosmetics [435–445]. Selected works showing the most recent advances in this field are detailed below.

6.1. Applications in Skincare

6.1.1. Moisturizers

As discussed in the introduction, one of the most important roles of the SC is to protect the body from dehydration by adjusting the transepidermal water loss (TEWL). Healthy skin water content is between 15 and 30% in the SC, and around 70% in the deeper skin layers. Reduction in this amount leads to dehydration, and, in extreme cases, to severe skin disorders. The main purpose of moisturizing creams is to decrease the TEWL and maintain skin hydration by blocking the openings on the skin surface with film-forming polymers as well as by promoting the permeation of natural moisturizing factors. These factors include ascorbyl palmitate, lactic acid, sodium lactate, natural oils, glycerol, urea, hyaluronic acid, and xanthan gum. For example, urea can form hydrophilic diffusion channels within the SC to facilitate hydration [446]. Glycerol was shown to have a strong fluidizing effect on the corneodesmosomes [447]. Recently, hyaluronic acid has also gained popularity as a moisturizing agent owing to its ability to retain water more than 1000 times its weight. All these substances can be incorporated into nanoparticulate delivery systems to improve their SC accumulation and activity [448–457]. For instance, Ribeiro et al., investigated an O/W nanoemulsion containing *opuntia ficus-indica* (L.) mill hydroglycolic extract, which is composed mainly of water and acts as a moisturizing factor and an anti-aging agent [458]. Nanoemulsion was able to increase the water content of the SC for 5 h after application and was stable for at least 2 months.

6.1.2. Anti-aging Creams

Numerous external and internal factors, such as pollution, chemical products, UV radiation, and stress, are responsible for the aging process of the skin. This leads to the loss of elasticity and volume, as well as to the reduction in collagen and water content. The anti-aging ingredients are intended to delay the aging process. For instance, retinoids are able to reduce wrinkles and lighten the dark spots by several mechanisms, including: (1) increasing the water content in the epidermis, (2) renewing the external cell layer, (3) boosting the

synthesis of collagen, and (4) inhibiting matrix metalloproteinases responsible for collagen breakdown [432,459–461]. Despite these benefits, retinoids are highly irritant and their continuous application may lead to redness, local inflammation and peeling off the skin. In addition, these compounds are easily degradable by light and oxidation [462,463]. Hence, the incorporation of retinoids in nanocarriers can reduce skin irritation, prolong the duration of their action and prevent their degradation. As mentioned in previous sections of this review, various nanocarriers were developed for retinoid delivery. It is important to note that in the European Union retinoids can be employed in cosmetic applications below certain concentrations: up to 0.05 % retinol equivalents for body lotions, and up to 0.3 % for hand and face creams [464]. Another important ingredient of anti-aging products is Coenzyme Q10 (CoQ10), owing to its ability to reduce oxidative stress and scavenge free radicals. As we age, the amount of the CoQ10 in our body decreases; and this compound is challenging to replenish because it is basically insoluble in water and has poor cutaneous permeability. Therefore a suitable nanocarrier system can greatly improve the topical delivery of CoQ10 [465]. El-Leithy et al. developed O/W CoQ10-containing nanoemulsion, which showed an enhanced skin permeation *ex vivo* and led to an effective reduction in wrinkles *in vivo*, in rat models [466]. Other common antioxidants include α -lipoic acid, vitamin C and vitamin E. Vitamin E also has poor aqueous solubility and is highly sensitive to oxygen, light, and heat. Eiras et al. developed hydrogel-based vitamin E-loaded NLC and showed that the formulation is biocompatible and non-irritant [467].

6.1.3. Anti-cellulite Creams

Cellulite is an appearance of dimpled skin caused by structural changes in the subcutaneous adipose tissue [468–470]. Cellulite creams are topically applied directly to the affected areas aiming for the active agent to permeate into the skin and reduce the size of hypertrophic fat cells, as well as smoothen the appearance of the dimples on the skin surface [468,471–473]. Active ingredients that are able to reduce the appearance of cellulite include xanthines, retinoids, and lactic acid. Caffeine is a xanthine compound with a pronounced activity on lipolysis [474]. Touitou et al. in 1993 pioneered in the delivery of caffeine into and across the skin using liposomes and permeation enhancers respectively [475]. Recently, Hamishehkar et al. prepared caffeine-loaded SLN by the hot homogenization technique [476]. The SLN had a mean particle size of below 100 nm, encapsulation efficiency of around 86%, and loading efficiency of about 29% for the optimized formulation. The *in vitro* permeation studies demonstrated that caffeine-loaded SLN incorporated into carbopol hydrogel exhibited a significantly higher deposition of caffeine in the skin (12%) compared with caffeine hydrogel (0.75%), but had lower systemic adsorption. Histological studies revealed the complete lysis of adipocyte membrane in the hypodermis caused by the administration of caffeine-SLN-hydrogel, compared with the plain caffeine-loaded hydrogel, which had no effect on adipocytes lysis. Moreover, there was a significant reduction of fat tissue mass in the areas treated with caffeine loaded SLN after 1 and 3 weeks of treatment compared with the skin areas treated with the plain caffeine-loaded hydrogel or untreated skin (Figure 10).

6.1.4. Sunscreens

Sunlight is considered to be the best source of vitamin D and natural tanning. Ultraviolet A (UVA) radiation is responsible for skin tanning, while UVB provides the energy to produce vitamin D from cholesterol. However, extensive exposure to UV radiation harms the skin and stimulates aging, actinic keratosis, and the formation of free radicals that can lead to skin cancer [477,478]. Therefore, sunscreens are cosmetic products of utmost importance, capable of protecting the skin from these harmful effects. The most effective sunscreens today are mineral compounds based on zinc oxide (ZnO) and titanium oxide (TiO₂). They form a physical screen on the skin that reflects the UV radiation and prevents it from penetrating to the deeper layers [479]. In addition, there are active substances such as benzophenone derivatives, vegetable oils, octyl methoxycinnamate, safranal, phenols,

and others that can absorb and dissipate UV radiation [480]. There have been some recent concerns about the systemic hazards of frequent topical applications of classical chemical sunscreens, such as benzophenone derivatives or octyl methoxycinnamate. Benzophenone derivatives can be absorbed through the skin and exhibit estrogenic and antiandrogenic activities, while octyl-methoxycinnamate can photogenerate highly destructive reactive oxygen species in the skin [481]. In 2008 Touitou and Godin overcame these potential hazards by immobilization of UV-absorbing moieties in the jojoba oil chemical backbone to prevent their penetration [481]. Recently Badea et al. employed several vegetable oils to design NLC for the entrapment of a synthetic sunscreen compound, diethylamino hydroxybenzoyl hexyl benzoate (DHHB) [482]. These oils themselves served to provide broad-spectrum sun protection and antioxidant activity. The NLC were prepared by hot high-pressure homogenization and had a mean particle size between 100 nm and 145 nm, and strongly negative zeta potential. The NLC showed enhanced photoprotective and antioxidant properties.

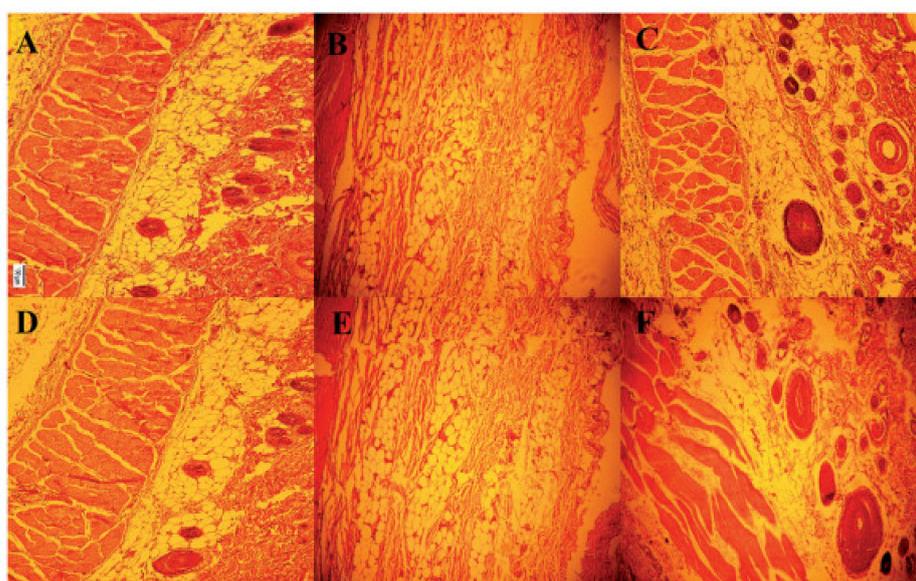


Figure 10. Histopathology images of the skin: (1) without a treatment after 7 days (A) and 21 days (D); (2) treated with caffeine hydrogel after 7 days (B) and 21 days (E); and (3) treated with caffeine-SLN-hydrogel after 7 days (C) and 21 days (F). Reproduced with permission from [476] [Copyright Clearance Center], [Drug Development and Industrial Pharmacy]; published by [Taylor & Francis, 2015].

6.1.5. Anti-hyper Pigmentation Activity

Hydroquinone is a tyrosinase inhibitor that has strong depigmenting properties and is used to lighten areas of darkened skin, such as freckles, age spots, chloasma, and melisma [483]. It is banned from the use in cosmetic products in Europe and the UK because of the acute and chronic adverse effects associated with its use. Deoxyarbutin (4-[(tetrahydro-2H-pyran-2-yl)oxy]phenol) is a relatively new tyrosinase inhibitor, with stronger inhibitory potency than hydroquinone, but with decreased cytotoxicity. Tofani et al. developed deoxyarbutin-containing NLC for the treatment of hyperpigmentation and compared their skin penetration enhancement in dispersion and in hydroxypropyl methylcellulose gel to deoxyarbutin loaded nanoemulsion and the commercial cream emulsion [483]. The permeation of deoxyarbutin across the synthetic sebum membrane was the highest from the NLC incorporated into the gel. The permeation from the gel-NLC was comparable to the one from the nanoemulsion during the first two hours following the application, however later surpassed it. These kinetics was explained by the higher fluidity and elasticity of the nanoemulsion droplets on one hand, but the superior potential of NLC to release greater amounts of the drug over a prolonged period of time, on the other.

Additional recent advances in this field are summarized in Table 5.

Table 5. Recent studies on nanoparticulate cutaneous drug delivery systems in cosmetics and skincare.

Type of Nanosystem	Drug/Active Material	Purpose	Reference
SLN	Beeswax	Formulation of beeswax loaded solid lipid nanoparticles to improve damaged skin barrier function	[484]
SLN	Hydroquinone (banned in EU)	Preparation of solid lipid nanoparticles containing hydroquinone to treat hyperpigmentation	[485]
SLN	Curcumin	Preparation of curcumin loaded solid lipid nanoparticles-encapsulated topical gel for the treatment of pigmentation and irritant contact dermatitis	[486]
SLN	N-Acetyl-d-glucosamine	Development of solid lipid nanoparticles containing n-acetyl-d-glucosamine for hyperpigmentation treatment	[487]
NLC	Deoxyarbutin	Development of deoxyarbutin loaded nanostructured lipid carriers for hyperpigmentation treatment	[483]
NLC	MHY908 tyrosinase inhibitor	Development of MHY908 loaded nanostructured lipid carriers for hyperpigmentation treatment	[488]
NLC	N-Acetyl-glucosamine	Development of n-acetyl-glucosamine loaded nanostructured lipid carriers for hyperpigmentation treatment	[489]
NLC	Resveratrol	Development of resveratrol loaded nanostructured lipid carriers for hyperpigmentation and melanogenesis treatments	[490]
SLN	Safranal	Development of safranal loaded solid lipid nanoparticles for sunscreen and moisturizing potential for topical applications	[491]
SLN	Aloe vera	Formulation of photoprotective solid lipid nanoparticles containing aloe vera as sunscreen cream	[492]
SLN	Green tea	Preparation of solid lipid nanoparticles containing green tea leaves (<i>Camellia sinensis</i> L. Kuntze) extract as sunscreen	[493]
SLN	Octyl methoxycinnamate	Formulating octyl methoxycinnamate in hybrid lipid-silica nanoparticles as UV skin protection product	[494]
NLC	Vegetable oils	Preparation of nanostructured lipid carriers containing various vegetable oils for UV protection and antioxidant activity	[482]
NLC	Naringenin	Development of naringenin loaded nanostructured lipid carriers as a sunscreen product	[495]
NLC	Acrocomia aculeata (arecaceae oil)	Production of acrocomia aculeata (arecaceae oil) loaded nanostructured lipid carriers for photoprotective activity	[496]
NLC	Amaranth and pumpkin seed oils	Design of amaranth and pumpkin seed oils loaded nanostructured lipid carriers as a new cosmetic formulation with broad photoprotective and antioxidative activities	[497]

Table 5. Cont.

Type of Nanosystem	Drug/Active Material	Purpose	Reference
NLC	Carnauba wax, beeswax, and kenaf seed oil	Formulation of novel nanostructured lipid carriers made from carnauba wax, beeswax, and kenaf seed oil as a photoprotective product	[498]
NLC	Octyl methoxycinnamate	Synthesis and characterization of octyl p-methoxycinnamate loaded nanostructured lipid carriers for enhanced sun protection factor (SPF) for sunscreen	[499]
NLC	Protocatechuic acid and ethyl protocatechuate	Evaluation of lipid nanoparticles containing protocatechuic acid and ethyl protocatechuate as a new photoprotection strategy	[500]
SLN	Heptapeptide	Development of heptapeptide loaded solid lipid nanoparticles for cosmetic anti-aging applications	[501]
SLN	N-6-furfuryl adenine	Development and evaluation of solid lipid nanoparticles containing N-6-furfuryl adenine for prevention of photoaging	[502]
SLN	Proanthocyanidins	Formulation of grape seed-derived proanthocyanidins loaded solid lipid nanoparticles to alleviate oxidative stress and inflammation in airway epithelial cells	[503]
SLN	Resveratrol	Evolution of resveratrol loaded solid lipid nanoparticles for anti-aging activities	[504]
NLC	Coenzyme Q10	Development of coenzyme Q10 loaded nanostructured lipid carriers as an inducer of the skin fibroblast cell for anti-aging activity	[505]
NLC	Folic acid	Preparation of folic acid loaded lipid nanocarriers with promoted skin anti-aging and antioxidant efficacy	[506]
NLC	Hesperidin	Formulation of nanostructured lipid carrier containing hesperidin from the orange residue as anti-aging	[507]
NLC	α -Tocopherol	Design of fatty acids based α -tocopherol loaded nanostructured lipid carrier gel for moisturizing and anti-aging effects	[508]
NLC	Coenzyme Q10 and myrica esculenta leaves extract	Preparation of nanostructured lipid carriers containing coenzyme Q10 and myrica esculenta leaves extract for anti-aging activity	[509]
NLC	Vitamin E	Characterization and biocompatibility evaluation of cutaneous formulations containing vitamin E loaded nanostructured lipid carriers for anti-aging activity	[467]
SLN	Serine	Preparation serine loaded solid lipid nanoparticles and polysaccharide-rich extract of root Phragmites communis incorporated in hydrogel bases for a moisturizing effect	[510]
SLN	Jojoba oil and grape seed oil	Synthesis and characterization of valacyclovir HCl hybrid solid lipid nanoparticles containing natural oils such as jojoba oil and grape oil for antioxidant and moisturizing activity	[511]

Table 5. Cont.

Type of Nanosystem	Drug/Active Material	Purpose	Reference
NLC	Curcumin	Development of nanostructured lipid carriers based on monoacyl-phosphatidylcholine containing curcumin for natural moisturizing	[512]
NLC	Ellagic acid	Formulation of ellagic acid loaded nanostructured lipid carriers for topical antioxidant activity	[513]
Niosomes	Caffeine	Preparation and evaluation of niosomes containing caffeine as an anti-cellulite drug	[514]
Liposomes	Azelaic acid	Development of new effective azelaic acid liposomal gel formulation of enhanced pharmaceutical bioavailability for anti-acne treatments	[515]
Niosomes	Rosmarinic acid	Development of a novel anti-acne niosomal gel of rosmarinic acid	[516]
Liposomes	Sodium copper chlorophyllin	Preparation of liposomal sodium copper chlorophyllin complex for anti-acne activities	[517]
Liposomes	Phenols recovered from olive mill wastewater	Formulation of liposomes containing phenols recovered from olive mill wastewater as UV booster in cosmetics	[518]
Liposomes	Epigallocatechin-3-gallate	Preparation of epigallocatechin-3-gallate loaded liposomes against UV irradiation	[519]
Liposomes	Isooctyl p-methoxycinnamate	Encapsulation of isooctyl p-methoxycinnamate with sodium deoxycholate mediated liposomes endocytosis for enhanced antioxidation and photo protecting	[520]
Liposomes	methyl-2-acetylamino-3-(4-hydroxyl-3,5-dimethoxybenzoylthio) propanoate	Development of methyl-2-acetylamino-3-(4-hydroxyl-3,5-dimethoxybenzoylthio) propanoate loaded liposomes for hyperpigmentation treatments	[352]
Ethosomes	Epigallocatechin-3-gallate	Formulation of nanoethosomal suspensions of (-)-epigallocatechin gallate for enhancing the effectiveness against UVB	[521]
Niosomes	Octyl methoxycinnamate	Formulations for photoprotective niosomes containing octyl methoxycinnamate	[522]
Ethosomes	Naringin	Preparation of naringin loaded nanoethosomal novel sunscreen creams	[523]
Transfersomes	Epigallocatechin-3-gallate and hyaluronic acid	Design of epigallocatechin-3-gallate and hyaluronic acid loaded nanotransfersomes for antioxidant and anti-aging effects in UV radiation-induced skin damage	[524]
Liposomes	Polygonum aviculare extract	Preparation of cell-penetrating peptide conjugated polygonum aviculare extract loaded liposomes as a delivery system for anti-aging activity	[525]
Niosomes	Coenzyme Q10	Development of coenzyme Q10 loaded niosomes for treatment of photoinduced aging	[526]
Niosomes	Gallic acid	Formulation of gallic acid loaded in cationic surfactant (cetrimonium bromide) niosomes for anti-aging activity	[527]

Table 5. Cont.

Type of Nanosystem	Drug/Active Material	Purpose	Reference
Ethosomes	Gamma oryzanol	Formulation of ethosomes containing gamma oryzanol for skin-aging protection and wrinkle improvement	[528]
Liposomes	Ascorbic acid derivative	Development of ascorbic acid derivative loaded liposomes for anti-aging activity	[529]
Ethosomes and liposomes	Rosmarinic acid	Formulation of rosmarinic acid loaded ethosomes and liposomes as an anti-aging product	[530]
Liposomes	Vitamin D3 (banned in EU)	Preparation of liposomes containing vitamin D3 as an anti-aging agent for the skin	[531]
Niosomes	Curcumin	Formulation of niosomes containing curcumin for anti-aging activity	[532]
Niosomes	Volvariella volvacea extract	Development of delivery enhancement of gel containing niosomes containing volvariella volvacea extract for anti-aging applications	[533]
Transfersomes	Gotu kola leaves extract	Formulation of transfersomes gel containing gotu kola leaves extract for anti-aging applications	[534]
Liposomes	Argan oil and phospholipids	Preparation of a mix of argan oil and phospholipids for the development of an effective liposomal system to improve skin hydration and allantoin dermal delivery	[535]
Transfersomes	Tocopherol	Preparation of tocopherol loaded transfersomes for skin regeneration	[536]
Ethosomes	Rutin	Formulation of rutin loaded ethosomes as an antioxidant agent	[537]
Transfersomes	Photocomplexes from grape seeds	Development of transfersomes containing photocomplexes extracted from grape seeds for the treatment of skin damages	[538]
Nanoemulsion	Centella asiatica L. and zingiber officinale	Design of nanoemulsion containing centella asiatica L. and zingiber officinale combination to promote collagen synthesis and decrease the diameter of adipocyte cells for anti-cellulite treatment	[539]
Nanoemulsion	Caffeine	Development of nanoemulsion containing caffeine for cellulite treatment	[540]
Nanoemulsion	Origanum vulgare L. essential oil	Formulation of origanum vulgare L. essential oil loaded nanoemulsion as a potential anti-acne drug	[541]
Nanoemulsion	Polyphenol-rich ethyl acetate	Development of photoprotection by Punica granatum seed oil nanoemulsion entrapping polyphenol-rich ethyl acetate fraction against UVB	[542]
Nanoemulsion	Chitosan	Preparation of a photoprotective and antioxidant nanoemulsion containing chitosan as an agent for improving skin retention	[543]
Nanoemulsion	Sunflower oil	Preparation and evaluation of sunflower oil nanoemulsion as a sunscreen product	[544]

Table 5. Cont.

Type of Nanosystem	Drug/Active Material	Purpose	Reference
Nanoemulsion	Soybean oil, avobenzone, and octyl methoxycinnamate	Preparation and evaluation of sunscreen nanoemulsions containing soybean oil, avobenzone, and octyl methoxycinnamate, with synergistic efficacy on SPF	[545]
Nanoemulsion	Rambutan fruit peel extracts	Formulation of gel nanoemulsion of rambutan for sunscreen protecting and antioxidant activity	[546]
Nanoemulsion	Vitamin E and genistein	Development of vitamin E-enriched nanoemulsion containing genistein for chemoprevention against UVB	[547]
Nanoemulsion	Quercetin tetraethyl ether	Preparation and characterization of a quercetin tetraethyl ether loaded nanoemulsion as photoprotective product	[548]
Microemulsion	Resveratrol	Microemulsion containing polyoxyethylene sorbitan trioleate and resveratrol for skin protection against UV	[301]
Microemulsion	Quercetin	Formulation of quercetin loaded microemulsion for topical sunscreen application	[549]
Microemulsion	Octyl p-methoxycinnamate	Preparation of octyl p-methoxycinnamate loaded microemulsion based on ocimum basilicum essential oil for potential cosmetic applications such as sunscreen	[550]
Nanoemulsion	Kojic monooleate	Development of kojic monooleate loaded nanoemulsion for hyperpigmentation treatments	[551]
Nanoemulsion	Azelaic acid with hyaluronic acid	Development of azelaic acid with hyaluronic acid loaded nanoemulsion for hyperpigmentation treatments	[552]
Nanoemulsion	Vitamin C	Development of vitamin C loaded nanoemulsion for hyperpigmentation treatments	[553]
Nanoemulsion	Adlay bran oil	Development of adlay bran oil loaded nanoemulsion for hyperpigmentation treatments	[554]
Microemulsion	Kojic acid and arbutin	Development of kojic acid and arbutin loaded microemulsion for hyperpigmentation treatments	[555]
Microemulsion	Cistanche tubulosa phenylethanoid glycosides	Preparation and evaluation of microemulsion containing cistanche tubulosa phenylethanoid glycosides for skin lightning activity	[556]
Microemulsion	Dibenzoylmethane	Development of microemulsion containing dibenzoylmethane for treatment of UV induced photoaging	[557]
Microemulsion	Melaleuca cajuputi essential oil	Formulation of microemulsion containing extract from melaleuca cajuputi essential oil using nonionic surfactant for sunscreen activity	[558]
Microemulsion	Mangosteen pericarp (Garcinia mangostana Linn.)	Development of microemulsion gel containing n-hexane fraction of mangosteen pericarp as a sunscreen product	[559]

Table 5. Cont.

Type of Nanosystem	Drug/Active Material	Purpose	Reference
Nanoemulsion	Grapeseed oil	Evaluation of the effect of antioxidant of grapeseed oil loaded nanoemulsion for skin anti-aging purposes	[560]
Nanoemulsion	Coenzyme Q10	Design of coenzyme Q10 loaded nanoemulsion with improved skin permeability and anti-wrinkle efficiency	[466]
Nanoemulsion	Copper peptide and virgin coconut oil	Formulation of nanoemulsion based virgin coconut oil containing copper peptide for anti-aging activity	[561]
Microemulsion	Camellia assamica seed oil	Development of camellia assamica seed oil loaded microemulsion for antioxidant and moisturizing activities	[562]
Microemulsion	Binahong leaf extract	Formulation of binahong (<i>Anredera cordifolia steenis</i>) leaf extract loaded microemulsion as anti-aging	[563]
Nanoemulsion	<i>Opuntia ficus-indica</i> (L.) mill extract	Production of cosmetic nanoemulsions containing <i>Opuntia ficus-indica</i> L. mill extracts for moisturizing activity	[458]
Nanoemulsion	Agave sisalana	Preparation of agave sisalana as a new cosmetic raw material loaded nanoemulsion to improve skin moisturizing	[564]
Nanoemulsion	Exotic vegetable oils	Development of exotic vegetable oils loaded O/W nanoemulsions for moisturizing applications	[565]
Nanoemulsion	Sweet fennel essential oil	Formulation of O/W nanoemulsion containing sweet fennel essential oil for antioxidant applications	[566]
Nanoemulsion	<i>Achyrocline satureioides</i> extract	Development of nanoemulsion containing <i>Achyrocline satureioides</i> extract for treatment against UV-induced skin damage	[567]
Nanoemulsion	Tea tree oil	Formulation of tea tree oil loaded nanoemulsion for antimicrobial applications	[568]
Nanocapsules	Rose-hip oil	Formulation of nanocapsules based on eudragit RS100 containing rose-hip oil for skin regeneration	[569]
Nanocapsules	Benzophenone-3	Development of a new sunscreen formulation based on benzophenone-3 loaded poly(ϵ -caprolactone) nanocapsules	[570]
Nanospheres	5-Hydroxymethylfurfural	Formulation of mesosilica-supported 5-hydroxymethylfurfural nanospheres to protect against UV-induced aging of human dermal fibroblasts	[571]
Nanocapsules	Dead sea water and retinyl palmitate	Formulation of dead sea water and retinyl palmitate loaded poly(3-hydroxybutyrate-co-3-hydroxyvalerate) micro/nanocapsules for the treatment of psoriasis, aging, or UV damage	[572]
Microcapsules	Grape seed oil	Formulation of ethylcellulose microcapsules containing grape seed oil for skin moisturizing activity	[534]

Table 5. Cont.

Type of Nanosystem	Drug/Active Material	Purpose	Reference
Microspheres	olive leaf extract	Preparation of olive leaf extract loaded chitosan microspheres for moisturizing activity	[573]
Microspheres	Glutathione	Development of glutathione loaded alginate microspheres for topical anti-aging activity	[574]
Microspheres	Lignin	Fabrication of light-colored lignin microspheres for developing natural sunscreens	[575]
Microspheres	4-Methylbenzylidene camphor I	Formulation of 4-methylbenzylidene camphor loaded microspheres based on hydrophilic (chitosan and gelatine) and hydrophobic (polymethylmetacrylate) polymers for sunscreen activity	[576]
Microcapsules	Octyl methoxycinnamate	Preparation and characterization of microcapsules based on gelatin and sodium polyphosphate encapsulating octyl methoxycinnamate for sunscreen applications	[577]
Nanospheres	Lignin and benzophenone	Formulation of lignin nanospheres with broad-spectrum UV adsorption and excellent antioxidant properties containing benzophenone for sunscreen activity	[578]
Nanospheres	Vitamin C	Preparation of nanospheres based on ethyl cellulose encapsulating vitamin C for hyperpigmentation treatments	[160]

7. Conclusions

It is evident from this immense number of recent works that nanomaterials play the most significant role in the contemporary dermal delivery research. Nanocarriers can effectively protect active materials from degradation on the skin surface, increase their concentration in the upper skin layers and enable gradual release, thus creating a prolonged local concentration gradient in the skin. It is important to remember though, that the permeation enhancement effect of nanomaterials rarely stems from the ability of the whole particle to penetrate deeper than the epidermis (with the exceptions of soft vesicles, deformable particles, and nanodroplets), but mostly from the capacity to create favorable conditions for the permeation of the active compound itself. In transdermal delivery, nanocarriers were shown to maintain the therapeutic concentrations of drug in plasma for prolonged periods of time, as well as to increase the overall drug amount that reaches the bloodstream over time. This effect can be explained by: (1) the sustained release of the drug from the skin by creating a concentrated drug depot within the skin, (2) the avoidance of the first-pass effect that takes place in oral administration of many drugs. Main challenges in the development of cutaneous nanometric delivery systems include: (1) incorporation and the effective cutaneous release of active compounds with a wide spectrum of physicochemical properties, (2) ensuring low skin irritability of nanocarriers and permeation enhancers, (3) precise delivery to various skin strata and across the skin depending on the final target, (4) overcoming toxicity concerns regarding nanomaterials in topical medical formulations and cosmetics.

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