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REVIEW

Potential of nanoparticulate carriers for improved drug delivery via skin

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Abstract

Skin as a delivery route for drugs has attracted a great attention in recent decades as it avoids many of the limitations of oral and parenteral administration. However, the excellent barrier property of skin is a major obstacle in the effective transport of drugs through this route. The topmost layer of skin, the "stratum corneum" is the tightest one and is responsible for most of the resistance offered. This necessitates breaching the resistance of the stratum corneum reversibly and transiently in order to achieve a therapeutically meaningful level in systemic circulation or local skin. In last few decades, a number of approaches have been developed to improve the limited drug permeability through stratum corneum. One promising approach is the use of nanoparticulate carriers as they not only facilitate drug delivery across skin but also avoid the drawbacks of conventional skin formulations. This review focuses on nanoparticulate carriers including conventional liposomes, deformable liposomes, ethosomes, niosomes and lipid nanoparticles developed for topical and transdermal drug delivery. A special emphasis is placed on their composition, structure, mechanism of penetration and recent application. The presented data demonstrate the potential of these nanoparticulate carriers for dermal and transdermal delivery.

Keywords Nanoparticulate carriers · Skin permeation · Liposomes · Deformable liposomes · Ethosomes · Niosomes · Lipid nanoparticles

Introduction

Skin is the major organ of the human body that serves as a unique and ultimate interface between the body and the external environment. It has been extensively investigated for drug delivery due to its easy accessibility and large surface area. As a drug administration route, skin has mainly been utilized for topical (dermal) delivery where a drug is localized in skin layers, or transdermal delivery where a drug passes through the skin and reaches blood circulation (Neubert 2011). Transdermal drug delivery has several advantages over conventional routes of administration. The key benefits of transdermal drug delivery are convenience, better patient compliance, noninvasiveness, low cost, and an easily accessible and large skin surface area for drug absorption. This type of delivery also permits bypassing the first pass metabolism thereby improving drug's bioavailability, circumventing the factors associated with variable drug absorption in the gastrointestinal tract (influence of pH, food, enzymes, GI motility), eschewing serious side effects of drugs, providing lower fluctuations in drug plasma levels, and abstaining patient phobia, risk factors and inconvenience associated with parenteral delivery (Barry 2004; Ranade and Cannon 2011). However, transdermal delivery of drugs has certain limitations too. The major one is the excellent barrier property of the outermost layer of skin, the "stratum corneum" which resists most of drug molecules to pass through it (Barry 1983; El Maghraby et al. 2001). Therefore, the stringent physicochemical conditions such as molecular weight, partition coefficient, lipophilicity and

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ionization imposed by this route restricts its use to only a few drugs with a specific set of properties (Khan et al. 2015; Prausnitz et al. 2004). The principal aim of this review is to describe in detail the hurdles associated with efficient skin delivery and to present the most promising types of nanoparticulate carriers and their applications in overcoming the skin barrier for drug delivery.

Skin structure

Skin is the largest organ of the human body, making up about 15% of total body mass with a surface area of about 2 m^2 (Hadgraft 2001; Kanitakis 2002). It represents a primary barrier between the body and the external environment (Hadgraft 2004). It functions to protect the body against external elements, maintain homeostasis and perform sensory role (Kenneth and Michael 2002). Skin structure is composed of three layers: the epidermis, dermis and hypodermis (Kenneth and Michael 2002) and associated appendages including the hair follicles, sebaceous glands, sweat glands and nails (Barry 2001; Rosen 2005). A diagrammatic illustration of skin structure is presented in Fig. 1a.

The epidermis is the topmost, 50–100 μm thick layer of skin that separates the interior of the human body from the outer milieu. It consists of keratinocytes, which are specialized epithelial cells producing keratin, and is regularly renewed through the process of desquamation and cell growth (Khan et al. 2015). The epidermis is an avascular layer and is conveniently divided (from top to bottom) into the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basale. These epidermal layers show different levels of keratinocyte differentiation. Keratinocytes in the stratum basale are single layered, columnar shaped and mitotically active, while the topmost 15–20 layers of polygonal shaped, fully differentiated, dead and non-nucleated keratinocytes (now known as corneocytes) form the least permeable "stratum corneum" of the skin (Christophers 1971; Menon 2002). Corneocytes are embedded in a matrix of lipid bilayers mainly consisting of ceramides, cholesterol, free fatty acids, triglycerides, cholesterol sulfate and sterol (Bouwstra and Ponec 2006). A 10–15 μm thick stratum corneum is made up of about 5–15% lipids and 75–85% proteins on a dry weight basis (Pegoraro et al. 2012).

The dermis is a 3–5 mm thick layer beneath the epidermis, comprising of a network of collagen and elastin fibers with an interfibrillar gel of glycosaminoglycans, salts and water (El Maghraby et al. 2008). The dermis supplies nutrition and provides a structural support to the skin as well as shelters a number of structures including blood vessels, lymph vessels, hair follicles, sweat and sebaceous glands, sense receptors and nerve endings (Cevc et al. 1996; Cevc and Vierl 2010). The hypodermis is the deepest layer of skin comprising of adipose and loose connective tissues that functions as an insulator and shock absorber (Pegoraro et al. 2012).

Drug permeation pathways through the skin

The stratum corneum represents the principal permeability barrier that controls drug transport across the skin (Scheuplein 1976). Drug transport via skin mainly occurs by two macro diffusional routes (Fig. 1b), namely trans-epidermal and trans-appendageal pathways (Hadgraft 2001; Trommer and Neubert 2006).

Trans-epidermal transport implies the transport of drugs via an intact stratum corneum and includes transcellular and intercellular micro routes. Transcellular transport involves the passage of drugs through a relatively hydrophilic environment of corneocytes followed by passage via the highly lipophilic intercellular lipid matrix (Trommer and Neubert 2006). Although it offers the shortest

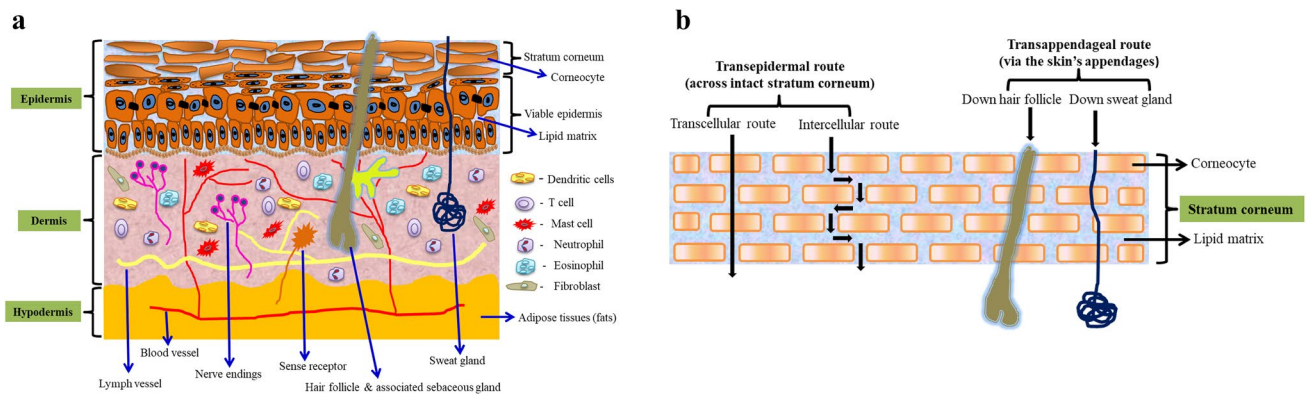

Fig. 1 Diagrammatic illustration of **a** skin's structure and **b** routes of drug permeation through the skin

route and is predominantly favored for the transport of hydrophilic molecules, such drugs are also required to pass through the intercellular hydrophobic domain (Benson 2006). The intercellular route of drug transport offers a continuous and tortuous pathway through the lipophilic matrix between the corneocytes. The intercellular route is regarded as the main route of drug transport for small, uncharged and lipophilic molecules (Johnson et al. 1997). Drug transport through the skin's appendages including the sweat glands, hair follicles and sebaceous glands constitutes the trans-appendageal or "shunt" route. It offers a highly permeable and continuous conduit directly across the stratum corneum. However, it is responsible for a very low contribution in overall drug transport via skin as appendages occupy only 0.1% of the skin's total area (Barry 2002; Moser et al. 2001). The shunt route is of relative importance for the passage of ions and large polar molecules through hair follicles (Barry 2002; Scheuplein 1965). In a particular transport, more than one of these pathways might be contributing simultaneously with the relative importance of any route being dictated by the physicochemical properties of that permeant (El Maghraby et al. 2008).

Nanoparticulate carriers for skin delivery

In the past few decades, nanoparticulate carriers have been the focus of great attention across a broad range of fields including pharmaceutical technology. In the context of drug delivery, nanoparticulate carriers generally refer to colloidal particulate systems with a size range below 500 nm (Neubert 2011). Nanoparticulate carriers can be utilized to alter the physicochemical properties of drugs and their interactions with physiological systems. Application of nanoparticulate carriers for skin delivery is especially important because it not only circumvents the limitations of conventional delivery systems but also enhances the skin permeation of drugs (Uchechi et al. 2014). Nanoparticulate carriers can improve drug transport across the skin by ensuring direct contact with the stratum corneum and skin appendages, controlling drug release, increasing contact time with the skin and protecting drugs against physical and chemical instabilities (Contri et al. 2011). The permeation of drugs after incorporation into nanoparticulate carriers is controlled by the physicochemical properties of the carriers such as the composition, method of preparation, particle size, particle shape, surface charge and flexibility. The skin permeation potential of some promising nanoparticulate carriers is described in this section along with a summary of studies showing improved drug delivery through various skin models (Tables 1, 2, 3, 4, 5).

Conventional liposomes

Liposomes are hollow, self-enclosing lipid colloidal particles arranged in a bilayer confirmation surrounding an aqueous volume as illustrated in Fig. 2a (El Maghraby et al. 2006). Phospholipids, usually egg yolk or soy phosphatidylcholine, are the main constituents of conventional liposomes, while the addition of cholesterol in lipid bilayers increases the stability and rigidity of bilayer membranes (Elsayed et al. 2007). The hydro-soluble molecules find their place in the central aqueous core and the aqueous phase between the lipid bilayers, while the lipid soluble molecules are incorporated into one or more concentric lipid bilayers via hydrophobic interactions (Honeywell-Nguyen and Bouwstra 2005). Since their development in the 1960s by Alec Bangham, conventional liposomes have gained widespread attention in drug delivery and biomedical applications (Torchilin 2005). In the last two decades, a number of liposomal products and technologies have received approval for practical use. The clinical applications of liposomal drug delivery are well-recognized with a number of drug products available in the market or under clinical trials. Recently, a number of advancements have been made in basic liposomes structure aimed to reduce problems with liposomal drug delivery and to incorporate attractive features to liposomal delivery. A few examples of these developments include long circulatory liposomes, immuno-liposomes, targeted liposomes and pH-sensitive liposomes (Torchilin 2005).

Conventional liposomes for skin delivery and the mechanisms of permeation

As a pharmaceutical nanocarrier, liposomes were first investigated for skin drug delivery in the 1980s where lotion incorporating liposomal triamcinolone acetonide had a greater deposition of drug in skin layers compared with the conventional dosage form (Mezei and Gulasekharam 1980). Since the first report, a large number of contradictory results have been published regarding the effectiveness of conventional liposomes in improving the skin permeation of drugs. Most of the published data supports the hypothesis that conventional liposomes only enhance drug deposition in the upper skin layers with little effect on skin permeation into blood circulation (Honeywell-Nguyen and Bouwstra 2005). Numerous mechanisms have been proposed for the skin penetration of conventional liposomes including *free drug mechanism* where drug penetrate the skin solitary after it is released from the vesicles, *penetration enhancement mechanism* whereby the liposomes disrupt the intercellular lipids of the stratum corneum by acting as a permeation

Table 1 Summary of representative studies using conventional liposomes for skin drug delivery

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Retinoic acid	EPC:retinoic acid (4:1 molar ratio) and EPC: DOTAP:retinoic acid (2:2:1 molar ratio)	Solvent evaporation and sonication method	To evaluate the potential of cationic liposomes for enhanced skin delivery of retinoic acid	Cationic DOTAP liposomes had a mean diameter of 108 nm	Twofold enhanced delivery of retinoic acid across the guinea pig dorsal skin using EPC liposomes compared to its solution in isopropyl myristate Addition of DOTAP into liposomes increases the skin delivery of retinoic acid by 3.7-fold compared to liposomes without DOTAP	Kitagawa and Kasamaki (2006)
Paromomycin	SPC:CH (1:1 molar ratio)	Solvent evaporation method for MLVs and reverse phase evaporation method for LUVs	To study the potential of paromomycin containing liposomes for topical delivery	LUVs showed a drug E.E of 20.4% MLVs exhibited an E.E of 7.5%	A higher drug E.E was achieved for LUVs than MLVs Liposomes (LUVs) showed higher drug permeation (1.55%) across hairless mice skin compared with an aqueous drug solution (0.50%)	Ferreira et al. (2004)
Ethyl hexyl methoxycinnamate (Sun filter)	Lipid (PC, HPC or IWL):Sun filter (5 and 2.5%, respectively)	Thin film hydration method	To determine the effects of various liposomes with different lipids on the skin penetration of a lipophilic sun filter, both in vitro and in vivo	Particle size for PC, HPC and IWL liposomes were 278, 339 and 221 nm, respectively PC, HPC and IWL liposomes showed a PDI of 0.21, 0.69 and 0.50, respectively	The in vitro percutaneous absorption in pig skin (after 16 h exposure) obtained from PC, HPC and IWL liposomes was 5.15, 1.21 and 2.09 μg/cm^2, respectively, compared with 1.85 μg/cm^2 for conventional O/W emulsion In vivo distribution of the sun filter in human stratum corneum (after 30 min exposure) from PC, HPC and IWL liposomes was 12.86, 4.07 and 6.26% of the applied dose compared with 4.43% for O/W emulsion	Ramon et al. (2005)

Table 1 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Indomethacin	DPPC:CH (9:1 molar ratio)	Extrusion method followed by incorporation into hydrogels	To investigate the in vivo anti-inflammatory effects of indomethacin-loaded liposomal gel formulation applied topically	Mean diameter of LUVs was 200 nm and PDI was 0.03 LUVs showed a drug E.E of 84%	Indomethacin-loaded liposomal gel formulation exhibited prolonged in vivo anti-inflammatory activity in healthy human volunteers compared to plain indomethacin gel formulation	Puglia et al. (2004)
5-Aminolevulinic acid	5-Aminolevulinic acid to lipid ratio was 1:3 (w/w). Lipid was a mixture consisting of ceramide (50%), cholesterol (28%), palmitic acid (17%) and cholesteryl sulfate (5%, w/w)	Reverse phase evaporation technique	To study the skin permeation and retention of 5-aminolevulinic acid from liposomes based on stratum corneum lipids and to optimize its skin delivery in photodynamic therapy	Particle size and PDI of drug loaded liposomes was 400 nm and 0.570, respectively Drug encapsulation efficiency was 5.7%	The amount of 5-aminolevulinic acid permeated across full thickness hairless mouse skin after 36 h from liposomes (500.9 µg) was lower compared to that of aqueous solution (3681.0 µg) 5-Aminolevulinic acid liposomes showed significantly higher skin retention in the stratum corneum removed epidermis and dermis layers in comparison to its aqueous solution	Pierre et al. (2001)
Vitamin E	Phospholipid:CH:vitamin E (50:6:12, mg). Phospholipid used was Phospholipon 80N	Ethanol injection method	To improve the topical delivery of vitamin E by its encapsulation in liposomes and subsequent loading into Carbopol 980NF gel (0.3%, w/w)	Optimized vitamin E loaded liposomes showed particle size, PDI and Z.P of 136 nm, 0.211 and − 35 mV, respectively E.E was found to be 100%	The optimized liposome formulation showed a significantly higher amount of vitamin E deposited (13.31 µg/cm^2) in rat skin after 24 h compared with that from aqueous dispersion of vitamin E (6.91 µg/cm^2) Vitamin E-loaded liposomal (5.54 µg/cm^2) gel demonstrated 12- and fivefold higher drug deposition compared to vitamin E plain gel (0.44 µg/cm^2) and marketed cream (1.15 µg/cm^2), respectively	Padamwar and Pokharkar (2006)

Table 1 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Benzoyl peroxide	Benzoyl peroxide:EPC:CH (1:6.38:0.63, molar ratio)	Lipid film hydration technique	To study the effects of benzoyl peroxide-loaded liposomal gel on local irritation and clinical efficacy in the treatment of acne	The optimized liposomal formulation of benzoyl peroxide showed a particle size and E.E of 2.52 µm and 76%, respectively	Clinical efficacy study in acne patients showed that liposomal benzoyl peroxide gel resulted in twofold reductions in the number of skin lesions compared to the patients treated with plain benzoyl peroxide gel Liposomal benzoyl peroxide gel demonstrated less irritation compared to non-liposomal gel	Patel et al. (2001)
Acyclovir palmitate	The optimized liposomes had a composition of bovine brain ceramide:CH:cholesteryl sulfate: palmitic acid (4:2.5:2.5:1, w/w) Total lipid concentration was 20 mg/ml with 0.5% (w/v) acyclovir palmitate	Modified reverse phase evaporation technique	To study the in vitro skin permeation of acyclovir palmitate from various liposomal formulations through hairless rat skin	Particle size, PDI and Z.P of various liposome formulations were found to be in between 570 and 620 nm, 0.18–0.20 and 49–85 mV	Liposome formulations with different compositions displayed superior skin permeation profiles compared to ointment formulation Liposome prepared from skin lipids showed the highest cumulative amount of acyclovir palmitate permeated after 48 h (4.93%), flux (4.47 µg/cm^2/h) and intradermal retention (1.67%) compared to that of ointment (1.67%, 0.37 µg/cm^2/h and 0.20%), respectively	Liu et al. (2004)

EPC egg yolk phosphatidylcholine, *DOTAP* 1,2-dioleoyl-3-trimethylammonium propane, *SPC* soybean phosphatidylcholine, *CH* cholesterol, *E.E* entrapment efficiency, *LUVs* large unilamellar vesicles, *MLVs* multilamellar vesicles, *PC* phosphatidylcholine, *HPC* hydrogenated phosphatidylcholine, *IWL* internal wool lipid, *PDI* polydispersity index, *Z.P* zeta potential, *DPPC* dipalmitoyl-L-α-phosphatidylcholine

Table 2 Applications of deformable liposomes to drug delivery through skin

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Pentoxifylline	The composition of the optimized formulation was pentoxifylline:phospholipon 90G:SC (100:800:150, mg)	Modified vortexing–sonication method	To develop pentoxifylline-loaded transfersomes for improved transdermal delivery	The optimized formulation exhibited a mean vesicle size of 690 nm, PDI of 0.11, Z.P of −34.9 and E.E of 74.9% Vesicle elasticity was found to be 145 mg/s/cm^2	Permeation flux from the optimized formulation across rat skin (56.28 µg/cm^2/h) was enhanced by 9.1-fold compared with 1 mg/mL pentoxifylline aqueous solution used as the control (6.2 µg/cm^2/h) Cumulative permeation after 12 h from transfersomes was 599 µg/cm^2 in comparison to 70.7 µg/cm^2 exhibited by the control In vivo pharmacokinetics study in male volunteers demonstrated that transfersomes increased drug absorption and prolonged its half-life compared to the commercial oral sustained release SR tablets (Trental™, 400 mg)	Shuwaili et al. (2016)
Diclofenac	Drug:SPC in proprietary lotion like formulation (Transfenac) containing transfersomes was between 1/4 and 1/9	Sonication and extrusion method	To formulate diclofenac-loaded transfersomes and compare its pharmacokinetics and biodistribution in mice, rats and pigs with commercially available hydrogel	Particle size of transfersomes was between 100 and 200 nm	Transfersomal lotion based product (Transfenac) was superior to the best available topical hydrogel formulation of diclofenac Within a reasonable dose range in mice, Transfenac was at least 5 times more potent and significantly more site-specific than the competing topical diclofenac formulations	Cevc and Blume (2001)

Table 2 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Diclofenac	Diclofenac:SPC:SC (100:440:150, w/w) with 10% ethanol	Lipid film hydration followed by sonication	To investigate the potential of deformable lecithin vesicles for topical delivery of diclofenac	Mean size of the optimized vesicles was 77.2 nm Z.P was found to be − 52.8 mV	The optimized deformable vesicles exhibited enhanced permeation across human epidermis with a cumulative amount of diclofenac permeated and flux after 18 h reaching 69.7 µg and 4.77 µg/cm^2/h, respectively In comparison to deformable lecithin vesicles, various commercially available topical formulations of diclofenac showed cumulative permeation and flux ranges from 2.46 to 29.9 µg and 0.53 to 3.61 µg/cm^2/h, respectively	Boinpally et al. (2003)
Melatonin	SPC:SDC (86:14, %w/w) with 1% w/w melatonin	Modified extrusion method	To develop elastic liposomes of melatonin for efficient transdermal delivery	Mean particle diameter, PDI and E.E of elastic liposomes was 118 nm, 0.035 and 67.1%, respectively Deformability index of elastic liposomes was 63.2 in comparison to 6.4 of conventional liposomes	Transdermal flux exhibited by elastic liposomes (51.2 µg/cm^2/h) across human cadaver skin was 4.7- and 12.2-times higher than those of conventional liposomes (10.9 µg/cm^2/h) and plain drug solution (4.2 µg/cm^2/h), respectively Elastic liposomes showed lower lag time (1.1 h) compared to conventional liposomes (2.7 h) and drug solution (2.9 h) Drug deposition from elastic vesicles was also increased (9.14%) compared to liposomes (4.12%) and drug solution (2.19%)	Dubey et al. (2006)

Table 2 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Retinol	EPC (15 µmol) and retinol (2 µmol) dispersed in 0.5 mL buffer containing 0.25% Tween 20 as the edge activator	Thin film hydration followed by extrusion method	To formulate Tween 20-based deformable liposomes for efficient transdermal delivery of retinol	Tween 20-based deformable liposomes showed a particle size of 97.5 nm Tween 20-based liposomes were 8.45 times more deformable than conventional liposomes	Permeation of retinol across human cadaver skin and a keratinocyte model was significantly enhanced with deformable liposomes compared to neutral and negatively charged conventional liposomes	Oh et al. (2006)
Griseofulvin	Phospholipon 90G:Span 85:griseofulvin (150:26.4:10, mg)	Thin film hydration method	To encapsulate griseofulvin in deformable liposomes for dermal delivery to treat fungal infections	The optimized deformable liposomes showed vesicle size, PDI, Z.P and E.E of 284.6 nm, 0.295, − 22 mV and 63.44%, respectively After passing through the polycarbonate membrane, deformable liposomes showed a smaller change (17%) in their initial size compared to conventional liposomes with a 58% decrease in vesicle size, indicating relative elasticity of deformable liposomes	Deformable liposomes exhibited a higher permeation rate (18.64 µg/cm^2/h) across mice skin compared to conventional liposomes (13.41 µg/cm^2/h), conventional cream base (4.35 µg/cm^2/h) and aqueous suspension of griseofulvin (2.37 µg/cm^2/h) Skin deposition after 24 h was also higher from deformable liposomes (37.1 µg/cm^2) compared to conventional liposomes (16.2 µg/cm^2), conventional cream base (11.1 µg/cm^2) and aqueous suspension (0.74 µg/cm^2) Deformable liposomes exhibited higher in vitro antifungal efficacy than conventional liposomes against different fungal strains Deformable liposomes successfully treated fungal infection after 10 days in infected guinea pigs	Aggarwal and Goindi (2012)

Table 2 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Triamcinolone acetonide	SPC:Tween 80 (11:9, w/w) with 0.005–0.5% of drug per mL of vesicle suspension	Sonication and homogenization method	To develop a novel formulation of triamcinolone acetonide transfersomes for transdermal delivery	Particle size of transfersomes was between 100 and 200 nm	Prolonged anti-inflammatory activity of triamcinolone acetonide was achieved with skin delivery of transfersomes in comparison to commercial cream and ointment Transfersomes resulted in a reduced dose of triamcinolone acetonide (0.2 µg/cm^2) to suppress 75% of murine ear edema for 48 h compared to the dose of conventional formulation (2 µg/cm^2) required to produce similar biological activity	Cevc and Blume (2003)
Betamethasone	SPC:SDC (87:13, %w/w)	Film hydration method	To investigate the potential of betamethasone-cyclodextrin inclusion complex loaded in deformable liposomes for topical delivery	Mean particle diameter was between 206 and 280 nm, and PDI was less than 0.2 Deformable vesicles showed increased deformation as their microviscosity was decreased (169.2 mPa s) compared to classical liposomes (206 mPa s)	Cyclodextrin complexes increased the aqueous solubility of betamethasone and thereby its encapsulation in deformable liposomes Deformable liposomes containing SDC as the edge activator increased the drug's encapsulation efficiency by 1.8 times and in vitro permeation across 50 nm pore size polycarbonate membrane by 1.3 times compared to their conventional, non-deformable liposomes	Gillet et al. (2009)

Table 2 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Cyclosporin A	Soy lecithin:cyclosporine A (7.5:3.75, %w/w) SC to lecithin weight ratio was fixed at 0.28	Thin film hydration and sonication method	To formulate flexible vesicular carriers of cyclosporin A for transdermal delivery	Flexible lecithin vesicles showed a particle size of 61.8 nm and PDI of 50.6%	Flexible vesicle transported 1.88 µg/cm^2 of drug across mice skin after 24 h, while conventional vesicles and SC micelles could not deliver a detectable amount of drug in to the receptor chamber Flexible vesicles deposited a higher amount of cyclosporin A (1.78 µg/cm^2) in mice skin after 24 h compared to conventional liposomes (0.72 µg/cm^2) and SC micelles (0.15 µg/cm^2) In vivo studies in mice showed that flexible vesicles were able to achieve a serum drug concentration of 154 ng/mL after 6 h of application in normal skin and 364 ng/mL after 4 h in stratum corneum destroyed skin, while conventional vesicles could not transport a detectable amount into the serum	Guo et al. Guo et al. (2000)

Table 2 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Propranolol HCl	SPC:Span 80 (85:15, %w/w) with final lipid and drug concentrations of 5% and 0.4% (w/v) in all UDLs formulations	Conventional rotary evaporation method	To investigate propranolol HCl-entrapped UDLs for enhanced transdermal delivery	Mean vesicle size, PDI and E.E of optimal UDLs were 128 nm, 0.047 and 60.2% UDLs showed a deformability index of 51.2 compared to 6.4 of classical liposomes	Propranolol HCl-entrapped UDLs showed higher transdermal flux (16.2 μg/cm^2/h) across human cadaver skin, lower lag time (0.7 h) and greater skin deposition after 24 h (11.4%) compared to conventional liposomes (3.2 μg/cm^2/h, 2.4 h and 6.6%) and plain drug solution (1.82 μg/cm^2/h, 2.6 h and 3.84%), respectively In vivo pharmacokinetics study in rats showed that C_{max} and AUC exhibited by UDLs after application to the skin was higher (92 ng/mL and 1659 ng h/mL) than those of conventional liposomes (35 ng/mL and 579 ng h/mL) and plain drug solution (25 ng/mL and 315 ng h/mL), respectively	Mishra et al. (2007)
Methotrexate	EPC:Tween 80:methotrexate (7:3:1.5, mg/mL)	Extrusion method	To prepare and optimize methotrexate-entrapped UDLs for potential transdermal delivery as possible rheumatoid arthritis therapeutics	The optimal UDLs had a mean diameter, PDI, Z.P and E.E of 87.7 nm, 0.048, −14.7 mV and 34.5%, respectively Deformability index of the optimized UDLs was 81.2 compared to 15.8 of conventional liposomes	The cumulative permeation after 24 h across rat skin was significantly increased by UDLS (470 μg) compared to methotrexate-loaded conventional vesicles (192 μg) and free methotrexate solution (81 μg) Steady-state flux exhibited by methotrexate UDLs was 2.3- and 5.2-times higher than those of conventional liposomes and free drug solution, respectively UDLs showed lower lag time than conventional liposomes and drug solution	Zeb et al. (2016)

Table 2 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Methotrexate	EPC:Tween 80:methotrexate (7:3:1.5, mg/mL) followed by incorporation into 1% Carbopol gel	Extrusion method	To study the in vivo anti-rheumatic activity of methotrexate-entrapped UDLs incorporated gel	UDLs incorporated gel showed drug content of 99%, neutral pH and non-Newtonian flow behavior	Ultra deformable liposomal gel of methotrexate significantly reduced edema volume (0.56 mL) after 36 days in arthritis rat model compared to gels incorporated with conventional liposomes (1 mL) and plain drug (1.03 mL) Methotrexate-UDLs gel exhibited enhanced anti-inflammatory and anti-rheumatic effects indicated by a substantial reduction in paw edema level, leukocytes infiltration, neutrophil count and expression levels of inflammatory cytokines compared to other treatment groups	Zeb et al. (2017b)
Paclitaxel	PC:Span 80 (85:15, %w/w) with lipid contents of 50 mg/mL and paclitaxel concentration of 6 mg/mL of vesicular suspension	Rotary evaporation sonication method	To investigate elastic liposomes of paclitaxel for localized delivery	Mean particle size of optimal elastic vesicles was 168 nm, PDI was 0.036, and E.E of 73.5% Elasticity index of the optimized vesicles was 58.2 compared to 2.1 of conventional liposomes	Elastic liposomes demonstrated an enhanced permeation rate of 5.2 and 10.8-times across rat skin in comparison to conventional liposomes and drug solution, respectively Skin deposition by elastic liposomes was also increased 5.31 and 15-times, respectively, compared to conventional liposomes and drug solution Toxicity studies indicated that elastic liposomes were less toxic as it caused only 11.2% hemolysis compared to 38% caused by commercial formulation	Utreja et al. (2011)

SC sodium cholate, *PDI* polydispersity index, *Z.P* zeta potential, *E.E* entrapment efficiency, *SPC* soy phosphatidylcholine, *SDC* sodium deoxycholate, *EPC* egg yolk phosphatidylcholine, *UDLs* ultradeformable liposomes, *PC* phosphatidylcholine

Table 3 Summary of studies investigating the potential of ethosomes for skin drug delivery

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Methotrexate	SPC (3%, w/v), methotrexate (1%, w/v) and ethanol (45%, v/v)	Mechanical dispersion method	To evaluate the potential of methotrexate-loaded ethosomes for transdermal delivery	Ethosomes showed a mean particle diameter of 143 nm, PDI of 0.097 and E.E of 68.7%	Transdermal flux across human cadaver skin from methotrexate-loaded ethosomes was increased to 57.2 μg/cm^2/h compared with conventional liposomes (14.6 μg/cm^2/h), 45% hydroethanolic solution (22.4 μg/cm^2/h) and aqueous dispersion (2.2 μg/cm^2/h), respectively Ethosomes decreased the lag time (0.9 h) by 2.78-, 1.55- and 3.22-times, respectively against conventional liposomes, hydroethanolic solution, and aqueous dispersion Methotrexate skin deposition was also increased by ethosomes (31.2%) than conventional liposomes (8.1%), hydroethanolic solution (6.4%) and aqueous dispersion (2.2%)	Dubey et al. (2007a)
Trihexyphenidyl HCl	SPC (2%, w/w), trihexyphenidyl HCl (1%, w/w) and ethanol (30%, w/w)	Classical mixing method	To compare the transdermal permeation of trihexyphenidyl HCl-loaded ethosomes with that of conventional liposomes	Optimal ethosomes had a mean particle size of 109 nm, Z.P of 7.2 mV and E.E of 75%	Transdermal flux from ethosomes (212 μg/cm^2/h) across mouse skin was increased 87-, 51- and 4.5-times compared to classical liposomes, phosphate buffer and 30% hydroethanolic solution of trihexyphenidyl Quantity of trihexyphenidyl deposited in mouse skin after 18 h was also enhanced from ethosomal vesicles (586 μg/cm^2) than those of classical liposomes (416 μg/cm^2), hydroethanolic solution (415 μg/cm^2) and phosphate buffer(127 μg/cm^2)	Dayan and Touitou (2000)

Table 3 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Melatonin	SPC (2%, w/w), melatonin (1%, w/w) and ethanol (30%, w/w)	Classical mixing method	To investigate the possibility of melatonin-bearing ethosomes for transdermal delivery	Ethosomes showed particle size, PDI, Z.P and E.E of 122 nm, 0.032, 70.7%, respectively	Permeation rate of melatonin through human cadaver skin from ethosomes was increased to 59.2 μg/cm^2/h compared to 22.4 and 10.9 μg/cm^2/h respectively, of 30% hydroethanolic solution and conventional liposomes of melatonin Skin deposition of melatonin from ethosomes was higher (9.46%) than hydroethanolic solution (6.44%) and liposomes (4.12%) Lag time from ethosomes (0.9 h) was reduced by 3- and 2.3-times in comparison to conventional liposomes and hydroethanolic solution	Dubey et al. (2007b)
Psoralen	SPC (5%, w/v), psoralen (2%, w/v) and ethanol (40%, v/v)	Modified injection method	To improve psoralen skin permeation and deposition via ethosomal vesicles	Optimal ethosomes had particle size of 122.7 nm and E.E of 85.6%	Ethosomes improved the permeation flux (38.9 μg/cm^2/h) and deposition (3.6 μg/cm^2) in rat skin compared to tincture (13.5 μg/cm^2/h and 0.55 μg/cm^2) In vivo pharmacokinetics via skin micro-dialysis revealed that ethosomes exhibited 3.37- and 2.34-times higher peak concentration and AUC compared to psoralen tincture	Zhang et al. (2014)

Table 3 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Lamivudine	SPC (2%, w/w), lamivudine (0.4%, w/w) and ethanol (45%, w/w)	Classical mixing method	To investigate the transdermal potential of lamivudine enclosed ethosomes	Optimal ethosomes showed a particle size of 102 nm, Z.P of −8.2 mV and E.E of 57.2% Elasticity index of ethosomes was 38.6 compared to 4.96 of liposomes	Transdermal flux of lamivudine through rat skin from optimal ethosomes (68.4 µg/cm^2/h) was 7.51, 10.52, 13.68 and 24.4-times higher than 2% SPC solution in ethanol, ethanolic solution, 45% hydroethanolic solution and PBS solution of drug, respectively Ethosomes exhibited lower lag time (3.1 h) compared to all other test formulations Cellular uptake of lamivudine in T-lymphoid cell lines from ethosomes (85.7%) was higher than those of drug solution (24.9%), liposomes and marketed product	Jain et al. (2007)
Griseofulvin	SPC (0.5%, w/v), Griseofulvin (0.1%, w/w) and ethanol (45%, v/v)	Classical mixing method	To evaluate ethosomes as a novel delivery system for transdermal delivery of griseofulvin	Optimal ethosomes showed a particle size of 154 nm, Z.P of −26 mV and E.E of 70%	Ethosomes deposited ~40% of the applied dose of griseofulvin (~ 100 µg/cm^2) in stratum corneum of new born pig skin after 24 h with minimal permeation compared to ~5 µg/cm^2 from solution Skin diffusion revealed potential of ethosomes for dermatophytes targeting Ethosomes showed significant in vitro antifungal activity against selected strains	Marto et al. (2016)

Table 3 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Ammonium glycyrrhizinate	Lecithin (2%, w/v), Ammonium glycyrrhizinate (0.3%, w/v) and ethanol (45%, v/v)	Classical mixing method	To investigate ammonium glycyrrhizinate ethosomes for in vitro skin and in vivo anti-inflammatory activity	Mean vesicle size was 109 nm, PDI was 0.109 and E.E was 78.9%	Ethosomes showed the highest cumulative permeation (63.2%) of ammonium glycyrrhizinate through human skin epidermis after 24 h than its aqueous and hydroethanolic solutions Ethosomes displayed good tolerability in human volunteers even after 48 h of application Ethosomes enhanced the in vivo anti-inflammatory activity of ammonium glycyrrhizinate via sustained release of the drug in erythema inhibition studies	(Paolino et al. 2005)
Paclitaxel	Phospholipon 90G (1%, w/v), paclitaxel (0.666 mg/mL) and ethanol (45%, w/v)	Classical mixing method	To assess the potential of paclitaxel-loaded ethosomes for topical delivery to treat squamous cell carcinoma	Paclitaxel-loaded ethosomes showed mean particle size, PDI and E.E of 240 nm, 0.145 and 82%, respectively	Percutaneous flux achieved by ethosomes (8.2 µg/cm^2/h) across human stratum corneum and viable epidermis was ~3.2 and ~23.2-fold higher than the physical mixture of paclitaxel and empty liposomes and its hydroethanolic suspension Amount of paclitaxel deposited by ethosomes in dermis after 24 h was also enhanced (103.5 µg/cm^2) compared to the physical mixture (20.35 µg/cm^2) and hydroethanolic suspension (4.31 µg/cm^2) Enhanced in vitro antiproliferative effect in human squamous carcinoma cells (DMJ1) was observed with paclitaxel-ethosomes compared to free paclitaxel	Paolino et al. (2012)

Table 3 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Rutin	EPC (2%, w/v), rutin (0.03%, w/v) and ethanol (20%, v/v)	Thin film hydration method	To evaluate rutin-loaded ethosomes for enhanced skin delivery	Rutin-loaded ethosomes showed mean vesicle diameter of 190 nm and loading efficiency of 73.8% Ethosomes were found 2.6-times more elastic than conventional liposomes	Cumulative permeation of rutin through mouse skin after 24 h was higher from ethosomes (61.3%) than ethanolic solution (44.2%), liposomes (37.8%) and aqueous solution of rutin (18.3%) Rutin deposition in the stratum corneum after 24 h was also higher from ethosomes (31.2%) compared to ethanolic solution (24.3%), liposomes (23.4%), and aqueous solution of rutin (7.8%)	Park et al. (2014b)

SPC soy phosphatidylcholine, *PDI* polydispersity index, *Z.P* zeta potential, *E.E* entrapment efficiency, *EPC* egg yolk phosphatidylcholine

enhancer and hence facilitating drug permeation via a structurally compromised skin barrier, *vesicles absorption and fusion with the stratum corneum* where the vesicles adsorb onto the stratum corneum thereby transferring their payload directly to the skin or fusing with lipids of the stratum corneum to enhance partitioning of the drug in skin and the *intact vesicle penetration mechanism* where the liposomes penetrate the skin in intact form by compromising its structural integrity (Elsayed et al. 2007).

Factors affecting the skin delivery of conventional liposomes

A number of factors including the liposomal size, surface charge, lamellarity, lipid composition and thermodynamic state of the lipid bilayers have been reported to affect skin drug delivery of conventional liposomes (Elsayed et al. 2007). Kitagawa and Kasamaki (2006) compared the effect of neutral liposomes [egg yolk phosphatidylcholine (egg yolk PC) liposomes] and cationic liposomes [1,2-dioleoyl-3-trimethylammonium propane (DOTAP) liposomes] on the skin delivery of retinoic acid in excised guinea pig skin. Egg yolk PC liposomes were two times more effective in increasing the skin delivery of retinoic acid than its solution in isopropyl myristate. Moreover, cationic DOTAP liposomes were 3.7-fold more effective in the skin delivery of retinoic acid compared with their neutral counterparts without DOTAP. It was concluded from the study that the surface charge of liposomes has an effect on the skin deposition and permeation of drugs. Similarly, Park et al. (2014a) studied the effect of liposome's zeta potential on the skin permeation of resveratrol. The study aimed to investigate enhanced transdermal delivery of resveratrol via chitosan-coated liposomes. The skin permeation of resveratrol from 0.1% chitosan-coated egg PC liposomes (zeta potential + 26.5 mV) was found to be 126.93 µg/cm^2 (40.4%) compared with 96.85 µg/cm^2 (30.8%) with uncoated liposomes (zeta potential − 9.4 mV). The enhanced skin permeation of chitosan-coated liposomes was attributed to the stronger interaction between the negatively charged lipids of the stratum corneum with the positively charged liposomes.

The lipid composition (liquid-state or gel-state phospholipids) of liposomes also affects skin drug delivery. In a study, the influence of the fluidity of phospholipids on the skin permeation of liposomes was investigated (Perez-Cullell et al. 2000). Skin penetration of sodium fluorescein from liposomes prepared with unsaturated phosphatidylcholine (PC) and saturated, hydrogenated phosphatidylcholine (HPC) were compared. The ability of unsaturated PC liposomes to penetrate the skin was observed to be higher than those prepared with HPC due to the existence of PC in a liquid-state at the operating temperature of the study compared with the gel-state of HPC liposomes. The gel-state of

Table 4 Summary of reported studies applying niosomes to skin drug delivery

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Minoxidil	The optimal composition was Span 20 + CH (34.6 mg, 1:1 molar ratio), DCP (8.2 mg) and minoxidil (25 mg)	Thin film hydration method	To investigate the possibility of minoxidil-loaded niosomes for enhanced skin delivery	Optimal niosomes showed a mean particle diameter, PDI, Z.P. and E.E of 214 nm, 0.334, −37.54 mV and ~45%	Niosomes were able to deposit a higher amount (59.4 µg/cm^2) of minoxidil in hairless mouse skin after 24 h than those of 5 mg/mL control solution (3.8 µg/cm^2) and 5% minoxidil marketed formulation (10.3 µg/cm^2)	Balakrishnan et al. (2009)
Ellagic acid	Span 60:Tween 60:CH (500:250:750, µmol), Solulan C24 (5 mol%), ellagic acid (1 mol%) and PEG 400 (15%, v/v)	Reverse phase evaporation method	To develop niosomal vesicles for dermal delivery of ellagic acid	Optimized niosomes showed a mean size of 457 nm, PDI of 0.335 and E.E of 26.75%	Amount of ellagic acid deposited in human skin after 24 h was higher from niosomes (~310 ng/cm^2) than that of ellagic acid solution (~40 ng/cm^2) Permeation of ellagic acid into the receptor compartment from niosomal formulation was also higher (~90 ng/cm^2) than the control solution with no detectable permeation across the skin	Junyaprasert et al. (2012)
Aceclofenac	Span 60:CH (7:4, molar ratio) with 50 mg of aceclofenac	Thin film hydration technique	To evaluate aceclofenac-loaded niosomes for enhanced anti-inflammatory effects via topical delivery	Optimal MLVs niosomes had a mean diameter of 850 nm, Polydispersity/SPAN index of 0.66 and E.E of 31.6% Cumulative release of aceclofenac after 8 h from optimal formulation was 49%	Aceclofenac-loaded niosomes showed sustained and higher anti-inflammatory activity in carrageenan-induced rat paw edema model as indicated by their higher edema inhibition rate (41.4%) after 8 h compared to liposomes (28.6%) and marketed formulation of aceclofenac (9.6%)	Nasr et al. (2008)

Table 4 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
5-Fluorouracil	Bola:Span 80:CH (2:5:2 molar ratio, total amount of mixture was ~44 mg) with 10 mM 5-fluorouracil	Thin layer evaporation and sonication technique	To prepare and evaluate 5-fluorouracil loaded niosomes for topical delivery to treat skin cancer	Mean particle size of niosomes was 229 nm, PDI was 0.102 and loading capacity was 40.7%	Percutaneous permeation of 5-fluorouracil across human stratum corneum and viable epidermis after 24 h was about 8- and 4-times higher for niosomes (468 μg/cm^2) than those of aqueous solution (58 μg/cm^2) and physical mixture of drug and empty niosomes (130 μg/cm^2) 5-fluourouracil loaded niosomes exhibited significantly higher cytotoxicity against human melanoma cells (SKMEL-28) and squamous carcinoma cells (HaCaT) at much lower concentrations than those of free drug solution	Paolino et al. (2008)
Capsaicin	Tween 80:Span 80 (94.32:12, mg) with 0.75% w/v capsaicin	Thin film hydration method	To investigate capsaicin-loaded niosomes as novel carriers for topical delivery	Optimal niosomes exhibited a mean particle diameter of 377 nm, PDI of 0.278 and E.E of 86.7%	Capsaicin-loaded niosomes demonstrated highest cumulative permeation (~45%) across rabbit ear skin after 12 h compared to microemulsion (9%) and hydroethanolic solution of the drug (4%)	Tavano et al. (2011)

Table 4 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Resveratrol, α-tocopherol and curcumin	Tween 60 (100 µmol), resveratrol (1.03 µmol) α-Tocopherol (1 µmol), curcumin (1.03 µmol)	Thin film hydration method	Co-encapsulating antioxidants in niosomes for enhanced antioxidant activity via percutaneous delivery	Mean particle diameter was between 455 and 571 nm and PDI 0.1–0.2	Resveratrol permeation across rabbit ear skin after 12 h was higher from different niosomal formulations (71–93%) than simple drug solution (15%) Curcumin permeation from various niosomal formulations was 19–35% in comparison to 5% from curcumin solution Co-encapsulation of antioxidants played a synergistic role in reducing free radical formation compared with single antioxidant	Tavano et al. (2014)
Salidroside	Span 40:CH (10:7.5 mmol/L, or 4:3 molar ratio), salidroside (2 mg/mL), and SDS (0.1 mg/mL)	Conventional mechanical dispersion method	To assess the cutaneous absorption of salidroside from niosomes	Optimal niosomes exhibited a mean particle size of 233 nm, Z.P of −45.3 mV and E.E of 33.74%	Transdermal flux and skin deposition of salidroside in rat skin from optimal niosomes was about 2.3- and 2-times higher, respectively than that of salidroside aqueous solution Niosomes showed a good safety profile for 7 days of application with no signs of edema or erythema	Zhang et al. (2015)

CH cholesterol, *DCP* dicetyl phosphate, *PDI* polydispersity index, *Z.P* zeta potential, *E.E* entrapment efficiency, *PEG 400* polyethylene glycol 400, *MLVs* multilamellar vesicles, *SDS* sodium dodecyl sulfate

Table 5 Applications of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) for improving skin drug delivery

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Isotretinoin	Precirol ATO 5:soy lecithin:Tween 80:isotretinoin (3:4:4.5:0.06, %w/w)	Hot homogenization method	To develop isotretinoin-loaded SLNs for targeted skin delivery	Isotretinoin-loaded SLNs showed a particle size of 42.7 nm, PDI of 0.258, Z.P of −13.73 mV and E.E of 82.62%	Optimized SLNs formulation showed enhanced skin targeting with 30% more uptake of isotretinoin in skin than that of 0.06% tincture used as control SLNs can avoid systemic uptake of isotretinoin as no drug from SLNs was detectable in the receptor medium	Liu et al. (2007)
Quercetin	Palmitic acid:Tween 80:quercetin (5:2:0.5, %w/v)	Homogenization and ultra-centrifugation method	To assess the potential of SLNs for transdermal delivery of quercetin	Mean particle diameter of optimized SLNs was 274 nm, Z.P was −31.3 mV and E.E was 46.2%	Amount of quercetin permeated across dorsal skin of mice after 24 h was higher from SLNs (29.4 μg/cm^2) than quercetin solution in propylene glycol (1.5 μg/cm^2)	Han et al. (2014)
Flurbiprofen	Stearic acid:coconut oil:soy lecithin:flurbiprofen (300:200:100:50, mg) per 10 mL of dispersion	Emulsification-homogenization and sonication method	To evaluate the potential of flurbiprofen-loaded NLCs for transdermal delivery	Mean particle size of optimized NLCs was 214 nm, PDI was 0.225, Z.P was −30.7 mV and E.E was 92.58%	In vitro skin permeation studies across full-thickness albino wistar rat skin revealed a rapid released of drug from NLCs in the first 2 h followed by prolonged release of drug for 24 h compared to commercial gel with 100% permeation in the first 6 h In vivo pharmacokinetic studies indicated about 1.7–times higher bioavailability from NLCs compared to commercial gel with prolonged and controlled drug delivery (higher t_{max} and higher elimination rate constant) In vivo anti-inflammatory studies in carrageenan-induced rat paw edema model showed that NLCs achieved a quick onset and maintained edema inhibition of 23% after 24 h, indicating a sustained anti-inflammatory effect compared to commercial gel	Kawadkar et al. (2013)
Avanafil	Compritol ATO:castor oil:CH:Tween 80 (6.36:46.82:0.83:7.64, %w/v) with 200 mg of avanafil	Homogenization and ultrasonication technique	To formulate avanafil-loaded SLNs with subsequent loading into hydrogel films for transdermal delivery	Mean particle size was 86 nm and E.E was 85%	Avanafil-SLNs loaded into HPMC films exhibited higher cumulative drug permeation (327.39 μg, 65.48%) and flux (4.5 μg/cm^2/h) across rat skin after 24 h compared to avanafil plain HMPC hydrogel film (72.5 μg, 14.5% and 0.85 μg/cm^2/h)	Kurakula et al. (2016)

Table 5 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
Triptolide	Tristearin glyceride:soy lecithin:PEG 400 monostrearate (5:1.2:3.6, %w/w)	Emulsification and sonication method	To formulate triptolide-loaded SLNs for transdermal drug delivery	Optimal SLNs showed particle size, PDI, Z.P of 123 nm, 0.19 and −45 mV, respectively	Permeation flux of triptolide across full-thickness abdominal rat skin was higher from SLNs (3.1 μg/cm^2/h) than triptolide solution (0.9 μg/cm^2/h) SLNs showed enhanced suppression of carrageenan-induced inflammation as indicated by higher edema inhibition rate (45.9%) after 6 h compared to triptolide solution (13.1%), microemulsion formulation (24.3%) and commercial diclofenac emulgel (28.6%)	Mei et al. (2003)
Idebenone	Cetyl palmitate:glyceryl oleate:Brij 58:idebenone (7:3.7:7.5:1.1, %w/w)	Phase inversion temperature method	To assess the feasibility of idebenone-loaded SLNs for targeting upper skin layers via topical delivery	Optimal SLNs showed a mean particle size of 33.3% and PDI of 0.140	Application of idebenone-loaded SLNs with optimal composition on excited newborn pig skin resulted in threefold higher drug content in the stratum corneum than in theepidermis, indicating targeting of SLNs to the upper skin layers	Montenegro et al. (2012)
Doxorubicin	Precirol ATO (2 g), poloxamer 407 (3%) and doxorubicin (20 mg)	Hot homogenization method	To investigate the potential of doxorubicin-loaded SLNs for topical delivery to treat skin cancer	Mean particle diameter of the optimized SLNs was 92 nm and E.E was 86%	In vitro cytotoxicity in melanoma cell lines showed enhanced permeability and a sufficient decrease in the viability of tumor cells at varying concentrations of doxorubicin-SLNs Topically applied doxorubicin-SLNs resulted a significant reduction in tumor volume after 40 days compared to free doxorubicin in the in vivo antitumor study conducted in mice	Tupal et al. (2016)

Table 5 (continued)

Drug	Composition	Preparation method	Purpose of investigation	Physicochemical characteristics	Key findings	References
5-Fluorouracil	Stearic acid (100 mg), lecithin (25 mg), poloxamer 188 (1.6% w/v) and 5-fluorouracil (10 mg)	Hot homogenization method	To develop 5-fluorouracil-loaded SLNs to target tumor cells in skin carcinoma via topical delivery	Optimal SLNs showed a mean particle size of 137 nm, PDI of 0.110, Z.P of − 19.7 mV and E.E of 40.8%	Optimal SLNs exhibited higher cumulative permeation (269 μg/cm^2) and lower lag time (26 min) through cellulose nitrate membrane after 24 h compared to free drug solution (122 μg/cm^2 and 80 min) SLNs incorporated into NaCMC gel showed superior permeation compared to that of plain drug in NaCMC gel 5-fluorouracil-SLNs incorporated into NaCMC gel showed a significant reduction in inflammatory reaction, degree of keratosis and symptoms of angiogenesis in comparison to plain 5-fluorouracil NaCMC gel in in vivo carcinoma-bearing mice model	Khallaf et al. (2016)

SLNs solid lipid nanoparticles, *NLCs* nanostructured lipid carriers, *PDI* polydispersity index, *Z.P* zeta potential, *E.E* entrapment efficiency, *CH* cholesterol, *PEG 400* polyethylene glycol 400

phospholipids in the vesicles render them rigid and reduce their penetrability across the skin. In another study, Sinico et al. (2005) reported that unilamellar vesicles (ULVs) resulted in a higher amount of tretinoin deposited in a newborn pig skin after 9 h than those of multilamellar vesicles (MLVs) in both positive (23.5 vs. 13.5 μg) and negatively charged vesicles (32.7 vs. 30.4 μg).

Deformable liposomes

Deformable liposomes were introduced for the first time in 1992 and were designed to improve the skin permeation of drug-loaded lipid vesicles across skin (Cevc and Blume 1992). This newer class of liposomes was firstly named Transfersomes® and is a proprietary technology of the Germany-based company, IDEA AG. Later on, the terms ultradeformable, elastic and ultraflexible liposomes emerged to represent these vesicles. This is a newer domain of liposomes with properties of pliability or deformability due to the presence of surfactant or "edge activator" along with double chain phospholipids (Fig. 2b), which makes them different from conventional liposomes in terms of composition (El Maghraby et al. 1999; Trotta et al. 2004). Deformable liposomes have the ability to preserve their structural integrity during passage through the tightest junctions of skin and carry their payload into systemic circulation. The function of the edge activator in deformable liposomes is to destabilize the lipid bilayer thereby increasing the deformability of the vesicle and enhancing their penetration through the skin (Gillet et al. 2011). The usual composition of deformable liposomes consists of phospholipid (70–95%) and edge activator (5–30%) such as the bile salts of cholic acids, Tweens, Spans, and dipotassium glycyrrhizinate (Benson 2006). For effective skin permeation, deformable liposomes are applied under non-occlusive conditions on the skin. Increased in vitro skin delivery and in vivo penetration is reported for a number of drugs utilizing deformable liposomes as they are capable of permeating through skin as intact vesicles (Cevc et al. 2002).

Deformable liposomes for skin delivery and the mechanisms of permeation

Deformable liposomes have the ability to squeeze themselves through pores much smaller than their own diameter. This unique capability is attributed to their inherent property of deforming and adapting their shape under stressful conditions such as increased pressure or a dry surface, thereby reaching the deeper skin unfragmented (Cevc et al. 2002). Application of deformable liposomes on a skin surface under non-occlusive condition provides them with the opportunity to follow an osmotic gradient between a relatively dry stratum corneum and hydrated viable epidermis

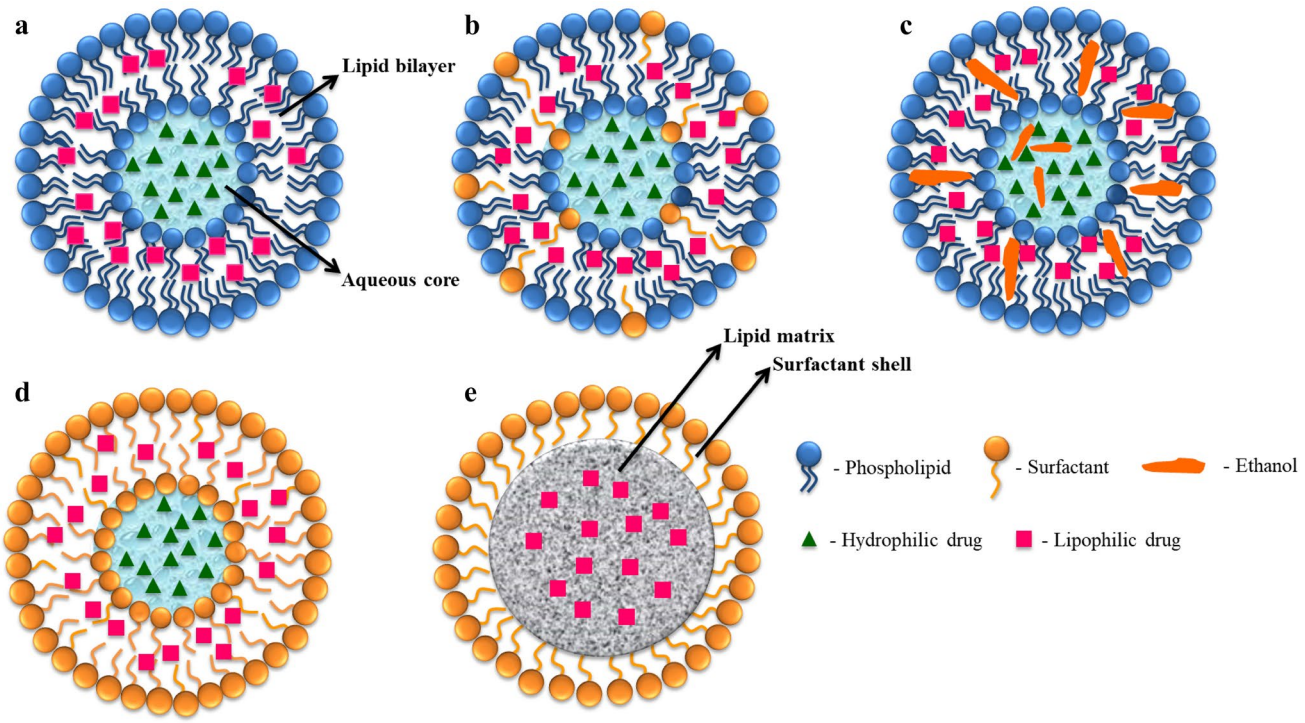

Fig. 2 Structure of **a** conventional liposomes, **b** deformable liposomes, **c** ethosomes, **d** niosomes and **e** lipid nanoparticles

(Cevc and Blume 1992). An occlusive application eliminates the deformable action by disrupting the osmotic gradient and hence demolishing the driving force to transport these vesicles across the skin. Contrary to deformable liposomes, rigid phospholipid bilayers of conventional liposomes confine them to the upper skin layer with diminished skin permeation (El Maghraby et al. 2008). Deformability and shape transformation in deformable liposomes are due to the incorporation of the edge activator, which causes local readjustments of the components of the lipid bilayer (Fig. 3). Exposure of deformable liposomes to space confinement or mechanical stress results in repositioning of the edge activator in zones of higher curvature and phospholipids in zones of smaller curvature. This repositioning brings about a reduction in the elastic energy of the lipid bilayers of vesicles and allows deformable liposomes to transform their shapes at much lower energy (Cevc 2012; Perez et al. 2016). Furthermore, it has also been proposed that deformable liposomes interact with the intercellular lipids of the stratum corneum to destabilize them and thereby produce a permeation enhancement effect (Elsayed et al. 2006). Combined together, deformable liposomes have enhanced the skin permeation of a number of drugs, irrespective of the mechanism of transport across skin.

Factors affecting the skin delivery of deformable liposomes

Factors that can influence the skin permeation of deformable liposomes include the type and amount of edge activator, fluidity and particle size. It has been reported that an increase in the concentration of the edge activator up to 15% resulted in an increase in the elasticity of the vesicles, while a further increase in concentration decreased the flexibility due to the formation of less deformable micellar structures along with the bilayer vesicles (Chaudhary et al. 2013). Similarly, the type of edge activator also has an influence on the skin permeation of deformable liposomes. Tween 80-incorporated deformable liposomes exhibited higher cumulative permeation and flux (470 μg and 20.2 μg/cm^2/h) after 24 h than those of deformable liposomes containing sodium cholate (406 μg and 17.4 μg/cm^2/h) as an edge activator (Zeb et al. 2016). The difference in the permeation profiles was attributed to their chemical structures, which in turn affect the deformability indices of deformable liposomes and permeation across skin. Verma et al. (2003) investigated the effect of particle size of deformable liposomes on the penetration of a hydrophilic dye (carboxyfluorescein, CF) into and across human skin. Smaller vesicles with a particle size of 120 nm resulted in a higher amount of CF accumulated in the stratum corneum (72.9%) than those with larger vesicles of 191 nm (65.2%), 377 nm (61.2%) and 810 nm (39.9%). The amount of CF accumulated by the smaller vesicles

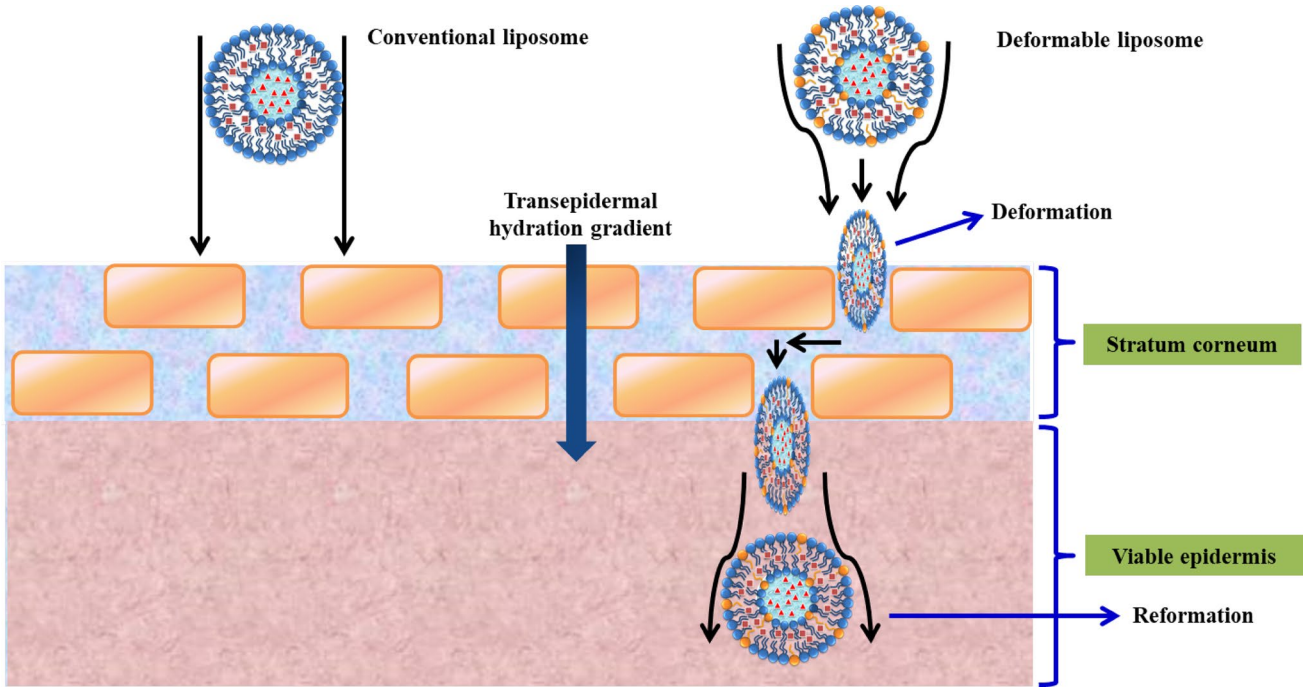

Fig. 3 Mechanism of deformable liposomes permeation through the skin

(120 nm) in the deeper layers was also enhanced by 4.68-, 7.29- and 33.57-fold compared with larger vesicles (191, 377 and 810 nm), respectively. The amount of CF permeated across the skin into the receptor fluid exhibited a similar trend. Particle size had similar effect on the penetration of a lipophilic dye in the same study. In another study, liposomal fluidity was reported to have an increasing effect on the skin penetration of entrapped dye (Subongkot and Ngawhirunpat 2015).

Ethosomes

Ethosomes are fluidic lipid vesicles containing a higher concentration of ethanol with the potential for transdermal drug delivery (Touitou et al. 2000a). Ethosomes were first introduced by Touitou and coworkers for enhancing skin delivery of drugs and are composed of 2–5% phospholipid, 20–45% ethanol and water up to 100% (Touitou 1996). The structure of ethosome is illustrated in Fig. 2c. The incorporation of ethanol makes them soft and pliable colloidal carriers with unilamellar or multilamellar structure and concentric phospholipid bilayers surrounding an aqueous phase and entrapped drugs (Mbah et al. 2014). The function of ethanol is to impart membrane flexibility to ethosomes as that of the edge activator in deformable liposomes and confers 10-times more flexibility by fluidizing their lipid bilayers (Godin and Touitou 2003). It has been proposed that phospholipids form closed bilayer vesicles in up to 45% of ethanol; however, concentrations above 45% may solubilize the phospholipid contents (Romero and Morilla 2013). Ethosomal vesicles have a particle size much smaller than conventional liposomes and the presence of high ethanol contents makes their size independent of phospholipid concentration. It was reported that the particle size of ethosomes decreased from 193 to 103 nm as the concentration of ethanol was increased from 20 to 45%. In contrast, the increase in phospholipid concentration from 0.5 to 4% (eight-fold increase) increased the particle size from 118 to 249 nm (only two-fold), indicating the limited dependence of particle size on phospholipid concentration (Touitou et al. 2000a). In another study, increasing phospholipid concentration from 1 to 3% (w/v) at 45% (v/v) ethanol content brought about a very small increase in particle size from 111 to 143 nm (Dubey et al. 2007a). The smaller particle diameter of the ethosomal vesicles is due to the presence of a high quantity of ethanol with a resultant negative zeta potential (Lopez-Pinto et al. 2005). Ethosomes have been shown to increase the delivery of a number of hydrophilic and hydrophobic drugs into deeper layers of skin and to systemic circulation compared to conventional liposomes, ethanol, hydro-ethanolic solution and ethanolic phospholipid solution. In contrary to deformable liposomes, ethosomes can be applied occlusively in the form of patches where particle size and its distribution remains constant for up to 2 years (Touitou et al. 2000b).

Ethosomes for skin delivery and the mechanisms of permeation

Ethosomes possess malleable and less tightly packed phospholipid bilayer membranes due to the presence of ethanol and have superior skin permeation compared to conventional liposomes. The enhanced drug delivery via ethosomes is attributed to the cumulative effects of vesicles pliability, the fluidization effect of ethanol on stratum corneum lipids and vesicle membranes, a smaller vesicle diameter and the facilitated interaction of ethosomal vesicles with stratum corneum components (Touitou et al. 2000a). Ethanol has been used as an effective skin permeation enhancer to disrupt lipid organization in the stratum corneum and extract its lipidic layers with a subsequent reduction in lipid density and the skin's impermeability towards the permeants (Barry 2001). The fluidization of lipid bilayers in the stratum corneum by ethanol makes it easy for small and malleable ethosomes to penetrate into the deeper skin layers (Mbah et al. 2014). In comparison to the structural adaptability mechanism of deformable liposomes, ethosomes mainly enhance drug permeation by interacting and disrupting the lipophilic barrier of skin (Van der Merwe and Riviere 2005). The capability of ethosomes to transport their payload to and through the skin has been widely investigated and found to be much greater than conventional liposomes, which remained in the upper layers of skin (Touitou et al. 2001).

Factors affecting the skin delivery of ethosomes

The skin permeation capacity of ethosomes is governed by ethanol concentration, vesicular size, phospholipid and cholesterol content. Ethanol binds to the polar heads of lipids thereby lowering the melting point of lipids in the stratum corneum and enhancing membrane fluidity and penetrability (Harris et al. 1987). On increasing ethanol concentration from 15 to 45%, the vesicular elasticity and skin permeation flux of drugs from ethosomes was reported to be increased from 20.3 to 38.6 and 24.8 to 68.4 μg/cm^2/h, respectively (Jain et al. 2007). The increased skin permeation of drug was ascribed to a significantly reduced particle size at 45% ethanol content and higher membrane elasticity compared to ethosomes with 15% ethanol. However, the transdermal flux was reduced to 12.5 μg/cm^2/h with a further increase in ethanol to 60% due to membrane solubilizing and the deteriorating effects of ethanol at higher concentrations. The addition of cholesterol in the lipid bilayers of ethosomes increases membrane rigidity and particle size, resulting in low deformability and skin permeation (Jain et al. 2007; Lopez-Pinto et al. 2005). In another study, variation in the amount of phospholipid did not show any significantly effect on the transdermal flux of ketoprofen (Chourasia et al. 2011). Transdermal flux was reduced from 207 to 192 μg/cm^2/h by increasing phospholipid concentration from 1 to 3%, indicating a non-significant influence. Taking these factors together, the overall composition of ethosomes contributes to the interaction of these vesicles with stratum corneum lipids and transport into and across the skin with ethanol being the most influential factor (Dayan and Touitou 2000).

Niosomes

Niosomes are nanosized colloidal vesicular structures formed by the self-assembly of non-ionic surfactants in an aqueous environment resulting in a bilayer configuration (Uchegbu and Vyas 1998). Non-ionic surfactants form a bilayer configuration by orienting their polar groups towards water and nonpolar groups facing each other (Fig. 2d). This vesicular morphology allow niosomes to accommodate hydrophilic drugs in aqueous volumes and lipophilic drugs in bilayer domains (Moghassemi and Hadjizadeh 2014). Some commonly used non-ionic surfactants include alkyl ethers, alkyl amides, alkyl esters, alkyl glyceryl ethers and esters of fatty acids (Kumar and Rajeshwarrao 2011). Non-ionic surfactants are preferred as they have less potential to cause irritation compared with their cationic and anionic counterparts (Moghassemi and Hadjizadeh 2014). Niosomal vesicles are either unilamellar or multi-lamellar in structure and have similar physical properties and preparation methods as those of conventional liposomes. Drug encapsulation efficiency and the formation of vesicles is dependent on the HLB value of surfactants. Surfactants with HLB values of 4–8 form vesicular structures, while surfactants with high HLB values (14–17) are not suitable for niosomes production as their high aqueous solubility hinder the association of freely hydrated surfactant into a lamellar structure (Marianecci et al. 2014). The first niosomal vesicular system based on the hydration of single alkyl chain non-ionic surfactant with cholesterol was reported in 1979 for cosmetic application (Handjani-Vila et al. 1979). Later on, niosomes received great attention for drug delivery applications compared to liposomal vesicles because of their advantages such as low cost, superior chemical stability, and easy scale up and large scale production (Alsarra et al. 2005). Niosomes have been successfully utilized for drug delivery to various organs such as the skin, liver, lungs, brain, tumor organs and ocular systems (Hamishehkar et al. 2013).

Niosomes for skin delivery and the mechanisms of permeation

Niosomes have the potential for skin delivery of drugs for a number of attractive reasons including increased skin permeation, sustained drug release via local depot and controlling systemic drug absorption through the skin (Muzzalupo

and Tavano 2015). The skin deposition and permeation of a number of drugs have been enhanced by using niosomal vesicles. A number of mechanisms have been proposed for enhanced drug transfer into and across the skin by niosomes. Niosomal vesicles may act as a permeation enhancer to disrupt the intercellular organization of lipids in the stratum corneum, making the lipid barrier permeable (Fang et al. 2001). Adhesion and fusion of niosomes on a skin surface creates a high thermodynamic activity gradient of drugs at the niosome-stratum corneum interface, providing a driving force for enhanced permeation of drugs (Mali et al. 2013). Reduction of transepidermal water loss to increase skin hydration, diffusion of intact niosomes across the skin and reformation of niosomes into smaller vesicles are some alternative proposed mechanisms to explain the enhanced skin permeation of niosomes (Muzzalupo and Tavano 2015). Furthermore, the permeation enhancing effects of non-ionic surfactants themselves might also contribute to the enhanced skin permeation of niosomal vesicles (Javadzadeh et al. 2010).

Factors affecting the skin delivery of niosomes

There are certain factors that might influence the formation, performance and hence permeation of niosomes through the stratum corneum. Some of these factors include the type of surfactant used, phase transition temperature of the surfactant, particle size of the niosomes, cholesterol content, encapsulation efficiency of the drug, presence of a solubilizer and HLB value of the surfactant. Non-ionic surfactants producing steric hindrance and electrostatic repulsion are desirable for the preparation of niosomes to prevent vesicle aggregation, as particle agglomerates of a larger size cannot permeate through the narrow channels of corneocytes (Solanki et al. 2010). It has also been suggested that surfactants with low phase transition temperatures produce vesicles with more flexible membranes and hence show better skin penetration than those formed from high phase transition temperature surfactants (Uchegbu and Vyas 1998). Smaller niosomal vesicles have shown better skin penetration than larger vesicles. In a study, Span 20 and Span 40 niosomes (214–252 nm) showed higher skin deposition of minoxidil compared to Brij 52 and Span 60 niosomes (1160–1240 nm), which was attributed to the smaller particle size and low phase transition temperatures of Span 20 and Span 40 (Balakrishnan et al. 2009). Cholesterol contents affect the structure, physical properties and elasticity of the niosomal membrane, which in turn affects the skin permeation of drugs. Higher cholesterol content produces a rigid vesicle, which reduces skin penetration (Balakrishnan et al. 2009; Liu et al. 2000). Higher entrapment efficiency of drug and the addition of solubilizers such as propylene glycol and polyethylene glycol 400 in niosomes have been reported to enhance skin penetration of drugs (Junyaprasert et al. 2012). The HLB values of surfactants also influence the physiochemical characteristics and skin permeation of niosomes. The percutaneous permeation of Span 80 niosomes was superior compared to those of Tween 80 niosomes due to its lower HLB value and better interaction with stratum corneum lipids. Furthermore, a proper balance between hydrophilic and hydrophobic surfactants was suggested for optimal performance of niosomes (Tavano et al. 2011).

Lipid nanoparticles

Solid lipid nanoparticles were introduced as first generation lipid nanoparticles in the early 1990s as alternative nanocarriers to liposomes, emulsions and polymeric nanoparticles (Muller et al. 1995). These colloidal carriers provide a highly lipophilic matrix for controlled drug release by restricting their mobility (Müller et al. 2000; Qureshi et al. 2017). Solid lipid nanoparticles are composed of solid lipids such as mono-, di- and triglycerides, fatty acids, steroids and waxes (Uner and Yener 2007). Surfactants including polaxamers, polysorbates and phospholipids have been utilized to provide steric stabilization to solid lipid nanoparticles (Zeb et al. 2017a). A diagrammatic illustration of a lipid nanoparticles composed of lipid matrix and surfactant shell is presented in Fig. 2e. With advantages of industrial large scale production, a sustained release effect, improved bioavailability and in vivo tolerability, solid lipid nanoparticles have been used as a potential colloidal carrier system for delivering active pharmaceutical ingredients to the brain, lungs, nose and skin (Din et al. 2017; Mehnert and Mäder 2012; Müller et al. 2000). The second generation of lipid nanoparticles, known as nanostructured lipid carriers, were introduced to overcome the drawbacks of drug leakage from solid lipid nanoparticles during storage (Wissing et al. 2004; Zeb et al. 2017a). Nanostructured lipid carriers contain oily nano-compartments in a solid lipid matrix (Han et al. 2008). The increased solubility of drug in a mixture of solid and liquid lipids significantly enhances drug encapsulation efficiency in nanostructured lipid carriers and reduces drug expulsion by providing an imperfect crystal (Müller et al. 2002a). Since their development, solid lipid nanoparticles and nanostructured lipid carriers have been extensively investigated for drug delivery applications to a number of inaccessible targets including skin.

Lipid nanoparticles for skin delivery and the mechanisms of permeation

Lipid nanoparticles have been the focus of research as carriers for the topical delivery of cosmeceuticals as well as

active pharmaceutical ingredients (Müller et al. 2002b). Lipid nanoparticles possess some valuable features for skin delivery such as controlled drug release, better tolerability, green chemistry and active ingredient stability over conventional topical formulations such as ointments, creams, lotions and tinctures (Wissing and Müller 2003). Topical use of lipid nanoparticles enhances skin penetration by maintaining a sustained release effect and close contact to the stratum corneum (Maia et al. 2000; zur Mühlen et al. 1998). The enhanced skin penetration of lipid nanoparticles is attributed to the formation of a lipid film on the skin's surface owing to their inherent adhesive effect. Lipid film produces an occlusive effect to retard the escape of water and improves skin hydration with the resultant promoting effect on skin delivery of drugs (Choi et al. 2010). Furthermore, the smaller particle size of lipid nanoparticles offers a high surface area to ensure close contact of particles with the stratum corneum for effective drug delivery (Jenning et al. 2000). The combination of the effects of these contributing factors results in enhanced skin penetration of drugs through the skin barrier.

Factors affecting skin delivery of lipid nanoparticles

The particle size of lipid nanoparticles, nature and concentration of surfactants, surface charge on the particles and state of the lipid (liquid vs. solid) in nanoparticle's core are the parameters that can affect the permeation of drugs across the skin. Skin penetration of lipid nanoparticles is based on an occlusive effect by forming a lipid film. Smaller particles produce increased adhesion and occlusion compared to larger particles, which in turn increase the skin permeation of drugs (Choi et al. 2010). In a study, an increase in particle size from 123 to 173 nm caused a reduction in the permeation flux from 3.1 to 1.9 μg/cm^2/h (Mei et al. 2003). The surface charge on the lipid nanoparticles also influences the penetration of drugs to the deeper skin layers. The stratum corneum carries a negative charge; therefore, the application of positively charged lipid nanoparticles results in their interaction with a superficial layer of skin with limited penetration to deeper layers. Furthermore, the negative charge of the stratum corneum hinders the diffusion of negatively charged lipid nanoparticles into the skin. For these reasons, nanoparticles with a net neutral surface charge are suggested in order to perform effectively compared to their positively or negatively charged counterparts (Tupal et al. 2016). The type and concentration of the surfactant in lipid nanoparticle formulation plays a key role in penetration of skin. In a study, Tween 80 and soybean lecithin in different concentrations were used as the surfactant and the co-surfactant. The results reveal that skin uptake of lipid nanoparticles increased with increasing concentration of Tween 80, while skin penetration was decreased with an increase in lecithin concentration (Liu et al. 2007). Increased incorporation efficiency of drugs in lipid nanoparticles is also suggested to enhance skin penetration and reduce skin irritation (Liu et al. 2007). Solid lipid core (SLNs) or nanostructured lipid carriers (NLCs) with a binary mixture core of solid and liquid lipid also affect skin permeation of the lipid nanoparticles. It has been reported that NLCs and NLCs-loaded gel showed higher amount of cyclosporine and calcipotriol deposited in the pig ear skin compared to their SLNs counterparts (Arora et al. 2017). In addition, the severity of inflammation in terms of serum cytokines level and skin morphology was markedly reduced by drug-loaded NLCs in comparison to SLNs in psoriatic mice model. In another study, meloxicam-loaded NLCs exhibited enhanced anti-inflammatory activity having better erythema score (3 ± 0.0) compared to meloxicam-loaded SLNs (erythema score of 2.67 ± 0.5) in UV-induced erythema rats model (Khalil et al. 2014). These results suggest a higher skin penetration potential of lipid nanoparticles with a binary mixture core of solid and liquid lipid than those with a solid lipid core only.

Conclusion

In recent years, research in transdermal delivery has been revolutionized due to better understanding of the structure of the stratum corneum on a molecular level and the pathways of drug permeation across skin. Nanotechnology has recently been established as a promising tool to overcome the barrier function of skin. In this article, we discussed some of the attractive nanoparticulate carriers with their applications in enhancing drug transport across skin. The aforementioned results indicated the superior interaction of nanoparticulate carriers with skin structures to promote drug delivery. In this regard, a deformable liposomes-based product (Transfenac®) developed by IDEA, Germany, has already proven its capability to carry a therapeutically significant amount of diclofenac into systemic circulation. A number of products based on nanoparticulate carriers and intended for skin delivery are in various phases of clinical trials. With advancements in material engineering, fabrication and characterization techniques, research has been focused on the development of newer nanoparticulate carriers with favorable properties for skin applications. Based on the amount of interest and research, it can be concluded that clinics might see more

effective and safer transdermal formulations as an alternative to oral delivery in the near future.

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Compliance with ethical standards

Statement of human and animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

Aggarwal N, Goindi S (2012) Preparation and evaluation of antifungal efficacy of griseofulvin loaded deformable membrane vesicles in optimized guinea pig model of *Microsporum canis*—dermatophytosis. Int J Pharm 437:277–287

Alsarra IA, Bosela AA, Ahmed SM, Mahrous GM (2005) Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur J Pharm Biopharm 59:485–490

Arora R, Katiyar SS, Kushwah V, Jain S (2017) Solid lipid nanoparticles and nanostructured lipid carrier-based nanotherapeutics in treatment of psoriasis: a comparative study. Expert Opin Drug Deliv 14:165–177

Balakrishnan P, Shanmugam S, Lee WS, Lee WM, Kim JO, Oh DH, Kim D-D, Kim JS, Yoo BK, Choi H-G (2009) Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery. Int J Pharm 377:1–8

Barry BW (1983) Dermatological formulations: percutaneous absorption. Marcel Dekker, New York

Barry BW (2001) Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 14:101–114

Barry BW (2002) Drug delivery routes in skin: a novel approach. Adv Drug Deliv Rev 54(Supplement):S31–S40

Barry BW (2004) Breaching the skin's barrier to drugs. Nat Biotechnol 22:165–167

Benson HA (2006) Transfersomes for transdermal drug delivery. Expert Opin Drug Deliv 3:727–737

Boinpally RR, Zhou S-L, Poondru S, Devraj G, Jasti BR (2003) Lecithin vesicles for topical delivery of diclofenac. Eur J Pharm Biopharm 56:389–392

Bouwstra JA, Ponec M (2006) The skin barrier in healthy and diseased state. Biochim Biophys Acta 1758:2080–2095

Cevc G (2012) Rational design of new product candidates: the next generation of highly deformable bilayer vesicles for noninvasive, targeted therapy. J Control Release 160:135–146

Cevc G, Blume G (1992) Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochim Biophys Acta 1104:226–232

Cevc G, Blume G (2001) New, highly efficient formulation of diclofenac for the topical, transdermal administration in ultradeformable drug carriers, transfersomes. Biochim Biophys Acta 1514:191–205

Cevc G, Blume G (2003) Biological activity and characteristics of triamcinolone-acetonide formulated with the self-regulating drug carriers, transfersomes®. Biochim Biophys Acta 1614:156–164

Cevc G, Vierl U (2010) Nanotechnology and the transdermal route: A state of the art review and critical appraisal. J Control Release 141:277–299

Cevc G, Blume G, Schätzlein A, Gebauer D, Paul A (1996) The skin: a pathway for systemic treatment with patches and lipid-based agent carriers. Adv Drug Deliv Rev 18:349–378

Cevc G, Schätzlein A, Richardsen H (2002) Ultradeformable lipid vesicles can penetrate the skin and other semi-permeable barriers unfragmented. Evidence from double label CLSM experiments and direct size measurements. Biochim Biophys Acta 1564:21–30

Chaudhary H, Kohli K, Kumar V (2013) Nano-transfersomes as a novel carrier for transdermal delivery. Int J Pharm 454:367–380

Choi W-S, Cho H-I, Lee H-Y, Lee S-H, Choi Y-W (2010) Enhanced occlusiveness of nanostructured lipid carrier (NLC)-based carbogel as a skin moisturizing vehicle. J Pharm Investig 40:373–378

Chourasia MK, Kang L, Chan SY (2011) Nanosized ethosomes bearing ketoprofen for improved transdermal delivery. Results Pharm Sci 1:60–67

Christophers E (1971) Cellular architecture of the stratum corneum. J Investig Dermatol 56:165–169

Contri RV, Fiel LA, Pohlmann AR, Guterres SS, Beck RCR (2011) Transport of substances and nanoparticles across the skin and in vitro models to evaluate skin permeation and/or penetration. In: Beck R, Guterres S, Pohlmann A (eds) Nanocosmetics and nanomedicines. Springer, Berlin, pp 3–35

Dayan N, Touitou E (2000) Carriers for skin delivery of trihexyphenidyl HCl: ethosomes vs. liposomes. Biomaterials 21:1879–1885

Din FU, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S, Zeb A (2017) Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int J Nanomed 12:7291–7309

Dubey V, Mishra D, Asthana A, Jain NK (2006) Transdermal delivery of a pineal hormone: melatonin via elastic liposomes. Biomaterials 27:3491–3496

Dubey V, Mishra D, Dutta T, Nahar M, Saraf DK, Jain NK (2007a) Dermal and transdermal delivery of an anti-psoriatic agent via ethanolic liposomes. J Control Release 123:148–154

Dubey V, Mishra D, Jain NK (2007b) Melatonin loaded ethanolic liposomes: physicochemical characterization and enhanced transdermal delivery. Eur J Pharm Biopharm 67:398–405

El Maghraby GMM, Williams AC, Barry BW (1999) Skin delivery of oestradiol from deformable and traditional liposomes: mechanistic studies. J Pharm Pharmacol 51:1123–1134

El Maghraby GMM, Williams AC, Barry BW (2001) Skin hydration and possible shunt route penetration in controlled estradiol delivery from ultradeformable and standard liposomes. J Pharm Pharmacol 53:1311–1322

El Maghraby GMM, Williams AC, Barry BW (2006) Can drug-bearing liposomes penetrate intact skin? J Pharm Pharmacol 58:415–429

El Maghraby GM, Barry BW, Williams AC (2008) Liposomes and skin: from drug delivery to model membranes. Eur J Pharm Sci 34:203–222

Elsayed MMA, Abdallah OY, Naggar VF, Khalafallah NM (2006) Deformable liposomes and ethosomes: mechanism of enhanced skin delivery. Int J Pharm 322:60–66

Elsayed MMA, Abdallah OY, Naggar VF, Khalafallah NM (2007) Lipid vesicles for skin delivery of drugs: reviewing three decades of research. Int J Pharm 332:1–16

Fang J-Y, Hong C-T, Chiu W-T, Wang Y-Y (2001) Effect of liposomes and niosomes on skin permeation of enoxacin. Int J Pharm 219:61–72

Ferreira LS, Ramaldes GA, Nunan EA, Ferreira LA (2004) In vitro skin permeation and retention of paromomycin from liposomes for topical treatment of the cutaneous leishmaniasis. Drug Dev Ind Pharm 30:289–296

Gillet A, Grammenos A, Compère P, Evrard B, Piel G (2009) Development of a new topical system: drug-in-cyclodextrin-in-deformable liposome. Int J Pharm 380:174–180

Gillet A, Lecomte F, Hubert P, Ducat E, Evrard B, Piel G (2011) Skin penetration behaviour of liposomes as a function of their composition. Eur J Pharm Biopharm 79:43–53

Godin B, Touitou E (2003) Ethosomes: new prospects in transdermal delivery. Crit Rev Ther Drug Carrier Syst 20:63–102

Guo J, Ping Q, Sun G, Jiao C (2000) Lecithin vesicular carriers for transdermal delivery of cyclosporin A. Int J Pharm 194:201–207

Hadgraft J (2001) Skin, the final frontier. Int J Pharm 224:1–18

Hadgraft J (2004) Skin deep. Eur J Pharm Biopharm 58:291–299

Hamishehkar H, Rahimpour Y, Kouhsoltani M (2013) Niosomes as a propitious carrier for topical drug delivery. Expert Opin Drug Deliv 10:261–272

Han F, Li S, Yin R, Shi X, Jia Q (2008) Investigation of nanostructured lipid carriers for transdermal delivery of flurbiprofen. Drug Dev Ind Pharm 34:453–458

Han S, Kwon S, Jeong Y, Yu E, Park S (2014) Physical characterization and in vitro skin permeation of solid lipid nanoparticles for transdermal delivery of quercetin. Int J Cosmet Sci 36:588–597

Handjani-Vila R, Ribier A, Rondot B, Vanlerberghie G (1979) Dispersions of lamellar phases of non-ionic lipids in cosmetic products. Int J Cosmet Sci 1:303–314

Harris RA, Burnett R, McQuilkin S, McClard A, Simon FR (1987) Effects of ethanol on membrane order: fluorescence studies. Ann N Y Acad Sci 492:125–135

Honeywell-Nguyen PL, Bouwstra JA (2005) Vesicles as a tool for transdermal and dermal delivery. Drug Discov Today Technol 2:67–74

Jain S, Tiwary AK, Sapra B, Jain NK (2007) Formulation and evaluation of ethosomes for transdermal delivery of lamivudine. AAPS PharmSciTech 8:E111

Javadzadeh Y, Shokri J, Hallaj-Nezhadi S, Hamishehkar H, Nokhodchi A (2010) Enhancement of percutaneous absorption of finasteride by cosolvents, cosurfactant and surfactants. Pharm Dev Technol 15:619–625

Jenning V, Schäfer-Korting M, Gohla S (2000) Vitamin A-loaded solid lipid nanoparticles for topical use: drug release properties. J Control Release 66:115–126

Johnson ME, Blankschtein D, Langer R (1997) Evaluation of solute permeation through the stratum corneum: lateral bilayer diffusion as the primary transport mechanism. J Pharm Sci 86:1162–1172

Junyaprasert VB, Singhsa P, Suksiriworapong J, Chantasart D (2012) Physicochemical properties and skin permeation of Span 60/Tween 60 niosomes of ellagic acid. Int J Pharm 423:303–311

Kanitakis J (2002) Anatomy, histology and immunohistochemistry of normal human skin. Eur J Dermatol 12:390–399 **(quiz 400–391)**

Kawadkar J, Pathak A, Kishore R, Chauhan MK (2013) Formulation, characterization and in vitro–in vivo evaluation of flurbiprofen-loaded nanostructured lipid carriers for transdermal delivery. Drug Dev Ind Pharm 39:569–578

Kenneth AW, Michael SR (2002) The structure and function of skin. In: Kenneth AW (Ed.) Dermatological and transdermal formulations. CRC Press, Boca Raton, pp 1–39

Khalil RM, Abd-Elbary A, Kassem MA, Ghorab MM, Basha M (2014) Nanostructured lipid carriers (NLCs) versus solid lipid nanoparticles (SLNs) for topical delivery of meloxicam. Pharm Dev Technol 19:304–314

Khallaf RA, Salem HF, Abdelbary A (2016) 5-Fluorouracil shell-enriched solid lipid nanoparticles (SLN) for effective skin carcinoma treatment. Drug Deliv 23:3452–3460

Khan NR, Harun MS, Nawaz A, Harjoh N, Wong TW (2015) Nanocarriers and their actions to improve skin permeability and transdermal drug delivery. Curr Pharm Des 21:2848–2866

Kitagawa S, Kasamaki M (2006) Enhanced delivery of retinoic acid to skin by cationic liposomes. Chem Pharm Bull 54:242–244

Kumar GP, Rajeshwarrao P (2011) Nonionic surfactant vesicular systems for effective drug delivery—an overview. Acta Pharm Sin B 1:208–219

Kurakula M, Ahmed OA, Fahmy UA, Ahmed TA (2016) Solid lipid nanoparticles for transdermal delivery of avanafil: optimization, formulation, in-vitro and ex-vivo studies. J Liposome Res 26:288–296

Liu D-Z, Chen W-Y, Tasi L-M, Yang S-P (2000) Microcalorimetric and shear studies on the effects of cholesterol on the physical stability of lipid vesicles. Colloids Surf A Physicochem Eng Asp 172:57–67

Liu H, Pan W-S, Tang R, Luo S-D (2004) Topical delivery of different acyclovir palmitate liposome formulations through rat skin in vitro. Pharmazie 59:203–206

Liu J, Hu W, Chen H, Ni Q, Xu H, Yang X (2007) Isotretinoin-loaded solid lipid nanoparticles with skin targeting for topical delivery. Int J Pharm 328:191–195

Lopez-Pinto J, Gonzalez-Rodriguez M, Rabasco A (2005) Effect of cholesterol and ethanol on dermal delivery from DPPC liposomes. Int J Pharm 298:1–12

Maia CS, Mehnert W, Schäfer-Korting M (2000) Solid lipid nanoparticles as drug carriers for topical glucocorticoids. Int J Pharm 196:165–167

Mali N, Darandale S, Vavia P (2013) Niosomes as a vesicular carrier for topical administration of minoxidil: formulation and in vitro assessment. Drug Deliv Transl Res 3:587–592

Marianecci C, Di Marzio L, Rinaldi F, Celia C, Paolino D, Alhaique F, Esposito S, Carafa M (2014) Niosomes from 80 s to present: the state of the art. Adv Colloid Interface Sci 205:187–206

Marto J, Vitor C, Guerreiro A, Severino C, Eleuterio C, Ascenso A, Simoes S (2016) Ethosomes for enhanced skin delivery of griseofulvin. Colloids Surf B Biointerfaces 146:616–623

Mbah CC, Builders PF, Attama AA (2014) Nanovesicular carriers as alternative drug delivery systems: ethosomes in focus. Expert Opin Drug Deliv 11:45–59

Mehnert W, Mäder K (2012) Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev 64:83–101

Mei Z, Chen H, Weng T, Yang Y, Yang X (2003) Solid lipid nanoparticle and microemulsion for topical delivery of triptolide. Eur J Pharm Biopharm 56:189–196

Menon GK (2002) New insights into skin structure: scratching the surface. Adv Drug Deliv Rev 54(Supplement):S3–S17

Mezei M, Gulasekharam V (1980) Liposomes-a selective drug delivery system for the topical route of administration. Lotion dosage form. Life Sci 26:1473–1477

Mishra D, Garg M, Dubey V, Jain S, Jain N (2007) Elastic liposomes mediated transdermal delivery of an anti-hypertensive agent: propranolol hydrochloride. J Pharm Sci 96:145–155

Moghassemi S, Hadjizadeh A (2014) Nano-niosomes as nanoscale drug delivery systems: an illustrated review. J Control Release 185:22–36

Montenegro L, Sinico C, Castangia I, Carbone C, Puglisi G (2012) Idebenone-loaded solid lipid nanoparticles for drug delivery to the skin: in vitro evaluation. Int J Pharm 434:169–174

Moser K, Kriwet K, Naik A, Kalia YN, Guy RH (2001) Passive skin penetration enhancement and its quantification in vitro. Eur J Pharm Biopharm 52:103–112

Muller RH, Mehnert W, Lucks JS, Schwarz C, Zur Muhlen A, Weyhers H, Freitas C, Ruhl D (1995) Solid lipid nanoparticles (SLN)—an alternative colloidal carrier system for controlled drug delivery. Eur J Pharm Biopharm 41:62–69

Müller RH, Mäder K, Gohla S (2000) Solid lipid nanoparticles (SLN) for controlled drug delivery—a review of the state of the art. Eur J Pharm Biopharm 50:161–177

Müller RH, Radtke M, Wissing SA (2002a) Nanostructured lipid matrices for improved microencapsulation of drugs. Int J Pharm 242:121–128

Müller RH, Radtke M, Wissing SA (2002b) Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev 54(Supplement):S131–S155

Muzzalupo R, Tavano L (2015) Niosomal drug delivery for transdermal targeting: recent advances. Res Rep Transderm Drug Deliv 4:23–33

Nasr M, Mansour S, Mortada ND, Elshamy A (2008) Vesicular aceclofenac systems: a comparative study between liposomes and niosomes. J Microencapsul 25:499–512

Neubert RHH (2011) Potentials of new nanocarriers for dermal and transdermal drug delivery. Eur J Pharm Biopharm 77:1–2

Oh YK, Kim MY, Shin JY, Kim TW, Yun MO, Yang SJ, Choi SS, Jung WW, Kim J, Choi HG (2006) Skin permeation of retinol in Tween 20-based deformable liposomes: in-vitro evaluation in human skin and keratinocyte models. J Pharm Pharmacol 58:161–166

Padamwar MN, Pokharkar VB (2006) Development of vitamin loaded topical liposomal formulation using factorial design approach: drug deposition and stability. Int J Pharm 320:37–44

Paolino D, Lucania G, Mardente D, Alhaique F, Fresta M (2005) Ethosomes for skin delivery of ammonium glycyrrhizinate: in vitro percutaneous permeation through human skin and in vivo anti-inflammatory activity on human volunteers. J Control Release 106:99–110

Paolino D, Cosco D, Muzzalupo R, Trapasso E, Picci N, Fresta M (2008) Innovative bola-surfactant niosomes as topical delivery systems of 5-fluorouracil for the treatment of skin cancer. Int J Pharm 353:233–242

Paolino D, Celia C, Trapasso E, Cilurzo F, Fresta M (2012) Paclitaxel-loaded ethosomes®: potential treatment of squamous cell carcinoma, a malignant transformation of actinic keratoses. Eur J Pharm Biopharm 81:102–112

Park SN, Jo NR, Jeon SH (2014a) Chitosan-coated liposomes for enhanced skin permeation of resveratrol. J Ind Eng Chem 20:1481–1485

Park SN, Lee HJ, Gu HA (2014b) Enhanced skin delivery and characterization of rutin-loaded ethosomes. Korean J Chem Eng 31:485–489

Patel V, Misra A, Marfatia Y (2001) Preparation and comparative clinical evaluation of liposomal gel of benzoyl peroxide for acne. Drug Dev Ind Pharm 27:863–870

Pegoraro C, MacNeil S, Battaglia G (2012) Transdermal drug delivery: from micro to nano. Nanoscale 4:1881–1894

Perez AP, Altube MJ, Schilrreff P, Apezteguia G, Celes FS, Zacchino S, de Oliveira CI, Romero EL, Morilla MJ (2016) Topical amphotericin B in ultradeformable liposomes: formulation, skin penetration study, antifungal and antileishmanial activity in vitro. Colloids Surf B Biointerfaces 139:190–198

Perez-Cullell N, Coderch L, de la Maza A, Parra JL, Estelrich J (2000) Influence of the fluidity of liposome compositions on percutaneous absorption. Drug Deliv 7:7–13

Pierre MBR, Tedesco AC, Marchetti JM, Bentley MVLB (2001) Stratum corneum lipids liposomes for the topical delivery of 5-aminolevulinic acid in photodynamic therapy of skin cancer: preparation and in vitro permeation study. BMC Dermatol 1:5–5

Prausnitz MR, Mitragotri S, Langer R (2004) Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov 3:115–124

Puglia C, Trombetta D, Venuti V, Saija A, Bonina F (2004) Evaluation of in-vivo topical anti-inflammatory activity of indometacin from liposomal vesicles. J Pharm Pharmacol 56:1225–1232

Qureshi OS, Kim HS, Zeb A, Choi JS, Kim HS, Kwon JE, Kim MS, Kang JH, Ryou C, Park JS, Kim JK (2017) Sustained release docetaxel-incorporated lipid nanoparticles with improved pharmacokinetics for oral and parenteral administration. J Microencapsul 34:250–261

Ramon E, Alonso C, Coderch L, de la Maza A, Lopez O, Parra JL, Notario J (2005) Liposomes as alternative vehicles for sun filter formulations. Drug Deliv 12:83–88

Ranade VV, Cannon JB (2011) Drug delivery systems, 3 rd edn. CRC Press, Boca Raton

Romero EL, Morilla MJ (2013) Highly deformable and highly fluid vesicles as potential drug delivery systems: theoretical and practical considerations. Int J Nanomedi 8:3171–3186

Rosen MR (2005) Delivery system handbook for personal care and cosmetic products: technology, applications and formulation, 1st ed. William Andrew, Norwich

Scheuplein RJ (1965) Mechanism of percutaneous absorption. 1. Routes of penetration and the influence of solubility. J Investig Dermatol 45:334–346

Scheuplein RJ (1976) Permeability of the skin: a review of major concepts and some new developments. J Investig Dermatol 67:672–676

Shuwaili AHA, Rasool BKA, Abdulrasool AA (2016) Optimization of elastic transfersomes formulations for transdermal delivery of pentoxifylline. Eur J Pharm Biopharm 102:101–114

Sinico C, Manconi M, Peppi M, Lai F, Valenti D, Fadda AM (2005) Liposomes as carriers for dermal delivery of tretinoin: in vitro evaluation of drug permeation and vesicle–skin interaction. J Control Release 103:123–136

Solanki AB, Parikh JR, Parikh RH, Patel MR (2010) Evaluation of different compositions of niosomes to optimize aceclofenac transdermal delivery. Asian J Pharm Sci 5:87–95

Subongkot T, Ngawhirunpat T (2015) Effect of liposomal fluidity on skin permeation of sodium fluorescein entrapped in liposomes. Int J Nanomed 10:4581–4592

Tavano L, Alfano P, Muzzalupo R, de Cindio B (2011) Niosomes vs microemulsions: new carriers for topical delivery of capsaicin. Colloids Surf B Biointerfaces 87:333–339

Tavano L, Muzzalupo R, Picci N, de Cindio B (2014) Co-encapsulation of lipophilic antioxidants into niosomal carriers: percutaneous permeation studies for cosmeceutical applications. Colloids Surf B Biointerfaces 114:144–149

Torchilin VP (2005) Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov 4:145–160

Touitou E (1996) Compositions for applying active substances to or through the skin. US patent 5,540,934

Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M (2000a) Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release 65:403–418

Touitou E, Godin B, Weiss C (2000b) Enhanced delivery of drugs into and across the skin by ethosomal carriers. Drug Dev Res 50:406–415

Touitou E, Godin B, Dayan N, Weiss C, Piliponsky A, Levi-Schaffer F (2001) Intracellular delivery mediated by an ethosomal carrier. Biomaterials 22:3053–3059

Trommer H, Neubert RH (2006) Overcoming the stratum corneum: the modulation of skin penetration. A review. Skin Pharmacol Physiol 19:106–121

Trotta M, Peira E, Carlotti ME, Gallarate M (2004) Deformable liposomes for dermal administration of methotrexate. Int J Pharm 270:119–125

Tupal A, Sabzichi M, Ramezani F, Kouhsoltani M, Hamishehkar H (2016) Dermal delivery of doxorubicin-loaded solid lipid nanoparticles for the treatment of skin cancer. J Microencapsul 33:372–380

Uchechi O, Ogbonna JD, Attama AA (2014) Nanoparticles for dermal and transdermal drug delivery. In: Sezer AD (Ed.) Nanotechnology and nanomaterials: application of nanotechnology in drug delivery. InTech, Rijeka, pp 193–235

Uchegbu IF, Vyas SP (1998) Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm 172:33–70

Uner M, Yener G (2007) Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomed 2:289–300

Utreja P, Jain S, Tiwary A (2011) Localized delivery of paclitaxel using elastic liposomes: formulation development and evaluation. Drug Deliv 18:367–376

Van der Merwe D, Riviere JE (2005) Comparative studies on the effects of water, ethanol and water/ethanol mixtures on chemical partitioning into porcine stratum corneum and silastic membrane. Toxicol In Vitro 19:69–77

Verma DD, Verma S, Blume G, Fahr A (2003) Particle size of liposomes influences dermal delivery of substances into skin. Int J Pharm 258:141–151

Wissing SA, Müller RH (2003) Cosmetic applications for solid lipid nanoparticles (SLN). Int J Pharm 254:65–68

Wissing S, Kayser O, Müller R (2004) Solid lipid nanoparticles for parenteral drug delivery. Adv Drug Deliv Rev 56:1257–1272

Zeb A, Qureshi OS, Kim H-S, Cha J-H, Kim H-S, Kim J-K (2016) Improved skin permeation of methotrexate via nanosized ultradeformable liposomes. Int J Nanomed 11:3813

Zeb A, Qureshi OS, Kim HS, Kim MS, Kang JH, Park JS, Kim JK (2017a) High payload itraconazole-incorporated lipid nanoparticles with modulated release property for oral and parenteral administration. J Pharm Pharmacol 69:955–966

Zeb A, Qureshi OS, Yu C-H, Akram M, Kim H-S, Kim M-S, Kang J-H, Majid A, Chang S-Y, Bae O-N (2017b) Enhanced anti-rheumatic activity of methotrexate-entrapped ultradeformable liposomal gel in adjuvant-induced arthritis rat model. Int J Pharm 525:92–100

Zhang Y-T, Shen L-N, Zhao J-H, Feng N-P (2014) Evaluation of psoralen ethosomes for topical delivery in rats by using in vivo microdialysis. Int J Nanomed 9:669–678

Zhang Y, Zhang K, Wu Z, Guo T, Ye B, Lu M, Zhao J, Zhu C, Feng N (2015) Evaluation of transdermal salidroside delivery using niosomes via in vitro cellular uptake. Int J Pharm 478:138–146

zur Mühlen A, Schwarz C, Mehnert W (1998) Solid lipid nanoparticles (SLN) for controlled drug delivery—drug release and release mechanism. Eur J Pharm Biopharm 45:149–155