Review Article

TIPS Trends in Pharmaceutical Sciences 2019: 5(1): 25-40.

Passive Enhancement of Transdermal Drug Delivery: Lipid-Based Nanocarriers as Emerging Technology Platform

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Abstract

Transdermal drug delivery (TDD) is an attractive approach to minimize the limitations encountered by other drug administration routes such as oral and parenteral. Apart from specialized devices fabricated for modifying the barrier properties of the stratum corneum such as iontophoresis, sonophoresis and microneedles, there are several passive methods applied through physicochemical manipulations in drug formulation, including prodrugs, ion-pairs, supersaturated solutions, inclusion complexes, eutectic mixtures, ionic liquids and use of chemical penetration enhancers. More recently, colloidal carriers due to their small size, high specific surface area, unique structural and biochemical features, are suggested for the skin penetration enhancement through transcellular or shunt routes. This review considers challenges and achievements of colloidal TDD systems, either used alone or in combination with other techniques, with a special concern about lipid-based vesicular nanocarriers including liposomes, niosomes, transfersomes, pharmacosomes, ethosomes, catesomes, and invasomes.

Keywords: Colloidal systems, Liposomes, Passive enhancement, Transdermal drug delivery.

1. Introduction

Transdermal drug delivery (TDD) has been evolved as an attractive and patient acceptable drug delivery method that can minimize the limitations associated with oral and intravenous administration routes (1). TDD involves an extensive range of non-invasive or minimally invasive approaches for delivering drugs and vaccines into or through the skin (2). The main advantages of this route include avoiding hepatic first pass effect, uniform plasma levels, longer duration of action, reduction of side effects and easy termination of therapy (3). Lipophilic potent drugs with molecular weight less than 500 Da are ideal candidates for TDD, so the stratum corneum (SC) acts as the main physical barrier to transport of such drugs (4).

Over last decades, numerous researches have been done in order to overcome the skin barrier property though disrupting highly organized lipid structure by using of special chemicals (formulation modification) or physical (device) techniques. Based on whether an external source of energy is used for skin permeation enhancement or not, the presented techniques are divided into passive and active methods (2, 5). Passive techniques involves the effects of drug and vehicle interactions on skin barrier function (6, 7). It is generally believed that the passive methods do not greatly

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Recieved: 27/01/2019; Accepted: 28/02/2019

increase the permeation of drugs, so the amount of delivered drug is still limited. Moreover, there is a delay in drug action due to the lag time required for drug molecules to reach into the blood circulation. In contrast, active methods offer more controls over the delivery profile and can provide rapid onset of drug action (2, 8).

Many drug molecules are unable to penetrate SC due to inappropriate physicochemical properties such as unfavorable partition coefficient and poor solubility. Therefore, several techniques have been introduced for passive enhancement of the skin permeation. For pharmaceutical semisolid and liquid formulations, enhancement in TDD can be achieved by either conventional (non-colloidal) or colloidal systems (9). Chemical penetration enhancers (CPEs) can perturb temporarily the barrier function of skin. On the other hand, physicochemical properties of drug molecule can be modified by several techniques such as prodrugs, ion-pairs, supersaturated solutions, eutectic mixtures, ionic liquids and inclusion complexes to enhance TDD. More recently, colloidal carriers such as vesicular systems (liposomes, niosomes, transfersomes, pharmacosomes, ethosomes, catesomes, and invasomes), solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), nanoemulsions and microemulsions have gained the scientists' attention for passive TDD (9) that will be discussed with a special concern about vesicular systems in this paper. Moreover, an attempt was made to reference successful combinatorial TDD systems as reported in the literature.

2. Non-colloidal enhancement methods

2.1. Chemical enhancers

Chemical penetration enhancers (CPEs) including alcohols, glycols, surfactants, fatty acids, fatty alcohols, sulphoxides, Azon, pyrrolidones and terpenes are widely used in TDD formulations. The mechanisms by which they exert skin penetration enhancement are mainly through altering intercellular lipid bilayer, intracellular keratin, desmosome connections between corneocytes, drug solubility in the vehicle and partitioning into skin (10). CPEs are potentially skin irritant and only few of them are in the marketed products such as ethanol, propylene glycol, sodium lauryl sulfate. Terpenes are also gained scientists' attention for TDD as they are less toxic and irritant than other surfactants. Apart from CPEs, there are several approaches to modulate the physicochemical property of drug for topical skin formulation such as prodrugs, ion-pairs, supersaturated solutions, eutectic mixtures, ionic liquids and inclusion complexes.

2.2. Prodrugs

Prodrugs are often known as pharmacologically inactive compound that will transform into a pharmacologically active metabolite after administration. This approach is usually seeking modifications which are adding a moiety to parent drugs for enhancing their solubility or partition coefficient. For example, steroid esterification (e.g. betamethasone 17-valerate) provides greater topical anti-inflammatory effect than the parent drug (11). Also, N-acyl derivatives of polar 5-fluorouracil causes a reasonable skin permeability (12, 13).

2.3. Ion-pairs

Ion-pair formation is a promising chemical approach for enhancing transdermal delivery of charged drug molecules. In this case, adding an oppositely charged species to the drug molecule will result in an ion-pair that can partition and penetrate through the SC. Unlike prodrugs, ion-pairs do not change the drug chemical structure and pharmacologic action. Diclofenac diethylamine topical gel is an example of commercially available ion-pair formulation. This approach is also used to control the skin permeation of escitalopram and bisoprolol skin patch preparations (14, 15).

2.4. Supersaturation

Supersaturated solutions are formed by mixing the drugs with co-solvents or evaporating the solvent from the warm skin (11, 16). In addition, skin absorbed water molecules can act as anti-solvent to form supersaturated solutions (17). High driving force for leaking drug out of the supersaturated solution formulation causes enhanced TDD without interfering the barrier properties of the SC (18). For example, penetration of estradiol across human skin increases 18-folds by using supersaturated solution. However, these systems suf-

fer from low chemical stability and require anti-nucleating agents to improve their stability.

2.5. Eutectic mixtures

Eutectic mixtures are defined as physical mixtures of two or more substances with a certain part inhibiting each other crystal formation. Although mechanism of the eutectic mixture in transdermal drug delivery is not well understood, it may act by reducing drug melting point to below skin temperature that leads to enhanced drug solubility and permeability or it may act by pore formation as a result of leaching the lipids through the skin (19). For example, 1:1 eutectic mixture of lignocaine-prilocaine forms an oily phase which is then formulated as EMLA cream, thereby it provides high local anesthesia. In another case, various ratios of meloxicam and thymol mixture resulted in eutectic mixtures with more skin permeation than pure meloxicam (20).

2.6. Deep eutectic solvents and ionic liquids

Deep eutectic solvents (DES) are eutectic systems formed from mixture of Bronsted or Lewis acids and bases. Several fundamental characteristics of DES forming through strong hydrogen bonds or interactions between partially ionized or non-ionized species include viscosity, miscibility, low volatility and possible penetration enhancement that can be controlled through careful selection of components and their mixing ratio. For example, choline and geranic acid form a deep eutectic solvent enhancing permeability of insulin across porcine skin (21).

Ionic liquids (ILs) are a group of compounds composed of low-melting ions. The cation is generally a bulky organic agent such as quaternary ammonium, imidazolium, pyrrolidinium, pyridinium and phosphonium, whereas the anion is a small compound. 1-octyl-3-methylimidazolium-based ILs have been conventionally used for TDD, which has been replaced by bioinspired choline based ILs with favorable biodegradation and low toxicity. Several enhancement mechanisms are proposed for ILs: a) drug solubilization in vehicle, b) fluidization of the lipid bilayer, c) disruption of the cellular matrix by acting on keratin and d) extraction of the SC lipid components. ILs can be used in pre-treatment interventions, various conventional and colloidal formulations such as microemulsions, and as active pharmaceutical ingredient (API-ILs) (22). For example, transdermal absorption of lidocaine enhances by the ionic liquid lidocainium docusate compound (23).

2.7. Inclusion complexes

Inclusion complex formation with cyclodextrins (CDs), cyclic oligosaccharides composed of glucopyranosyl units, is among the methods used for enhancing solubility, dissolution rate, stability and biomembrane permeability of guest drug molecules (24). For example, to improve curcumin solubility for the preparation of a transparent gel and also to enhance the skin permeability, β-cyclodextrin–CD complex has been prepared (25). β-CD is also useful for enhancing skin permeability of hydrophilic drugs, which is attributed to extraction of SC lipids by β-CD (26). Moreover, combination of hydroxypropyl-β-CD with elastic liposomes containing Tego® care 450 as edge activator provides a sustained caffeic acid release and higher skin permeability than free caffeic acid solution (27).

3. Colloidal systems

3.1. Microemulsions

Microemulsions (MEs) are thermodynamically stable transparent dispersions of oil, water and relatively high concentration of surfactants. Their small particle size (<100–200 nm), capability to spontaneous formation, transparency, low viscosity, increased drug solubility and bioavailability are among the most interesting advantages. The permeation enhancement depends on the choice and concentration of suitable oily phase, surfactant and co-surfactant (28). Several excellent reviews provide examples of MEs for TDD of wide variety of drugs (28-32).They can enhance TDD by disrupting the skin lipid structure or improving drug stability in formulations (33). Gupta et al. showed that transdermal flux of 5-fluorouracil increases up to 6 folds using MEs of sodium bis (2-ethylhexyl) sulfosuccinate: water: isopropyl myristate in comparison to an aqueous solution (34). Similarly, enhanced transdermal flux of tetracaine hydrochloride from lecithin/ n-propanol/

isopropyl myristate/ water MEs was reported (35). Zhu et al. showed that skin permeation of penciclovir from MEs containing oleic acid/ Cremophor EL/ ethanol/ water can be 3.5 folds higher than commercial creams (36). Tabosa et al. also reported a range of MEs containing a mixture of Cremophor EL, Tween 20, oleic acid and water for the enhancement of skin permeability of lapachol (37). Gallarate et al. revealed that stability of ascorbic acid against oxidation increases in w/o/w MEs in comparison to the aqueous formulations (38). It has been shown that the in vivo efficacy of lidocaine/ prilocaine eutectic mixture can be augmented by phospholipid ME hydrogel (39). In another study, eutectic mixture of menthol and camphor (1:1 w/w) was used for preparing o/w ME of glabridin. A synergistic enhancement of the skin permeation has been found for the combination of the eutectic mixture and ME in the formulation (40).

3.2. Nanoemulsions

Nanoemulsions (NEs) are a certain type of emulsions with droplet sizes in range of 20-200 nm. Unlike MEs, they are thermodynamically unstable and generally require external energy for their preparation. They contain oily phase (natural or synthetic lipids, fatty acids, oils, triglycerides, etc.), emulsifiers (lecithins, Cremophor EL, glycerides, polyethylene oxide sorbitan ester, etc.), additives (buffers, antioxidants, preservatives) and active pharmaceutical ingredient. NEs are superior to MEs because of lower skin irritation due to the lower amount of surfactant needed for their preparation. They offer also several advantages for TDD such as potential for skin hydration, high drug loading, skin penetration enhancement, extended drug release and depot action. Moreover, it is believed that incorporation of cationic lipids such as phytosphingosine may play an essential role for attachment of NE oily droplets to SC for successful TDD (41). NEs have been applied for transdermal delivery of a broad range of drugs such as ropinirole hydrochloride (42), glycyrrhizin (43), carvedilol (44) and aceclofenac (45). Enhanced skin delivery of minoxidil loaded in NEs containing oleic acid or eucalyptol as CPEs has been reported by Benson et al (46). The NE formulation enhances both the drug solubility and the skin diffusivity, causing high skin permeation of minoxidil significantly more than aqueous drug solution. In another study, a topical film containing o/w NE formulation of carvedilol was prepared that showed a substantial increases in the steady state flux and permeability coefficient of the drug (47).

3.3. Pickering emulsion

Pickering emulsions (PEs) are a type of emulsions, being developed in order to reduce surfactant-induced toxicity, a common problem in nano- and micro-emulsions (48). They are emulsions stabilized with solid colloidal particles (rather than chemical surfactants) such as zein, starch, silica, titanium dioxide and clay particles to prevent droplet coalescence (49, 50). Despite the potential application of PEs for TDD, no marketed product uses this technology possibly due to lack of toxicological information (51).

3.4. Lipid nanoparticles

SLNs and NLCs are the main classes of lipid nanoparticles presenting enhanced skin permeation (52, 53). SLNs are modifications of o/w NEs in which the oily phase is replaced by a physiologically biocompatible solid lipid or a blend of lipids such as fatty acids or triglycerides. Compared with emulsions, SLNs exhibit negligible higher stability, skin irritation, and more control over the drug release (54). Biocompatibility of triglycerides bypass the toxicity challenges and make SLNs well suited for inflamed and abraded skins. SLNs also have several advantages as TDD such as: 1) their occlusive effect on skin causes skin hydration (55), 2) crystal lattice of SLNs can protect labile agents from degradation (56), 3) high loading of lipophilic substances (57), 4) slow drug release and 5) small particle size which leads to close contact to SC and enhanced skin penetration (58). In contrast to SLNs, NLCs comprise mixture of liquid and solid lipids (59). They not only present SLNs advantages, but also overcome their limitations such as unfavorable drug leakage during the preparation process (i.e. low drug loading or expulsion) and possible burst effect (60, 61).

Application of SLNs and NLCs for TDD have increased during recent years. Lipid

nanoparticles are successfully used for the skin penetration enhancement of a wide range of drugs such as triptolide (62), flurbiprofen (63), metformin (64), lornoxicam (65), safranal (66) and olanzapine (67). For example, tape stripping method shows enhanced skin penetration of coenzyme Q10 by SLN and NLC structures in comparison with liquid paraffin and isopropanol mixture (68). In another study, podophyllotoxin-loaded SLNs increases drug accumulation in the SC of porcine skin to nearly 3.5 times in comparison to 0.15% tincture (69). Similarly, application of SLNs in the treatment of atopic dermatitis shows the prednicarbate loaded SLNs can induce nearly 4-fold more epidermal localization than standard cream and ointment (70). In another study, the tacrolimus loaded NLCs were prepared and their penetration rates through the hairless mouse skin were investigated, showing that the penetration rates of NLCs were greater than the conventional formulation, Prototopic® (71). SLN and NLC preparations can also enhance transdermal drug bioavailability as attained 4.4 folds for flurbiprofen. SLN and NLC dispersions can also provide a sustained drug release especially if they are combined with gel formulation (72). By SLN encapsulation, a better protection from hydrolysis and improved permeation into SC can be achieved as shown for all-trans retinoic acid (atRA) which causes irritation, erythema and has poor stability in combination with hydroquinone (73). Topical preparation of the piroxicam loaded SLN shows higher skin permeation of the drug in comparison to commercial gel formulation. In addition, it has been revealed that the particle size can influence on the skin permeation rate (74). To target hair follicle, various fabrication factors including surfactant/lipid ratio, mixing rate and addition time of the organic to aqueous phase have been considered for the preparation of cyproterone loaded NLCs with different sizes. NLCs with the diameter of 300 nm accumulate in the hair follicles more significantly and show a sustained drug release (75).

Lipid nanoparticles can also be combined with other permeation enhancement methods. For example, synergistic effects of skin micro-needling and co-administration of NLCs loaded with total alkaloid extracts from Aconitum sinomontanum has been explored (76).

4. Vesicular lipid formulations

Vesicular lipid carriers are among the most popular formulation for TDD. Vesicles are aqueous-filled colloidal bilayer forming carriers with amphiphilic shell(s) (77). Hydrophilic drugs can be encapsulated in the internal aqueous core, whereas lipophilic and amphiphilic drugs can be incorporated in the lipid bilayer(s) by hydrophobic or electrostatic interactions (78). Lipid-based vesicles have some favorable properties for TDD applications, including:

Table 1. Recent investigations on the lipid-based vesicular carriers for transdermal drug delivery and their achievements.

Type	Drug	Vesicle composition	Achievements	Ref.
Liposome	Ibuprofen	lecithin, cholesterol, dicetyl phosphate	higher transdermal flux	(79)
Peptide-modified liposome	Vemurafenib	lecithin, sodium cholate, cholesterol	high cellular uptake and skin permeability in-vitro, enhanced antitumor activity and safety in-vivo	(80)
pH-sensitive liposomes	Quercetin	egg lecithin, N-succinyl-chitosan, chitosan oligosaccharide	increased stability against surfactants, controlled drug release, enhanced skin permeation	(81)
Liposome	Finasteride	egg lecithin, cholesterol, dicetylphosphate	enhanced delivery to the pilosebaceous units	(82)
Transferosome	Cytarabine	soy lecithin, sodium deoxycholate	higher transdermal flux	(83)
Transferosome	Miconazole nitrate	soy lecithin, sodium deoxycholate, Span 80, Span 60, Tween 80	higher skin permeation, enhanced antifungal performance	(84)

Continued Table 1.

Type	Drug	Vesicle composition	Achievements	Ref.
Transferosome	Imperatorin (Chinese herbal medicine)	lecithin, cholesterol, dicetyl phosphate, stearylamine	sustained drug release, enhanced transdermal flux	(85)
Proniosome	Mefenamic acid	Span 80, cholesterol	reduction of rat paw edema	(86)
Niosome	Febuxostat	Span 60, cholesterol	prolonged drug permeation	(87)
Noisome	Lacidipine	Span 60, cholesterol, soy lecithin	higher skin permeation, higher reduction in blood pressure	(88)
Ethosome	Testosterone propionate	lecithin, Cremophor EL	higher transdermal flux	(89)
Ethosomal gel	Raloxifen	soy plecithin, cholesterol, saponin, Tween 20, Triton X-100	higher transdermal flux, higher bioavailability	(90)
Invasome	Olmesartan	lecithin, b-citronellene (terpene)	higher transdermal flux and bioavailability	(91)
Invasome	Isradipine	lecithin, b-citronellene (terpene)	high transdermal flux	(92)

a) act as drug carriers for delivering drug into or across skin layers,
b) can change the intercellular lipids within the SC,
c) solubilize lipophilic drugs,
d) serve as a depot for sustained drug release,
e) serve as rate-limiting membrane barriers to control TDD and systemic absorption.

Although there are few marketed topical drug products containing vesicular lipids, various systems are introduced as drug carriers for TDD. Table 1 summarizes lipid-based vesicular carriers including liposomes, niosomes, deformable liposomes or transfersomes, ethosomes, catesome, and invasome, which will be explained in the following sections.

4.1. Liposomes

Liposomes have received huge attentions for drug delivery. They have shown to be clinically more preferable to conventional dosage forms for intravenous and topical routes of administration (93-95). They also present a good potential to provide high local drug concentrations within the skin (9, 96). In most cases, they are composed of phosphatidylcholine (lecithin) extracted from soybean or egg yolk (97). Addition of cholesterol to the formulation stabilizes the resulting vesicles though increasing the rigidity of lipid bilayer. The mechanism by which liposomes can enhance skin permeation has not been clearly understood yet. They may penetrate the SC, interact with the skin lipids and release the loaded drug into SC. Liposomes are suitable for drug delivery to upper skin layers, as they only accumulate in the SC with minimal drug penetration to the deeper tissues and systemic circulation (98-100). Pevaryl lipogel® is the first topical liposomal product containing econazole that has been introduced into the market since 1988 for the treatment of dermatomycosis. Daylong Actinica® is a liposomal sunscreen product that reduces the risk of actinic keratosis lesions and severe skin lesions. Psoriatic patients also benefit from the use of topical gel of liposomal dithranol. Earlier liposome researches are focused on the potential use of liposomes for topical delivery of steroids such as triamcinolone acetonide (101, 102), triamcinolone acetonide-2-palmitate (103), hydrocortisone (101, 104), betamethasone dipropionate (104), cortisol (105), progesterone (106-109), dihydrotestosterone (110), bunazosin hydrochloride (111), flufenamic acid (112), dyphylline (113), clindamycin hydrochloride (114) and ibuprofen (79). Recent studies show the applicability of liposomes for delivery of macromolecules such as interferon (115), gene delivery (116) and cutaneous vaccination (117). Peptide-modified liposomes were applied to delivery of vemurafenib through skin for the treatment of melanoma. The cubic-shaped liposomes showed high cellular

uptake and skin permeability in vitro. Moreover, more enhanced antitumor activity and safety were reported for the peptide targeted liposomal vemurafenib in comparison to oral administration or I.V. injection (80). Surfactant-stable, pH-sensitive liposomes containing quercetin were prepared using layer-by-layer coating technology with N-succinylchitosan and chitosan oligosaccharide. This formulation can be applied to increase stability against surfactants, to control drug release and to enhance the skin penetration of quercetin (81). In another study, it was shown that the physical state of liposomes or niosomes can influence on the extent of finasteride permeation through and deposition into skin. Results revealed that the vesicular finasteride (especially in liquid crystalline state) had a lower skin permeation, but an enhanced delivery to the pilosebaceous units (82).

Some studies have been carried out to investigate the adding value of liposome technology in combination with other passive or active enhancement methods (11). Combination of liposomes with physical enhancement techniques such as electroporation and iontophoresis have been reported (118, 119). For example, Zorec et al. combined the liposomal formulation of drug with the physical methods. The results showed that conventional liposomes have little or no value on TDD; however their combination with electroporation and sonoporation considerably enhances drug efflux across SC (120).

4.2. Transferosomes

Transferosomes are a special type of elastic or ultra-deformable liposomes that consists of lecithin and also an edge activator for increasing deformability of the bilayers. Sodium cholate, sodium deoxycholate, Span 60, 65 and 80, Tween 20, 60 and 80 are the mostly used edge activators (37, 63). It was claimed that they are squeezed through channels in the SC and penetrate into deeper skin because of the presence of edge activator. Also, gradient of water between the skin surface and viable epidermis is generally believed as the driving force for skin penetration of Transferosomes across dermal layers (37). Due to their capability to bypass skin barriers, Transferosomes are successfully used for the skin penetration enhancement of a broad range of drugs including 5-fluorouracil (121), lidocaine (121, 122), tetracaine (122), cyclosporin A (123), insulin (124), diclofenac (125, 126), triamcinolone acetonide (127), hydrocortisone (128), dexamethasone (129), levonorgestrel (130), estradiol (131), low molecular weight heparin (132), methotrexate (133), zidovudine (134), ketoprofen (135) and cytarabine (83). For example, Transferosome technology has been employed for transdermal delivery of micronazole nitrate (a widely used antifungal agent) that shows higher rate of drug transfer through the skin and more enhanced antifungal performance than conventional liposomes or free drug solution (84). In another study, Transfersomes loading imperatorin (Chinese herbal medicine) was developed by the thin-film hydration technique. The results showed that cationic Transferosomes have satisfactory encapsulation efficiency, particle size, elasticity, sustained drug release and enhanced transdermal flux of imperatorin (85).

Application of Transferosomes in combination with chemical penetration enhancers can also lead to more efficient TDD of hydrophilic agents. For example, the lyophilized Transfersomal gel formulation composed of Tween 20 (as an edge activator), oleic acid (as a penetration enhancer), mannitol (as a cryopretectant) and a gelling agent (HPMC, CMC or sodium alginate) was successfully employed for transdermal delivery of buspirone HCl (a hydrophilic anxiolytic model drug) (136).

4.3. Niosomes (nonionic surfactant vesicles)

Niosomes are vesiclular carriers composed of non-ionic alkyl or dialkyl polyglycerol ether surfactants with cholesterol. Nonionic surfactants such as Span 60, 40 and 80, Tween 20, 40 and 80, Brij 52, 58, 35 and 30 form closed bilayer vesicles while cholesterol gives shape and rigidity to them (137). Niosomes are regarded as efficient TDD vehicles since they can be successfully applied for a prolonged and enhanced skin permeation (138) as shown for various drugs such as mefenamic acid (86), febuxostat (87) and lacidipine (128). In one study, lidocaine hydrochloride entrapped in the Niosomal formulation composed of Tween 20 and cholesterol that shows better local anesthetic

performance in comparison with liposomes (139). To avoid systemic adverse effects such as hepatotoxicity, the Niosomal methotrexate in chitosan gel has been formulated, showing significant reduction in psoriatic lesion after 12 weeks (140). In another example, gallic acid was prepared in two forms of elastic and non-elastic Niosomes for antiaging topical application that shows more enhanced permeation of the loaded gallic acid through rat skin for the elastic Niosomes (141). Niosomal gel of celecoxib shows 6.5 times higher drug deposition in deep skin layer than the drug solution (142). To overcome side effects of topically administered benzyl peroxide used for treating acne, the Niosomal formulation was prepared and then incorporated into HPMC gel. The results indicate favorable drug permeation through skin, extended drug release and reduced adverse effects such as itching, skin redness and irritation (143). One of the promising dermal treatment for acne is gallidermin (a cyclic peptide antibiotic). Anionic Niosomal gel formulation composed of cholesterol, Tween60 and diacetyl phosphate not only enhances chemical stability of gallidermin, but also provides efficient localization and favorable skin permeation (138). In another study, Narcissus tazetta extract (Traditional Persian Medicine) loaded Niosomal formulations composed of Span 60, Tween 60 and cholesterol are proposed for wound healing application. In-vitro experiment on human dermal fibroblasts (the scratch test) showed superior action of the Niosomal formulation (144).

4.4. Ethosomes

Ethosomes are vesicular carriers composed of phospholipid, water and ethanol (123). Because of the interdigitation effect on lipid bilayers, high ethanol concentrations (20-45%) results in particle sizes smaller than liposomes. It has been shown that presence of ethanol causes high encapsulation efficiency due to solubilizing activity of ethanol for a wide range of lipophilic drugs (123, 145-147). It also reduces the melting temperature of SC lipids and increases their fluidity (148). Ethosomes have been used for delivery of various drugs across skin such as minoxidil (145), testosterone (145), acyclovir (149), cannabidiol (150), erythromycin (151), ammonium glycyrrhizinate (152), sotalol (153), sodium salicylate (153), propranolol (153), trihexyphenidyl (154), zidovudine (155), azelaic acid (156), ketotifen (147), clonazepam (157) and aceclofenac (158). Ethosomal carbomer gel containing 30% ethanol was applied for transdermal delivery of antigen (89). In another study, surfactant-modified testosterone propionate loaded Ethosomes show higher entrapment efficiency and stability than liposomal preparations. Furthermore, higher transdermal flux and lower lag time than the liposomal preparation were shown (159). Similarly, raloxifene loaded ethosomal formulations show higher transdermal flux than the conventional liposomes and higher systemic bioavailability in comparison with the oral formulation (90).

Ethosomal formulations can be used in combination with CPEs. For example, fluconazole-loaded liposomal formulation and Ethosomes containing turpentine (as a penetration enhancer) leads to smaller vesicles, suitable encapsulation efficiency, enhanced skin permeation and antifungal activity in-vitro (160).

4.5. Catezomes

Catezomes are non-phospholipid based vesicles composed of fatty acid salts of quaternary amines (161). They can load and release both hydrophobic and hydrophilic compounds, which may be altered by changing the medium ionic strength. Catezomes can keep active materials on the skin surface due to their cationic surface charge; however, due to their minimal skin penetration, they are suitable for delivery to the superficial layers of skin as intended for sunscreens, fragrances, or enzymes (162).

4.6. Invasomes

Penetration enhancer-containing vesicles (PEVs), also called Invasomes, are composed of phosphatidylcholine, ethanol and a mixture of terpenes (163). It has been proposed they enhance synergistically skin penetration of minoxidil (163) and diclofenac (164) by combinatorial use of elastic vesicles and terpenes. Invasomes containing olmesartan and β-citronellene (as a penetration enhancer) were prepared in order to overcome the short half-life, and low oral bioavailability. The

results showed high transdermal flux and high bioavailability of olmesartan in comparison with the marketed tablet formulation (91). In another study, high transdermal flux of isradipine was achieved for the Invasomes composed of lecithin, β-citronellene and ethanol (92).

5. Conclusion

TDDs are a good alternative to overcome the problems associated with the other routes of administration such as intravenous or oral, especially these delivery systems have other advantages including dosage flexibility and patient compliance. Unfortunately, transdermal flux of drugs is often too low through the SC that requires temporary changing of the skin barrier function by variety of enhancement methods. Nanoemulsions, lipid nanoparticles and vesicles are among the passive approaches with favorable biocompatibility, capacity to load both hydrophobic and hydrophilic drugs, controlled drug release, skin penetration, retention and permeation. Furthermore, recent investigations have suggested possibility of loading bioactive peptides, proteins or nucleic acids and targeted delivery to skin components and cells. Certainly, comprehensive physicochemical characterization of such nanocarriers are required for a better understanding of the underlying penetration enhancement mechanisms. Moreover, combination of lipid-based colloidal systems with other techniques (even active methods) can provide a possibility for synergistic TDD.

Conflict of Interest

None declared.

6. References

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