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Chapter 6

Hydrogels and Their Combination with Liposomes, Niosomes, or Transfersomes for Dermal and Transdermal Drug Delivery

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Abstract

Polymeric networks that retain and absorb substantial amount of water or biological fluids and resemble as a biological tissue are defined as hydrogels. On the other hand, liposomes, transfersomes and niosomes are lipid carriers, which represent one of the major research and development focus areas of the pharmaceutical industry. They have great potential as lipid vehicles that are able to enhance permeation of drugs across the intact skin and can act as local depot for the drug to sustain and control its delivery. Lipid carrier and hydrogel combinations offer transdermal drug delivery of great potential to enhance systemic effects of both hydrophilic and lipophilic drugs. Also, lipid carriers can target drugs to skin appendages and improve transdermal delivery. Lipid carrier proform systems in the form of gelly liquid crystals can also be used transdermally for better drug absorption enhancement. This review highlights the potential of hydrogels and emulgels with or without lipid nanocarriers for dermal and transdermal application.

Keywords: hydrogel, emulgel, liposome, niosome, transfersomes

1. Introduction

Lipid carriers such as liposomes, niosomes, and transferesomes can be brought into gel formulations either in their proforms or in hydrogel vehicles and applied transdermally. They offer the capability of controlling drug release, enhancing drug transdermal absorption and increasing drug bioavailability compared to the plain gels [1]. Pharmaceutical gel preparations such as hydrogels, organogels, and emulgels have been extensively used to deliver both

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hydrophilic and lipophilic drugs for dermatological and transdermal use. Gels are cross-linked assembly containing both solid and liquid components within its configuration, which were considered as gelling agents and called gelators [2]. When the gelators are dispersed in appropriate solvent, they were associated together forming network of three-dimensional structure, which immobilize the surrounding aqueous media [2]. These results are followed by a series of the interactions to form the polymeric cross-linked network structures, which retained certain amount of the water [3]. The synthetic or natural gelators have ability to form this series of interactions producing macromolecular chain reaction. It was declared that the hydrophilic groups of the polymers build up gel like structure upon the hydration in the liquid environment. The gelation process stated that the polymer chains connected together to form large branched soluble polymers, which are called 'sol'. Afterward, the aggregation process leads to an increase in the branched polymer length with decreasing of the solubility of the polymers. This macrobranched polymer is called "gel". Then the gelation effect is called 'sol-gel transition' and the gel point is defined as the first point of gel formation [4]. Therefore, it is recognized that the ideal gels were developed following the incorporation of gelator molecules and the proper liquid phase resultant of self aggregation in the environmental medium. Thus, the gels were formed because of physical and chemical interaction between polymers chains. These interactions might form irreversible or reversible links producing permanent or temporary bonds. Hydrogen bonding, van der Waals force, hydrophobic interactions, ð-ð interactions, lamellar microcrystals, glassy nodules or double and triple helices blocks copolymer micelles and ionic associations are the physical interactions included in hydrogel formulations [5].

Hydrogels are polymeric networks, which can absorb and retain substantial amount of water or biological fluids within their porous structure. Several natural and synthetic polymers either solely or cross-linked are used in formulating hydrogels. Crosslinking of polymers provides high physical integrity to the network structure as well as to control the release of drug molecules. Newer ligands and different types of crosslinking allow the development of ideal hydrogel systems with appropriate release characteristics for the successful delivery of drugs, such as nucleic acids, proteins and peptides. The hydrogels have extended their applications in targeted drug delivery and as constituents for preparation of protein or enzyme conjugates. Also, the chemical process may involve a range of interactions such as: formation of covalent bonds always resulting in a strong gel. The three main chemical gelation processes were noticed: (1) condensation, (2) vulcanization, and (3) addition polymerization [5]. These types of bonds have great important roles in the controlling of the physical and chemical characterizations, properties, and structure of the gels. The key for the classification of gels into organogel or hydrogel was based on the type of solvent, polymer used, and polymer chain interactions. If the solvent is organic in nature, then the gel is considered as organogel, else hydrogel [6]. On the other hand, emulgel is a semisolid vehicle that is composed of hydrophilic surfactant (s), oil, water, and gelling agent, "an emulsion transformed to a gel by gelling agent" [7]. Emulgel bases offer the advantage that of being capable of incorporating aqueous and oleaginous ingredients, and their rheological properties can be controlled easily.

The focus of the current chapter in gel drug delivery with or without a carrier system is to increase the range of products, which can effectively deliver the drug with specific release

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characteristics. The properties of certain gels to undergo sharp volume or sol-gel phase transition in specific environment have provided their importance in drug delivery with new promising applications. Progresses in polymer chemistry and gel technology have extended the prospective of gels in transdermal drug delivery.

2. Hydrogels and lipid carriers for drug delivery

2.1. Hydrogels

Hydrogels offer several favorable characteristics, which are crucial for designing suitable drug delivery systems. Typically, they are polymeric matrices, which are capable of imbibing greater amount of water, due to the good thermodynamic compatability which allow them to swell to a higher extent. These hydrogels emerged as a promising option for drug delivery scientists mainly due to their significant physicochemical and biological properties such as reversible swelling and shrinking, good sorption capacity, mechanical strength, considerable biocompatibility, desired drug release, tissue like physical properties, accommodating wide range of molecules, better compatibility, easy to fabricate, good oxygen permeability, low interfacial tension, nontoxic, etc. In addition, they offer several other characteristics like bioadhesion, mucoadhesion, rapid deformation, ease of surface modification, conforming the shape of surface which they are applied, which make them ideal for drug delivery vehicles for targeted drug delivery [8]. However, the physical properties of hydrogels are usually influenced by the charge of polymer, molecular weight of polymer, density of crosslinking, etc.

The biocompatibility of hydrogels is primarily owing to their higher water content and physicochemical similarity to the native extracellular matrix. They resemble more biological tissues probably due to their high water content, soft consistency and three-dimensional polymeric network. Indeed, the existence of three-dimensional structure of hydrogels could be employed in the design and development of different drug delivery systems. Moreover, the rubbery nature will minimize the mechanical irritation of the polymer to the surrounding body tissues. Further, hydrogels are highly compatible with most of the drugs, proteins and peptides. They can be modified and fabricated into desired formulations of specific size or shape. Thus, hydrogels appeared to be the ideal vehicle for dermal as well as transdermal delivery and different transdermal formulations like matrix patch, reservoir system, gel and carrier system. On the other hand, there are some few limitations, which confine the applications of hydrogels in drug delivery such as relatively low tensile strength, nonuniformity in drug loading of hydrophobic drugs and rapid drug release [9].

2.2. Lipid carriers

Lipid carriers such as liposomes, niosomes, and transfersomes have many applications expanded from conventional drugs to hormones, peptides, immunoglobulin, vaccination, and gene therapy. These drug delivery carriers employ different rate-controlling mechanisms such

as membrane diffusion, diffusion through matrices, osmosis and biodegradation. An explosion in research in drug delivery by nonconventional routes such as transdermal, nasal, ocular, pulmonary, and intraarterial routes has been reported.

2.2.1. Liposomes/niosomes and their pro-forms

Liposomes are the microscopic spherical phospholipids vesicles that form spontaneously when mixed in water under low shear conditions [10]. The phospholipid molecules arranged in layers or sheets and the molecules aligned side by side, in which the hydrophilic heads of phospholipid and their hydrophobic tails down. These phospholipid layers then formed bilayer membranes that encapsulate some of the aqueous vehicles inside a lipid sphere (**Figure 1**).

Liposomes are structurally related to cell membrane "phospholipid bilayer" and have been used in the study of biological membranes instead of using cadaver skin of human [11]. Moreover, liposomes as lipid carriers have been extensively evaluated as delivery vehicles for drugs, genes and/or cosmetics [12]. Liposomes undergo the problem of both chemical and physical instability; hence, the concept of proliposomes was introduced [13]. Proliposomes with least or no water content were prepared in three different forms: dry free-flowing granular product, mixed micellar proliposomes, and liquid crystalline proliposomes for reconstitution immediately at time of use (**Figure 2**). The proliposome liquid crystal type formulae were used successfully for transdermal drug delivery [14].

On the other hand, niosomes are nonionic surfactant vesicles of multilamellar or unilamellar bilayer membrane structures such as liposomes. They can encapsulate both hydrophilic

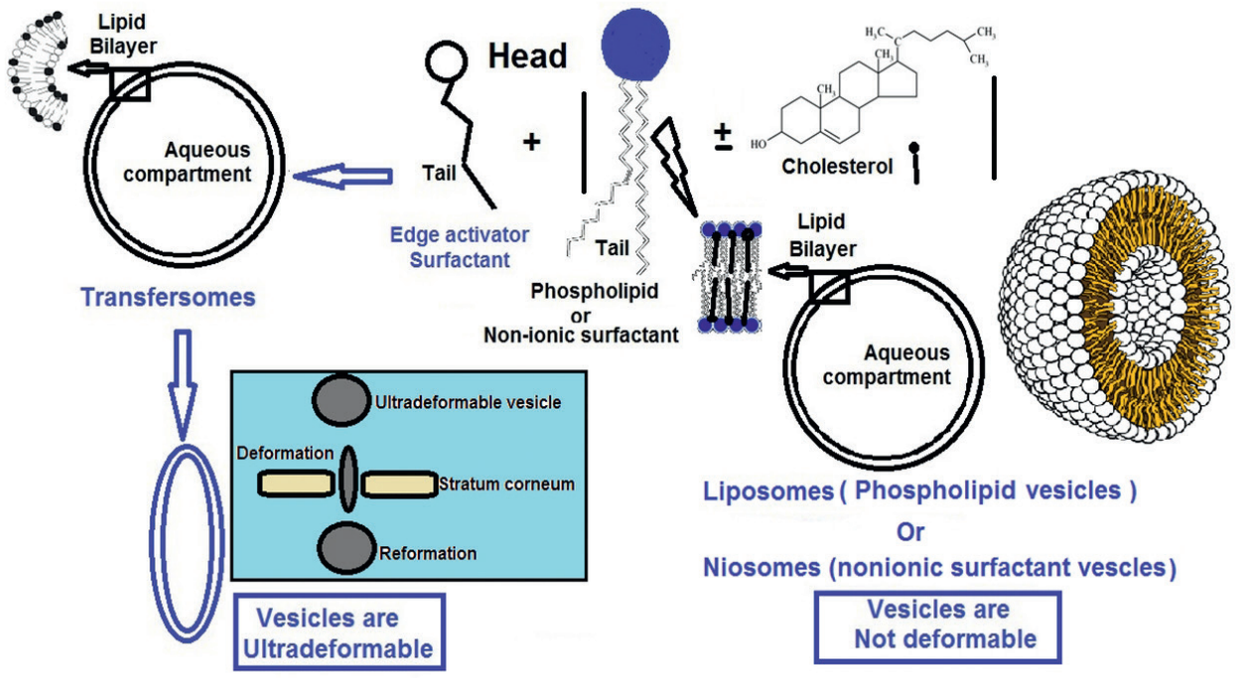


Figure 1. Schematic representation of lipid carriers "liposomes, niosomes, and transfersomes" structure and composition.

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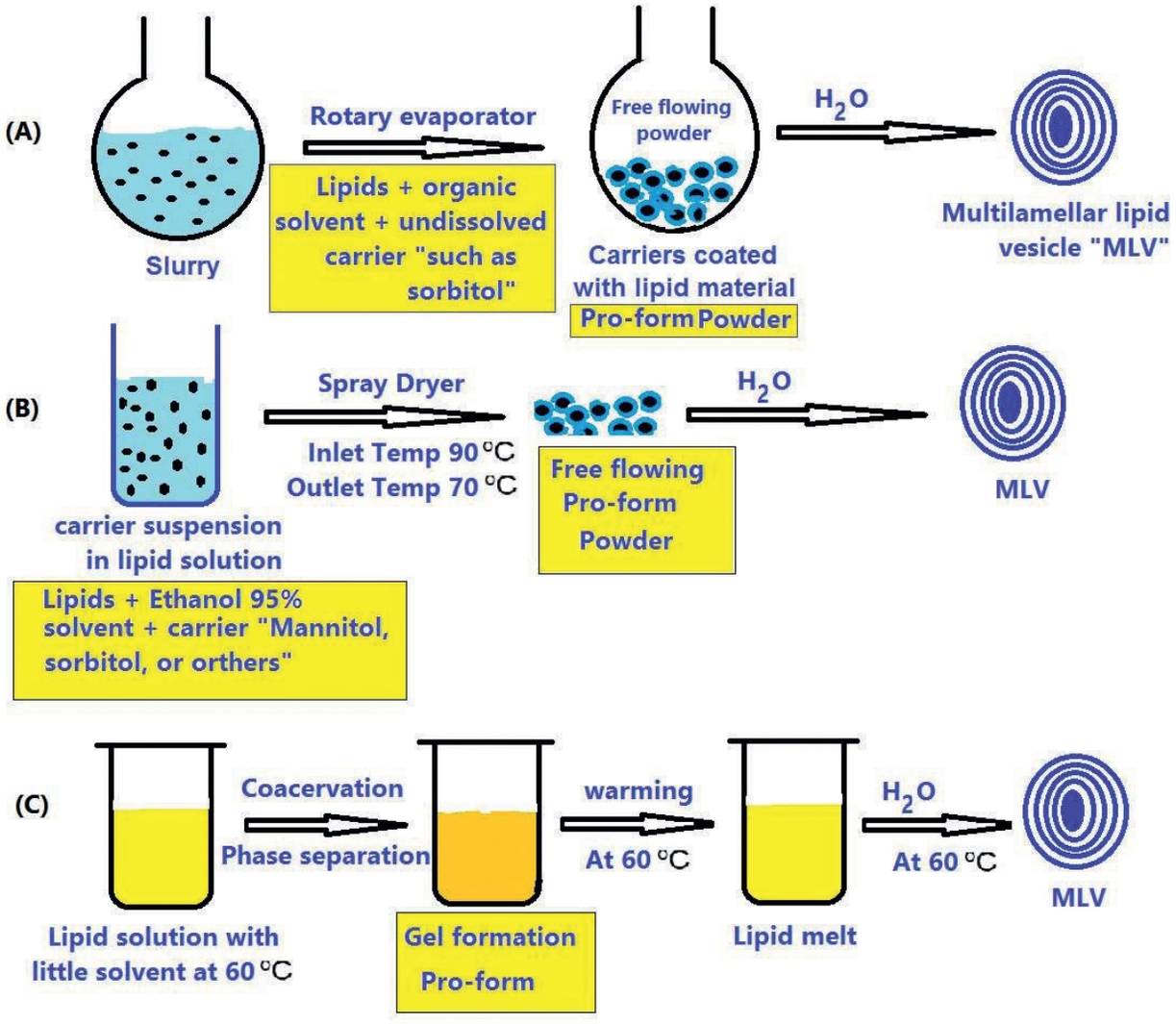


Figure 2. Different procedures of proforms preparation. (A) Slurry method, (B) spray drying method, and (C) coacervation phase separation method.

and hydrophobic molecules in the aqueous compartment and in the bilayer lipid membrane, respectively [15]. These niosomes are chemically stable, and no special conditions are required while preparation or storage, such as nitrogen atmosphere or low temperature. Niosomes are inexpensive alternatives of nonbiological origin to liposomes which are widely studied *in vivo* [16]. Moreover, they are extensively used as lipid carrier similar to liposomes physically, with particular properties, which can be exploited to attain different release characteristics and drug distributions [16]. Preliminary studies indicated that niosomes could prolong the plasma circulation of an entrapped drug and alter its distribution pattern and its metabolic stability [17]. Also, niosomal systems could prolong the contact time of a drug with the applied membranes in case of topical and transdermal applications [18]. Niosomes have many advantages over liposomes such as the lower cost, the greater chemical stability, and the ease of preparation and storage. Theoretically, a niosome formulation requires the presence of a particular class of nonionic amphiphiles dispersed in aqueous vehicle. Cholesterol as well as

fatty alcohols (e.g., myristyl, lauryl, cetyl, steryl, and cetosteryl alcohols) are added in order to prepare vesicles, which are more stable and less leaky [19]. Many investigators had reported a decrease in drug permeability across niosomal membranes as cholesterol concentration increased in the bilayers of niosomal vesicles [20]. In addition, stabilizers to enhance physical stability of niosomal dispersions might be included in formulations of niosomes to inhibit aggregation of vesicles by steric, electrostatic, or repulsive effects. Often a charged surfactant is included in the niosomal bilayers to create electrostatic charges, hence, repulsion between vesicles, thereby increasing their physical stability. The addition of dicetyl phosphate (negatively charging agent) or stearyl amine (positively charging agent) to the bilayers prevents the aggregation of the vesicles [21]. Stability of the niosomal vesicles can also be improved by using a substance (e.g., poly-24-oxyethylene cholesteryl ether (solulan C24)) providing steric barrier on the vesicle surface, which can prevent vesicles aggregation [22].

An increasing number of nonionic surfactants have been found to form niosomes for the encapsulation of hydrophobic and/or hydrophilic solutes [23]. The nonionic surfactants for preparing niosomal vesicles are usually single-alkyl chain surfactant and/or sorbitan esters. There are many examples belonging to different classes of nonionic surfactants that could be used in niosomes production such as crown ethers, glucosyldialkylether, polyglycerol alkylethers, and polyoxyethylene alkyl esters and ethers. These nonionic surfactant vesicles are prepared in the same way like liposomes and under different conditions give rise to either unilamellar type vesicles or multilamellar vesicles according to the method of production [24].

Proliposomes, proniosomes were introduced as free flowing powder and as liquid crystalline preparations for reconstitution just before use [13, 25]. Proniosomes are alternatives to proliposomes and are important from technical view point as they possess greater chemical stability and do not require special preparation or storage conditions as vacuum or nitrogen atmosphere (**Figure 2**).

2.2.2. Transfersomes

Transfersomes "the carrying bodies" are designed lipid vesicles especially for transdermal and/or topical delivery of wide variety of drug molecules. They offer an excellent approach for topical drug application especially the topical immunization. Transfersomes are analogous to liposomes vesicles but contain detergent "the edge activator" in their bilayers composition (**Figure 1**). They are called the ultradeformable carrier systems because they have high capacity of changing their shape via deformation and reformation mechanism, and passing through the natural pores in the stratum corneum (SC) (**Figures 1** and **3**). They can penetrate into the skin deeply and even reach the blood circulation. Transfersomes "the ultradeformable vesicles" containing reasonable amounts of detergent "the edge activator" did not produce lyses of human RBCs. They are very effective in transferring the bioactive drug molecules across the SC. They have the ability to penetrate through small pores "having a diameter of fivefold lower than their own diameter" present in the skin membrane. This indicates that a transfersome vesicle of diameter equaling 500 nm can pass across a membrane pore of 100 nm diameter or more.

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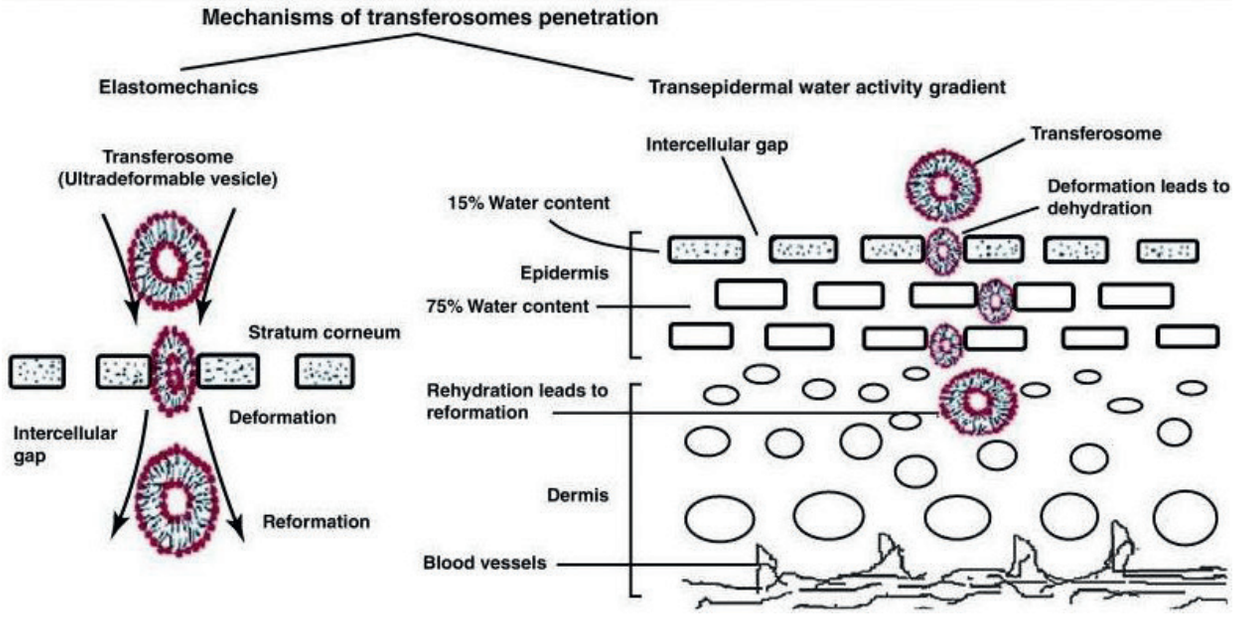


Figure 3. A schematic representation of an ultradeformable, mixed lipid vesicle (transfersome) penetrating a narrow pore. Adapted from Kumar, et al [111].

3. Formulation of gels containing lipid vesicles

For the preparation of gels containing liposomes, transferesomes or niosomes, a portion of the buffer required to form polymer hydrogels will be replaced by concentrated lipid vesicle dispersions loaded with the drug. The gels will be prepared by sprinkling the required amount of gelling agent gradually over the surface of that buffer containing the drug/lipid vesicles and mixed until homogenous gel was obtained [26–27].

3.1. The proposed mechanisms of enhancement of drug permeability using lipid vesicles

Several mechanisms have been proposed in order to explain the enhancement of the drug permeability across the skin membranes using lipid vesicles. El Maghraby et al. had fully described these mechanisms and here we will give short account on it [28].The possible mechanisms for drug and/or vesicular transport through the tough skin layers are shown in **Figure 4**.

1. **Free drug mechanism:** The mechanism concluded that the drug permeates the skin independently after releasing from the vesicles. Thus, the amount of drug that permeated the skin could be due to its own physicochemical properties and not due to the lipid vesicle composition. Many researchers do not support this mechanism as the vast majority recommended the effect of vesicles size and composition on the overall amount of the drug transport [28].
2. **Mechanism of penetration enhancing effects:** It was proven that surface-active agents, which are the backbone of the formulated lipid vesicles, could enhance the transdermal

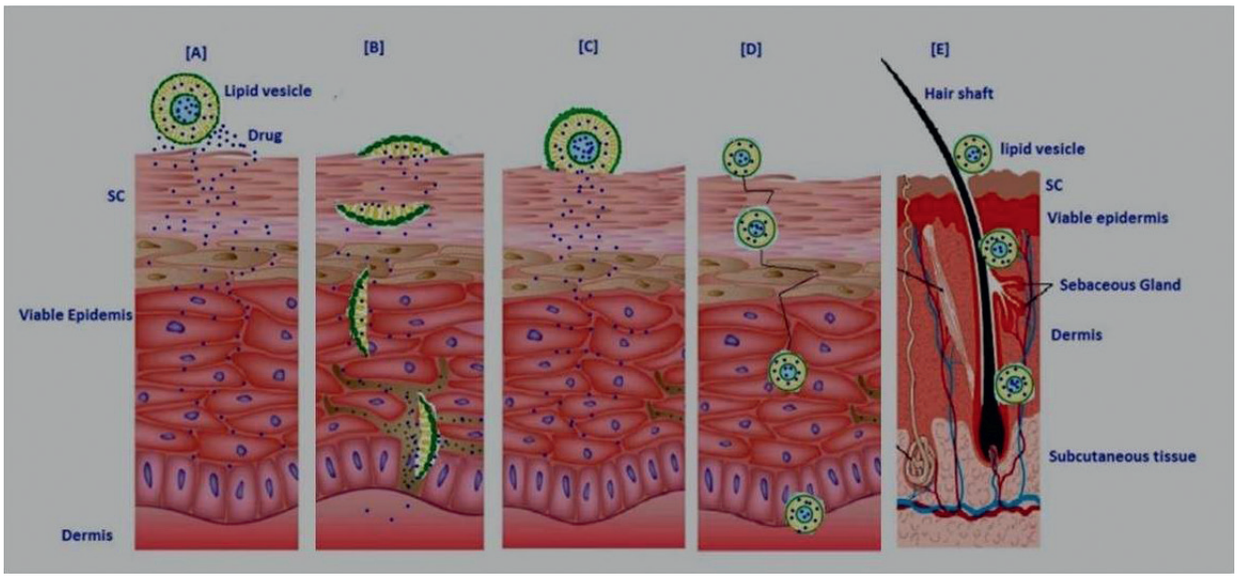


Figure 4. Possible mechanisms of action of liposomes as skin drug delivery systems. (A) It is the free drug mechanism, (B) it is the penetration enhancing process of liposome components, (C) it indicates vesicle adsorption to and/or fusion with the stratum corneum (SC), (D) it illustrates intact vesicle penetration into or into and through the intact skin (not to scale), and (E) Illustrates the penetration of the vesicles through hair follicle. Adapted from El Maghraby et al. [78].

delivery of drugs by lowering the permeability barrier of the skin and interacting with the SC *in vitro* [29]. On the other hand, studies also reported that for the drug molecules to be effectively transported across the SC, they must be entrapped within the lipid vesicles, suggesting that the vesicles are not considered as penetration enhancers, but they act as drug carrier systems [1].

3. **Fusion with the SC and/or vesicle adsorption to cells of SC:** The cells of SC may fuse and mix with lipid vesicles increasing drug partitioning into the skin. Otherwise, the lipid vesicles may adhere to the SC surface via adsorption mechanism and subsequently, drug partition inside the SC cells could happen. Thus, lipid vesicles could fuse with SC where they dissolve and unite with the membrane structure [30].
4. **Intact vesicular penetration mechanism into the skin**: Studies on liposomes based on electron micrography showed intact liposomal vesicles deep in the dermis. In these studies, the authors postulated that liposomal drug carriers could penetrate the epidermis. In addition, it was shown that vesicles can penetrate a ruptured or diseased SC as in case of eczema but cannot transport a skin with psoriasis or hyperkeratosis conditions [31]. On the other hand, Zellmer et al. [32], and Korting et al. [33] indicated that there was no evidence of intact liposomal carrier penetration after skin application of liposomes made from DMPC "1,2-dimyristoyl-sn-glycero-3-phosphocholine" or soy-lecithin.
5. **Mechanism of transfersome transport through the stratum corneum:** Transfersomes are of high surface hydrophilicity which respond to the hydration gradient across dermal tissue. They propel the vesicles through the transcutaneous channels giving transfersome vesicles the chance to act as noninvasive drug carriers. This is due to the fact that transfersome vesicles are of high bilayer membrane flexibility and sufficient skin permeability

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where the trans-barrier gradient acts on all skin membrane ingredients simultaneously but not to the same extent. As a result, the membrane changes its local composition under the influence of an anisotropic local (dehydration/hydration) stress, thus acting as a responsible, and smart material. The transfersomal vesicle thus deforms and passes through pores much smaller than the average vesicle diameter spontaneously in a self-regulated manner [34]. Then the hydrostatic pressure difference is responsible for the penetration of intact transfersome vesicles across the SC, i.e., the penetration of ultradeformable vesicles is a result of hydrotaxis and the permeation is governed by principles of elastomechanics [35].

6. **The process of noninvasive transport across the skin consequently involves:**

1. Reversible vesicle mediated opening between epidermal cells and/or lipids "intercellular hydrophilic pathways".
2. Strong response of transfersome vesicles "applied transdermally" to skin hydration gradient which is naturally occurring or an external transdermal electrical gradient.

4. Applications of hydrogels without and with lipid carriers for transdermal delivery of drugs

The different pharmaceutical applications of hydrogels, nanocarriers and their potential combinations are summarized in **Tables 1** and **2**.

4.1. Hydrogels for transdermal delivery of drugs

Application of formulation on skin surface is generally meant for the topical use of dermatological drugs for skin diseases. In this context, hydrogels have been widely studied for topical delivery of drug moieties. Several antifungal and antiinflammatory agents have been successfully formulated into hydrogel products using different polymers [36, 37]. Recently, adhesive hydrogel patches were fabricated, using sodium polyacrylate and carboxymethyl cellulose, for the topical delivery of triclosan in treating acne. *In vitro* permeation studies using hairless mouse skin revealed that a greater amount of drug has been transported into the skin layers [38].

Another application of hydrogel is its usefulness in treating wounds due to burn. The healing rate of these types of wounds is more rapid in a moist environment as compared to the dry technique. Thus, the biocompatible hydrogel polymers are likely to provide moist and healing environment in addition to its potential to protect the wound from bacterial infection. Moreover, these hydrogels could promote fibroblast proliferation and compensate fluid loss from body due to wound exudation. The hydrogels also allow greater entrapment of drug and provide controlled release, which favor rapid healing. Several hydrogel based formulations have demonstrated their potential in healing the skin wounds. Chitosan hydrogels have been widely used in wound healing applications, where they are not only a vehicle but also a medicament [39]. The ideal characteristics such as hemostasis,

Polymer	Type	Drug	Membrane /animal	Formulation type	Inference	References
Agarose	Natural	Alfuzoisn	Sprague-Dawley rats	Hydrogel patch	Prototype transdermal patch prepared with agarose successfully delivered alfuzosin in rats using iontophoresis	[68]
Chitosan	Natural	Berberine	Wistar rat skin	Hydrogel	Increased the permeation and skin deposition in presence of enhancers	[45]
		Liodocaine	Human	Hydrogel	Combination of chitosan membrane and chitosan hydrogel is a good transparent system for controlled drug delivery	[49]
		Diltiazem	Albino rats	Matrix/ membrane	Prolonged steady state drug plasma concentration was observed in membrane permeation controlled system	[46]
		Propranolol	Porcine skin	Hydrogel	Chitosan-laurate and chitosan-myristate hydrogels enhanced the drug diffusion through the skin	[48]
Dextran	Natural	Vitamin E	Rabbit skin	Hydrogel	Enhance the deposition in the skin and increase the stability	[50]
HEC/HPC	Natural	Prochlorperazine	DDY mice	Hydrogel	Pharmacodynamic activity shows the strong inhibitory effects after 4 h of application and extended over a period of time	[52]
Pectin	Natural	Chloroquine	Sprague-Dawley rat	Matrix patch	Plasma concentration of chlorquine by transdermal delivery was comparable to IV infusion	[51]
Poloxamer	Synthetic	Insulin	Sprague-Dawley rats	Hydrogel	Poloxamer hydrogels system could be used for the transdermal iontophoretic delivery of insulin	[119]
		Capsaicin	Wistar rats	Hydrogel	Significant enhancement in capsaicin delivery and greater pharmacodynamic effect by hydrogels compared to cream	[66]

Polymer	Type	Drug	Membrane /animal	Formulation type	Inference	References
Polyvinyl alcohol	Synthetic	Captopril	Wistar rat	Hydrogel	Transdermal delivery of captopril is significantly improved by iontophoresis	[69]
		Testosterone	Sprague-Dawley rats	Hydrogel	Controlled transdermal delivery systems can be developed using polyvinyl alcohol	[57]
Polyacrylamide	Synthetic	Salicylic acid	Hairless pig skin	Hydrogel	The diffusion of salicylic acid from the hydrogel is influenced by the cross-linking density, and applied electric field strength	[70]
pHEMA	Synthetic	Theophylline	Human	Hydrogel disc	Single application of the hydrogel disc provides therapeutically effective concentration of theophylline in 24 h and is maintained for days	[53]
Polyacrylamide, pHEMA, carbopol 934	Synthetic	Peptides	Hairless rat skin	Hydrogel	Permeability coefficient decreases with increase in molecular weight	[71]
PVP, HPC	Synthetic	Nalbuphine	Hairless mice	Hydrogel	Iontophoresis significantly increased the permeation nalbuphine from the formulated hydrogels	[72]
Alginate-Pluronic F127 composite	Semi synthetic	Selegiline	Porcine skin and nude mouse skin	Hydrogel	Linear permeation profile observed suggests the successful transdermal delivery of selegiline	[67]

Abbreviations: HEC, hydroxyethyl cellulose; HPC, hydroxypropyl cellulose; pHEMA, poly(2-hydroxyethyl methacrylate); PVP, poly vinyl pyrrolidone.

Table 1. Particulars of selected transdermal permeation studies carried out using hydrogels.

bacteriostasis, biocompatibility, biodegradability, etc. have made hydrogels an excellent material for wound dressing. Polyvinyl pyrrolidone-based hydrogels were also developed and employed for the successful application of honey in wound treatment, which exhibited greater healing compared with silver sulphadiazine cream [40]. This hydrogel is also utilized in the application of iodine [41]. Hydrogels of alginate, cellulose, and poloxamer were also used in the treatment of wounds [42–44].

The transdermal route is considered a promising path for delivery of molecules into the systemic circulation. This route overcomes major limitations of oral therapy and provides steady state drug delivery. In this context, hydrogels have played an integral role in the progress of

Formulation	Drugs	Model used	Major outcome	References
Chitosan hydrogel	Berberine	*In vitro*	Treatment of Leishmaniasis	[45]
		In vivo		
Chitosan hydrogel	Diltiazem HCl	Diffusion controlled	Systems are capable of achieving the effective plasma concentration for a prolonged period	[46]
		Membrane controlled		
Chitosan hydrogel	Propranolol HCl	*In vitro* permeation	Hydrogels provided more transcutaneous permeation of propranolol hydrochloride than the corresponding solution	[48]
Dextran hydrogels TTS	Vitamin E	*In vitro*	Improved Vitamin E poor stability and increased its topical delivery	[50]
Pectin hydrogel	Chloroquine	*In vivo*	The transdermal management of malaria	[51]
Acrylate hydrogel discs	Theophylline	Clinical study in preterm infants	Therapeutic concentrations of theophylline were achieved and maintained for up to 15 days after repeated application of discs	[53]
Poloxamer hydrogel	Piroxicam	*In vitro*	Various nonionic surfactants improved drug permeation across rat skin	[61]
Liposome suspension	Curcuminoids	*In vitro*	Increased cellular uptake and transdermal delivery of curcuminoids	[76]
			Enhanced and prolonged cytotoxic effects of curcuminoids	
Liposome gel	Triamcinolone acetonide	*In vitro*	Liposomal gel increased the concentration of triamcinolone acetonide five times higher in the epidermis and three times higher in the dermis, than application of the free drug gel	[79]
Liposome suspension and emulsion vehicle	Interferon	*In vivo* antimicrobial activity	Liposomes were better than w/o emulsion for treatment of cutaneous Herpes in guinea pigs	[80]
Liposomes; Cream	Tetracaiene	Clinical study	Liposomal tetracaine-produced anesthesia, which lasted at least 4 h after 1 h application under occlusion	[83]
			The cream formula has no effect	
Liposomal suspension	Miconazole nitrate	*In vitro*	Enhanced skin permeation and retention using liposomes compared to commercial cream	[85]
Liposomes suspension	Carboxyfluorescein	*In vitro*	Selective targeting into pilosebaceous units of hamster ears	[86]
Liposomes in chitosan/gelatin crosslinked with glutaraldehyde hydrogels	Calcein	*In vitro*	Controlled release	[92]

Formulation	Drugs	Model used	Major outcome	References
Liposomes in carbopol hydrogel and hydroxyethyl cellulose gels	Calcein and greseofulvin	*In vitro*	Improved release from carbopol gels compared to hydroxyethyl cellulose gels	[93]
Liposomes in chitosan gel	Carboxyfluorescein	*In vitro*	Delayed release	[94]
Proliposome monophasic system and PEG based ointment	Levonorgestrel	*In vitro* *In vivo*	The higher potential of proliposomal system for efficacious transdermal delivery of hydrophobic drugs compared to PEG ointments	[96]
Proliposomal gel	Exemestane	*In vivo*	Efficient carriers with high potential for the enhanced transdermal delivery	[97]
Niosomes, liposomes, and transferesomes	Tetanus toxoid	*In vivo*	Niosomes and liposomes showed weak immune response transdermally compared to transferesomes in albino rats	[99]
Proniosome gel	Estradiol	*In vitro*	Encapsulation efficiency was 100% High skin permeability	[100]
Niosomes	Lidocaine	*In vitro*	High flux across model lipophilic membrane High flux and shorter lag time across mouse abdominal skin compared with liposomes	[16]
Niosomes in chitosan gel	Methotrexate	Clinical study	Enhanced treatment of psoriasis	[101]
Niosomes in carbopol gel	Celecoxib	*In vitro* *In vivo*	Improved drug localization in deep skin layers and muscles Significant reduction in rat paw edema compared to conventional carbopol gels	[102]
Niosomes and liposomes	Tretinoin	*In vitro* *Ex vivo*	Niosomes give higher cutaneous drug retention than both liposomes and Retin A®commercial formulation	[105]
Proniosome in carbopol, CMC, and HPMC hydrogels	Ketorolac	*In vitro*	Enhanced drug release from niosomes prepared with Span 60 Improved absorption of celecoxib Improved bioavailability	[106]
Niosomes in sodium alginate and CMC hydrogels, emulgels and proniosomes	Ketorolac tromethamine	*In vitro*	Improved skin permeability from niosomal gels and emulgels Delayed drug permeability from proniosomes Enhanced antiinfalmmatory effects using rat paw edema model	[27]

Formulation	Drugs	Model used	Major outcome	References
Transferesomes "Transfersulin"	Insulin	*In vivo*	Only transfersulin produced marked hypoglycaemic effects in mice however, mixed micelles, liposomes, or insulin solution did not produce any hypoglycemic effect after transdermal application	[108]
		Clinical study	Transfersulin could be administered over an area of 40 cm^2 or less to deliver the basal daily supply of insulin to a typical type I diabetes patient	
Transfersomes	Triamcinolone acetonide	*In vivo*	Transfersomes of Triamcinolone-acetonide suppresses arachidonic acid-induced skin edema longer than the marketed products for topical treatment	[113]
Transfersomes	Hydrocortisone	*In vivo*	Therapeutic concentration lowered significantly to 0.1% after topical application to mice	[114]
Transfersomes	Dexamethasone	*In vivo*	Therapeutic concentration lowered to below 0.01% after topical application to mice	[114]
Transfersomes "cationic type"	DNA vaccines	*In vivo*	Induced strong humoral and cellular immune response after topical application to mice	[115]
Tranfersomes in carbopol hydrogel	Sertraline	*In vitro*	Enhanced release and permeability of poor soluble drug	[116]
		In vivo	No skin irritation after topical application to guinea pigs	
			Better antidepressant activity of transferosomal gel compared to the control gel	
Protransfersome gel	Levonorgestrel	*In vitro*	Better entrapment efficiency, better skin permeation and better stability compared to proliposomes	[117]
Proliposomal gel		*In vivo*	Eight-fold increase in peak plasma concentration of levonorgestrel after topical application to female rats	
Protransfersome gel	Cisplatin	*In vitro*	Improved site-specific and localized drug action in the skin	[118]
		In vivo	Protection against cisplatin genotoxicity and cytotoxicity	

Table 2. Pharmaceutical application of hydrogels, nanocarriers and their combinations.

transdermal drug delivery. This versatile hydrogel drug delivery system has been successfully utilized for the delivery of molecules into and through the skin. The use of hydrogels in transdermal delivery is primarily owing to their intrinsic properties such as controlled/sustained drug release for transdermal transport, higher stability, greater percutaneous absorption, desired functionality, and nontoxic nature. Additional advantages such as ease

of application, better skin compliance, skin hydration, improved drug effectiveness, convenience, compliance, safety and ease of fabrication of patch, and greater swelling have made them to triumph over other polymeric materials. Both passive and active delivery approaches have been used for the transdermal delivery of molecules by fabricating patches or gels or carriers using hydrogels (**Table 1**).

Prospective of hydrogels in the transdermal delivery of drug molecules by passive process has been extensively studied in the last few decades. Both natural and synthetic polymers were widely used in developing transdermal delivery system for passive delivery. The potential of chitosan in developing hydrogel-based transdermal drug delivery systems was demonstrated in several investigations. Tsai et al. have successfully delivered berberine through the skin by incorporating in a hydrogel formulation for the treatment of leishmaniasis [45]. This polymer was also utilized in developing hydrogel-based matrix diffusion controlled and membrane permeation controlled transdermal systems of diltiazem. The *in vivo* permeation studies in rat model signified the prospective of this polymer to deliver effective concentration of drug for a prolonged period of time [46]. Several studies were also reported wherein chitosan-based hydrogel transdermal systems have been successfully utilized [47]. Hydrogels of this polymer prepared by physical crosslinking method were utilized for transdermal delivery of propranolol [48]. Multiple functions of chitosan as a rate controlling membrane and as reservoir in the transdermal delivery system were also demonstrated [49].

Cassano et al. have developed dextran hydrogel transdermal system, which deposits greater amount of vitamin E in the skin and enhances the vitamin stability [50]. This transdermal system was prepared by adding the methacrylic groups on dextran and the product (methacrylated dextran) was further copolymerized with aminoethyl methacrylate. This is then esterified with transferulic acid to protect the vitamin E from photodegradation. Pectin, another polysaccharide, was also utilized in developing hydrogel matrix patch for the transdermal delivery of chloroquine [51]. Similarly, hydrogels of cellulose polymers (hydroxyethyl cellulose and hydroxypropyl cellulose) have also demonstrated their prospective in preparing different transdermal delivery systems [52].

Acrylate polymers were also extensively studied for their potential in developing various transdermal systems. A hydrogel disc consisting of 90% w/w poly-2-hydroxyethyl methacrylate, crosslinked with 10% w/w polytetramethylene oxide was used for the transdermal delivery of theophylline in infants (**Figure 5**). The repeated application of discs has delivered therapeutic concentrations of theophylline and maintained for a period of 2 weeks [53]. In another attempt, various poly(hydroxyethyl methacrylate) copolymeric hydrogels were synthesized using 2-hydroxyethyl methacrylate, methacrylic acid and *N*-[3-(dimethylamino)propyl] methacrylamide by redox free radical bulk polymerization technique and assessed for their prospective in transdermal delivery system using salbutamol sulphate [54]. Hydrogel prepared with different latex particles (polyacrylic acid-*co* sodiumacrylate, polyacrylic acid-*co*-2-ethylhexyl acrylate and poly*N*-isopropylacrylamide) within carboxymethyl cellulose matrix displayed thermosresponsive release of caffeine, signifying its potential in developing transdermal delivery systems [55]. There are reports wherein composite membrane of crosslinked poly(2-hydroxyethyl methacrylate) has been developed and successfully employed as rate controlling barrier for membrane transdermal drug delivery systems [56].



Figure 5. Hydrogel disc occluded with a transparent dressing on the abdomen of an infant of 29 weeks gestation. Adapted from Cartwright et al. [54].

Polyvinyl alcohol-based hydrogels were also developed and evaluated for the transdermal delivery of testosterone, both *in vitro* and *in vivo*. It was observed that the prepared hydrogel effectively delivering drug into the systemic circulation indicates the potential of this polymer in developing a transdermal system [57]. pH sensitive hydrogels have also been developed using poly-electrolyte, poly(acrylamide: maleic acid) for the delivery of terbinafine (cationic) wherein drug release was influenced by pH of media [58]. Alternatively, ionic polymers like N vinyl-2-pyrrolidone and methylene succinic acid have been successfully employed in developing the transdermal drug delivery systems [59]. Reports also exist wherein hydrogels are used to fabricate transdermal patch for the delivery of vaccine [60].

Poloxamer is probably one of the most extensively studied polymers in transdermal drug delivery. This polymer has demonstrated its potential as a transdermal vehicle for delivery by passive and active approaches [61, 62]. Several molecules of different categories are successively delivered using this polymer. The ideal concentration for the topical application of this polymer was found to be ~20% [63]. The prospective of this polymer in enhancing the transdermal delivery of molecules, providing controlled zero order release, prolonging therapeutic effect, delivering macromolecules was documented in the literature [64–66]. Composite thermogels of poloxamer were also utilized in transdermal delivery of certain molecules [67–72].

4.2. Liposomes for transdermal delivery of drugs

Liposomes are widely used as carriers due to the small size, both hydrophobic and hydrophilic properties, biodegradability, and high safety [73]. Several studies demonstrated the

great potential of liposomes as lipid vehicles, which are able to enhance drug permeation through the skin and also can act as local depot for the drug to sustain and control its delivery [74, 75].

A recent investigation showed that liposomes were induced to deliver and release very poor water-soluble drugs such as curcuminoids at a controlled rate to targeted cells [76]. Authors have evaluated and proved the contribution of liposomal curcuminoids to the antiproliferation as well as to the apoptosis of breast cancer cell lines. Another investigation done by El Maghraby et al. about the effects of liposomes after topical application indicated that liposomes could exert different functions, which may be local or enhanced systemic absorption [77]. They can improve drug deposition into the skin at the site of action providing local effects and reducing systemic absorption and drug side effects. Moreover, the liposomes as a drug carrier can provide high potential for transdermal delivery and targeted delivery to skin appendages. Liposomes as lipid carriers for triamcinolone acetonide showed increased drug concentration in SC as well as in the dermis by fivefold compared with a standard ointment of the same drug [78]. In one more research by the same authors, the incorporation of these liposomes encapsulating triamcinolone acetonide in a gel dosage form resulted in nonsignificant differences in drug concentrations in SC and dermis when compared with a gel containing liposome components as well as the free drug at the same concentrations [79]. Moreover, the topical delivery of interferon (peptide drug) from liposomes was greater than that from emulsion form (w/o) or aqueous solution when *in vivo* applied to cutaneous herpes simplex virus guinea pig model [80]. Egbaria et al. had employed a tape striping technique on guinea pig skin *in vitro* and liposomes showed increased deposition and accumulation of interferon into SC and deeper stratum [81]. It has been demonstrated that liposomes with lipophilic drugs such as progesterone or hydrocortisone "entrapped in the bilayer structure of the lipid vesicles" permeate the skin like the free drug itself. Conversely, glucose (highly polar molecule) enclosed in the aqueous compartment of liposomal vesicle was found not available for transport across the skin. It was suggested that direct transfer of the drug molecule from liposomal suspension to the skin occurs only when the drug is entrapped within the lipid bilayer [82]. Liposomes can also improve the local anesthetic activity of tetracaine and lidocaine where the cream formula has no effects [83, 84]. Ethanol containing liposomes (Ethosomes) enhanced the intensity and duration of benzocaine local anaesthetic effect [75]. The localizing effects or efficiency of liposomes was dependent on the lipid composition and method of preparation. In addition, the liposomal miconazole nitrate has shown to facilitate the localized drug delivery and improved its availability by a controlled release pattern, which enhanced the treatment of deep fungal infections [85]. In addition to the enhanced localized accumulation effects of liposomes, they can target drugs to skin appendages and improved transdermal delivery of drugs. Lieb et al. showed selective carboxyfluoresce in liposomes targeting into the pilosebaceous follicles of the hamster ears when compared with aqueous or alcoholic solutions containing 10% ethanol or even with 0.05% sodium lauryl sulphate, or propylene glycol donor vehicles [86]. Due to the highest follicular density in hamster skin and hairless mice skin as compared to human skin, a higher drug accumulation was observed in their skin suggesting the drug deposition from liposomes through the

follicular pathway [87]. This is true for hydrophilic drugs encapsulated into liposomes; however, highly lipophilic drugs could target the sebaceous gland and no significant differences in drug accumulation was observed when liposomes were compared with mixed micelles or ethanolic gels [88].

Liposomes as nanocarriers were reported to improve transdermal delivery of drugs. Ganesan et al. observed that after finite dose applications of lipophilic drugs to hairless mouse skin, greater amounts were delivered from liposomal vesicles compared to aqueous vehicles [82]. In addition, vesicles of fluid liposomes produced high percutaneous absorption and tissue distribution rather than skin accumulation [89]. Conversely, there are some reports which generally excluded a liposome transport process across the skin where they attributed their positive influence on increased skin permeability to a localizing effect as the drugs accumulated on skin surface or the upper layers of SC, hence, favoring their diffusion. This was done for lipophilic drugs such as ketoprofen where the drug was first complex with cyclodextrin and then encapsulated into liposomes [90, 91].The major aim of inclusion of liposomes into a hydrogel was to control the release of drugs and to stabilize the liposomal bilayer structure by creating a protective film on surfaces of liposomal vesicles. Ciobanu et al. had formulated chitosan/gelatin hydrogel by double crosslinking with glutaraldehyde and sodium sulphate/sodium tripolyphosphate to be used as matrices for the inclusion of calcein loaded liposomes [92]. Calcein, a model hydrophilic drug in small unilamellar vesicles (SUVs) and multilamellar vesicles (MLVs), was released from polymeric hydrogels for several days to weeks. In another study, liposomes prepared from phosphatidylcholine (PC) or distearoylglycero-PC and cholesterol (DSPC/Chol), and incorporating calcein or greseofulvin were formulated by thin film hydration technique. Calcein and greseofulvin release from liposomal gels using carbopol polymer was faster compared to hydroxyethyl cellulose and mixture gels [93]. Billard et al. prepared an innovative hybrid formulation, which was composed of a water-soluble model molecule "carboxyfluorescein" in liposomal vesicles and dispersed in tridimensional matrix of chitosan hydrogel [94]. Liposome dispersions in chitosan gel in water did not affect the gelation process absolutely. The release of carboxyfluorescein was delayed from the hybrid liposomes in hydrogel systems compared to the hydrogel matrix without lipid vesicles.

Taking into consideration the potential use of proliposomes for transdermal delivery of drugs, topical application of nicotine-loaded proliposomes under occlusive conditions was evident to sustain nicotine delivery across the skin [95]. In addition, Deo et al. had proven that the system proliposomes was superior to PEG-based ointment for the transdermal delivery of levonorgestrel (model hydrophobic drug) [96]. Moreover, proliposomal gels prepared and evaluated for transdermal bioavailability of exemestane (a novel steroidal aromatase inactivator used in the treatment of advanced breast cancer) were compared with control oral suspension of the drug [97]. Proliposomal gels offered high potential and was efficient carriers for the enhanced sustained transdermal delivery of Exemestane. Proliposomal gel showed greater percentage of inhibition of edema when compared to marketed diclofenac gel in the treatment of rheumatoid arthritis. They also exhibited superior stability when compared to traditional liposomes, thereby increasing its potential application in transdermal delivery systems [98].

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4.3. Niosomes for transdermal delivery of drugs

One of the most useful advantages of niosomes is that they greatly enhance the uptake of drugs via transdermal route. Transdermal drug delivery using niosomes is widely used in cosmetics. Niosome-entrapped antibiotics were successfully used to treat acne. The penetration of drugs into the skin was greatly enhanced as compared to unentrapped drug. The noninvasive transdermal vaccination via topical application of niosomes is also being researched. Gupta et al. has shown that niosomes of tetanus toxoid (along with liposomes and transfersomes) can be used for transdermal immunization [99]. However, the current results of niosomal topical immunization allow only a weak immune response, and thus more research needs to be done in this field. The encapsulation efficiency of estradiol in proniosomes made from Span 40, Span 60 was 100%, and the permeability of the drug across the nude mouse skin was high as reported by Fang et al. [100]. Lidocaine and lidocaine hydrochloride loaded nonionic surfactant vesicles were formulated using Tween 20 and cholesterol, and tested for their local anesthetic effects [16]. The diffusion experiments indicated high flux of charged lidocaine (lidocaine hydrochloride) through a model lipophilic (Silastic™) membrane and found to be possible only after vesicle formation. In addition, the permeation of the drug from niosomes through mouse abdominal skin showed higher flux and shorter lag times compared with liposome formulations. Methotrexate-loaded niosomal vesicles in chitosan gel were used in the treatment of psoriasis by double blind, placebo controlled study on healthy human volunteers and psoriasis patients [101]. Kaur et al. showed 6.5 times higher drug deposition in deep skin layers and muscles from celecoxib niosomal gels compared with carbopol gel indicating better drug localization with niosomal gel [102]. In the same study, a significant reduction of rat paw edema was resulted after administration of niosomal formulation compared to that of applying conventional gel. Psoriasis area severity index (PASI) was the measure for the severity of the disease. The reduction in PASI scores after 12 weeks of niosomal methotrexate gel topical application was found to be threefold with better clinical efficacy, tolerability and patient compliance. Niosomes were also included in the treatment of vitiligo. Elastic cationic niosomes composed of tween 61/cholesterol/dimethyl dioctadecyl ammonium bromide at 1:1:0.5 molar ratio were effectively used for the dermal delivery of tyrosinase encoding plasmid. Their percutaneous absorption across exercised rat skin showed greater flux compared with the nonelastic niosomes. The application of pMEL34-loaded elastic cationic niosomes in melanoma cell lines gave four times increase in tyrosinase gene expression compared with the free and the plasmid in nonelastic niosomes which lead to efficient topical delivery in vitiligo therapy [103]. Tretinoin (vitamin A metabolite), is topically applied for the treatment of skin diseases such as acne, psoriasis, and photoaging. The drug has high chemical instability and skin irritation, which limited its topical administration [104]. However, the drug transdermal delivery using niosomes and liposomes as vehicle carriers showed more upper cutaneous drug retention than commercial formulation "RetinA®" [105].

Ketorolac proniosomes of Span 60 and Tween 20 and mixed with carbobol, carboxymethyl cellulose (CMC) or hydroxypropylmethyl cellulose (HPMC) hydrogels were evaluated by Alsarra et al. [106]. They found that the drug release was higher from niosomes prepared with Span 60 than from the HPMC gel as control due to the formation of elution channels

and loss of vesicular structure. However, authors did not give any scientific reason for that explanation. Conversely, Mokhtar and Shehata showed the formation of greater vesicles after niosome/hydrogel admixture and explained this by the vesicles crack and reformation during the preparation procedure, which improved ketorolac tromethamine leakage to the outside vehicle (**Figure 6**) [27]. A recent study indicated that no percutaneous permeation

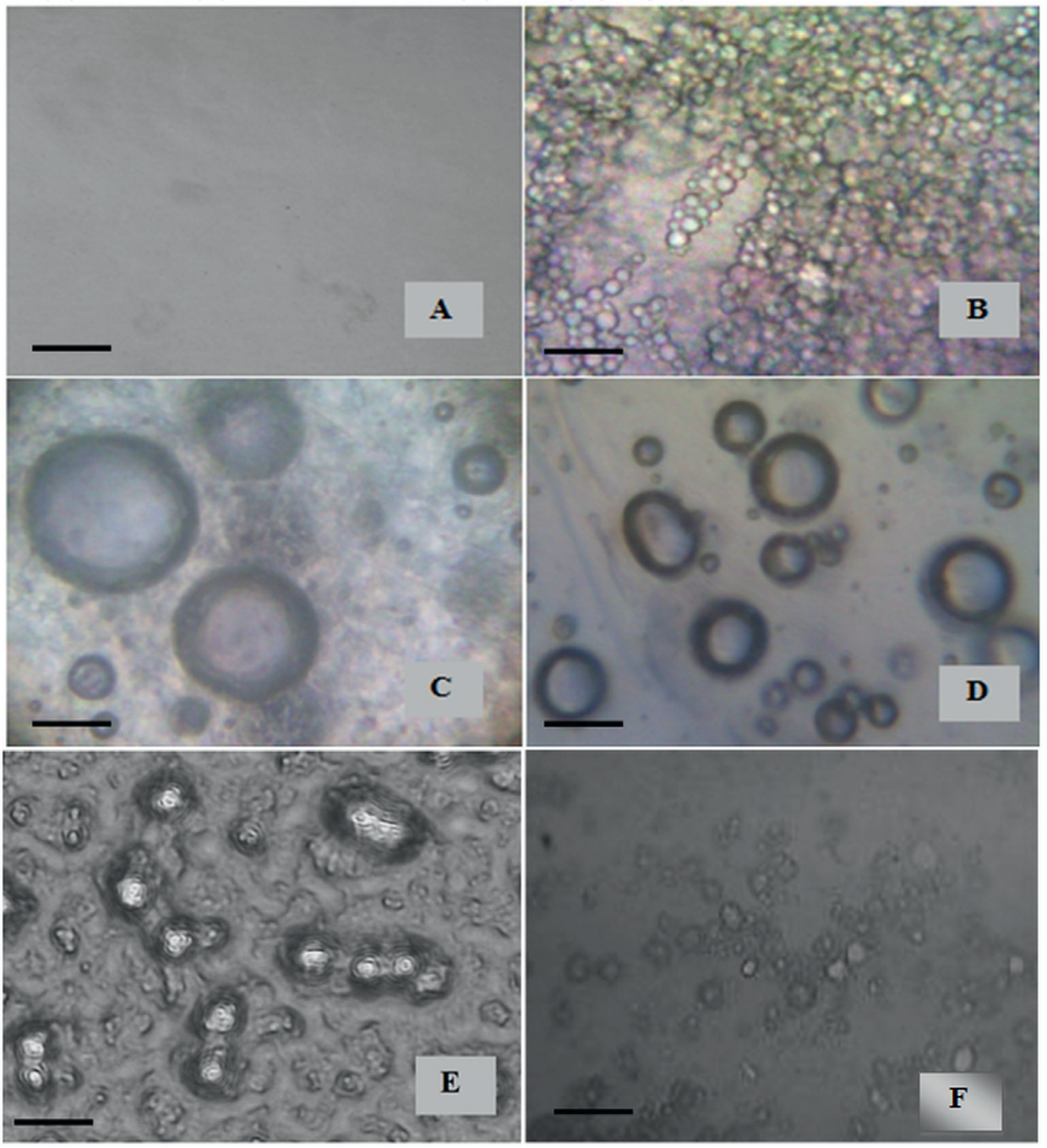


Figure 6. Micrographs (magnification power is 40×) of alginate gel (A), emulgel (B), niosomal gel (C), niosomalemulgel (D), proniosomes (E) and niosomes suspension (F). Adapted from Mokhtar and Shehata, its first publication in J Drug Del Sci Tech. With copywriter permission [27].

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was achieved when using submicellar solution of pluronic and sucrose esters containing free Sulfadiazine sodium or when the skin was pretreated with blank niosomes or submicellar solutions of the surfactant free of the drug and only the drug niosomal vesicles can do enhancing the skin permeability [107].

4.4. Transfersomes for transdermal delivery of drugs

The use of transfersomes technology is an innovative approach to increase the transport of substances through the skin. Nonocclusive administration of drug moieties using transfersomes is useful for noninvasive drug delivery of therapeutic proteins transdermally. Transdermal administration of diverse molecules with ultradeformable vesicles also permits targeted skin delivery or preferential delivery into the deep tissue of the dermis under the site of application.

Transferesomes have high suspension-driving pressures, which can eliminate the mismatch effect of carrier and pore size. This can be considered true for the transfersomes with a size not more than threefold the size of transdermal pores. The transcutaneous glands or hair follicles are well known to play a role in the process of molecular diffusion across the skin. However, such channels are too impermeable to large molecule such as insulin transdermally [108]. This could explain why a topically applied insulin in the mixed-lipid micelles or liposomes had nonsignificant antidiabetic effects. Transfersomes have a higher flexibility and stability than liposomes which allows them to penetrate through the human skin. The incorporation of insulin molecules into the vesicle of these lipid particles (transfersulin) results in a considerable insulin transport through the skin into the blood stream in mice and to a lower extent in humans [108]. Moreover, transfersomes can deliver an antigen to the lymphatics from where they can be transferred to lymph nodes. The antigens are then phagocytosed and presented to the T-cells in the lymph nodes. Thus, transfersomes are very important carriers for transdermal delivery of antigens and are under investigation for use in human vaccination development [109–110]. The transdermal enhancement of drug permeability using these ultradeformable vesicles does not depend upon the concentration gradient and mainly work on the principle of hydrotaxis and elastomechanics as reported by Kumar et al. [110].

The transfersomes deform and reform but remain intact during the transportation of the loaded drug to the target tissues under the skin application site. These carriers which are driven by the local water gradient across the skin barrier could be engineered to achieve a localized and high drug concentration at the application sites and deep inside the dermis. This way of drug administration can abolish any local and/or systemic adverse drug effects, and often increase the drug potency. Also, the local clearance through the cutaneous microcirculation is avoided, which permits the drug delivery deep into the muscles or joints. Therefore, transfersomes greatly increase the ratio of drug concentration in the target tissue more than the systemic drug concentration when compared to other formulations "liposomes or niosomes of the drug", which inherently enhances the drug safety profiles. In addition, the transfersomes could be targeted to the macrophages if suitably designed, thus, they have sufficient immune-adjuvant action. After topical application of transfersomes, they showed comparable titer values with their intradermal counterparts; however, they required lesser dosages [109]. Transfersomes encapsulating bacterial gap junction proteins gave rise

to circulatory antibodies against the gap junction proteins when applied topically. It was interesting that the antibodies titer value was found to be greater than that produced after subcutaneous injection of the gap junction proteins [111].

The study done by Kim et al. has vividly shown that the ultradeformable cationic vesicle (cationic transfersomes) formulation has several characteristics of being a good nonviral vector system, for instance, high transfection activity and long retention time [112]. This formulation was prepared using a cationic lipid, 1,2-dioleoyl-3-trimethyl- ammonium propane chloride (DOTAP) and sodium cholate, and it was found to be capable of transfecting several cell lines as well as penetrating the intact skin of mice when transdermally applied. In addition, this formulation is found to be stable and has shown 6 days of gene expression, an essential factor for an efficient gene therapy. Therefore, it is developed further as either invasive or noninvasive gene delivery system.

Topical usage of triamcinolone acetonide with ultradeformable vesicles resulted in reduction of the necessary drug dose to the levels of 0.01 wt% (10-fold lower drug dosage compared to cream or lotion preparations). Epicutaneous drug administration of these highly deformable carriers was also observed to prolong the biological response time markedly and to increase the reproducibility of the biological drug action [113]. In another study done by Cevc and Blume, either hydrocortisone or dexamethasone formulations in a suspension of very deformable vesicles (transfersomes) have significantly lowered the therapeutically relevant concentration range to 0.1 wt% and may be lower than 0.01 wt%, respectively [114]. This is lower than the respective concentrations used in commercial hydrocortisone and dexamethasone products "0.25–2.5 wt% (mainly 1%) and 0.03–0.1 wt%, respectively". The biological response time for the local corticosteroid action was prolonged and the sensitivity of dexamethasone in very deformable vesicles to abrasion was diminished. These findings confirmed the expectation that very deformable carriers offer several advantages for transdermal delivery of corticosteroids into the skin. Cationic transfersomes were formulated and tested for topical immunization using cationic transfersomes based DNA vaccine. They were capable of inducing strong humoral and cellular immune response and offered all the advantages of DNA vaccines, and overcome the disadvantages of classical invasive methods of vaccination [115]. Transfersomal gels prepared by Gupta et al. using Span 80, soya lecithin, and carbopol was found to enhance skin delivery of sertraline (antidepressant drug) due to excellent release and permeation of the drug [116]. They found no skin irritation after transdermal application of the gel formulation containing transfersomes. Since a properly designed ultradeformable vesicles could even claim the transport of drug (of different sizes, even large peptide or DNA) equivalent to the subcutaneous injection and this technology may provide effective tool for noninvasive therapy. The enhanced transdermal delivery of bioactive molecules by transferesomes also opens new challenges for the development of novel therapies.

Protransfersomal gels of levonorgestrel were developed for transdermal contraceptive use [117]. Authors indicated that the protransfersomal gels possessed better stability, better skin permeability, and greater encapsulation efficiency than proliposomal formulation. Recently, protransfersome showed better noninvasive delivery of cisplatin in cutaneous squamous cell carcinoma [118]. They have improved site-specific and localized drug action in the skin; hence, they provide a better option for dealing with serious diseases of skin such as squamous cell carcinoma. In addition, they had high potential as topical drug delivery system with protection against genotoxicity and cytotoxicity of cisplatin.

5. Conclusion

This review article provides valuable information regarding the hydrogels, emulgels and their combination with lipid nanocarriers "liposomes, niosomes and transferesomes" for topical and transdermal drug delivery. It has been shown that all of these systems have great potentials, being able to deliver both lipophilic and/or hydrophilic active ingredient via transdermal route of administration. The inclusion of lipid vesicles into hydrogels could enhance their stability, prolong drug release, enhance transdermal permeability, and increase localization of the drug in the skin. Proforms of the lipid vesicles could also improve site-specific and localized drug action in the skin. In order to optimize these drug delivery vehicles, a greater understanding of polymer and biological interaction mechanisms is required. Hydrogel combinations with lipid nanocarriers could be of great potential for increasing transdermal drug delivery and clinical research in the future.

Declaration of interest

Authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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