REVIEW ARTICLE

Dermal delivery of drugs using different vesicular carriers: A comparative review

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Many skin diseases are based in the dermal layer of the skin like-acne, alopecia, psoriasis, herpes zoster, etc. Conventional topical formulations have not proved to be effective in managing these conditions because of poor retention in the skin. Some formulations do not penetrate through the stratum corneum and some pass through the skin very quickly. Therefore, there is need to develop a strategy to deliver drugs to the dermis for better management of these conditions. Vesicular systems like liposomes, niosomes, ethosomes and transfersomes have been used by many researchers to localize drugs in the dermal layer and have been fairly successful. Some vesicles were found to be more effective in retaining drug to the skin and some were more effective in transdermal delivery. This article summarizes and compares the work done in the last decade on this topic and provides a conclusion.

Key words: *Dermal delivery, ethosome, liposome, niosome, transfersome, transdermal*

INTRODUCTION

Substantial research has been carried out in recent years on bilayer vesicle systems for dermal and transdermal drug delivery. Liposomes, niosomes, tranferosomes, ethosomes are some of the prominently studied types of these vesicles made from different types of material. Initially, they were extensively researched with the approach to deliver drugs to systemic circulation through skin by Honeywell-Nguyen.[1-3] But in many cases they were not found to be effective in doing so, rather they retarded the rate of penetration of the drug through skin and created a localization effect.[4,5] Many authors have reported such effect and a few reviews have also been published on this topic.[6,7] These vesicles are very versatile and have shown encouraging results in topical preparations. Today they are one of the most popular strategies to overcome penetration problems through the skin.

There are several pathological and cosmetic problems that have their origin in the skin and require the drugs to be delivered to the different layers of our skin. Some of these conditions are not life-threatening but have significant effect on an individual's appearance, such as acne, alopecia, hirsuitism, dermatitis, vitiligo and psoriasis. Some conditions are infectious such as herpes simplex, herpes zoster, plantar warts, scabies and fungal infections, and some are cancerous in nature such as Bowen's disease, basal cell carcinoma, squamous cell carcinoma, etc. Formulations using suitable vesicular carriers can be prepared for the treatment of these conditions and can have better results than conventional topical formulations.

The scope of this article is to discuss the various carrier systems and their suitability as agents for enhancing drug retention in the skin.

Skin

We will briefly review the structure of skin before proceeding to the vesicular systems. The skin can be broadly divided into the epidermis, dermis and subcutaneous fat layer [Figure 1]. The topmost layer of the epidermis is the stratum corneum (SC), which is also the main hurdle in dermal and transdermal drug delivery. Its barrier properties can be attributed to its structure that represents a 'brick and mortar' arrangement.[8] It is made of 25-30 layers of flat dead cells called corneocytes which are analogous to bricks

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Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.107558

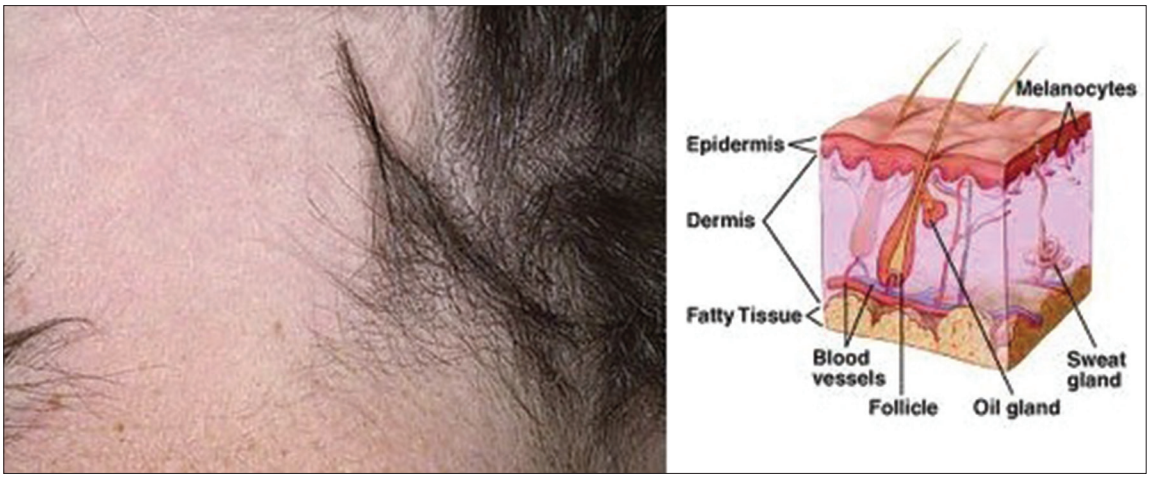

Figure 1: Different layers of skin and hair loss in alopecia

and the intercellular space is filled with lipids which are analogous to the mortar. The lipids are released from the lower lying lamellar bodies and are composed of ceramides, cholesterol and large chain fatty acids. The second layer is the stratum lucidum which is present only in some regions like fingertips, palms and soles. It consists of 3-5 layers of corneocytes with thickened plasma membranes. The middle layer is known as stratum granulosum. Here the keratinocytes undergo apoptosis (programmed cell death). This layer contains the lamellar granules which effuse the lipid-rich secretion which fills the intercellular space of the above lying layers. The second last layer is the stratum spinosum. This layer is also referred to as the "spinous" or "prickle-cell" layer. This appearance is due to desmosomal connections of adjacent cells. Keratinization begins in the stratum spinosum.

The bottommost layer, stratum basale, has cells that are shaped like columns. This layer has some stem cells that divide and push already formed cells into higher layers. As the cells move into the higher layers, they flatten and eventually die.[8]

Liposomes

Liposomes are vesicles made of lipid bilayers. They were discovered by Bangham and colleagues.[9] Both natural and synthetic phospholipids are used as the major component of liposomes. Cholesterol is added in most formulations as a structure stabilizer which acts by providing rigidity to the bilayer membrane above the phase transition temperature (Tg) and makes the membrane less ordered below the Tg.[9] The drug can be entrapped in the aqueous region inside the vesicle or in the bilayer membrane depending on its nature. Hydrophilic drugs are entrapped in the aqueous volume inside the vesicle and hydrophobic drugs dissolve in the lipid membrane.

The first reported work on liposomes for dermal delivery was by Mezei and Gulasekharam.[10,11] They compared the retention of triamcinolone acetonide in the epidermis and dermis using a liposomal-based lotion and gel with conventional lotion and gel of the free drug. With the liposomal gel the retention was five times higher in the epidermis and three times higher in the dermis for the model drug.

A lot of researchers reported the potential of a liposomal local anesthetic formulation to provide topical anesthesia of the skin.[12] Tetracaine base (0.5%) was encapsulated into multilamellar phospholipid vesicles. The topical anesthetic effects of the liposomal and a control (Pontocaine® cream) preparation were evaluated by pinprick technique in adult volunteers. Liposomal tetracaine produced anesthesia, which lasted at least 4 hours after 1 hour application under occlusion. Pontocaine cream was ineffective. The liposomal formulation appeared to be suitable to provide long lasting anesthesia of the skin with low drug concentration.

In 1994 Fisher R.[13] measured the plasma tetracaine concentration versus time profiles for liposome-encapsulated tetracaine (LET) versus nonliposome-encapsulated tetracaine (NLET) after topical application to open wounds in six rabbits (three in LET and three in NLET). H3-tetracaine preparations of LET or NLET were applied randomly to uniform dermal lacerations in anesthetized rabbits. Plasma tetracaine concentrations (ng/mL) of arterial blood samples obtained were measured at predetermined intervals by isotope tracer assay. Results showed the peak plasma tetracaine concentration (Cmax) and the time to Cmax were 40.8 ± 5.1 ng/mL and 40.1 ± 7.3 minutes for LET, and 117.8 ± 9.7 ng/mL and 49.1 ± 50.2 minutes for NLET. Plasma tetracaine concentrations at all samples times were significantly lower for LET versus NLET. Liposome encapsulation of topically applied tetracaine significantly decreases both the peak and overall plasma tetracaine concentrations compared with the nonencapsulated form. The data suggest that liposome encapsulation of topically applied local anesthetics such as a solution of tetracaine, adrenaline, and cocaine, might reduce the potential systemic toxicity caused by rapid absorption of these compounds.

In another study by Foldvary, *et al*.[14-16] the fate of liposomes and the encapsulated drug was studied after topical application in human. Lidocaine applied on the forearm of human volunteers produced greater local anesthetic effect in the liposomal form than in the cream form ($P \leq 0.001$ after 1 h application). Autoradiography demonstrated higher concentration of [14] C-lidocaine in the epidermis and dermis of guinea pigs treated with liposome-encapsulated lidocaine as opposed to lidocaine in Dermabase® cream. Electron microscopic observations, using colloidal iron as an electrondense marker, indicated that intact liposomes penetrated into the skin and deposited in the dermis where they acted as a slow release depot system. A liposomal reservoir system bearing the local anesthetic, benzocaine, was also developed for controlled and localized delivery via topical route.[17] The liposomal suspension was incorporated into an ointment and gel base. The developed systems were studied for various physical and kinetic attributes *in vitro*. The systems delivered the drug at a controlled rate over 24 hours whereas plain drug ointment showed a rapidly decreased release rate over 24 hours, with more than 92% released. The drug delivery across human cadaver skin following liposomal ointment application was noted to be considerably slow. The *in vivo* study revealed a longer duration of action in the case of liposomal formulations. An effort was made to study the effect of ultrasound as a reversible means to effect pulsatile delivery of the drug from the liposomal depot. The work proved the potential of liposomes as a slow release vehicle which follows apparent zero order kinetics. In a recent study, Manconi[18] conducted *ex vivo* studies for diclofenac entrapped in liposomes. On addition of Transcutol®, diethylene glycol monoethyl ether (Registered product of Gattefosse), a solubilizer for poorly soluble drug to liposomal preparation, better permeation and less skin retention was observed. Similarly, minoxidil liposomes containing Transcutol also reduced skin retention.[19] Therefore use of penetration enhancers with liposomes reduces their ability to retain drugs in the skin for long time.

Fresta and Puglisi in 1997[20] worked on liposomes prepared from skin-lipids to improve corticosteroid delivery in the deep layers of skin and hence, improve their therapeutic effectiveness. In this study, skin-lipid liposome formulations and phospholipid-based liposomes were prepared by hydrating a thin lipid film followed by extrusion through polycarbonate filters. The liposomes produced from this process were unilamellar with a mean size of 100 nm and a narrow size distribution. The steroidal anti-inflammatory drugs selected were situated in the bilayer structures of the vesicles. Skin-lipid liposomes provided the highest drug disposition within the deeper skin layers, i.e., in the epidermis and dermis. The therapeutic effectiveness was evaluated by measurement of the blanching effect following UV-induced erythema. Skin-lipid liposomes showed a 6 and 1.3 times higher blanching effect than that obtained with a control formulation ointment and the phospholipid-based liposome formulation, respectively. Skin-lipid liposomes also produced a reduction in drug levels in the blood and urine. These findings were supported by the body distribution of the drugs in guinea pigs after topical treatment. In particular, skin-lipid liposomes provided a corticosteroid uptake in the thalamic region (site of corticosteroid collateral effects) 5.1 times lower than the control formulation. Skin-lipid liposomes appeared to be a suitable corticosteroid delivery system, increasing the pharmacological effectiveness and reducing possible side effects.

Niosomes

Niosomes are also bilayer vesicles almost similar to liposomes except the fact that they are made up of nonionic surfactants rather than phospholipids. They were introduced by Handjani Vila, *et al*. in 1979.[21] The most commonly used surfactants for making niosomes are Spans, Tweens and Brij. Some rarely used ones are Wasang®, Gemini and Bola surfactants.

Niosomes have certain advantages over the other types of vesicles particularly in terms of oxidation stability. They are more stable than carriers made from phospholipids and are not very susceptible to oxidation. They require nonionic surfactants which are cheaper than phospholipids and there is no need for expensive ingredients such as solubilizers like Transcutol or edge activators like egg phosphatidyl choline and bile salt.[22] They are also less immunogenic.

Tretinoin-loaded niosomes were prepared from Oramix® (CG110 and NS10) and Brij® 30 in the presence of cholesterol, dicetyl phosphate and stearyl amine by Manconi, *et al*., 2006.[23-25] MLVs and UVs were prepared of different compositions and charge. The study helped understand the thermodynamic activity of the drug, the morphology of niosomes and their skin retention ability. The different formulations were evaluated for their dermal delivery efficiency using newborn pig ear skin. The niosomal formulation made from Brij® 30/DCP showed the highest skin accumulation which was approx 2.5 times more than the highest skin accumulation achieved by a liposomal formulation made from P90/DCP. Similarly Tabbakhian, *et al*. in 2006[26] formulated noisomes (MLVs) from Brij® series and Span 40 with cholesterol and DCP. They also prepared liposomes from DMPC (dimyristoyl phosphatidylcholine) or egg lecithin with cholesterol and DCP. *In vitro* permeation and deposition studies were carried out using freshly sacrificed hamster flank skin. The amount of finasteride deposited in different compartments of the skin was lower in Brij 72 and Span 40 niosomes but higher in Brij 97, Brij 76: Brij 97 niosomes and DMPC liposomes. The results of the above two studies, reveal that the accumulation of drug in skin, depends on the nature of major constituents of the vesicles rather than its morphology.

Minoxidil niosomes have been prepared by Mura, *et al*. in 2007[19] and Balakrishnan, *et al*. in 2009.[27] S Mura prepared

Table 1: Comparative summary of *in vitro* studies for skin accumulation and permeation using niosomes and liposomes

Drug/Marker and Investigator	Model membrane for *in vitro* studies	Type of vesicle	Composition	Maximum skin retention	Maximum skin permeation
Tretenoin (TRA) Manconi *et al*., 2006[24]	Newborn porcine ear skin	Liposomes	P90/DCP	32.67±8.98 μg/cm^2	0.1226±0.004 μg/cm^2/h
		Niosomes	Oramix® Brij®30	79.47±8.44 μg/cm^2	0.0987±0.0066 μg/cm^2/h
Finasteride (FNS) Tabbakhian *et al*.[26]	Hamster flank skin	Liposomes	EL, DMPC	App. 88.2% of dose applied	1.7±0.3% of applied dose
		Niosomes	Brij 52/72/76/97 Span 40	App. 90.3% of dose	2.9±0.7% of applied dose
Minoxidil Mura *et al*.[19]	Human skin	Liposome	PL90, SL	29.7±9% of dose in epidermis 1.6±0.81% in dermis	Not detected
		Niosome	Oramix (NS10 and CGS110)	9.1±3.5 % in epidermis 0.54±0.24% in dermis	Not detected
Minoxidil Balakrishnan *et al*.[27]	Hairless mice skin	Niosomes	Brij52 Span20/40/ 60	19.41±4.04 % of applied dose	Not determined
Lidocaine Hal *et al*.,[28]	Human stratum corneum	Niosome	Wasag-7	Not reported	542±190μg/cm^2/h
Enoxacin Fang *et al*.,[62]	Intact mouse skin	Liposomes	PL90/75	74.06±7.35 ng/mg	44.97±8.25 μg/cm^2 in 48 h
		Niosomes	Span40/60/ 80	100.11±11.91 ng/mg	85.79±19.20 μg/cm^2 in 48 h

DCP: Dicetylphophate, PL90: Phospholipon 90, SL: Soya Lecithin, EL: Egg Lecithin

multilamellar liposomes (MLV) using soy phosphatidylcholine at different purity degrees (Phospholipon 90, 90% purity, soy lecithin, 75% purity) and cholesterol, whereas niosomes were made with two different commercial mixtures of alkylpolyglucoside surfactants (Oramix NS10, Oramix CG110), cholesterol and dicetyl phosphate. Skin penetration and permeation experiments were performed *in vitro* using vertical Franz diffusion cells and human skin. Penetration of minoxidil in epidermal and dermal layers was greater with liposomes than with niosomal formulations and the control solution. These differences might be attributed to the smaller size and the greater potential of liposomal carriers to target skin and skin appendages. Balakrishnan, *et al*. formed niosomes from polyoxyethylene alkyl ethers (Brij™) or sorbitan monoesters (Span™) with cholesterol. Skin permeation studies were performed using static vertical diffusion Franz cells and hairless mouse skin treated with either niosomes, control minoxidil solution (propylene glycol-water-ethanol at 20:30:50, v/v/v) or a leading topical minoxidil commercial formulation Minoxyl®. It was observed that both dialyzed and nondialyzed niosomal formulations enhanced the percentage of dose accumulated in the skin (1.03 ± 0.18 to 19.41 ± 4.04%) compared to commercial and control formulations (0.11 ± 0.03 to 0.48 ± 0.17%). The results also showed that the type of surfactant, cholesterol and amount of drug added altered the entrapment efficiency of niosomes.

In 1995 Hal, *et al*.[28] prepared nonionic surfactant vesicles (NSVs) from polyoxyethylene alkyl ether or a sucrose ester (Wasag® 7) containing charged and uncharged lidocaine. Comparative diffusion studies were carried out using human SC between niosome entrapped 9.2 mM of Lid: HCl (Lidocaine hydrochloride) and 5.8 mM of Lid: HCl solution. The results of the study showed that the flux from the NSV suspension (436 ± 175 ng/hour per cm^2) was not significantly different from the flux of the control solution (542 ± 190 ng/hour per cm^2). In 2002, Carafa, *et al*.[29] also prepared lidocaine containing niosomes from Tween 20 and cholesterol. Conventional liposomal formulation was also prepared and it showed better skin accumulation than the niosomes.

A summarized comparison between liposomes and niosomes is given in Table 1.

Transfersomes®

Transfersomes were developed by Cevc and Blume in 1992.[30-33] They are highly deformable type of liposomes. They can overcome the penetration barriers by squeezing themselves through the intercellular spaces packed with lipids. This flexibility is imparted to them by adding surface active agents along with phospholipids and cholesterol to conventional liposomes.[34,35] Some of these surface active agents also known as 'edge activators' used are- sodium cholate, sodium deoxycholate, dipotassium glycyrrhizinate and different types of Spans and Tweens. They have been delivered intact through the skin due to transdermal osmotic gradients and hydration force.[31]

Cevc and Blume have reported several studies on transfersomes in the past two decades. Their first reported work was in 1992[31] where they proposed the possible mechanism of transfersome penetration into the skin. According to their study the osmotic gradient present between the different layers of the skin created by the evaporation of water from its surface, plays an important role in providing the impetus required by the vesicles to penetrate into intact skin.[36,37] To prove this, transfersomes with radioactive triturated dipalmitoyl phosphatidyl choline were prepared and tested

under occluded and nonoccluded conditions. In occluded conditions, the radioactivity in the deeper layers of the skin and in the blood (<0.1%) was negligible. Whereas in nonoccluded conditions 50-90% of the applied dose was found in layers beyond the SC and 1-10% in blood stream after 8 hours of application. In 1998, Cevc and Blume[38] worked on vesicles containing insulin and tested them on NMRI mice and humans. Epicutaneous administration produced results similar to a subcutaneous injection in mice. Transfersome-associated insulin (Transfersulin®) was able to reduce the blood glucose levels by 20-30 % in mice within 2-4 hours. Human data also showed very similar results but with a delay of 45-145 min from comparable subcutaneous doses. In contrast a liposomal formulation and a micellar suspension were also prepared but proved to be ineffective in producing any hypoglycemic action in mice and humans. Transfersome-associated diclofenac (Transfenac®) was also developed by Cevc and Blume in 2001.[30] Transfenac achieved 10 times more concentration in the tissues under the skin than a commercial hydrogel formulation of the drug. Even when the dose of Transfenac (0.25-2 mg/kg of rat body weight) was lower than the commercial hydrogel (2-10 mg/kg of rat body weight), it managed to achieve higher concentrations in the underlying tissues depending on their depth. In their latest work[39] they managed to increase the effect of triamcinolone-acetonide in the treatment of murine ear edema. A transfersome-based triamcinolone-acetonide formulation of dose 0.8 μg/cm^2 was able to produce action for around 84 hours. And for a conventional lotion of similar dose, the duration of action was only around 2 hours which is 40 times less than the former. In 1992 Planas, *et al*.[12] prepared tranfersomes containing lidocaine and tetracaine which were tested *in vivo* on rats and human volunteers. The study showed that the anesthetic affect of topically applied transfersome formulation of these drugs were similar to their corresponding subcutaneous injections.[40] Thus their results were in coherence with the work done by Cevc and Blume.

On the other hand, the results reported by Guo, *et al*.[41] do not coincide with the results of Cevc and Blume. Guo, *et al*. prepared liposomes from phospholipids and transfersomes with addition of sodium cholate to the conventional vesicles. They were not able to deliver significant amounts of cyclosporine A using either vesicles into the receptor media in *in vitro* studies through mouse abdomen skin as well as in *in vivo* studies in mice. Both vesicles did show good accumulation in the skin. But in the same year they also published work on insulin. The transfersome-based formulation of insulin produced a good hypoglycemic effect (>50%) for up to 18 hours, whereas the insulin solution and conventional vesicles had no effect at all.

In 2004, deformable liposomes of methotrexate were investigated by Trotta, *et al*.,[42] for the treatment of psoriasis by topical administration. They used soya lecithin (Epikuron 200) and hydrogenated lecithin (Phospholipon 100) as lipids and dipotassium glycyrrhizinate as edge activator. Full thickness pig ear skin was used to study *in vitro* permeation and skin retention. The deformable liposomes showed better permeation in comparison to aqueous solution and conventional liposomes. Also the skin retention of tranfersomes was reported to be higher (almost 3 fold) than the others formulations after an interval of 24 hours. Work was also done for penetration of dipotassium glycyrhizinate.[43]

Another researcher[44] prepared protransfersome gel of levonorgestrel and tested them on Sprague-Dawley rats. The *in vitro* flux value from rat abdominal skin for protransfersomes (15.82 ± 0.37 μg/cm^2/hour) was three times higher than those from pro-liposome (5.90 ± 0.20 μg/cm^2/hour) and approximately 8 folds the value of mixed micelle formulation (1.82 ± 0.12 μg/cm^2/hour). These results were supported by *in vivo* studies in which the protransfersome formulation gave the best results in terms of increase in thickness of the uterine mucosal wall by the action of levonorgestrel. Acyclovir sodium transfersomes were prepared along with conventional liposomes by Jain, *et al*. in 2008.[45] The *in vitro* permeation of tranfersome-based formulation was higher than that of free drug and conventional liposomal formulation at both 8 hours and 24-hour interval. Amount of drug permeated after 8 hours of application from transfersome-based formulation was twice that of drug permeated from conventional liposomes and six times that of free drug.

In 2012 the work done by Badran, *et al*.[46] confirmed the effectiveness of transfersomes as agents for transdermal drug delivery and their ability to accumulate drugs in the skin. Carboxyfluorescein was chosen as the model drug because of its hydrophilic nature and poor permeability through the skin. Sodium cholate, tween 80 and cineol were used as edge activators. Formulation containing sodium cholate showed maximum permeation (0.29 ± 0.05%) into the receptor media through Wistar rat skin followed by formulation containing tween 80, cineol and ethanol, conventional liposomes and least permeation by PBS solution. Maximum skin retention was also shown by transfersomes (0.55 ± 0.17%) containing sodium cholate.

Ethosomes

Ethosomes are yet another modified form of liposomes. They are malleable vesicles made of phospholipids, alcohol (ethanol) in high concentrations (20-45%) and water. They were introduced by Touitou, *et al*. in 2000.[47] They may be unilamellar or multilamellar with sizes ranging from 30 nm to a few microns. The presence of ethanol which is a well known permeation enhancer helps ethosomes to permeate deeper into skin layers due its fluidizing effect and the interdigitization effect[48] of ethanol helps the vesicles to gain a flexible structure so that they can squeeze through the pores in the skin. The presence of ethanol also helps to entrap drugs of different physiochemical properties.[49,50]

One of the earliest works on this topic is reported by Kirjavainen, *et al*. in 1999.[51] They prepared liposomes with different types of phospholipids[52] (EPC, DOPE/CHEMS, DSPC/CHOL) containing different model drugs-sotalol, propranolol and sodium salicylate. They also prepared phospholipid-ethanol solutions of these model drugs and compared their permeation through human cadaver skin.[53] They conclude that ethanol increases heterogeneity of phospholipids and decreases the transition temperature. They also found that phospholipids liposomes reduced the permeability of sotalol and propranolol in the skin.

In the year 2000 Touitou, *et al*.[47] published their research on ethosomes (Phospholipon 90) containing rhodamine red (RR), minoxidil and testosterone. It was found using confocal scanning laser microscopy that ethosomes containing RR and hydroalcoholic solution of same concentration penetrated much deeper (140 μm) as compared to ethanol-free liposomal formulation. Similarly, the permeation of ethosomal minoxidil into the receptor chamber through nude mice abdominal skin, in comparison to the other formulations- 2% PL in EtOH, 30% EtOH and pure EtOH, was 10, 45 and 35 times higher, respectively. Also the skin retention was 2, 7 and 5 times higher in the same order. A patch containing testosterone loaded ethosomes (Testosome) was compared with a commercial patch-Testoderm®. Rabbit pinna skin was used as the model membrane for permeation and retention studies. The amount of testosterone permeated in 24 hours from Testosome was almost 30-fold higher than that from Testoderm® and the skin retention was almost 7 times higher.[49]

In a different study, Dayan and Touitou[54] compared ethosomes and liposomes loaded with trihexyphenidyl (THP) for their ability to deliver the drug. Nude mice skin was used as model membrane for determining permeability of four formulations- ethosomes, liposomes, phosphate buffer and hydroethanolic solution. THP flux from ethosomes (0.21 mg/cm^{2}h) was 87, 51 and 4.5 times higher than that from the liposomes, phosphate buffer and hydroethanolic solution respectively. After the 18 hour of experiment, THP retention in skin was 586 ± 77 μg/cm^2 for ethosomes, 416 ± 27 μg/cm^2 for liposomes and 415 ± 21 μg/cm^2 for hydroethanolic solution.[50] In 2005 Ainbinder and Touitou[55] published another work on testosterone ethosomes. They carried out *in vitro* studies on human skin under nonocclusive conditions and *in vivo* experiments were carried out on Sprague-Dawley rats. The amount of testosterone permeated through human skin from ethosomes was 594 ± 39.9 μg and from the marketed formulation AndroGel® was 92 ± 2.86 μg. The results from blood samples also showed significantly higher Cmax and AUC values for the ethosomal system as compared with AndroGel®.

Paolino, *et al*. in 2005 prepared ethosomal vesicles of ammonium glycyrrhizinate (AG) for the treatment of various inflammatory skin diseases.[56] Human SC and viable epidermis (SCE) was used for *in vitro* permeation studies. The aqueous solution of AG showed minimum permeation (8.9% of applied dose) followed by hydoalcoholic solution (22.3%) and maximum by ethosomal system (63.2 %). Skin retention of the drug was not analyzed. In the same year, Lopez-Pinto, *et al*.[57] studied the effects of ethanol and cholesterol on dermal delivery of minoxidil. They prepared ethosomal systems with different concentrations of cholesterol and compared them with conventional liposomes of similar compositions. After 24 hours permeation experiment using abdominal Wistar rat skin, it was observed that ethosomes delivered the highest percentage of applied dose to the receptor chamber (42.79 ± 1.57%). Liposomes delivered comparatively lower percentage of drug (33.31 ± 1.56%) but the highest flux was shown by the hydroalcoholic solution. It was also observed that increasing the amount of cholesterol in the vesicles increased their entrapment efficiency and permeability due to the stabilizing effect of cholesterol on bilayer structure.

In a recent study, Dubey, *et al*. 2007 prepared methotrexate ethosomes for the treatment of psoriasis.[58] They also compared the extent of penetration of ethosomes and liposomes loaded with rhodamine red (RR) by CLS microscopy. They found that ethosomes penetrated to a depth of 170 μm with fluorescence intensity (FI) of 160 AU, whereas liposomes penetrated only up to 80 μm with FI of 40 AU. On the other hand the flux of methotrexate ethosomes was found to be 57.2 ± 4.34 μg/cm^2/hour whereas the flux for hydroethanolic solution and liposomes was found to be 22.43 ± 0.24 μg/cm^2/hour and 14.6 ± 1.65 μg/cm^2/hour, respectively.

DISCUSSION AND CONCLUSIONS

The results from the above studies can help us to make an informed decision on "What type of carrier system should be used" for our model drug. The results are in many places ambiguous in nature but help us to derive some important facts. It is clear that liposomes and niosomes have moreover the same capabilities to localize drugs in the epidermis and dermis and this ability depends largely on the physico-chemical properties of the major constituent (lipid) of the vesicles and the entrapped drug. In some examples the liposomal formulation is more successful in accumulating the drug in the skin[29] and vice versa in others.[26,59] But when compared to ethosomes or transfersomes, they lack in their ability to penetrate deep skin layers. For example all types of vesicles have been made for minoxidil. It was found that liposomes were the best in retaining minoxidil in dermis and transfersomes showed the best permeation. It is clear from the data published by various other authors as well[38,41,44] that transfersomes are a promising technology to deliver drugs transdermally. The results also indicate that transfersomes are not suitable agents for dermal delivery as they deliver the drug into deeper layers of the skin and eventually into blood circulation. Tranfersomes should not be employed in

cases where systemic effect of the drug is highly undesirable. Similarly, ethosomes are also found to be more suitable for transdermal delivery rather than dermal delivery.[47,56]

There is a need to understand the exact mechanism of permeation of different vesicles[60,61] so that a more effective targeted delivery could be achieved. It is expected that more number of formulations based on vesicular carriers will be launched in the market in the coming years. These formulations clearly show better results than conventional formulations but their success in the market is largely dependent on their cost-effectiveness.

ACKNOWLEDGMENT

The authors are grateful to Prof. R. S. R. Murthy for kind guidance in the final outcome of this manuscript and Mr. Parveen Garg, Chairman, ISF College of Pharmacy, Moga, for providing facilities and financial assistance during the project.

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How to cite this article: Arora S, Lamba HS, Tiwari R. Dermal delivery of drugs using different vesicular carriers: A comparative review. Asian J Pharm 2012;6:237-44.

Source of Support: I. S. F. College of Pharmacy, Moga.
Conflict of Interest: None declared.