Review Article

Vesicular Systems emerging as Dermal and Transdermal Drug Delivery Systems

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ABSTRACT

The Dermal and Transdermal route of drug delivery have attracted researchers due to many biomedical advantages associated with it. The delivery of drugs *via* skin routes has been extensively investigated. Nevertheless, clinical applications are limited by the stratum corneum (SC), the predominant barrier of the skin. One of the possibilities for increasing skin absorption or permeation of drugs is the use of vesicular systems. Vesicular Systems may serve as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, as rate-limiting membrane barrier for the modulation of systemic absorption of drugs, or as to increase the systemic absorption of drugs. The aim of this review work is to focus on the recent innovations in Vesicular Systems for Dermal and Transdermal Drug Delivery Systems which can be a platform for the research and development of pharmaceutical drug dosage forms for Dermal and Transdermal Drug Delivery.

Keywords: Liposomes, Niosomes, Ethosomes, Transferosomes.

INTRODUCTION

Dermal drug delivery is the topical application of drugs to the skin in the treatment of skin diseases. This has the advantage that high concentration of drug can be localised at the site of action, reducing the systemic levels and therefore also reducing the systemic side effects. Transdermal drug delivery uses skin as an alternative route for reaching the drug to the systemic circulation. This drug delivery route has several advantages over the conventional oral and parental routes like avoidance of the risk and inconvenience of intravenous therapy (non invasive), avoidance of first pass hepatic metabolism (avoiding the deactivation by digestive and liver enzymes) thus increasing bioavailability and efficacy of drugs, no gastrointestinal degradation (pH, enzymatic activity, drug interaction with food, drink and other orally administered drugs), substitute for oral administration of medication when that route is unsuitable as with vomiting and diarrohea. But one of the major disadvantages in Transdermal drug delivery is the low penetration rate of substances through the skin. In short, in both Dermal and Transdermal routes absorption of drug by skin occurs but only in Transdermal route drug reaches the systemic circulation. A limited number of drugs can be formulated as Transdermal delivery products due to the functions of the stratum corneum (SC), which provides the principal barrier to skin permeation. Although a number of penetration enhancement techniques like Iontophorosis, Ultrasound (phonophorosis and sonophorosis), Magnetophoresis, Electroporation, Laser radiation and photomechanical waves have been used but still the number of drugs that can be given by Transdermal route are limited. However over the last 10-15 years, vesicular-encapsulated drug

delivery *via* the skin has undergone intense investigations and it sounds to be promising.[1-3]

The rationale for the use of lipid vesicles as topical and transdermal drug carriers are:

1) Phospholipids themselves can be the solubilizers to increase the solubility of lipophilic drugs.

2) They may serve as a local depot for the sustained release of dermally active compounds.

3) Phospholipids in liposomal systems can disrupt the bilayer fluidity in the SC, decreasing the barrier properties of the skin.

4) They may serve as rate-limiting membrane barrier for the modulation of systemic absorption.

5) As a drug carrier to deliver entrapped drug molecule into or across the skin.[4-5]

VESICULAR SYSTEMS EMPLOYED IN DERMAL AND TRANSDERMAL DRUG DELIVERY

Liposomes

Liposomes were introduced in 1965 by Bangham et al (Bangham et al., 1965). Initially, they were used as a model for membrane system studies. However, the topical application of liposomal systems has attracted increasing attention in dermatology since the first liposomal product, which was an econazole preparation for topical therapy of dermatomycosis, introduced into the market in 1988. Liposomes are microscopic vesicles consisting of amphipathic lipids arranged in one or more concentric bilayers. These thermodynamically stable, lamellar structures form spontaneously when a lipid is brought into contact with an aqueous phase. While

liposomes have been investigated for many years as parenteral drug carrier systems, particularly for the selective delivery of anticancer, antibiotic and antifungal agents, they have only for approximately one decade been considered for topical drug delivery, including ophthalmic, pulmonary and dermal/ transdermal delivery.[6-15]

Mezei and Gulasekharam were the first to demonstrate that liposomes loaded with triamcinolone acetonide, in both a lotion and gel dosage form facilitated 3-5-fold accumulation of radiolabelled drug within epidermis and dermis, while systemic drug levels were very low. These results were encouraging and sparked much interest in the use of liposomal drug preparations for topical application.[16-17]

The lipid components of liposomes are predominantly phosphatidylcholine (PC) derived from egg or soybean lecithins. There are two long alkyl chains in the structure of PC. The minor components in lecithin are phosphatidylserine, phosphatidic acid, phosphatidyl glycerol, phosphatidyl ethanolamine, and phosphatidylinositol. Because of their biphasic character, liposomes can act as carriers for both lipophilic and hydrophilic drugs. Depending upon their solubility and partitioning characteristics, the drug molecules are located differently in the liposomal environment and exhibit different entrapment and release properties. Lipophilic drugs are generally entrapped almost completely in the lipid bilayers of liposomes. Since they are very poorly soluble in water, problems like loss of an entrapped drug on storage are minimal with this class of drugs. Hydrophilic drugs may be entrapped inside the aqueous cores of liposomes. However, it is also possible that hydrophilic drugs may be located in the external water phase.[18-20]

Mechanism of action

The specific mechanism can fall into one of three categories, including the intact vesicular skin penetration, the penetration enhancing effect, and vesicle adsorption to and/or fusion with the SC [21].

The use of vesicles for transdermal drug delivery has been introduced in 1980. The statement that intact conventional liposomes can penetrate across the skin was received with skepticism. Some studies supported that intact vesicular penetration may be a possible mechanism for improved skin accumulation, while others indicated that intact liposomes did not penetrate the skin. Further evidence that liposomes penetrate no deeper than the stratum corneum layer has been provided by Lasch et al. who labelled liposomes with both a hydrophilic high molecular weight fluorescent marker (FITC-dextran, 70 000 M,) and a fluorescent lipid marker (NBD-DPPE). Fluorescence micrographs taken after 0.5, 5 and 24 h showed unequivocally that, despite a rapid dispersion within the stratum corneum, no further penetration of either label into epidermis, dermis or deeper layers of the

skin took place. Realistically, conventional liposomes such as colloids from an aqueous suspension can cross the skin barrier only through hydrophilic pathways (intercellular route or intercorneocyte pathway). However, intact skin contains only an insignificant number of pathways of sufficient width to allow passage of even small colloids. Hence, any colloids that are trying to penetrate through narrow pores of fixed size in the skin have to possess two capabilities: the colloid-induced opening of the very narrow (~0.4 nm) gaps between cells in the barrier to pores with a diameter greater than 30 nm, and self-adapting to the size of 20 to 30 nm without destruction. Obviously, conventional liposomes fall short of these prerequisites. As a result, it is almost impossible for large conventional liposomes to penetrate the densely packed SC in great numbers.[22-28]

In an elegant series of experiments, Ganesan et al. and Ho et al. demonstrated unequivocally in an in vitro hairless mouse skin system (finite dose diffusion cell) that neither liposomes nor phospholipid molecules diffuse across intact skin: **(i)** radiolabelled phospholipid could not be detected in the acceptor compartment and **(ii)** lipophilic drugs such as hydrocortisone and progesterone had practically identical skin transfer coefficients, whether they were incorporated within liposomes or not. Transport of progesterone was not affected by the acyl chain length of the phospholipids, nor by the presence of charged phospholipids in the vesicle membrane, supporting the conclusion that no fusion of vesicles with the skin took place. Most investigators have suggested that the direct transfer of a drug between the phospholipid bilayers of liposomes and the lipid contents of the skin is the main mechanism of enhancement of drug delivery *via* the skin. In this case, liposomes do not appear to function as permeation enhancers, but instead provide the needed physicochemical environment for the transfer of drugs into the skin. Some authors suggested that liposome lipids penetrate into the stratum corneum by adhering onto the surface of the skin and, subsequently destabilizing, and fusing or mixing with the lipid matrix. Thereafter, they may act as penetration enhancers, loosening the lipid structure of the stratum corneum and promoting impaired barrier function of these layers to the drug, with less well-packed intercellular lipid structure forms, and with subsequent increased skin partitioning of the drug.[29-30]

Physiochemical Factors of Liposomes affecting Liposomal Permeation:[31]

1) Thermodynamic activity

Hofland et al. and Abraham et al. suggested that liquid-state liposomes show greater skin penetration than those in the gel state, suggesting that there may be a relationship between the depth of penetration and the phase transition temperature. Kirjavainen et al showed that Egg PC (EPC), soybean PC (SPC), and dioleylphosphatidyl ethanolamine (DOPE) increase the drug permeation into the skin, and distearoylphosphatidyl

choline (DSPC) does not change or increase it. EPC, SPC, and DOPE have low values for the gel-liquid crystalline-phase transition temperature (Tc), and they are in a fluid state at the skin temperature of 32 °C. It seems that fluid-state phospholipids disturb the rigid bilayer structures of skin lipids leading to increased drug partitioning into the lipid phase.

2) Electrostatic Charge

The effect of electrostatic charge remained as a controversy. Positively charged liposomes provide significantly higher skin permeation compared to neutral or negatively charged liposomes for retinoic acid and triamcinolone delivery. The greater drug permeation observed using positively charged liposomes can be attributed to a greater accumulation of this type of liposome within the SC probably due to the negative charge of the skin surface at a physiological pH. The opposite results by Ogiso *et al.* and Fang *et al.* demonstrated that negatively charged liposomes diffused betahistine and tea catechins through the skin much faster than did positive vesicles. Negatively charged liposomes may experience a weak electrostatic repulsion in the intercellular domain of the SC. The repulsion ensures the rapid penetration of negative vesicles through the SC and follicles into viable skin by the driving force of excessive lipids.

3) Chemical Composition

In a very elegant set of experiments Knepp et al. showed that presence of free unsaturated fatty acids in the liposome formulations contributed to a 'fluidization' of the lipid domains within the stratum corneum which, in turn, facilitated transdermal flux of progesterone. Liposomes prepared from ceramides were more effective in penetrating into skin than liposomes prepared from phospholipids. The best results exerted may come from their optimum miscibility with the lipid layers of the SC, which thus facilitates the release of drugs from vesicles and transport of drugs *via* the skin.

4) Liposomal Size

Michel and colleagues examined the size dependence of liposomes on the percutaneous absorption of dl-tocopherol nicotinate, a model lipophilic drug. The data showed that there is only a weak dependence between the skin permeation of liposome-entrapped drug and the size of such liposomes. A vesicle size between 100 and 120 nm assures superior skin permeation. However Sentjurc et al showed that small vesicles with diameters of < 200 nm exhibited decreased transport of spin-labeled hydrophilic compounds. The authors proved this effect as the smaller vesicles were not stable and disintegrated immediately upon contact with the other surface.

5) Lamellarity

The influence of lamellarity of the liposomes on drug delivery should not be neglected. The unilamellar liposomes typically result in higher degrees of drug penetration than multilamellar liposomes.

Method of preparation

Egbaria et al. investigated effects of the preparation method and lipid composition on the disposition of drugs in, and diffusion across skin. Liposomes prepared by the dehydration-rehydration method were observed to penetrate deeper into skin strata than large unilamellar vesicles.

Niosomes

Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. Niosomes can be prepared both as unilamellar and multilamellar structures and can entrap hydrophilic, lipophilic, and amphiphilic molecules. Niosomes seems an interesting drug delivery system in the treatment of dermatological disorders. In fact, topically applied niosomes can increase the residence time of drugs in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. They are thought to improve the horny layer properties; both by reducing transepidermal water loss and by increasing smoothness via replenishing lost skin lipids. Span (sorbitan monoester) and Tween (polysorbate) non-ionic surfactants are mostly used as predominant ingredients for niosomes. The parameter of HLB is a good indicator of the noisome-forming ability of surfactants. With Span, an vesicle formation occurs easily. The water-soluble surfactant, Tween 20, also forms niosomes in the presence of cholesterol. This is despite the fact that the HLB number of this compound is 16.7, and it appears on first inspection to be too hydrophilic to form a bilayer membrane. However, with an optimum level of cholesterol, it seems that niosomes are indeed formed from Tween 20. Other surfactants such as polyoxyethylene lauryl ether (Brij 30), octyl/decyl polyglucoside (Triton CG110), glyceryl distearate, and PEG stearate are also used to form niosomal vesicles.

In recent years, attention has been focused on sugar-based surfactants for several types of applications like less toxic, highly biodegradable, which are also produced from renewable raw materials. It has also been suggested that sugar moieties may replace ethylene oxide as the polar head of amphiphiles and that sugar based amphiphiles may substitute ethylene oxide-based surfactants in several applications. In particular, alkyl polyglucosides (APGs) have been studied for several types of applications. Commercial available APGs are mixture of glucosides, which are obtained from degraded starch fractions. APGs are stable at high pH values, but sensitive to low pH where they hydrolise to glucose and fatty alcohol. The main APGs attractiveness lies in their favourable environmental profile: the rate of biodegradation is usually high while the aqueous toxicity is low. In addition, APGs show favourable dermatological properties, being very mild to the skin and eye. This mildness makes this surfactant class attractive for

cosmetic products although APGs have also found a wide range of technical applications. APGs have already shown their capability to form vesicular structures and their properties led us to explore the possibility of using APGs containing niosomes as carriers for the topical.[32-36]

Mechanism of action

Both a permeation enhancer effect and direct vesicle fusion with the SC may contribute to the enhanced permeation of drugs loaded in niosomes. Hofland et al. showed that, although pretreatment with vesicles resulted in higher estradiol fluxes compared to untreated stratum corneum, the fluxes were significantly lower than when estradiol was encapsulated in vesicles. Since these higher estradiol fluxes cannot be explained by penetration enhancement of the surfactant only, it was postulated that niosomes fuse at the interface of the stratum corneum and that the high local estradiol concentration in the vesicle bilayers generates a high thermodynamic activity of estradiol in the upper part of the stratum corneum. Fusion of niosome vesicles on the surface of skin has been demonstrated by electron microscopy. If this mechanism is valid, vesicles are a more promising carrier for lipophilic drugs than for hydrophilic drugs. This mechanism is further supported by Fang et al. who investigated the feasibility of niosomes for the transdermal administration of enoxacin. Enoxacin is formulated as suspensions containing the same amounts of niosomes, without any further preparation procedure. This physical mixture, produced by directly adding all of the components in the vehicles, was used to study the effect of niosomes on enoxacin permeation. The results clearly demonstrated that the physical mixture had a significantly lower permeation than niosomes. Therefore, factors other than the permeation enhancer effect, such as vesicle fusion to the SC, are likely involved in this enhancement.[37-38]

Advantages of Niosomes over liposomes

In fact, if compared with conventional liposomes (phospholipids) Niosomes (non ionic surfactant vesicles) offer higher chemical stability, lower costs, and great availability of surfactant classes. Fang et al. have showed that enhancing effect for skin permeation of enoxacin for niosomes was greater than that of liposomes composed of dimyristoyl phosphatidylcholine (DMPC). Manconi et al showed that higher tretinoin stability was obtained when it was incorporated in niosomes than in liposomes.[39]

Ethosomes

Touitou and colleagues developed a lipid vesicle system embodying ethanol in relatively high concentrations (20%-45%), in what are called ethosomes and which are very efficient at enhancing the skin permeation of a number of drugs. The effect of ethanol and its concentration on the physicochemical characteristics of the ethosomes have been investigated. As reported, ethanol can confer a net negative surface charge to the liposome, which in turn causes the size of vesicles to decrease. The decrease of ethanol concentration in the range of 20% to 45% can result in the increase in the size of ethosomes. The ethosomal lipids are in a more-fluid state than liposomes from the same components without ethanol. Thus the effect of ethanol, which is considered harmful to conventional liposomal formulations, may provide vesicles with soft flexible characteristics, which allow them to more-easily penetrate into deeper layers of the skin. Moreover, due to the multilamellarity of ethosomes, the presence of ethanol in ethosomes, and the solubility of many drugs, ethosomes can exhibit high encapsulation efficiency and drug loading. Because of their unique structure, ethosomes can entrap and effectively deliver highly lipophilic molecules and cationic drugs such as acyclovir, trihexyphenidyl, minoxidil, cannabinoids, zidovudine, propranolol and testosterone through the skin.

Mechanism of action

Although the exact process of skin drug delivery by ethosomes remains unclear, it appears that a synergistic mechanism between ethanol, lipid vesicles, and skin lipids facilitates drug delivery to the deeper skin layers or across the skin. At first, ethanol must be responsible for the enhanced skin drug delivery described. Ethanol is a well-known permeation enhancer. It can interact with intercellular lipid molecules in the polar head group region, thereby increasing their fluidity and decreasing the density of the lipid multilayer, which results in an increase in membrane permeability. Ethanol is also supposed to extract the SC lipids and these penetration enhancement effects may be referred to as "pulleffects". In addition, ethanol imparts flexibility to the ethosomal vesicles, which in turn facilitates skin permeation. Furthermore, ethanol can act as a "blending" agent for lipid vesicles, increasing their distribution in various skin layers. The ethanol effects are followed by the interaction between ethosome vesicles and the skin.[40]

However the effect of Ethosomes on enhancing skin permeation of drugs may depend on the physiochemical properties of the drug. In the case of trihexyphenidyl HCl (THP), the flux of THP through nude mouse skin from THP ethosomes was 87-, 51-, and 4.5-times higher than from conventional liposomes, phosphate buffer, and a hydroethanolic solution, respectively. The data clearly indicate that the ethosomal system is effective at delivering molecules deeply into and through the skin. But ethosomes didn't show a significantly enhanced skin delivery of temoprofin compared with ethanol solution and hydroethanolic solution. The authors concluded that the results may be due to the thermodynamic activity of temoprofin in ethosomes that is not equally increased compared with temoprofin hydroethanolic solution.[41]

Transferosomes

Liposomal as well as niosomal systems, are not suitable for transdermal delivery, because of their poor skin permeability, breaking of vesicles, leakage of drug,

aggregation, and fusion of vesicles (Cevc et al., 1997). To overcome these problems, a new type of carrier system called "transferosome", has recently been introduced, which is capable of transdermal delivery of low as well as high molecular weight drugs (Schatzlein et al., 1995). Transferosomes are specially optimized, ultradeformable (ultraflexible) lipid supramolecular aggregates, which are able to penetrate the mammalian skin intact. Liposomes are too large to pass through pores of less than 50nm in size; transfersomes up to 500nm can squeeze to penetrate the stratum corneum barrier spontaneously. Each transferosome consists of at least one inner aqueous compartment, which is surrounded by a lipid bilayer with specially tailored properties, due to the incorporation of "edge activators" into the vesicular membrane. Surfactants such as sodium cholate, sodium deoxycholate, span 80, and tween 80 have been used as edge activators. These novel carriers are applied in the form of semi-dilute suspension, without occlusion. Due to their deformability, transferosomes are good candidates for the non-invasive delivery of small, medium, and large sized drugs. Transferosomes are vesicles composed by phospholipids as the main ingredient (soya phosphatidylcholine, egg phosphatidylcholine, dipalmityl phosphatidylcholine, etc), 10- 25% surfactants for providing flexibility (sodium cholate, tween 80, span-80), 3-10% alcohol as a solvent (ethanol, methanol) and hydrating medium consisting of saline phosphate buffer (pH 6.5-7).[42]

Mechanism of penetration

Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of stratum corneum. At present, the mechanism of enhancing the delivery of active substances in and across the skin is not very well known. Two mechanisms of action have been proposed. First, transferosomes may act as drug carrier systems by which intact vesicles enter the SC carrying vesicle-bound drug into or across the skin. Direct supporting results have been published. Additional studies have shown that pretreatment of skin membranes with empty deformable liposomes did not enhance estradiol flux, while application of estradiol entrapped within vesicles resulted in a 14- to17-fold increase in estradiol flux relative to control. A reduction in vesicle size improved the deposition and penetration of two fluorescently labeled model substances with large structures improving the deposition only, and epidermal permeation enhancement via the vesicular components in a lipid solution in 90% propylene glycol in water was inferior, suggesting that ultraflexible liposomes may act as drug carriers and are better for lipid components to be applied in the form of vesicles. However, in case of accepting this mechanism, as mentioned before, two prerequisites are necessary: the sufficient carrier stability on the skin and hydrophilic pore opening in the skin by such vesicles. This is why only well designed ultraflexible liposomes can overcome the skin barrier posed by the SC. On the other hand, the water gradient was regarded as

the driving force for ultraflexible liposomes entering the skin. However, the water gradient across the skin may not be linear, consequently, as a result of the osmotic force such vesicles will not penetrate beyond the level of the lowest layers in the SC. Hence, the drugs will be released first from such vesicles and then penetrate alone to reach the systemic circulation.[43-54]

Second, vesicles may act as penetration enhancers, whereby membrane bilayers as vesicles interact with the SC and subsequently modify the intercellular lipid lamellae. It has been shown that deformable liposomes were able to carry both the entrapped and the nonentrapped carboxyfluorescein (albeit to a lesser extent) into the SC and possibly to deeper layers, enoxacin permeation across lecithine-treated skin was higher than that across nontreated skin after 12 hours of pretreatment, indicating that this mechanism is also reasonable. Hence, most possibly, both mechanisms play a role in the enhanced transdermal delivery of drugs by ultraflexible liposomes under nonocclusive conditions. It is possible that one of the two mechanisms might predominate according to the physicochemical properties of the drug considered. The effectiveness of Transfersomes was successfully demonstrated using model drugs, such as lidocaine, corticosteroids, diclofenac and high molecular weight compounds, such as insulin. Furthermore, it was suggested that Transfersomes could be used for noninvasive transdermal immunisation.[55-60]

CONCLUSION

In spite of certain drawbacks, the vesicular delivery system still plays an important role in the selective targeting, and the controlled delivery of various drugs. Researchers all over the world continue to put in their effort in improving the vesicular system by making them steady in nature, in their leaching of content, oxidation, and their uptake by mechanisms.

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