Transdermal drug delivery via colloidal systems: a review

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ABSTRACT: Transdermal administration of drugs is generally limited by the barrier function of the skin. Colloidal systems are one of the most contentious methods for transdermal delivery of active substances across the skin. The colloidal systems helps in overcoming the shortcomings associated with transdermal drug delivery systems and provide sustained and controlled release of drugs. This review presents the use of colloidal systems across skin as transdermal drug delivery tools.

Key words: Transdermal, drug, delivery, colloidal systems

INTRODUCTION:
The colloidal systems contain therapeutic compounds in colloidal state. Colloidal systems are dispersed into another medium. The dispersed phase particles have a size range of 1-1000 nm. Colloidal systems are use in transdermal drug delivery because of the fact that they act as drug carriers to deliver entrapped drug molecules across the skin, as well as penetration enhancers because of their composition. These vesicles also serve as a depot for the sustained release of active compounds in the case of topical formulations, as well as rate-limiting membrane barrier for the modulation of systemic absorption in the case of transdermal formulations.

COLLOIDAL SYSTEMS:

NIOSOMES:
Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic non-ionic surfactants, with or without incorporation of cholesterol or their lipids. They are vesicular systems resembling liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Noisome are promising vehicle for transdermal drug delivery and being non-ionic they are biodegradable, biocompatible and non-immunogenic and exhibit flexibility in their structural characterization.

- They have better availability to the particular site, by protecting the drug from biological environment.
- They exhibit flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
- They improve the bioavailability of the drug molecules.
- Niosomes surfactants are biodegradable, biocompatible and non-immunogenic.

Encapsulation of drug in niosomes prolongs the existence of drug in the systemic and enhances its penetration into target tissue. Niosomes have been widely evaluated for controlled release and targeted delivery for the treatment of cancer, viral infections and other microbial diseases. Various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral, transdermal, etc.

LIPOSOMES:
Mezei and Gulusekaram first proposed liposomes for drug topical administration to the skin more than 25 years ago. The basic components of liposomes are phospholipids (phosphatidylcholine, phosphatidyserine, dipalmitoyl phosphatidylcholine, etc), cholesterol, and water. Liposomes may vary significantly in terms of size (10 nm to microns) and structure. In liposomes, one or more concentric bilayers surround an aqueous core generating small or large unilamellar or multilamellar vesicles (SUV, LUV, MUV, respectively).

- Liposomes are biocompatible, completely biodegradable, non-toxic, flexible and nonimmunogenic for systemic and non-systemic administrations.
- Liposomes can be formulated as a suspension, as an aerosol, or in a semisolid form such as gel, cream and lotion, as a dry vesicular powder (proliposome) for reconstitution or they can be administered through most routes of administration including ocular, pulmonary, nasal, oral, intramuscular, subcutaneous, topical and intravenous.
- Liposomes could encapsulate not only small molecules but also macromolecules like superoxide dismutase, haemoglobin, erythropoietin, interleukin-2 and interferon-g.
- Liposomes are increased efficacy and therapeutic index of drug (Actinomycin-D).
- Liposomes help to reduce exposure of sensitive tissues to toxic drugs.
- Alter the pharmacokinetic and pharmacodynamic property of drugs (reduced elimination, increased circulation life time)
- Flexibility to couple with site-specific ligands to achieve active targeting (Anticancer and Antimicrobial drugs).
Different interpretations have been proposed concerning the mechanism of drug permeation through the skin in the case of liposomal formulations. The theories are as follows: liposomes penetrate intact into the skin\(^7,8\); vesicles are disintegrated on the skin surface and penetrate as individual lipid molecules through the stratum corneum, thus producing fluidization and modification of the wall-thickness barrier\(^9\); liposomes are absorbed on the skin surface and then fused with lipids in the stratum corneum, thus promoting a lipid exchange between phospholipids of bilayer and cellular skin lipids\(^10,11\), allowing a direct transfer of the drug to the stratum corneum; and liposomes have an occlusive effect on the stratum corneum\(^12\). Differences in permeation performance of liposomes through the skin can be explained by interaction models between vesicles and lipids of the stratum corneum. This effect is mediated by the physicochemical properties of colloidal systems. In particular, vesicle–lipid compositions, besides being able to modulate the elasticity and the thermodynamic state of the liposomal bilayer, are also able to modulate the transdermal permeation of drug compounds encapsulated in liposomes\(^13,14\).

**TRANSFERSOMES:**
Transfersomes are highly adaptable, stress-responsive and complex aggregates. Its preferred form is an ultradformable vesicle possessing an aqueous core surrounded by the complex lipid bilayer. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-optimizing. This enables the transfersomes to cross various transport barriers efficiently, and then act as a drug carrier for noninvasive targeted drug delivery and sustained release of therapeutic agents. The name means “carrying body”, and is derived from the Latin word 'transferrre', meaning ‘to carry across’.
- Transfersomes can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.
- They are biocompatible and biodegradable as they are made from natural phospholipids.
- They have high entrapment efficiency in case of lipophilic drug near to 90%.
- They protect the encapsulated drug from metabolic degradation.
- They act as depot, releasing their contents slowly and gradually.
- They can be used for both systemic as well as topical delivery of drug\(^15\).

Transfersomes 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\(^16-19\).
- Transfersomes act as drug vectors, remaining intact after entering the skin
- They act as penetration enhancers, disrupting the highly organized intercellular lipids from stratum corneum, and therefore facilitating the drug molecules penetration in and across the stratum corneum.

Some mechanisms, suggests that transfersomes penetrate the stratum corneum because of the transdermal hydration gradient, normally existing in the skin, and then, crossing the epidermis, they enter the systemic circulation. The recent studies propose that the penetration and permeation of the vesicles across the skin are due to the combination of the two mechanisms.

Depending on the nature of the active substance (lipophilic or hydrophilic) and the composition of the transfersomes, one of the two mechanisms prevails\(^20\).

**ETHOSOMES:**
Ethosomes are non-invasive delivery carriers that enable drugsto reach the deep skin layers and/or the systemic circulation\(^21\). These are soft, malleable vesicles tailored for enhanced delivery of active agents. They are composed mainly of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatidic acid), high concentration of ethanol and water\(^22,23\). The high concentration of ethanol makes the ethosomes unique, as ethanol is known for its disturbance of skin lipid bilayer organization; therefore, when integrated into a vesicle membrane, it gives that vesicle the ability to penetrate the stratum corneum. Also, because of their high ethanol concentration, the lipid membrane is packed less tightly than conventional vesicles but has equivalent stability, allowing a more malleable structure and improves drug distribution ability in stratum corneum lipids\(^24-27\).

- Enhanced permeation of drug through skin for transdermal and dermal delivery.
- Ethosomes are platform for the delivery of large and diverse group of drugs (peptides, protein molecules)
- Ethosomal composition is safe and the components are approved for pharmaceutical and cosmetic use..
- High patient compliance
- High market attractiveness for products with proprietary technology. Relatively simple to manufacture with no complicated technical investments required for production of Ethosomes.
- The Ethosomal system is passive, non-invasive and is available for immediate commercialization.

Ethosomes show a good permeation across the skin, taking advantage of the passive diffusion process. The presence of ethanol, besides giving fluidity, malleability and elasticity to the ethosomal bilayer, confers a soft structure and, interacting with the stratum corneum phospholipids, induces a temporary disorganization of their alchilic chains\(^28,29\). This phenomenon facilitates the crossing of the vesicles through the stratum corneum and, by the passive diffusion process, the active compounds loaded inside the carriers can reach the deeper skin layer where they can explicate their pharmacological action. Therefore, a path through the skin can be expected to result, permitting the fusion of ethosomes with the cells from the deepest skin layers\(^30,31\).
PHARMACOSOMES:
These are defined as colloidal dispersions of drugs covalently bound to lipids and may exist as ultrafine vesicular, micellar or hexagonal aggregates, depending on the chemical structure of drug-lipid complex. The prodrug joins hydrophilic and lipophilic properties and therefore acquires amphiphilic characters and was found to reduce interfacial tension and thus at higher concentrations exhibits mesomorphic behavior. Because the system is formed by linking a drug (pharmakon) to a carrier (soma), they are called pharmacosomes. Pharmacosomes bearing unique advantages over liposome and noisome vesicles have come up as potential alternative to conventional vesicles.

- They are an effective tool to achieve desired therapeutic goals such as drug targeting and controlled release.
- High and predetermined entrapment efficiency as drug and carrier form a stoichiometrically defined unit covalently linked together.
- Volume of inclusion doesn’t influence entrapment efficiency.
- No need of removing the free, unentrapped drug from the formulation which is required in the case of liposomes.
- Improves bioavailability especially in the case of poorly soluble drugs.
- Drug carriers such as liposomes, nanoparticles, microemulsions which have lead to low drug-loading efficiency, physical stability such as fusion, aggregation, sedimentation and drug leakage during preparation, preservation etc is absent in pharmacosomes.

CUBOSOMES:
Bicontinuous cubic liquid crystalline materials are active ingredients because they give the unique structural ends to control release applications. Amphiphilic molecules form bicontinuous water and oil channels, where “bicontinuous” refers to two distinct (continuous, but non-intersecting) hydrophilic regions separated by the bilayer. Cubosomes are discrete, sub micron, nanostructured particles of bicontinuous cubic liquid crystalline phase. Cubosomes possess the same microstructure as the parent cubic phase but have much larger specific surface area and their dispersions have much lower viscosity than the bulk cubic phase. The ability of cubic phases to exist as discrete dispersed colloidal particles or cubosomes is perhaps the most intriguing.

Whereas most concentrated surfactants that form cubic liquid crystals lose these phases to micelle formation at high dilutions, a few surfactants have optimal water insolubility. Their cubic phases exist in equilibrium with excess water and can be dispersed to form cubosomes. Cubosomes are typically produced by high-energy dispersion of bulk cubic phase, followed by colloidal stabilization using polymeric surfactants. After formation of the cubosomes, the dispersion is formulated into a product and then applied to a substrate of interest, usually bodily tissue.

- Cubic phase materials can be formed by simple combination of biologically compatible lipids and water and are thus well suited for use in treatments of skin, hair, and other body tissue.
- With respect to liposome, cubosome possesses a larger ratio between the bilayer area and the particle volume and a larger breaking resistance.

COLLOIDAL SYSTEMS USED IN TRANSDERMAL DRUG DELIVERY:
The transdermal drug delivery is a discrete mode of drug administration by using the intact skin in a controlled manner in to the systemic circulation. A steady infusion of drug for a prolonged period can be achieved by this route. This route is indeed a preferable route, but the major and only obstacle for the drug to diffuse through the skin is its barrier function. Achievement of a high and a constant drug flux across the skin is challenging. It is very difficult to deliver a drug compound through the skin, especially if it has hydrophilic physicochemical properties. Therefore, substances are normally used that improve the percutaneous diffusion, called penetration enhancers (i.e., ethanol). Unfortunately, these substances increase the percutaneous permeation of all the components, causing an increase in the collateral effects related to some substances (surfactants, preservatives etc.). To avoid these problems, innovative drug delivery systems have been developed. Currently, the colloidal drug delivery systems are highly preferred for administration through transdermal route as the route provides a direct approach to the systemic environmennt for delivering the drug moieties. Use of colloidal systems in transdermal drug delivery has created a new path development of non-invasive techniques by using their self regulating properties.
OVERVIEW OF COLLOIDAL SYSTEMS:

<table>
<thead>
<tr>
<th>TYPE</th>
<th>SIZE</th>
<th>STRUCTURAL COMPONENTS</th>
<th>TYPES OF DRUG PARTICLES</th>
<th>DRUG LOADING</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIOSOMES</td>
<td>1-1000nm</td>
<td>Nea-ionic surfactant, cholesterol and aqueous solvent</td>
<td>Hydrophilic, amphiphilic and lipophilic drug molecules</td>
<td>Drug loading is more than liposomes</td>
</tr>
<tr>
<td>LIPOSOMES</td>
<td>1-1000nm</td>
<td>Phospholipids, cholesterol and organic solvents</td>
<td>Lipophilic drug molecules</td>
<td>Low drug loading due to leakage of drug from the phospholipids</td>
</tr>
<tr>
<td>TRANSFERSOMES</td>
<td>1-1000nm</td>
<td>Phospholipids, surfactants, alcohol and buffering agents</td>
<td>Hydrophilic drug molecules</td>
<td>Drug loading is more than 90% in case of lipophilic drugs</td>
</tr>
<tr>
<td>ETHOSOMES</td>
<td>1-1000nm</td>
<td>Phospholipids, ethanol and water</td>
<td>Lipophilic drug molecules</td>
<td>Improved drug loading than liposomes</td>
</tr>
<tr>
<td>PHARMACOSOMES</td>
<td>1-1000nm</td>
<td>Phospholipids and organic solvent</td>
<td>Hydrophilic and lipophilic drugs</td>
<td>Drug loading is not only high but predetermined, because drug itself in conjugation with lipids forms vesicles</td>
</tr>
<tr>
<td>CUBOSOMES</td>
<td>1-1000nm</td>
<td>Lipids, surfactants (cationic and non-ionic) and polymers</td>
<td>Lipophilic, hydrophilic and amphiphilic drug molecules</td>
<td>High drug loading due to stability of the vesicles</td>
</tr>
</tbody>
</table>

STABILITY OF COLLOIDAL SYSTEMS

NIOSOMES
- They have various stability problems associated with them such as physical stability of fusion, aggregation, sedimentation and leakage on storage. The Hydrolysis of encapsulated drugs which limits the shelf life of the dispersion is also an issue for niosomes.

LIPOSOMES
- The main stability issues associated with liposomes are formation of ice crystals in, the subsequent instability of bilayers leads to the leakage of entrapped material.
- The physical instability is another problem faced by liposomes. The oxidation of cholesterol and phospholipids also leads to the formulation instability.
- Chemical instability primarily indicates hydrolysis and oxidation of lipids. Hydrolysis detaches the hydrophobic chains of ester bonds. Oxidation is more likely due to the presence of unsaturated chains. Adding antioxidants to the liposome formulation can usually protect the lipids from oxidation. The cationic liposomes can be stable at 4°C (refrigerator) for a long period of time if they are properly sterilized.
- Liposomes in plasma are prone to aggregation and exhibit leakage. The destabilization of liposomes is due to the lipid exchange between the liposomes and HDLs.

TRANSFERSOMES
- Transferosomes are chemically unstable because of their predisposition to oxidative degradation. Purity of natural phospholipids is another criterion responsible for instability of transfersomes. They are chemically unstable because of their predisposition to oxidative degradation, lack of purity of the natural phospholipids. These problems come in the way of adoption of transfersomes as drug delivery vehicles.

ETHOSOMES
- Ethosomes have initiated a new area in vesicular research for transdermal drug delivery which can provide better skin permeation and stability than liposomes. Application of ethosomes provides the advantages such as improved drug loading and physical stability.

PHARMACOSOMES
- Since the drug is covalently linked, loss due to leakage of drug, does not take place, hence pharmacosomes are stable drug delivery systems.

CUBOSOMES
- They have high physico-chemical stability and the stability of cubosomes is also enhanced by the presence of polymers.
MECHANISM OF DRUG TRANSPORT THROUGH SKIN BY COLLOIDS:
Several mechanisms mediating the colloid–skin interactions have been described in the literature. It has been suggested that colloid–skin interactions can occur either at the skin surface or in the deeper layers of the stratum corneum. Hofland et al. and Abraham et al. have demonstrated adsorption and fusion of vesicles onto the skin surface, resulting in the formation of lamellae and rough structures on top of the outermost corneocytes. Changes in the deeper layers of the stratum corneum were observed only after treatment of the skin with liquid-state liposomes and non-ionic surfactant vesicles. No ultrastructural changes in the skin were found when gel-state non-ionic surfactant vesicles were applied. The authors explained their results by a molecularly dispersed penetration of lipid or surfactant into the intercellular matrix. Studies with thermal analysis that enable to detect lipid phase transitions confirmed this mechanism. This suggests that components of liquid state vesicles can enter the deeper layers of the stratum corneum where they can modify the intercellular lipid lamellae, whereas the components of gel state vesicles remain on the skin surface. The superior mode of action of liquid-state vesicles for skin interactions is the most probable explanation for the fact that they are more effective in enhancing drug transport into and across the skin. This is in accordance with a study that found a correlation between the skin penetration and the fluidity of the vesicle bilayers determined by electron spin resonance. From the studies above there is no doubt that vesicular components can penetrate into the stratum corneum. However, it is still debated whether vesicles can enter the stratum corneum as intact entities. In fact only one group claimed that liposomes enter the stratum corneum intact. Remarkably, it was noticed that these liposomes are ‘very flexible lipid vesicles’. An increased deformability of the bilayers will have consequences for their interaction with skin. In general, one can conclude that rigid liquid- and gel-state vesicles do not enter the stratum corneum as intact entities.

CONCLUSION:
Colloidal drug delivery systems play an important role in the field of transdermal drug delivery systems. In our opinion all colloidal carriers present notable characteristics when applied transdermally. Classical liposomes, especially unilamellar, are able to deliver an active compound through the skin by means of absorption, lipid exchange and diffusion, and to increase the amount of permeated drugs compared with conventional formulations. Another important characteristic is related to the thermodynamic state of the liposomal bilayer (influenced by phospholipid and cholesterol percentages). The incorporation of a drug into liposomes in a gel state permits a slower skin-permeation rate than that for vesicles in a fluid state. The use of colloidal carrier- niosomes will increase in the near future because of the possibility of selecting characteristics by means of an accurate choice and synthesis of surfactants. Ultradeformable vesicles are another important class of carrier as the presence of an edge activator (conferring them elasticity and deformability of the bilayer structure) enables them to permeate narrow pores in the skin. Ethosomes present very encouraging characteristics and the presence of ethanol, intercalated in lipid bilayers, does not cause any damage to the skin. Novel Therapeutic Technology, Inc is a biopharmaceutical company that has developed a lot of pharmaceutical formulations based on ethosomes technology, including formulations for the treatment of alopecia, deep skin infection, herpes, hormone deficiencies, inflammation, postoperative nausea, atopic dermatitis and erectile dysfunction. So, taking into account all the formulation characteristics (mainly drug loading) of different colloidal systems, it can be evaluated that the newer colloidal systems like ethosomes, pharmacosomes, cubosomes, transfersomes are posing to better than the conventional vesicles. Form stability point of view, pharmacosomes, ethosomes and cubosomes are better than niosomes, transfersomes, liposomes and niosomes. The basic principle for this kind of carrier, which may be exploited in the future, is skin targeting to reduce systemic and, consequently, the adverse effects induced by the systemic absorption for some substances. An interesting topic of research for the future would be the delivery of biological drugs. The future will see a combination of these carriers and the creation of mixed carriers to exploit several positive aspects of each carrier and to enable their characteristics to be enhanced, especially for the delivery of biological drugs transdermally.

REFERENCES