VESICULAR NANOCARRIERS IN TRANSDERMAL DRUG DELIVERY

Abstract

Protein-based nanocarriers are promising because they occur naturally and generally show less cytotoxicity than synthetic molecules.Nanocarriers have been explored for drug delivery, especially in chemotherapy. They can target small pores, lower pH levels, and higher temperatures of cancer cells, potentially reducing the toxicity of many chemotherapeutic drugs.The skin protects the internal organs of human body with regard to the entry and exit of a large number of auxiliary products water salts and other metabolites. However, these barriers pose a challenge into the penetration of the drug into the skin and its diffusion across the membrane.Liposome preparations of anticancer drugs, antihypertensive drugs, steroidal and non-steroidal analgesic drugs, local anesthetic drugs, antimigraine and antiparkinsonian drugs, vaccines, and toxoids are administered through transdermal delivery.

Keywords: cancer cells, chemotherapeutic drugs, antiparkinsonian drugs, transdermal delivery

Introduction:

Nanocarriers are nanomaterials used to transport substances, such as drugs. These carriers are now being utilized in drug delivery, demonstrating their potential in chemotherapy. Common nanocarriers include polymers, liposomes, micelles, polymeric nanoparticles, dendrimers, lipid-based carriers, carbon-based materials, and gold nanoparticles. Examples of gold nanoparticles include nanocages and gold nanoshells. Various nanomaterials in nanocarriers enable delivery of both hydrophobic and hydrophilic drugs throughout the body. Given that the human body is mostly water, the efficient delivery of hydrophobic drugs is a significant therapeutic advantage of nanocarriers. Micelles can incorporate either hydrophobic or hydrophilic drugs based on the orientation of phospholipid molecules. Nanocarriers are nanotube arrays that can accommodate both types of drugs.

However, a potential issue with nanocarriers is the undesirable toxicity of the nanomaterials that are used. Inorganic nanomaterials can be toxic if they accumulate in certain organelles. Further research is ongoing to develop more efficient and safer nanocarriers. Protein-based nanocarriers are promising because they occur naturally and generally show less cytotoxicity than synthetic molecules.

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Nanocarriers have been explored for drug delivery, especially in chemotherapy. They can target small pores, lower pH levels, and higher temperatures of cancer cells, potentially reducing the toxicity of many chemotherapeutic drugs. As approximately 75% of antitumor drugs are hydrophobic and difficult to deliver into human cells, using micelles to maintain and mask the hydrophobic nature of these drugs offers new prospects for hydrophobic anticancer drugs[1].

Drug delivery through the skin

Drugsapplied to the skin can cross the epidermis through either the skin's appendages or the stratum corneum. The appendages cover only approximately 0.1% of the surface, so they contribute little to steady-state drug penetration, but they may be important for ions, large molecules, polymers, and colloidal particles. The stratum corneum, only 10-15 layers thick, is the main barrier for permeation. It has a "brick and mortar" structure with keratin-filled cells (bricks) in a matrix (mortar) made of long-chain ceramides, fatty acids, triglycerides, cholesterol, cholesterol sulfate, and sterol/wax esters. Proteins and desmosomes in the lipid layers add rigidity and resistance to diffusion. Most molecules pass through the lipid domains; therefore, most skin penetration enhancement methods focus on this route[2].

Table No. 1: Ideal properties of drugs for transdermal drug delivery[3]

S.No	Parameter	Properties
1	Dose	Should be low (less than 20mg/day)
2	Half-life	10 or less hours
3	Molecular weight	<400 Dalton
4	Partition coefficient	Log P (octanol -water) between 1.0 and 4.0
5	Skin permeability coefficient	>0.5 X 10^{-3} cm/h
6	Liophilicity	10 <Ko/w <1000
7	Oral bioavailability	Low
8	Therapeutic window	Low
9	Melting point	<200^{O}C
10	pH	Between 5.0 to 9.0

Barriers of the delivery of the drug through skin

The skin protects the internal organs of human body with regard to the entry and exit of a large number of auxiliary products water salts and other metabolites.However, these barriers pose a challenge into the penetration of the drug into the skin and its diffusion across the

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membrane.As the first layer of defense, the stratum corneum, topmost layer of the skin exposed to the environment, is usually considered a significant hurdle for a broad set of drugs. Highly lipophilic and small molecule drugs are easier to permeate but restricts other classes of compounds. Stratum corneum is mostly lined by corneocytes (to a large extent the keratin), and are responsible for the permeation of water during the standard homeostatic mechanisms[4].

Interestingly, both dermal and transdermal drug delivery involve similar steps. The drug must first deposit on the stratum corneum and then diffuse into the viable epidermis. In transdermal delivery, the drug also needs to pass through the dermis to reach the systemic circulation[5].

In dermal delivery, bypassing the stratum corneum to concentrate the drug in the epidermis sounds appealing, but it is rarely effective. The epidermis actively metabolizes drugs, and the drug may permeate into deeper layers, reducing its concentration within the skin. The drug might also diffuse into hair follicles and sweat glands, where it is further metabolized, decreasing transdermal permeation.

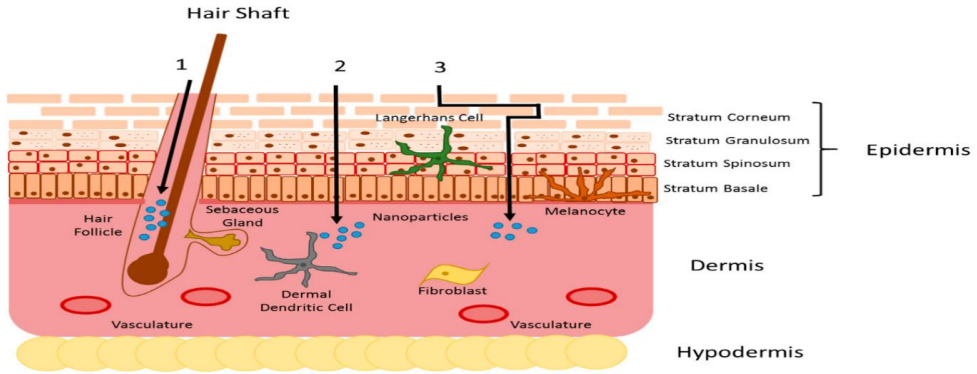

Figure 1: Routes of drug delivery through skin(1) through the appendageal route, (2) through the intracellular route, or (3) through the intercellular route[4].

Several successful strategies have been developed to enhance drug permeation within the skin, including physical and chemical methods, their combination, and micro- and nano-technological approaches. Recently, polymeric, lipidic, and surfactant-based nano-drug delivery platforms have gained attention. These nano-systems can provide the needed lipophilicity, occlusion, irritation masking, and stabilization during diffusion, depending on the drug[6]. Most dermal and transdermal drug formulations use lipid-based systems due to the lipidic nature of skin cells and tissues. However, many lipid-based systems require polymeric

bases for application, enhancing permeation and delivery. There are various types of vesicular and non-vesicular transdermal drug delivery systems.

RATIONALE FOR TRANSDERMAL DRUG DELIVERY

The skin is an excellent barrier to molecular transport, so the rationale for this delivery strategy must be clear. There are times when oral drug intake isn't possible, and alternatives are needed. While intravenous (IV) drug administration avoids issues like gastrointestinal and liver metabolism, it is invasive and uncomfortable, especially for long-term use. This has led to the exploration of other delivery routes.

Advantages:

- Allows easy and pain-free self-administration for patients.
- Reducesdosing frequency and prevents the fluctuations in drug levels.
- Drugs with a short half-life can be delivered effectively.
- It improves patient compliance, especially for long-term treatments like chronic pain and smoking cessation[7]
- It avoids the liver's first-pass metabolism and the GI tract for drugs with poor bioavailability.
- Transdermal systems are cheaper and can deliver drugs for 1 to 7 days.
- New programmable systems allow for multiple dosing and variable drug delivery, adding benefits to traditional patches.
- The transdermal route allows the use of potent drugs with minimal risk of system toxicity.
- In case of toxicity, the patient can simply remove the transdermal patch.

Disadvantages:

- Drugs needing high blood levels cannot be given this way.
- The adhesive may not stick well to all skin types.
- Drugs or formulations can cause skin irritation or allergies.
- Patches can be uncomfortable to wear.
- Manufacturing requires special equipment, expensive than traditional methods.
- There is a delay before the drug enters the bloodstream, so it's not good for drugs needing quick action[8].

Elasticliposome:

Elastic liposomes (EL) are some of the most flexible deformable amphiphilic vesicular systems containing biocompatible lipids and surfactants for the diffusion of many

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difficult molecules for curative, biochemical, and cosmetic applications. It has been used in several pharmaceutical technologies through topical, transdermal, nasal, and oral delivery systems for better and enhanced drug delivery. ELs are similar to conventional liposomes but contain an edge activator in the lipid bilayer structure to make it flexible. Els include deformable liposomes, ultra-deformable liposomes, flexible liposomes, ultra-flexible liposomes, and transfersomes. They are composed of phospholipids and surfactants such as edge activators (EA), and they have an internal water core that is enclosed within a lipid layer and can contain hydrophilic materials in the aqueous chamber and lipophilic materials in the lipid bilayer. However, other materials such as charged lipids, including cationic and anionic lipids; polyethylene glycol, which is also known as PEG or PEGylation; ethanol; cyclodextrin complexes; and gels. Composition causes changes in physicochemical characteristics and, hence, skin permeability behavior, and therefore the efficacy of a chemical structure. For instance, it should be mentioned that it is a noticeable fact that in vivo skin permeation performance reflects quite different results compared to in vitro data and cannot be explained by in vitro results[9].

Liposome preparations of anticancer drugs, antihypertensive drugs, steroidal and non-steroidal analgesic drugs, local anesthetic drugs, antimigraine and antiparkinsonian drugs, vaccines, and toxoids are administered through transdermal delivery (figure 2).

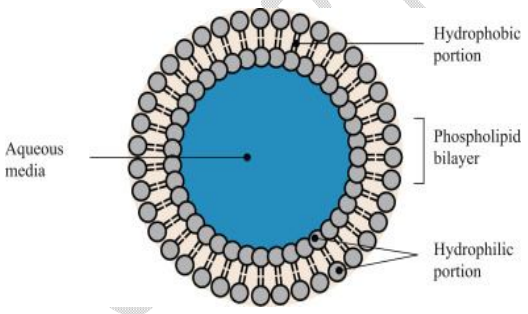

Figure 2: Structure of Liposomes

Niosomes:

Niosomes are vesicular nanocarriers. They possess lamellar (bilayer) structures composed of amphiphilic molecules with a surrounding aqueous phase (Fig. 3). Surfactants consist of both water-insoluble tails and water-soluble heads, which have self-assembling characteristics and form structures such as spheres or plate-like structures called micelles or lamellar bilayers. Some of the areas in surfactants that can be used in delivering drugs are

sorbitan esters and analogs depending on sugar-based, polyoxyethylene, or polyglycerol or crown ether based nonionic surfactants are widely used as they avoid skin irritation followed by anionic and cationic surfactants[10].

The structures of niosomes, which are considered vesicular systems, differ in their ability to entrap both hydrophilic and lipophilic materials. Hydrophilic drugs are either encapsulated in the inner aqueous core or adsorbed on bilayer surfaces, whereas lipophilic agents are incorporated into the lipid core of the bilayers through lipid solubility.

The preparation of vesicular assemblies depends on the supply of some form of energy; all examined techniques involve the hydration of one or more surfactants above the gel-to-liquid phase transition temperature of the system to form a colloidal dispersion. Owing to their possible capacity to encapsulate numerous chemotherapeutics, these vesicles are used as drug delivery systems to facilitate drug targeting, controlled release and permeation[11]. Niosomes can act as therapeutic reservoirs for delivering a drug in an effective manner, which in turn increases the bioavailability of the drug, to obtain the therapeutic spectrum of the drug for an even longer period of time. The niosomes can be altered in terms of components and composition, concentration of different additives, and the surface charge of components of the vesicles or membrane additive substances. Furthermore, it has been ascertained that drug ionization affects the physicochemical characteristics of vesicles as well as their percutaneous permeation profiles, and niosomes have been investigated in depth as potential carriers for sustained and targeted drug delivery, since they are easily derivatized to enhance vesicle versatility to improve the affinity for the target site[12].

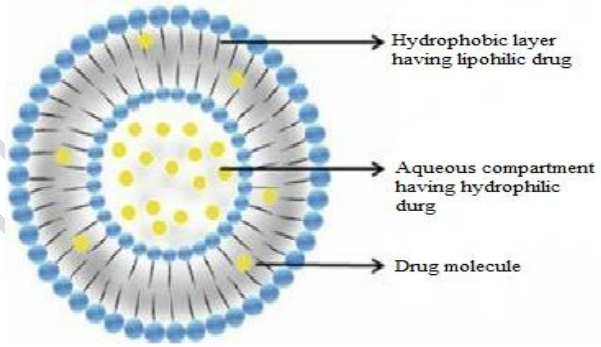

Figure 3: Structure of Niosomes

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Ethosomes:

Ethosomes are mucosal-targeted noninvasive preparations that allow drugs to penetrate into the dermal or systemic circulation. They are soft, easily deformable, and highly compatible with the deposition of active agents. They mainly consist of phospholipids: phosphacitin,

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phosphatidylserine, phosphatitic acid, and high concentrations of ethanol (45%w/w) and water (Figure 4). Ethosomes are characterized by a high concentration of ethanol, which is known for its ability to disturb the organization of the skin lipid bilayer; therefore, penetration of such vesicles through the stratum corneum is possible. Second, because ethanol content has been loaded high in lipid membranes, but compared with common vesicles, the lipid membrane is looser, yet carries equal stability, which enhances malleability and improves the drug distribution performance in the lipids of the stratum corneum. The molecular weights of the drugs incorporated into classical ethosomes fell within the range of 130. Ethosomes are adaptable for different uses in the pharmaceutical/biotechnology, veterinary, cosmeceutical, and functional food/nutraceutical fields. These "soft vesicles" can be considered new vesicular carriers with improved delivery to and through the skin. Ethosome vesicles can be made to range between tens of nanometers to particles of the micron range[13].

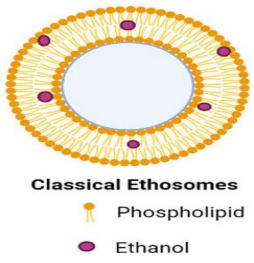

Figure 4: Structure of Ethosomes

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Transfersomes

Transfersomes, also called ultra-flexible liposomes or elastic vesicles, contain bilayers as their core and edge activators. Transfersomes are more sensitive to stress than are conventional liposomes. Therefore, the positive isotropic pressure and mixture of phospholipids and edge activators in an optimal ratio provide transfersomes with excellent deformability. These vesicles are relatively elastic in nature, primarily because of the action of the edge activator, which makes the lipoidal bilayer of vesicles flexible and deformable. Edge activitors are single-chain surfactants with high radii of curvature. Spans, tweens, dipotassium glycyrrhizinate, sodium cholate, and sodium deoxycholate were the major edge activators (figure 5). When administered through the transdermal route, transfersomes expand and enter deeper layers under the effect of a water gradient across the skin's horny layer, the stratum corneum, and settle in the subcutaneous tissue. Accumulated transfersomes help shield the built-in drug from cellular expulsion from the cutaneous circulation and the release

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of drugs into the systemic circulation, leading to increased circulation time and drug bioavailability[14].

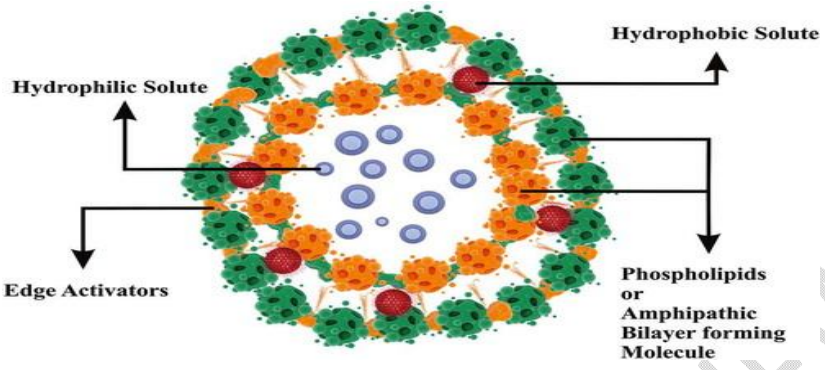

Figure 5: Structure of Transfersomes[15]

Invasome

Invasomes are also a modern vesicular system and are of vital importance for enhancing the penetration of active molecules of drugs through the skin as compared to other vesicles. These vesicles are formed from phospholipids, ethanol, terpenes, or a blend of two or more terpenes. These components have proven to be good transdermal penetrators with the required penetration characteristics. Invasosomes are soft liposomal vesicles containing insignificant amounts of ethanol and terpene or terpene combinations and are potential transporters that exhibit enhanced skin permeability. These lipidic carriers are consisted of phospholipids i.e. phosphatidylcholine, phosphatidylserine, soya phospholipid, egg lecithin, phosphatidylinositol, phosphatidic acid and phosphatidylglycerol), low concentration of ethanol (3%–3.3% v/v), terpenes or a mixture of terpenes (i.e. citral, cineole, limonene, eugenol; 1–5% v/v) and water (Figure 5). Terpenes have the general formula (C5H8)n, which enhances the rates of skin permeation of both hydrophilic and hydrophobic drugs. Terpenes are constituents of plant-derived essential oils and are used extensively as carriers or envisaged penetration enhancers. However, terpenes have other advantages, such as low skin irritation at lower concentrations. Moreover, according to FDA classes, terpenes are among the products generally considered safe to use[16].

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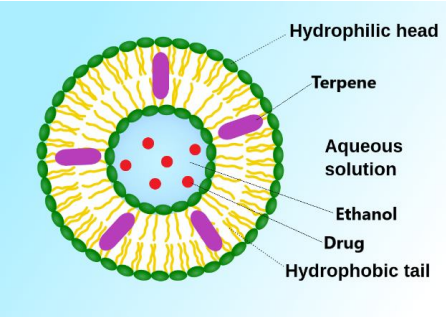

Figure 5: Structure of Invasome

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Glycerosomes:

Glycerosomes are bilayer structures used for dermal and transdermal drug delivery. Glycerol is a viscous liquid and an alcohol. It has three hydroxyl groups that make it naturally soluble in water, making it a polar molecule. Glycerol is a triglyceride present in animal fat and vegetable oils. This can be made directly during the course of soap production, or it can be a co-product derived from biodiesel production. It is used in the formulation of drugs as lubricants, humectant agents, edge promoters, and emulsifying agent.These vesicles are quite dissimilar to the common liposomes with regard to bilayer fluidity prepared by the incorporation of phospholipids and different concentrations of glycerol (10-30 % v/v). These vesicles effectively transport active ingredients across the skin tissue. Liposomes are less stable and less fluid than glycerosomes and are therefore commonly used in topical drug delivery systems. This is a relatively noninvasive and non-toxic procedure for drug administration. Because glycerol increases the deformability index of liposomal bilayers, there is better penetration into the skin. Liposomes, which are formed by phospholipids and cholesterol, glycerosomes are new vesicular systems. If phospholipids are dispersed in water, they rapidly self-organize into bilayer vesicle structures[17].

Cubosomes:

Cubosomes are a type of nanoparticle, but unlike solid particles, they are self-assembled liquid crystalline particles formed from certain surfactants mixed with water in the right ratio (**Figure 6)**. Their unique microstructure offers properties of significant practical interest. The discovery of cubosomes is intriguing and involves aspects of food science, differential geometry, biological membranes, and digestive processes. One of the most commonly used surfactants to create cubosomes is the monoglyceride glycerol monoolein. The bicontinuous cubic liquid crystalline phase, known for being optically clear and highly viscous, has a distinctive nanometer-scale structure. The term "bicontinuous" describes the separation of

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two continuous, non-intersecting aqueous regions by a lipid bilayer twisted into a space-filling form. Cubosomes are typically formed by hydrating a surfactant or polar lipid that forms a cubic phase and then dispersing the solid-like phase into smaller particles. There is significant interest in cubic phases due to their biologically compatible microstructure and ability to control the release of solubilized active ingredients, such as drugs and proteins[18].

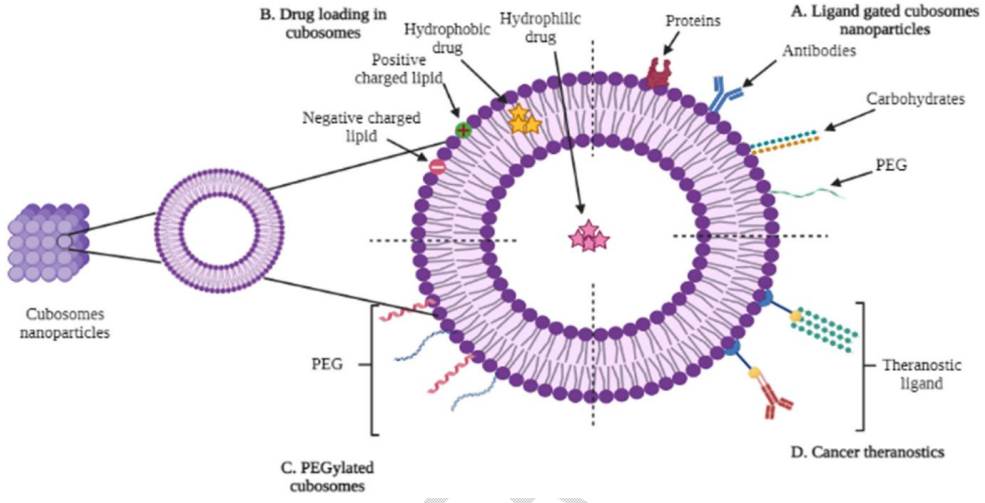

Figure 6: Structure of Cubosomes[18]

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