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AN IN-DEPTH REVIEW THAT INCLUDES A COMPARATIVE ANALYSIS OF LIPOSOMAL AND NIOSOMAL CARRIER SYSTEMS USED IN TRANSDERMAL DRUG DELIVERY SYSTEMS.

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ABSTRACT:

Transdermal drug delivery systems (TDDS) have emerged as a groundbreaking method for administering therapeutic agents, offering benefits such as non-invasiveness, bypassing of first-pass metabolism, and increased patient adherence. Nevertheless, the outer layer of the skin, known as the stratum corneum, acts as a significant barrier to drug absorption. To address this challenge, advanced nanocarrier systems such as liposomes and niosomes have been widely investigated. Liposomes, which are made from natural phospholipids, demonstrate excellent biocompatibility and can encapsulate both water-soluble and fat-soluble drugs. In contrast, niosomes, formed from non-ionic surfactants, show enhanced chemical stability, economic advantages, and ease of large-scale manufacture. This review provides a thorough comparison between liposomal and niosomal delivery systems in the field of TDDS, examining their structures, mechanisms of permeability, preparation techniques, benefits, and drawbacks. Particular attention is given to their roles in facilitating drug absorption through the skin and enhancing therapeutic effectiveness. Although both systems hold considerable potential, the choice of the right carrier is contingent on the properties of the drug, the specific application, and the goals of the formulation. Ongoing progress in nanotechnology and vesicular systems is anticipated to further enhance transdermal delivery methods and broaden their clinical uses.

KEYWORDS: niosomes, liposomes, nanotechnology, transdermal route.

INTRODUCTION:

Administering drugs through the skin is a highly effective method for drug delivery. The transdermal drug delivery system (TDDS) represents a groundbreaking method in pharmaceuticals for drug administration due to its numerous advantages compared to other delivery methods. Traditional drug delivery formulations often necessitate larger doses and regimens to obtain therapeutic effects, and prolonged treatment can lead to significant side effects and ultimately result in poor patient adherence. Although the oral route is typically seen as the most appropriate, convenient, and ideal method for drug administration due to its various benefits, it also has notable drawbacks. These include issues such as enzymatic breakdown within the gastrointestinal tract, irritation of the gastrointestinal lining, suboptimal absorption, and low bioavailability. Furthermore, certain drugs can pose safety risks when taken orally. Additionally, with drugs that are given by injection, needle phobia is a frequent psychological challenge for both children and adults, alongside the risk of infection during administration. TDDS emerges as the preferred solution for such medications to address these obstacles. [1]. Transdermal delivery is a patient-friendly, non-invasive, and painless method of administration. Despite its benefits, it is often less preferred due to inherent challenges. The skin acts as the primary barrier, limiting the successful permeation of Active Pharmaceutical Ingredients (APIs) into the systemic circulation at effective levels. One promising approach to overcome these obstacles is the use of nanoparticles, such as niosomes and liposomes, which benefit from their small size and ability to protect their cargo while controlling its release. [2]. Amidst the growing interest in a nutritious and effective lifestyle, numerous new chemical entities have led to discoveries with potential therapeutic effects on biological systems. However, formulating these chemicals often faces challenges due to physicochemical properties like low solubility, poor penetrability, and limited ability to produce therapeutic effects inside cells, which results in a lack of correlation between in vitro and in vivo outcomes. Consequently, innovative drug delivery systems have rapidly developed over recent decades. The modern idea of nano-bioactive materials stems from nanoscience and nanotechnology. Additionally, the term “nano” has become highly trendy within the pharmaceutical and cosmetics industries. Nanotechnology involves manipulating matter at the nanoscale (about 1/100,000 the diameter of a human hair) to create advanced products with significant societal impact. Key delivery systems utilizing nanotechnologies include nanoparticles, nanoliposomes, solid lipid nanoparticles, nanocrystals, nanocrystals, nano-suspensions, nano-emulsions, and niosomes. [3]. This review provides an extensive comparative study of liposomal and niosomal carrier systems, with a particular focus on transdermal drug delivery.

TRANSDERMAL DRUG DELIVERY SYSTEM:[4]

The skin serves as the body's primary line of defense and is also the largest organ for drug delivery; however, its main function limits its effectiveness in this role. The stratum corneum (SC), which is the outermost layer of the skin, acts as a barrier against foreign substances, hindering the transdermal absorption of medications. Administering drugs through the skin affects the nearby tissues and has an impact when distributed throughout the systemic circulation. Transdermal drug delivery provides numerous advantages compared to oral medication and hypodermic injections. The introduction of transdermal delivery has significantly influenced the delivery of various therapeutic agents, especially in the treatment of conditions such as cancer, diabetes, cardiovascular disorders, and central nervous system ailments. In 1979, the Food and Drug Administration (FDA) approved the first transdermal device, a patch designed to alleviate motion sickness. Subsequently, various methods have been developed, including structure-based, electrical-based, and velocity-based approaches. These advancements were created to overcome the obstacles associated with this method of drug administration, enhancing patient adherence.

Transdermal drug delivery systems, particularly patches, consist of several key components:

- A liner
- The drug itself
- An adhesive (pressure-sensitive adhesive)
- A membrane (comprising a polymer matrix/drug reservoir)
- Backing laminates
- Additional excipients such as permeation enhancers, plasticizers, and solvents.

The benefits of using transdermal drug delivery systems include:

- Thanks to ongoing technological advancements and the ability to directly deliver medication to the target area without disrupting the skin, transdermal delivery is becoming one of the most recognized methods for administering drugs.
- Avoidance of drug exposure to the gastrointestinal tract (GIT), first-pass hepatic metabolism, enzyme breakdown, and discomfort associated with the gastrointestinal system.
- Enhanced drug absorption and consistent drug concentration in the bloodstream over a specified period.
- Simplified scalability. Numerous medications are available as transdermal patches on the market.
- Increased patient adherence.
- Reduced variability among individuals.
- Lower overall doses required.
- Minimization of gastrointestinal (GI) adverse effects.
- The ability to easily stop treatment in cases where toxicity or side effects arise.
- Feasibility of drug administration even for unconscious patients.
- A larger area available for application compared to the buccal or nasal routes.

On the downside:

- Transdermal drug delivery systems cannot deliver ionic medications or drugs.
- Drugs weighing over 500 Daltons are unsuitable for transdermal delivery.
- They are unable to achieve high drug concentrations in blood or plasma.
- There is a risk of skin irritation, including erythema and itching.
- They cannot release drugs in a pulsatile manner.
- Prolonged wear can lead to discomfort for the patient.
- Sufficient solubility in both hydrophilic and hydrophobic environments, along with a log P value between 1 and 3, is necessary to penetrate the SC and the underlying aqueous layer.
- Drugs with low or high partition coefficients are unable to penetrate the bloodstream.
- This type of drug delivery system typically prefers lower dose candidates.

ANATOMY OF SKIN LAYER:

Gaining insight into the structure and function of the skin can facilitate the design and creation of effective drug delivery systems. In humans, the skin serves as the body's largest organ, covering an area of approximately 20 square feet and containing about one-third of the blood circulating throughout the body. The skin's anatomy is complex and consists of various layers, each with distinct roles, including the epidermis (the outermost layer), the dermis, and the subcutaneous layer. The uptake of substances happens through these different skin layers. Drug delivery into systemic circulation can occur via intercellular or transcellular pathways through the stratum corneum. Numerous factors influence transdermal drug delivery, including the skin's physiological characteristics, environmental conditions, and the drug's physicochemical properties, as well as the compatibility of any excipients used. The composition of human skin is made up of the epidermis, dermis, subcutaneous tissue, as well as sebaceous and sweat glands. The stratum corneum, the outer layer of the epidermis, is made up of multiple layers of spinous and granular cells. It contains about 15–20 layers of metabolically inactive cells and features a complex structure of proteins and lipids resembling a brick-and-mortar formation. Key lipids in this layer include fatty acids, cholesterol, and ceramides, with ceramides making up nearly half of the lipid content. Free fatty acids, which consist of 10–15% of the total lipids, are typically saturated and possess long carbon chains. The effectiveness of the stratum corneum as a barrier relies on these lipids. The stratum corneum is composed

of approximately 75–80% proteins, 5–15% lipids, and 5–10% unidentified materials. According to the brick-and-mortar model, corneocytes are flat, elongated, and polygonal cells that measure between 0.2 and 1.5 µm in thickness and 34.0 to 46.0 µm in diameter. These cells are surrounded by a lipid matrix, consisting of crystalline or gel lipid bilayers and lamellar structures. It is important to note that the mortar in this model is not a uniform substance; rather, the lipids are intricately linked with the lamellar components (the layers of lipid bilayers and water), alongside other lipid bilayers arranged in either crystalline or gel forms.

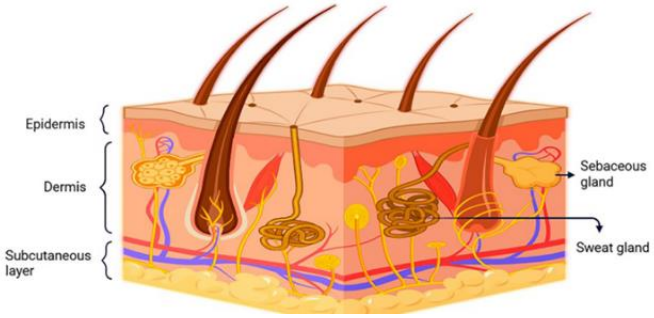

Fig no:1

MECHANISM OF DRUG PENETRATION PATHWAYS:

The essential requirement for achieving a therapeutic effect in transdermal drug delivery formulations is the permeability of the drug. The drug molecules in the formulation must traverse several layers of the skin and ultimately enter systemic circulation to elicit a therapeutic response. There are multiple pathways through which it can reach systemic circulation. They include:

A. Trans-epidermal pathways

i. Intracellular pathways (movement of molecules through the cells).

ii. Intercellular pathways (movement of molecules between the cells).

B. Trans-appendageal route (shunt pathways) [1].

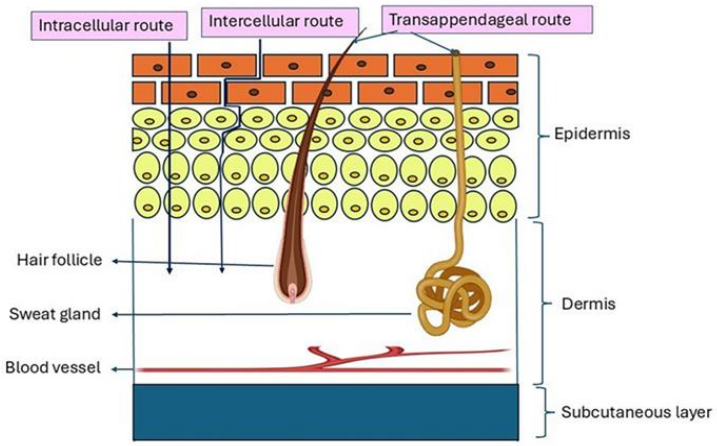

Fig no:2

OVERVIEW OF LIPOSOMES AND NIOSOMES:

NIOSOMES:

Niosomes are pseudo-spherical vesicles comprised of surfactants, classified according to their size and number of lipid layers. They are divided into small unilamellar vesicles (ranging from 10 to 100 nm), large unilamellar vesicles (between 100 and 300 nm), and multilamellar vesicles (exceeding 1000 nm). The distinction between unilamellar (which have a single surfactant bilayer) and multilamellar (which contain multiple bilayers) vesicles is based on their lamellarity. Niosomes present benefits such as osmotic stability, compatibility with biological systems, low immunogenic response, and ability to biodegrade. They enhance the solubility, absorption, and bioavailability of substances, particularly by improving the penetration of active pharmaceutical ingredients (APIs) through the skin. Their structural adaptability allows for lipophilic substances to be integrated within surfactant bilayers while hydrophilic substances are retained in their aqueous core. By attaching targeting ligands to their surface, they become suitable for specific applications. Niosomes can be administered through various routes, including oral, topical, and parenteral. Commonly employed in cosmetics for dermal delivery, niosomes also provide options for delayed and controlled drug release, acting as depot systems. They minimize adverse reactions to medications as they require a smaller amount of API to achieve the same therapeutic effect. Nevertheless, their scale-up faces challenges due to the necessity for

specialized equipment for their preparation and characterization. Additionally, problems such as aggregation, flocculation, and the leakage of encapsulated APIs jeopardize their physical stability and shelf-life, presenting further drawbacks for niosomes [3].

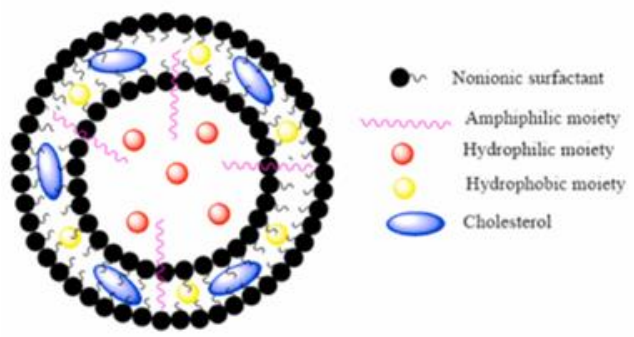

Fig no:3

LIPOSOMES:

The lipophilic effect chiefly governs the orientation of amphiphilic molecules like phospholipids in a way that reduces unfavorable thermodynamic interactions between the hydrophobic acyl chains and the surrounding water. Intermolecular forces such as Van der Waals interactions, hydrogen bonds, and electrostatic forces help to alleviate this effect. A microscopic vesicle that has an aqueous core and is composed of one or more layers of phospholipids is referred to as a liposome, which can trap hydrophilic, hydrophobic, and amphiphilic substances, leading to diverse applications. Liposomes are classified into five categories based on their chemical properties and cellular distribution: conventional, pH-sensitive, cationic, immunoliposomes, and long-circulating liposomes. The size of the vesicle is essential in determining the liposome's circulation duration, while the number and size of the bilayers influence the volume of drug they can carry. Consequently, liposomes are frequently categorized by their size and bilayer count into small unilamellar vesicles (SUV, 20–100 nm), large unilamellar vesicles (LUV, >100 nm), giant unilamellar vesicles (GUV, >1000 nm), oligolamellar vesicles (OLV, 100–500 nm), and multilamellar vesicles (MLV, <500 nm) [5].

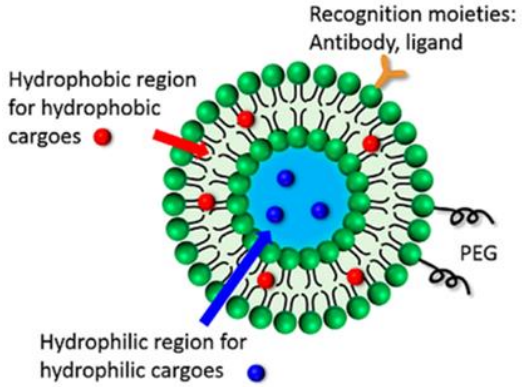

Fig no:4

ROLE OF CARRIER SYSTEM IN TRANSDERMAL DRUG DELIVERY SYSTEM:

LIPOSOMES:

The absorption pathways of liposomes vary based on the administration route. Oral intake can destabilize liposomes due to gastric enzymes, bile salts, and pancreatic secretions, although recent modifications, like using hydrogenated long-chain phospholipids, enhance their stability and bioavailability. The intranasal route allows for high permeability and bypasses the first-pass effect, improving drug delivery to the brain and preventing enzymatic degradation. Liposomes are also beneficial for transdermal delivery, enhancing drug passage through the skin's barrier and treating skin cancers.

Pulmonary delivery offers a systemic route with advantages like avoiding first-pass metabolism, as seen in studies using lipid inhalation of cisplatin for osteosarcoma. However, in vivo success depends on factors such as anatomy, physiology, liposome size, and charge. Intravenously, liposomes face challenges due to protein adsorption that affects circulation and biodistribution, often leading to rapid absorption by the reticuloendothelial system.

For specific tumors, intraperitoneal injection targets drugs within the abdominal cavity but may limit circulation time. Intramuscular injection allows broader distribution, though biodistribution varies by lipid composition, with anionic liposomes clearing quickly via lymphatics and cationic liposomes accumulating at the injection site.[6]

Liposomes, which are vesicular structures composed of phospholipid bilayers, are frequently used for delivering drugs through the skin both topically and transdermally. While conventional liposomes tend to remain in the upper layers of the stratum corneum, modified variants such as elastic (deformable) liposomes, propylene-glycol liposomes, and PEGylated liposomes can significantly enhance skin penetration. Elastic (Deformable) Liposomes: The incorporation of edge activators like Tween or bile salts enhances the flexibility of the bilayer. These vesicles can navigate through narrow intercellular

gaps and access deeper layers of skin without occlusion. Propylene Glycol Liposomes (PGLs): PGLs show increased drug permeability compared to standard deformable liposomes, probably due to improved hydration and fluidity of the bilayer, with a permeation coefficient of approximately 6.2 × 10^6 cm/s in contrast to 5.5 × 10^6 cm/s. PEGylated Liposomes: Altering the surface with PEG enhances the hydration of the stratum corneum, facilitating deeper penetration of hydrophilic drugs such as sodium fluorescein or calcipotriol.[7][8].

NIOSOMES:

In recent years, there has been a focus on using nanocarriers for drug encapsulation, particularly for oral and parenteral formulations. Growing interest also exists in their application for topical and transdermal delivery due to benefits like improved patient compliance, a larger absorption surface area, and avoidance of first-pass metabolism.

The dermal route allows localized delivery of therapeutics for skin conditions, minimizing systemic exposure and side effects, while the transdermal route enables active ingredients to enter systemic circulation via skin capillaries.

Niosomes enhance transdermal drug delivery through various mechanisms, including penetrating the stratum corneum intact or transforming into smaller vesicles. They may interact with the stratum corneum through adsorption or fusion. Adsorption can involve nonspecific interactions or receptor-ligand binding, allowing direct drug transfer, while fusion integrates the vesicle membrane with the cellular membrane for complete release into the cytoplasm. Niosomes can also act as penetration enhancers by modifying the stratum corneum's structure, increasing permeability, and reducing transepidermal water loss (TEWL) [3].

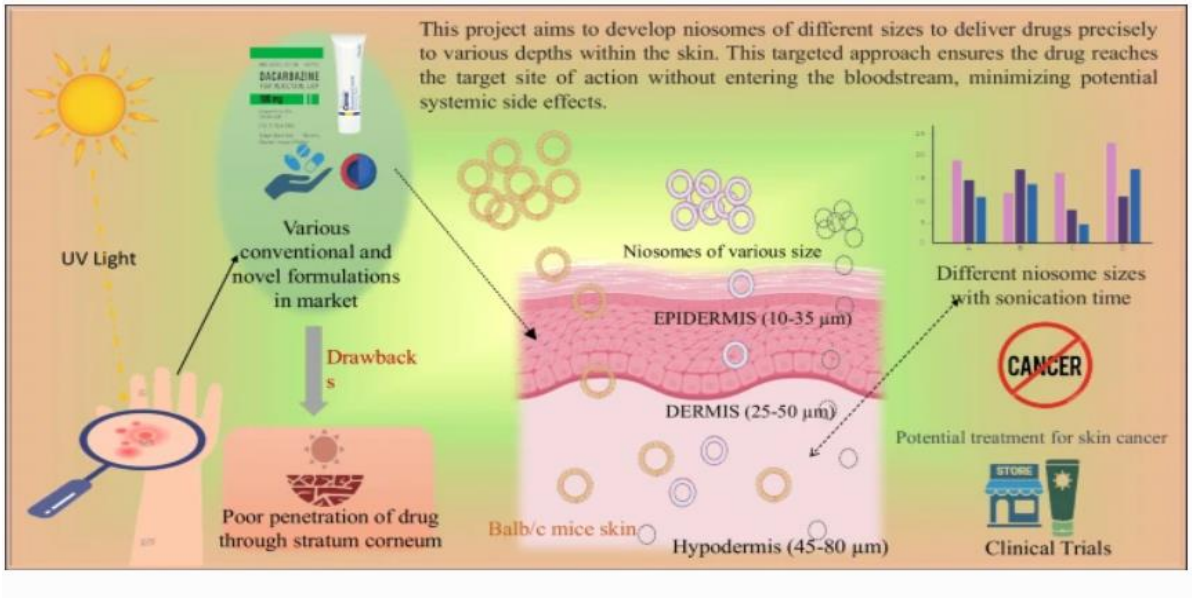

Fig. no: 5

PREPARATION OF CARRIER SYSTEM:

LIPOSOMES:[3]

Thin-Film Hydration-Sonication (TFHS) Method:

Phospholipids and lipophilic drugs are mixed in a polar solvent, evaporated above the phospholipid transition point, and left under vacuum to form a film. After hydration with distilled water or buffer, while stirring, the sample is sonicated for 1 hour to minimize vesicle size.

Ethanol Injection (EI) Method:

An ethanol solution of phospholipids is injected into a water phase with vigorous mixing and controlled temperature above the lipid transition point. The mixture is then stirred and evaporated to remove the remaining solvents.

Reverse Phase Evaporation (RPE) Method:

Lipid mixtures are solubilized using ultrasonication in RPE solvent and combined with stabilizers. A rotary evaporator removes the solvent to form a thick film, followed by a liquid solution for further homogenization.

Microfluidization:

The final mixture undergoes centrifugation, sonication, or dialysis in a nitrogen atmosphere to prevent degradation.

Detergent Dialysis:

Lipids dissolved in detergent form mixed micelles. Controlled dialysis removes detergent, yielding homogeneous unilamellar vesicles. Other methods, like calcium-induced fusion and nanoprecipitation, are also used for liposome creation.

Supercritical Fluid (SF) Method:

This method reduces organic solvent use for nanoliposome synthesis through supercritical solutions and supercritical antisolvent techniques. It relies on mixing in supercritical fluids to concentrate lipids and facilitate particle production.

Spray-Drying:

A straightforward process where a lipid-drug mixture is spray-dried after sonication. The dried sample is hydrated with phosphate-buffered saline (PBS), and the water phase quantity affects liposome size.

Freeze Drying:

Involves creating a homogeneous lipid dispersion with water-soluble carriers like sucrose in a tert-butyl alcohol/water co-solvent. This solution is freeze-dried and, upon rehydration, yields homogeneous liposomes. The lipid/carrier ratio influences liposome size and polydispersity.

NIOSOMES:

Thin Film Hydration Technique:

Dissolve a non-ionic surfactant (such as Span 60) along with cholesterol in a chloroform and methanol mixture (2:1). Evaporate the solvent using a rotary evaporator at 40–60 °C under reduced pressure to form a thin lipid film on the walls of the flask. Hydrate this lipid film with an aqueous solution (such as PBS or a drug solution) while rotating to create multilamellar niosomes. You can then use sonication or extrusion to decrease the vesicle size, resulting in small unilamellar vesicles (SUVs) [9].

Reverse Phase Evaporation Technique:

Create a mixture of cholesterol and surfactants in an organic solvent like chloroform. Use sonication to emulsify the aqueous drug solution into this organic phase. Finally, remove the organic solvent under reduced pressure to generate gel-like niosomal vesicles [10].

Microfluidization:

The aqueous and organic phases are passed through microchannels at high shear rates. Controlled laminar flow facilitates the creation of uniform and small niosomes (100–300 nm) [11].

RESULT AND DISCUSSION:

COMPARISON OF LIPOSOMAL AND NIOSOMAL CARRIER SYSTEM:

FEATURE	LIPOSOMES	NIOSOMES
Definition	Vesicular carriers made of natural phospholipids	Vesicular carriers made of non-ionic surfactants and cholesterol
Composition	Natural phospholipids (such as egg lecithin) and cholesterol	Artificial surfactants (like Span and Tween) are combined with cholesterol.
Stability	Prone to oxidation and hydrolysis; sensitive to storage conditions	Enhanced chemical and physical stability; extended shelf life
Permeation Mechanism	Integration with lipid membranes, increased hydration, and enhanced deformability for deeper penetration	Disturbance of stratum corneum lipids, increased hydration, and permeation facilitated by surfactants
Usual Permeation	Dependent on variables—not useful unless altered (e.g., ethanol, edge activators)	Reliable permeation; lower variability
Preparation Difficulty	Moderate to high (particularly for elastic varieties)	More scalable and economical.
Category of Vesicle	Amphiphilic structures composed of bilayers	Amphiphilic vesicles that can be bilayer or multilamellar
Entrapment	Hydrophilic & lipophilic drugs	Hydrophilic & lipophilic drugs
Biocompatibility	High (natural lipids)	Good (synthetic but generally non-toxic)
Preparation Methods	Thin-film hydration, reverse-phase evaporation, ethanol injection	Thin-film hydration, reverse-phase evaporation.
Size Range	Typically 50–300 nm	Typically 100–600 nm
Surface Charge	Neutral to negative (can be modified)	Can be modified with charged surfactants
Vesicle Flexibility	Offered in the form of elastic or deformable liposomes (such as transfersomes and ethosomes)	While they are less deformable compared to liposomes, they still can penetrate the skin.
Toxicity	Low (due to natural ingredients)	Low to minimal (varies with type and concentration of surfactant)
Scalability	More difficult (because of lipid sensitivity)	Simpler (thanks to more robust and stable components)

Expense	Elevated because of the source of phospholipids and the need for stability	Reduced costs for production and raw materials
Clinical Application	Recommended when deep tissue penetration and compatibility with biological systems are essential	Preferred for cost-effective or consistent transdermal formulations
List of Medications Provided	Diclofenac, Estradiol, Insulin, Acyclovir	Ketoconazole, Nimesulide, Paclitaxel, Insulin

CONCLUSION:

Transdermal drug delivery systems (TDDS) provide a non-invasive and user-friendly alternative to conventional drug administration methods, effectively addressing issues like poor oral bioavailability, first-pass metabolism, and complications associated with injections. Nevertheless, the barrier properties of the skin, particularly the stratum corneum, present significant challenges for efficient drug absorption. To tackle these challenges, vesicular nanocarriers such as liposomes and niosomes have emerged as effective delivery options. Liposomes, which are made of natural phospholipids, exhibit high biocompatibility and can encapsulate both hydrophilic and lipophilic medications. Variants such as elastic liposomes and PEGylated liposomes further improve their ability to penetrate more profound layers of the skin. However, despite these benefits, liposomes encounter challenges related to stability, cost, and scalability. In contrast, niosomes are created using non-ionic surfactants and cholesterol, providing enhanced physical and chemical stability, simpler production processes, and reduced manufacturing expenses. They are effective at improving skin permeability and demonstrate consistent performance, making them favorable for large-scale use. While their biocompatibility is somewhat lower than that of liposomes, they are still non-toxic and well-accepted. Both delivery systems considerably improve the absorption and therapeutic effectiveness of drugs administered transdermally. The decision to use either liposomes or niosomes is influenced by specific drug characteristics, target sites, the desired release profile, and cost considerations. In summary, liposomes and niosomes are crucial components in the progress of TDDS, and ongoing research into their optimization, hybrid formulations, and clinical application holds significant promise to transform the realm of non-invasive drug delivery.

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