A review on vesicular drug delivery systems

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ABSTRACT:

The skin, the body's largest organ, serves as a highly effective barrier—primarily due to the stratum corneum, a thin 10–20 µm layer that blocks over 90 percent of substances—making topical drug delivery particularly difficult. Conventional formulations while user-friendly, face major challenges such as poor skin penetration, susceptibility to environmental degradation, and inability to deliver drugs in a sustained manner. These limitations result in reduced therapeutic effectiveness and poor patient compliance. Recent advancements in nanotechnology have led to the development of vesicular drug delivery systems (VDDS), which are nanoscale, lipid-based carriers capable of traversing the stratum corneum to deliver active agents more effectively into deeper layers of the skin. VDDS improve drug absorption, protect sensitive molecules from degradation, enable sustained and targeted drug release, and minimize systemic exposure and side effects. VDDS are broadly classified into lipoidal and non-lipoidal carriers, each possessing distinct advantages and limitations. Lipoidal vesicles—such as liposomes, transferosomes, and ethosomes—mimic biological membranes and promote efficient dermal and transdermal delivery; however, they can be prone to oxidation, leakage, and require more complex and costly production. Non-lipoidal carriers—including niosomes, bilosomes, and aquasomes—offer better chemical stability and are well-suited for oral and protein-based therapeutics, though they may exhibit lower encapsulation efficiency and require precise formulation control. Drug release from VDDS occurs via mechanisms such as passive diffusion, osmotic pressure gradients, pH-triggered destabilization in acidic environments, and external stimuli like temperature or light to achieve localized, controlled delivery. In topical applications, VDDS have shown effectiveness across multiple conditions, including antimicrobial therapy, treatment of psoriasis and eczema, acne management, local anti-inflammatory interventions, and localized cancer therapy. Innovative developments—such as nanoparticle incorporation, stimuli-responsive ("smart") vesicles, gene delivery systems, and co-delivery of multiple therapeutics—promise to overcome pharmacokinetic challenges, enhance targeting precision, and reduce toxicity, positioning VDDS as a promising frontier in topical drug delivery.

KEYWORDS: Vesicular drug delivery systems (VDDS), drug encapsulation, transdermal delivery, topical drug Delivery, Nanocarriers, Bioavailability Enhancement.

1. INTRODUCTION

The skin is the largest and one of the most important organs in the human body. It works like a natural shield, protecting us from harmful things in the environment such as germs, chemicals, and sunlight. However, this same protective nature makes it hard for many medicines to pass through the skin, especially when they are applied as creams or ointments. This is mainly because of the stratum corneum, the outermost layer of the skin, which acts like a tight wall made of dead skin cells and fats[1]. Although it's very thin (just about 10 to 20 micrometers), it blocks over 90% of substances from getting inside[2]. As a result, most drugs—especially large or water-loving (hydrophilic) ones—can't easily pass through.

Traditional topical drug products like lotions, gels, creams, and ointments are popular because they are easy to use and can provide quick, local relief. But these products come with some serious limitations. They don't allow enough medicine to pass through the skin, especially if the drug doesn't dissolve well in water. They can also be sensitive to heat and may lose effectiveness when stored under different environmental conditions. Moreover, they usually don't offer controlled or long-lasting drug release, meaning the patient must apply them frequently. Overall, these challenges reduce how well the drug works and how comfortable the treatment is for the patient.

Cheers to new developments in nanotechnology, scientists have created special drug delivery systems called vesicular carriers to overcome these problems[3]. These systems are very small—at the nanometer scale—and can carry drugs deeper into the skin. Known as Vesicular Drug Delivery Systems (VDDS), they help improve how well drugs are absorbed through the skin, protect the drug from damage, and provide more effective and longer-lasting results, often with fewer side effects[4].

2. VESICULAR DRUG DELIVERY SYSTEMS (VDDS)

VDDS are tiny, bubble-like carriers made mostly of lipids (fats) that form one or more layers around a water-filled center. These bubbles, or vesicles, are very similar to the membranes that surround our body's cells. This makes them biocompatible, which means they are safe to use in the body and unlikely to cause irritation or harm[4].

One of the best things about VDDS is that they can carry both types of drugs: hydrophilic drugs (which dissolve in water) can be stored in the inner water core, while lipophilic drugs (which dissolve in fats) can be stored within the lipid layers. For example, doxorubicin, a water-loving cancer drug, can go inside the center, while paclitaxel, a fat-loving drug, fits into the outer layers. This dual ability makes VDDS very flexible for treating different conditions[5,6].

VDDS help medicines penetrate the skin more effectively by interacting with the skin's own fats. This leads to a higher amount of drug reaching the target area while reducing how much enters the bloodstream, which lowers the chance of side effects. These systems also release the drug slowly and steadily over time, improving treatment and reducing how often the drug needs to be applied. Additionally, they protect delicate drugs—like proteins and genetic materials—from getting broken down by enzymes or from degrading due to heat or light. This helps keep the medicine stable and extends its shelf life[7,8].

2.1 Advantages of Vesicular Drug Delivery Systems

- Encapsulation of both hydrophilic and lipophilic drugs

VDDS can carry both water-soluble and fat-soluble drugs at the same time. For e.g. Doxorubicin (water-soluble) fits inside the water core, while Paclitaxel (fat-soluble) is stored in the outer lipid layer. This allows for combination therapy in one system[9].

- Enhanced bioavailability and skin penetration

Because vesicles can change shape and mix well with the skin's lipids, they help drugs move through the outer skin layer much more efficiently than traditional formulations[10].

- Controlled and sustained drug release

The release of the drug can be fine-tuned by changing the vesicle's ingredients. This means drugs can be delivered slowly over time, which helps maintain their effect for longer and reduces the need for frequent application[11].

- Protection from enzymatic degradation

Some drugs, like proteins or DNA-based treatments, are easily broken down by enzymes. VDDS shield these drugs, allowing them to stay active and reach their target[12].

- Biocompatibility and reduced toxicity

Since VDDS are made from materials like phosphatidylcholine, which are naturally found in the body, they are generally safe and cause fewer side effects or allergic reactions[13].

- Improved stability and shelf-life

Drugs carried in vesicles are protected from damage caused by environmental factors like heat, light, and air. This improves the shelf life and reliability of the final product[14].

- Cost-effective and scalable

Many types of vesicles can be produced using standard pharmaceutical techniques. This makes them suitable for large-scale production and helps lower manufacturing costs[15].

2.2 Challenges and Limitations of VDDS

Although vesicular drug delivery systems offer many benefits—like better drug absorption, protection from degradation, and controlled release—they also face some important challenges, especially when moving from the lab to real-world use.

One major issue is stability. Vesicles like liposomes and niosomes can become unstable during storage. Over time, they might stick together (aggregate) or leak the drugs they carry, which reduces their effectiveness and shelf life. This makes it hard to keep the product safe and reliable for long-term use[16].

Another challenge is scalability. While it's easier to prepare vesicles in small quantities in a lab, producing them in large batches with the same quality is more complicated and costly. Ensuring that every batch has the same size, drug content, and stability requires advanced equipment and careful process control.

Immunogenicity, or the potential to trigger an immune response in the body, is also a concern. Although the vesicles are usually made from safe and biocompatible materials, some components or surface modifications can still cause allergic reactions or immune system activation, especially if the product is used over a long period.

Lastly, regulatory approval for these systems can be difficult. Since vesicular formulations are more complex than regular tablets or creams, they must go through extensive testing to prove they are safe, effective, and stable. This makes the approval process time-consuming and expensive, often delaying their availability in the market[17].

3. CLASSIFICATION OF VESICULAR DRUG DELIVERY SYSTEMS

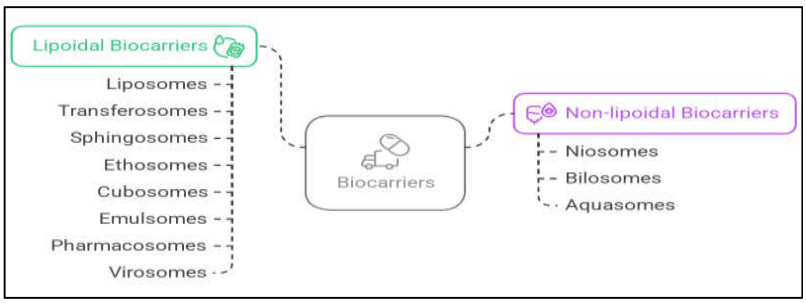

Figure 1: Comparison between Lipoidal and Non-lipoidal Drug Carriers

4. LIPOIDAL BIOCARRIERS

Lipoidal biocarriers are vesicular drug delivery systems composed primarily of lipid molecules, which mimic biological membranes. These carriers are particularly beneficial for topical, transdermal, parenteral, and oral delivery of drugs by enhancing permeation, improving bioavailability, and providing controlled drug release.

4.1 Liposomes

Liposomes are spherical vesicles comprising one or more phospholipid bilayers encapsulating an aqueous core. The primary components include phosphatidylcholine and cholesterol, which stabilize the bilayer and enhance membrane fluidity. These carriers can encapsulate both hydrophilic (in the aqueous core) and lipophilic drugs (within the bilayer)[18].

Liposomal amphotericin B (AmBisome®) has shown superior safety over conventional amphotericin B in systemic fungal infections, significantly reducing nephrotoxicity[19].

4.2 Transferosomes

Transferosomes are ultra-deformable lipid vesicles composed of phospholipids, edge activators (surfactants), and ethanol. Their deformable nature allows them to pass through the narrow pores of the skin, making them ideal for transdermal delivery[20].

Diclofenac-loaded transferosomes have demonstrated superior anti-inflammatory efficacy in arthritis therapy when compared to conventional topical gels[21].

4.3 Sphingosomes

Sphingosomes are lipid vesicles composed primarily of sphingolipids, which naturally occur in cell membranes. Their rigid and stable bilayer offers enhanced stability over conventional liposomes, and they are particularly suitable for encapsulating anticancer drugs[22].

Doxorubicin-loaded sphingosomes have shown improved efficacy and reduced cardiotoxicity in cancer therapy[23].

4.4 Ethosomes

Ethosomes are soft, malleable lipid vesicles composed of phospholipids, high concentrations of ethanol (20–45%), and water. Ethanol acts as a penetration enhancer, disrupting the stratum corneum lipid structure and allowing ethosomes to deliver drugs deep into the skin[24].

Acyclovir ethosomes have been used effectively for the treatment of herpes simplex virus infections, providing improved dermal delivery compared to conventional formulations[25].

4.5 Cubosomes

Cubosomes are nanostructured liquid crystalline particles with a bicontinuous cubic phase, composed of amphiphilic lipids like glyceryl monooleate and stabilizers. Their internal structure consists of two continuous but non-intersecting water channels separated by lipid bilayers[26].

Cubosomes loaded with curcumin have shown enhanced skin retention and controlled release for treating inflammatory skin conditions like psoriasis[27].

4.6 Emulsomes

Emulsomes are hybrid vesicular systems composed of a solid or semi-solid lipid core stabilized by a phospholipid bilayer, combining the advantages of emulsions and liposomes. They are particularly effective for the oral and parenteral delivery of lipophilic drugs[28].

Antifungal drugs like itraconazole and ketoconazole have been successfully delivered via emulsomes to increase bioavailability and sustain release[29].

4.7 Pharmacosomes

Pharmacosomes are drug-lipid conjugates that self-assemble into micelles, vesicles, or hexagonal aggregates, depending on the physicochemical properties. Unlike passive entrapment in liposomes, the drug is covalently bound to the lipid, increasing stability and control over release[30].

NSAIDs such as indomethacin have been formulated into pharmacosomes for arthritis treatment, reducing GI side effects and improving therapeutic efficacy[31].

4.8 Virosomes

Virosomes are virus-like vesicles formed by reconstituting viral envelopes (usually influenza) with phospholipids and viral glycoproteins (e.g., hemagglutinin, neuraminidase). They mimic the structure of a virus, enabling effective antigen presentation and immune activation[32].

Virosome-based Hepatitis A vaccines have shown improved immunogenicity and safety over conventional vaccines[33].

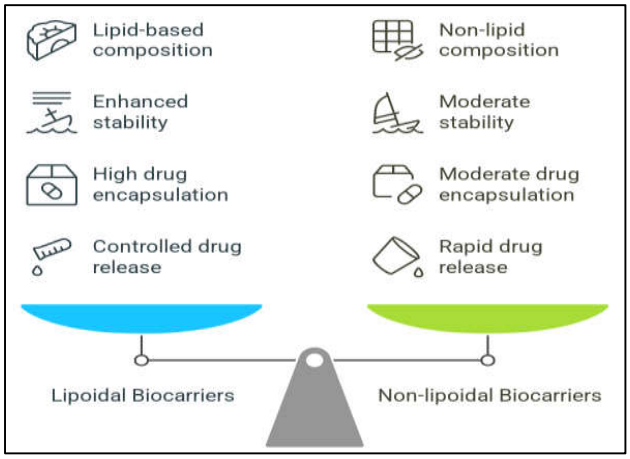

Figure 2: Comparison between Lipoidal and Non-lipoidal Drug Carriers

5. NON-LIPOIDAL BIOCARRIERS

Non-lipoidal biocarriers are vesicular systems not primarily composed of lipids, offering additional benefits like GI stability, increased flexibility in formulation, and enhanced drug protection for sensitive biomolecules.

5.1 Niosomes

Niosomes are non-ionic surfactant-based vesicles made from surfactants (e.g., Spans, Tweens) and cholesterol. They resemble liposomes in structure but are more stable and cost-effective, making them ideal for both topical and oral delivery[34].

Niosomal insulin formulations have been studied for oral delivery, protecting insulin from enzymatic degradation in the GI tract[34-36].

5.2 Bilosomes

Bilosomes are niosomes modified with bile salts (e.g., sodium deoxycholate) in their membrane. The presence of bile salts enhances their resistance to enzymatic degradation in the GI tract, making them suitable for oral vaccine delivery[37].

Bilosomes carrying polio antigens have shown enhanced mucosal and systemic immunity when administered orally[38].

5.3 Aquasomes

Aquasomes are three-layered nanoparticles consisting of a solid core (e.g., calcium phosphate or tin oxide), a carbohydrate coating, and a layer of bioactive molecules. Their structure maintains the structural integrity of fragile biomolecules like proteins and DNA[39].

Aquasomes have been used for oral insulin delivery and gene therapy applications due to their structural stability and ability to avoid immune recognition[40].

Table 1: Comparative Analysis of Lipoidal and Non-Lipoidal Vesicular Drug Carriers

Carrier Type	Advantages	Disadvantages
Lipoidal Vesicular Drug Carriers		
Liposomes	- Biocompatible and biodegradable - Protects from enzymatic degradation - Dual drug encapsulation - Improved therapeutic index	- Prone to leakage and oxidation - Expensive production - Limited shelf life - Requires cold storage
Transferosomes	- Excellent skin penetration - Non-invasive delivery - Suitable for peptides/proteins	- Sensitive to stress/storage - May cause irritation - Needs precise surfactant ratio
Sphingosomes	- Enhanced stability - Biocompatible and non-toxic - Controlled release	- Less flexible - Limited studies compared to liposomes
Ethosomes	- High skin penetration - Suitable for both hydrophilic and lipophilic drugs - Ethanol as permeation enhancer	- Ethanol may irritate skin - Sensitive to pH/temp - Stability issues
Cubosomes	- High drug loading - Controlled release - Thermodynamically stable	- Complex preparation - Burst release risk - Requires high-energy equipment
Emulsomes	- High stability from lipid core - Suitable for lipophilic drugs - Sustained release	- Limited use for hydrophilic drugs - Scale-up difficulty - Requires homogenization
Pharmacosomes	- Stable drug-lipid conjugate - Controlled release - Less leakage	- Limited flexibility (requires drug modification) - Complex synthesis
Virosomes	- High immunogenicity - Mimics viral structure for vaccine delivery - Safe (non-replicating)	- Expensive - Complex manufacturing - Potential immune reaction to viral proteins
Non-Lipoidal Vesicular Drug Carriers		
Niosomes	- Greater chemical stability - Cost-effective - Encapsulates both drug types	- Lower encapsulation efficiency - Possible aggregation - Surfactant irritation risk
Bilosomes	- Protects in GI environment - Stimulates systemic and mucosal immunity - Ideal for oral vaccines	- Bile salt formulation complexity - Stability varies in GI - Not widely commercialized
Aquasomes	- Preserves structure of delicate molecules - High surface area - Avoids immune detection	- Complex fabrication - Lower drug load vs. vesicles - Requires tight control of surface chemistry

Each vesicular system offers distinct advantages depending on drug type, route of administration, and target site, but must be matched carefully with its limitations and stability profile. Lipoidal carriers such as liposomes, transferosomes, and ethosomes are lipid-based and mimic biological membranes. Non-lipoidal carriers like niosomes, bilosomes, and aquasomes offer better chemical stability and are often suitable for oral and protein delivery.

Mechanisms of Drug Release:

The release of drugs from vesicular systems occurs through various mechanisms, depending on the nature of the vesicle and its environment[41,42]:

a) **Diffusion:** The most common mechanism where the drug moves from the internal aqueous core to the surrounding medium.
b) **Osmotic pressure:** The concentration gradient between the encapsulated drug and the external environment leads to drug release.

c) **pH-Dependent Release:** Some vesicular systems, such as pH-sensitive liposomes, release drugs when exposed to a specific pH environment, which is useful for targeted drug delivery to tumors or acidic areas.
d) **Thermal and light-sensitive Release:** Some vesicular systems can be triggered by temperature or light to release the drug at the site of action, providing spatial control over drug delivery.

6. APPLICATIONS OF VDDS IN TOPICAL DRUG DELIVERY

Vesicular systems have shown significant promise in managing a range of skin disorders and systemic infections through the topical route. This include[43-46]:

a) Antimicrobial Therapy

Vesicular drug delivery systems enhance the effectiveness of antimicrobial agents by improving their penetration into infected tissues and prolonging drug residence time at the site of infection. Liposomes, niosomes, and emulsomes can encapsulate antibiotics or antifungals, offering targeted delivery and reduced systemic toxicity. These systems are especially useful for treating skin infections caused by resistant pathogens and for minimizing side effects associated with conventional antimicrobial therapies.

b) Management of Psoriasis and Eczema

Psoriasis and eczema are chronic inflammatory skin disorders characterized by impaired skin barrier function. Vesicular carriers like transferosomes and ethosomes enhance the penetration of corticosteroids, immunosuppressants, and natural anti-inflammatory compounds into deeper skin layers. These systems allow for localized, sustained drug delivery, reducing the need for systemic therapy and minimizing potential side effects such as skin thinning or irritation.

c) Acne Treatment

Acne vulgaris involves bacterial infection (typically Cutibacterium acnes), inflammation, and excess sebum production. Vesicular formulations—especially liposomes and niosomes—can encapsulate retinoids, antibiotics (like clindamycin), or anti-inflammatory agents, ensuring deeper follicular penetration and controlled release. This targeted approach helps reduce bacterial resistance, improves therapeutic efficacy, and minimizes irritation commonly seen with conventional topical treatments.

d) Delivery of Anti-inflammatory Agents

Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids face limitations such as poor skin permeability and systemic side effects. VDDS like niosomes, transferosomes, and ethosomes facilitate enhanced dermal absorption and prolonged retention of these agents within inflamed tissues. This allows for effective local therapy in conditions like arthritis, dermatitis, or sports injuries while avoiding gastrointestinal or systemic complications.

e) Localized Cancer Treatment

Vesicular drug delivery systems offer a promising approach for localized cancer therapy by enabling the direct delivery of chemotherapeutic agents to tumor sites. Liposomes, cubosomes, and transfersomes can be engineered to exploit the enhanced permeability and retention (EPR) effect, ensuring drug accumulation in tumor tissues while sparing healthy cells. These systems also support sustained and controlled drug release, potentially increasing efficacy and reducing systemic toxicity in skin cancers or metastases accessible via the dermal route.

f) Recent Advances and Future Directions:

Recent developments in vesicular drug delivery systems have focused on improving their effectiveness through several innovative strategies. Incorporating nanoparticles into vesicles has been shown to enhance their stability, drug-loading capacity, and targeting ability. Researchers are also developing “smart” vesicles that respond to external triggers like pH, temperature, or light, enabling more precise and controlled drug release. In addition, vesicular systems are being explored for gene delivery, offering a safe and efficient way to transport genetic materials such as siRNA and DNA to specific cells. Another advancement is the use of liposomal and niosomal formulations for combination therapy, allowing the simultaneous delivery of multiple drugs, which is especially useful in treating complex conditions like cancer.

7. BROADER APPLICATIONS OF VESICULAR DRUG DELIVERY SYSTEMS

Vesicular drug delivery systems have found applications across a wide spectrum of medical fields due to their ability to enhance permeability, drug stability, and site-specific delivery while reducing toxicity. Below is an expanded overview of key applications, supported by relevant scientific literature.

Table 2: Therapeutic Applications of VDDS with Descriptions and References

Application Area	Vesicular Carrier	Example Drug(s)	Benefit	References
Antifungal Therapy	Liposomes, Emulsomes	Amphotericin B	Reduces nephrotoxicity associated with conventional formulations while improving efficacy in systemic and cutaneous fungal infections.	[47], [48]
Anti-inflammatory Agents	Niosomes, Transferosomes	Diclofenac	Enhances skin penetration, prolongs anti-inflammatory action, and reduces systemic exposure.	[49], [50]
Vaccination	Virosomes, Bilosomes	Hepatitis A, Oral Polio	Delivers antigens to immune-responsive sites, improves mucosal immunity, and protects from GI degradation (in oral vaccines).	[51], [52]
Cancer Therapy	Liposomes, Cubosomes	Doxorubicin	Enables targeted delivery to tumor tissues via the enhanced permeability and retention (EPR) effect, reducing toxicity to healthy cells.	[53], [54]
Hormone Therapy	Ethosomes, Niosomes	Testosterone	Facilitates deep skin penetration and provides sustained hormone release over an extended period.	[55], [56]

7.1 Antifungal Therapy

Amphotericin B, a broad-spectrum antifungal agent, is highly effective but traditionally associated with significant nephrotoxicity. Liposomal formulations (e.g., AmBisome®) and emulsomes encapsulate the drug, minimizing systemic toxicity and improving delivery to infected sites. These carriers enhance bioavailability and patient compliance in both systemic and topical fungal infections[47,48].

7.2 Anti-inflammatory Therapy

Non-steroidal anti-inflammatory drugs (NSAIDs) like diclofenac face challenges such as limited skin absorption and GI side effects when administered orally. Vesicular carriers such as niosomes and transferosomes increase drug residence time in skin layers, promoting deeper dermal penetration and a prolonged anti-inflammatory effect. Transferosomal diclofenac gels have been shown to be superior to conventional gels in arthritis treatment[49,50].

7.3 Vaccination

Virosomes (reconstituted viral envelopes) and bilosomes (bile-salt stabilized vesicles) have revolutionized vaccine delivery. Virosomes mimic native viruses and enhance antigen presentation, making them ideal for intranasal or parenteral vaccination (e.g., hepatitis A). Bilosomes enable oral delivery of vaccines, such as polio, by protecting antigens from degradation in the gastrointestinal tract and eliciting mucosal immunity[51,52].

7.4 Cancer Therapy

Cancer chemotherapeutics such as doxorubicin are well known for their efficacy but also for their systemic toxicity. Liposomal doxorubicin (e.g., Doxil®) has gained clinical acceptance due to its targeted tumor delivery and improved safety profile. Similarly, cubosomes, with their structured bicontinuous phase, are ideal for controlled release of anticancer agents directly to tumors[53,54].

7.5 Hormone Replacement Therapy

Transdermal delivery of hormones like testosterone avoids first-pass hepatic metabolism and provides stable plasma concentrations. Ethosomes, due to their high ethanol content, fluidize the skin lipids and enhance penetration, while niosomes provide sustained delivery through dermal layers. These vesicles offer an alternative to painful injections or orally administered hormone therapies[55,56].

8. CONCLUSION

Vesicular drug delivery systems represent a significant advancement in the field of transdermal and topical drug delivery. Their ability to encapsulate diverse drug molecules, enhance penetration, and provide controlled release positions them as a powerful alternative to conventional formulations. Continued research and development of newer vesicle types and novel systems are likely to expand the applicability of VDDS in both clinical and cosmetic dermatology.

CONFLICT OF INTEREST

The authors have no conflicts of interest about this review paper**.**

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