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VESICULAR DRUG DELIVERY: NEW FRONTIERS AND FUTURE PERSPECTIVES

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ABSTRACT

Vesicular drug delivery systems have become a fundamental part of modern pharmaceutical research because they offer a more targeted, controlled and reliable way to deliver medications. Carriers listing from liposomes and niosomes to ethosomes, transfersomes, phytosomes, cubosomes, and spanlastics have the ability to entrap drugs with either hydrophilic or lipophilic characteristics. Their basic structure, usually a lipid layer surrounding an aqueous core, gives them the flexibility to be used in many different applications. In recent years, these systems have been explored for a variety of delivery routes, including ocular, transdermal, pulmonary, oral, targeted and even herbal formulations. This growing interest is largely due to their ability to improve drug bioavailability, protect sensitive drugs from breaking down, control the release of therapeutic agents and reduce unwanted side effects.

Ongoing improvements in how these vesicles are designed, prepared and modified on their surfaces have only increased their usefulness. Despite these benefits, vesicular systems are not without limitations. Drug leakage, physical instability and limited drug-loading capacity are some of the issues that need to be addressed for consistent performance. Recent classification are based on how they work, their function, origin or historical development reflect the continuing effort to better understand and refine these systems. Their applications now range from treating eye diseases like glaucoma and fungal keratitis to enhancing skin

and lung delivery, supporting cancer therapy and improving the effectiveness of plant-based compounds.

KEYWORDS: Vesicular drug delivery; Liposomes; Niosomes; Phytosomes; Targeted Delivery.

INTRODUCTION

In recent decades, there has been growing interest in developing improved ways to deliver medications. These advanced drug delivery systems are intended to fulfill two criteria: To release medication at a rate that matches the body's needs during treatment, and to deliver the drug directly to the tissues or organs where it is required.[1] To attain targeted and controlled drug delivery, various novel vesicular drug delivery systems have been developed, utilizing different methods of administration. Targeted drug delivery refers to a strategy for directing a therapeutic agent specifically to the desired tissues while reducing its concentration in other areas, thus enhancing therapeutic effectiveness and minimizing side effects.[2] A new approach to drug delivery ensures that this not only improves the drug's effectiveness but also helps to reduce potential side effects. Additionally, this method ensures that the drug is released at a steady rate, maintain consistent drug levels in the body, and further minimize unwanted reactions.[3] Vesicular drug delivery systems, such as liposomes, niosomes, ethosomes, transfersomes, bilosomes, transethosomes, cubosomes, proniosomes, chitosomes, terpesome, phytosomes, discomes, and spanlastics, are capable of encapsulating both hydrophilic and lipophilic medications. The structural components of these vesicles, comprising an aqueous core and a lipid bilayer, facilitate the transport of both polar and non-polar drugs. Drugs that are contained within lipid vesicles can readily traverse cell membranes, thus influencing both the pace and extent of drug absorption, as well as the distribution of the drugs throughout the body.[4]

Advantages[5,6]

- **Improved Bioavailability:** By safeguarding medications from degradation in the gastrointestinal tract and facilitating absorption, vesicular systems can significantly boost the bioavailability of both hydrophilic and lipophilic drugs.
- **Controlled Release:** Vesicular systems can be designed to release their contents at a regulated pace, ensuring a prolonged therapeutic effect and decreasing the frequency of administration.

- **Targeted Delivery:** The capability of vesicular systems to hone in on particular tissues or cells limits the drug's exposure to non-target areas, thus reducing side effects.
- **Versatility:** These vesicular carriers can transport diverse types of drugs, including small molecules, peptides, proteins, and nucleic acids, making them suitable for a variety of therapeutic purposes.

Disadvantages[3]

- **Drug Leakage:** The drugs are loaded passively, which may cause leakage during preparation, storage, and in vivo transport.
- **Physical Instability:** Vesicles can aggregate, fuse, sediment or swell compromising their structural integrity and affecting drug delivery.
- **Oxidation:** Some components of vesicular systems may experience oxidation, which can influence their overall stability.
- **Low Drug Loading Efficiency:** The method of passively encasing drugs may lead to a minimal quantity of the drug being incorporated into the vesicles.

Classification of Vesicular Drug Delivery System

1. Mechanism-Based Classification

Mechanism-Based Class	Types	Basis of grouping
Permeation enhancers	Ethosomes, Transferosomes, Spanlastics	Enhance penetration across biological barriers
ImmuneResponse Modulators	Virosomes, Immunosomes	Stimulate or deliver antigens to the immune system
Controlled/Targeted release system	Cubosomes, Sphingosomes	Provide sustained, localized, or targeted delivery
Encapsulation	Liposomes, Niosomes	Protect drug from degradation, deliver to site
Bioenhancer	Phytosomes, Archaeosomes	Improve absorption/bioavailability of bioactives

2. Function-Oriented Classification

Challenge in Drug Delivery	Types	Mechanism
Poor bioavailability	Liposomes, Phytosomes	Improved solubility & absorption
Skin penetration barrier	Ethosomes, Transferosomes, Spanlastics	Elastic vesicles with skin flexibility
Targeted delivery	Virosomes, Sphingosomes, Immunosomes	Surface ligands, immune recognition
Stability issues	Niosomes, Archaeosomes	High chemical and thermal stability

3. Source based Classification

Type	Source	Structure
Liposomes	Synthetic	Bilayer
Phytosomes	Natural	Complex lipids
Virosomes	Viral proteins	Proteins Bilayer
Cubosomes	Synthetic	Liquid crystalline
Transferosomes	Synthetic	Deformable bilayer

4. Chronological Evolution Classification

Era	System Developed	Innovation
1960s-1970s	Liposomes	First lipid-based vesicles
1980s–1990s	Niosomes, Virosomes	Synthetic surfactant vesicles and immune carriers
2000s	Transferosomes, Ethosomes	Improved skin penetration
2010s–Now	Cubosomes, Phytosomes, Spanlastics	Nanotechnology, phytochemical integration, and flexible delivery systems

Vesicle Preparation Techniques for Drug Delivery: Various techniques have been developed for the preparation of vesicular drug delivery systems, each differing in principle, vesicle size, lamellarity, and encapsulation efficiency. The most commonly employed and well-established methods are described below.

1. Thin Film Hydration
2. Reverse Phase Evaporation
3. Ethanol Injection
4. Microfluidization
5. Freeze Thaw
6. Detergent Removal

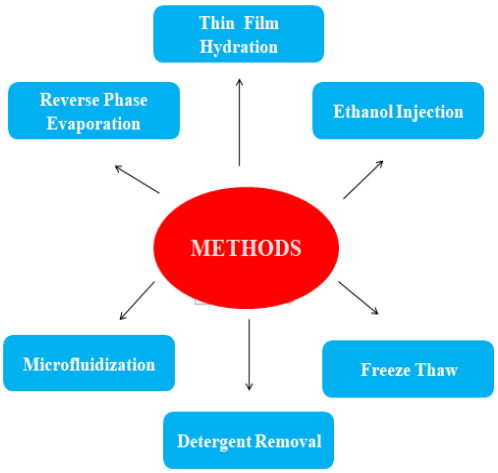

Fig. 1: Vesicle Preparation Techniques for Drug Delivery.

1. Thin Film Hydration: This is one of the technique used for preparation of vesicular system. This method is alternatively called the hand shaking method. This technique typically used for multilamellar vesicles.[15] This mixture of vesicles forming elements like surfactant and cholesterol are dissolved in volatile organic solvents like diethyl ether, chloroform or methanol in a round bottom flask. By using rotary evaporates the organic solvent removed at room temperature and it leaves a thin layer of solid mixture deposited on the wall of the flask.[12,16] The dried surfactant layer should be rehydrated. Rehydration is done with aqueous phase at 0-60°c with gentle agitation.

2. Reverse Phase Evaporation: This approach represents one of the established techniques for formulating vesicular systems. Here, cholesterol and the surfactant in equal proportions (1:1) are mixed and dissolved in a combined solvent system of ether and chloroform. The drug-containing aqueous phase is added, and the mixture is sonicated at 4–5 °C until two clear phases form. Afterward, a small volume of phosphate-buffered saline (PBS) is introduced, and the resulting gel is further sonicated. The organic phase is removed at 40°c under low pressure. The resulting viscous suspension is diluted with PBS and heated on a water bath at 60°c for 10 minutes to yield vesicles.[16]

3. Ethanol Injection: Through the ethanol injection approach, phospholipids that are dissolved in ethanol are swiftly introduced into pre-heated distilled water or buffer. The ethanol's dilution in the water solution below a certain threshold promotes the self-assembly of the dissolved lipids in the aqueous environment. The rapid dilution of ethanol within the aqueous phase also encourages the precipitation of lipid molecules and the subsequent creation of bilayer planar fragments (stacks) that enclose the aqueous phase. Ultimately, the evaporation of ethanol facilitates the merging of lipid fragments and the eventual formation of closed unilamellar vesicles.[17]

4. Microfluidization: This method is based on the submerged jet principle to produce small and uniform unilamellar vesicles. The two phases (aqueous phase and lipid-dispersed phase) are forced into a membrane and pressurized vessel at extremely high pressure and velocity using pneumatic pumps, where they meet. The membrane together with the pressurized chamber acts as a continuous micro-channel, promoting intense mixing and maintaining a stable pressure profile even under extremely high pressures. This controlled environment is crucial for producing niosomes with a narrow size range. The method provides advantages

such as better uniformity, smaller particle size, higher encapsulation of the aqueous phase, and efficient large-scale production.[18]

5. Freeze Thaw: This method involves the extrusion of multilamellar vesicles using 20,000psi pressure at 4°C through a small orifice. An important feature of the freeze thaw method is that the proteins do not seem to be significantly affected as in sonication process so it is widely used for encapsulation of proteins. The method provides several advantages over sonication method like simplicity, reproducibility and involves gentle handling of unstable materials.[19]

6. Detergent Removal: The method is based on the formation of detergent-lipid micelles, followed by the removal of the detergent to form vesicles. Micelles composed of lipids and detergent can be produced by adding a detergent solution to dry lipids or by evaporating a combined lipid–detergent mixture and then rehydrating it. The detergent molecules shield the lipid's hydrophobic parts from the water, promoting the formation of micelles rather than vesicles. The formation of vesicles occurs after the detergent is eliminated from the micellar solution, which can be achieved through methods such as 10–100-fold dilution, dialysis, column chromatography or adsorption.[20]

Applications of Vesicular Drug Delivery System

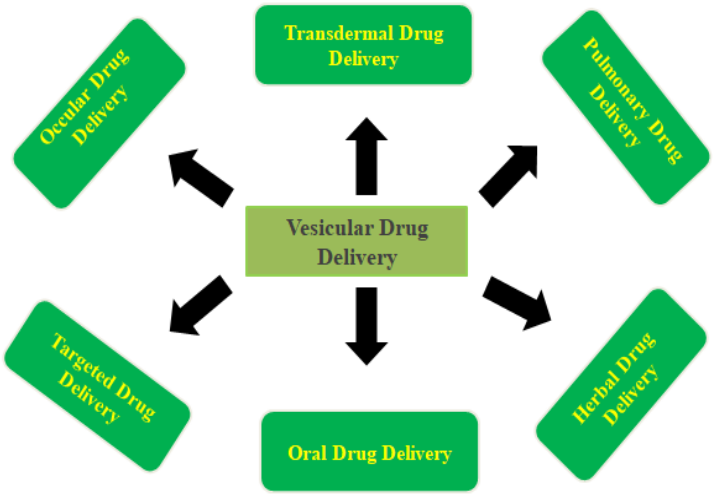

Fig: 2 Applications of Vesicular Drug Delivery System.

1. Occular Drug Delivery

Vesicular drug-delivery platforms provide targeted action in the eye along with greater stability, prolonged drug release, and improved bioavailability and tissue penetration. Systems such as liposomes, niosomes, ethosomes, transfersomes, and newer variants including bilosomes, transethosomes, cubosomes, proniosomes, chitosomes, terpesomes, phytosomes, discomes, and spanlastics can enclose both water-soluble and lipid-soluble therapeutic agents. By forming protective vesicles, these carriers enable controlled release at the ocular surface, help shield drugs from metabolic enzymes present in the tear film and corneal epithelium, and ultimately support sustained therapeutic effects on the cornea.[4,39] For examples; Niosomal timolol maleate for glaucoma[23], Liposomal fluconazole for fungal keratitis.[24]

2. Transdermal Drug Delivery

Vesicular Drug Delivery systems play an important role in the dermal and transdermal domain overcoming the limitations associated with the physical and chemical methods of permeation enhancement.[22] Slow penetration of drug through skin is the major drawback of the transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in vesicles.[21] For examples; Tretinoin-loaded liposomes for anti acne therapy[25], Ketoconazole niosomes for antifungal activity.[26]

3. Pulmonary Drug Delivery

Vesicular drug delivery systems such as liposomes, niosomes, transfersomes, ethosomes, exosomes, and polymersomes have recently emerged as promising carriers for pulmonary drug delivery Because they can entrap a variety of therapeutic agents, increase lung residence time, and improve intracellular uptake, vesicular drug delivery.[28] For examples; Liposomal ciprofloxacin for chronic lung infections[29], Exosome-mediated siRNA delivery to alveolar cells for lung infection.[30]

4. Targeted Drug Delivery

Delivering a medication to a specific location while having little or no impact on nontargeted cells or tissues is known as targeted drug delivery. In order to improve target specificity, vesicular drug delivery systems have been investigated as the best drug delivery vehicles. Drugs pass via intricate pathways and must overcome several obstacles in order to reach their target. because of their site-specific drug delivery, biocompatibility, minimal toxicity, and capacity to capture both hydrophilic and lipophilic medications. Both as a commercial drug

delivery device and as an experimental technology, vesicular systems show higher rates.[31, 40] For examples; Folate-targeted Liposomes for anticancer.[32]

5. Oral Drug Delivery

Vesicular delivery systems are increasingly used to overcome factors associate with oral drug delivery system such as poor solubility, enzymatic degradation, low permeability, instability in gastric fluids, and first-pass metabolism and enhance the oral bioavailability of a wide range of therapeutic agents.[33] For examples; Oral delivery of insulin[34], Omeprazole niosomes for the enhancement of solubility and stability of Omeprazole hydrochloride.[35]

6. Herbal Drug Delivery

Vesicular drug delivery systems such as Phytosomes that consist of complexes formed by conjugating phytoconstituents with phospholipids. Plant active ingredients become more soluble and bioavailable as a result, increasing their potency as medicinal agents. They stand out as a specific formulation for improving the distribution of phytoconstituents with possible therapeutic advantages due to their distinctive feature of integrating plant extracts.[36] For examples; Curcumin liposomes – improve solubility and bioavailability of curcumin[37], Neem extract niosomes – improved antimicrobial activity.[38]

CONCLUSION

Vesicular systems have proven to be very useful as drug carriers in many areas of research. They can be easily modified for different purposes, which is why they have been widely studied for drug delivery. Even though they have some limitations, these systems still play an important role in helping deliver drugs to specific sites in the body and controlling how the drug is released. Systems such as liposomes, niosomes, ethosomes, transferosomes, phytosomes, and cubosomes have shown good results in many types of drug delivery, including eye drops, skin applications, inhalation, oral use, and targeted therapies. Still, there are challenges like drug leakage, instability, oxidation, and limits on how much drug they can hold that need to be addressed for reliable use and large-scale production. Overall, these systems continue to improve and offer a lot of promise with the goal of ensuring that therapies are safer, work better, and place less burden on patients.

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