The New Era of Vesicular Drug Delivery System: A Review

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Abstract **- The article provides an up-to-date review of several vesicular drug delivery systems, which are designed to administer drugs at a controlled pace determined by the body's needs. Vesicular drug delivery systems are primarily utilized for medication targeting by localizing the drug action in the sick or inflamed tissue, location, or organ of action through the use of various pharmaceutical carriers. Novel Vesicular drug administration has been employed to improve the therapeutic index, solubility, and speed of drug breakdown. This vesicular system prolongs the presence of the drug in the circulatory system by releasing the drug in a controlled manner, as well as reducing the drug's toxicity. Thus, a variety of vesicular systems, such as Niosomes, Liposomes, Transferosomes, Ethosomes, Aquasomes, Cubosomes, and Ufasomes, have been designed to improve the potential of new therapeutic compounds by encapsulating an active ingredient within the vesicular structure of a system. To offer the drug in the form of a novel drug delivery system, several carriers such as polymeric micelles or vesicular systems, particulate systems or colloidal carrier systems, and macro and micromolecules are used. In this study, we will focus on various forms of novel vesicular systems in terms of their types, advantages, shortcomings, possibilities of vesicular drug delivery system in gel form, and recent applications. In this study, we will focus on many forms of innovative vesicular systems in terms of their types, benefits, drawbacks, possibilities of vesicular drug delivery system in gel form, and recent applications in Pharmaceutical sciences.**

Index Terms **- Vesicular drug delivery systems, Niosomes, Liposomes, Colloids, Drug Targeting.**

INTRODUCTION

There has been a lot of interest in developing a novel drug delivery system. This delivery method intends to distribute the drug at a rate determined by the body's needs throughout treatment and to channel the active substance to the site of action. To achieve regulated and targeted medication delivery, numerous unique approaches in drug delivery systems have arisen, including multiple routes of administration. Encapsulation of the drug in vesicular structures is one such approach that, if selective absorption is achieved, can be projected to prolong the drug's presence in systemic circulation while minimising toxicity. [1]. Aquasomes, Cubosomes, Ethosomes, Liposomes, Niosomes, Pharmacosomes, Sphingosomes, Transferosomes, and Ufasomes are vesicular systems that are utilised to improve the therapeutic index of both existing and new pharmacological molecules by encapsulating an active medicament inside a vesicular structure. It increases the drug's time in systemic circulation and, as a result, lessens its toxicity. These various approaches are frequently used in gene delivery, tumour targeting, oral formulations, and medication stability and permeability issues. [2].

Vesicles are colloidal particles that are composed of a bilayer of amphiphilic molecules surrounded by an aqueous compartment. They are a handy carrier for both hydrophobic and hydrophilic drug delivery (associated with the lipid bilayer which is encapsulated in the interior aqueous compartment). These vesicles made of natural or manufactured phospholipids are referred to as liposomes, whilst those built of nonionic surfactants (e.g. alkyl ethers and alkyl esters) and cholesterol form a nonionic surfactant vesicular system referred to as niosomes. [3-7]. Bilosomes are niosomes that contain bile acids and have improved stability in the presence of bile salts in the gastrointestinal system. Vesicle composition influences physicochemical properties such as size, charge, lamellarity, elasticity, and thermodynamic phase. The vesicular structure can also be altered to offer sustained or regulated medication administration for extended periods of time. [5, 8, 9].

The goal of a novel drug delivery system is to provide some control over the release of drugs in the body, whether that control is temporal, spatial, or both.

Novel approaches seek to either sustain medication activity at a predefined rate or to maintain a generally constant, effective drug level in the body while minimising undesired side effects. It can also localise drug action by spatially positioning controlled release systems close to or within the sick tissue or organ, or target drug action by employing carriers or chemical derivatization to deliver medication to a specific target cell type.

There are various types of pharmaceutical carriers. Particulate, polymeric, macromolecular, and cellular carriers are the four types. Particulate carriers, also known as colloidal carriers, comprise lipid particles (low and high density lipoprotein-LDL and HDL, respectively), microspheres, nanoparticles, polymeric micelles, and vesicular-like niosomes, pharmacosomes, virosomes, and so on. [10-13].

NEW ERAS OF VESICULAR DRUG DELIVERY SYSTEMS

Liposomes

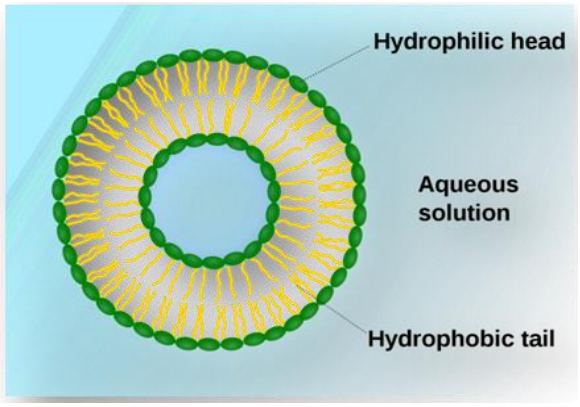

Fig.1 Liposome structure [14]

Lipids, like proteins and nucleic acids, are necessary biomolecules for the structure and function of biological things. The majority of lipids are fats and waxes, but this thesis concentrates on amphiphilic lipids. This type of lipid is the most common building block of biological membranes and liposomes. Liposomes are self-closed spherical structures made up of curved lipid bilayers that enclose a portion of the surrounding solvent in their interior. Liposomes range in size from around 20 nm to several micrometres and are made up of one or more concentric membranes with a thickness of about 4 nm. [15]. Because of the amphiphilic nature of the lipids, liposomes have unique features that make them excellent for medication administration.

Advantages [16]

1. Amphiphatic in nature so entrap both kind of drugs either water soluble or insoluble.
2. Increased efficacy and therapeutic index of drug.
3. Non ionic.
4. Liposome helps to reduce exposure of sensitive tissues to toxic drugs.

Disadvantages [17]

1. Low solubility
2. Short half life
3. Production cost is high
4. Leakage and fusion of encapsulated drug may occur
5. Oxidation of phospholipids may occur.

Niosomes

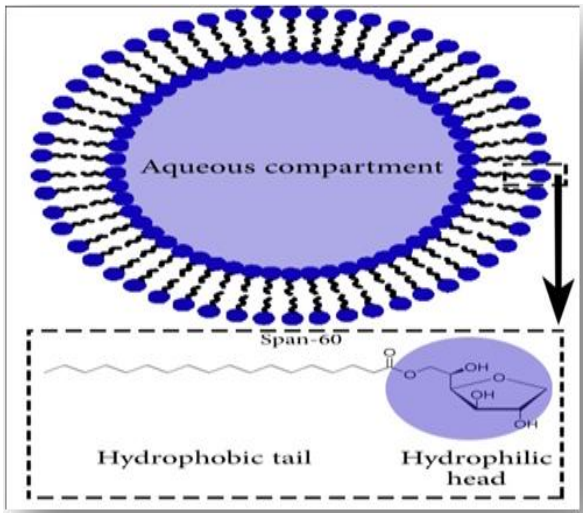

Fig.2 Schematic representation of Niosome[14]

Niosomes are nonionic surfactant vesicles with a tiny lamellar bilayer structure generated by the self-association of hydrated surfactant monomers. Niosomes' multilamellar or unilamellar structure is created by combining nonionic surfactant, cholesterol, and diethyl ether, followed by hydration in aqueous media. As a carrier controlled drug delivery system, niosomes can entrap both hydrophilic and lipophilic medicines in the aqueous layer and vesicular membrane, respectively. Niosomes are made up of an inner and outer hydrophilic layer, with a sandwiched lipophilic layer in between. [18, 19].

Advantages

1. The use of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and therapeutics may provide various benefits.
2. They boost drug molecules' therapeutic performance by delaying clearance from circulation, shielding the drug from the biological environment, and limiting effects to target cells.
3. They are osmotically active and stable, and they improve the entrapped drug's stability.
4. Surfactant handling and storage do not necessitate any particular precautions.
5. 5.They improve the oral bioavailability of poorly absorbed medicines and increase drug penetration via the skin.

Disadvantages

1. Physical instability
2. Aggregation
3. Fusion
4. Leaking of entrapped drug
5. Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion [20-23].

Transferosomes

Transferosome is a registered brand of the German business IDEA AG. According to its parent Latin and Greek names, "transferred" and "soma," the word denotes a "carrying body." The term "transferred" refers to the act of carrying something across, whereas "soma" refers to a body. An artificial vesicle is built in such a way that it behaves like a cell engaged in exocytosis, making it suitable for controlled and targeted drug administration. [25].

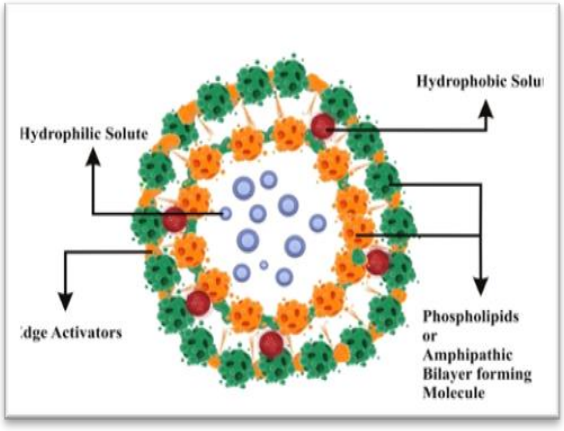

Fig. 3 Structure of Transferosomes [24]

Advantages:

1. Because of the existence of hydrophilic - hydrophobic moieties in their infrastructure, they can accommodate medications with varied solubility.
2. They can distort themselves and pass through thin constrictions (5-10 times smaller than their diameter) without suffering major losses.
3. They can act as a vehicle for medications of any molecular weight.
4. They are biocompatible and formed of natural phospholipids.
5. They provide adequate degradation protection for the encapsulated medication. This is especially important for proteins and peptides.They gradually discharge their contents, serving as a depot. [26].

Disadvantages:

1. They are susceptible to oxidative degradation, which may cause them to become unstable.
2. The purity of phospholipids complicates the use of transfersomes as drug delivery vehicles.
3. Manufacturing and processing are both costly. [27,28].

Pharmacosomes

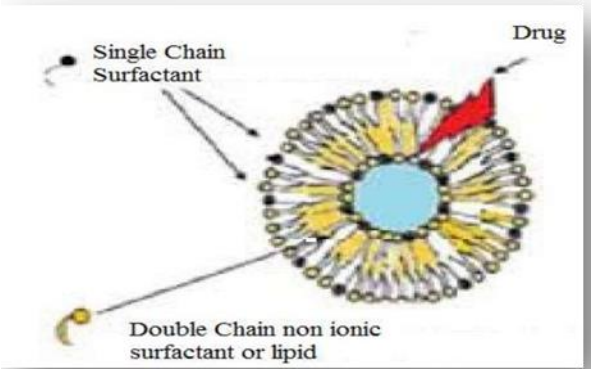

Fig.4 Structure of Pharmacosomes.

Pharmacosomes are characterized as “a colloidal dispersion of pharmaceuticals covalently bonded to lipids that may exist as ultrafine vesicular, micellae, or hexagonal aggregates depending on the chemical nature of the drug-lipid complex.” The name "pharmacosomes" is derived from the active principle pharmacon and the carrier soma. The concept of vesicular pharmacosomes is based on the surface and bulk interactions of lipids with water [29].

Advantages [30-31]

1. Entrapment efficiency is not only high, but also preset, because the drug forms vesicles when conjugated with lipids.
2. Unlike liposomes, there is no need to go through the time-consuming and difficult process of extracting the free, unentrapped drug from the formulation.
3. Because the medicine is covalently bonded, there is no loss owing to drug leakage. Hydrolysis, on the other hand, may result in loss.
4. There are no issues with drug incorporation.
5. Hydrolysis is used to liberate the medication from the Pharmacosomes (including enzymatic).

Disadvantages:

1. The amphiphilic character of the molecule is responsible for its production.
2. Covalent bonding is essential to prevent medication leakage.
3. The underlying idea of pharmacosomes is the surface and bulk interaction of lipid with drug.
4. Pharmacosomes suffer fusion, aggregation, and chemical hydrolysis during storage.
5. Pharmacosomes can only encapsulate water-insoluble pharmaceuticals in very small hydrobic areas inside the membrane bilayer, rather than on a larger surface.

Ethosomes

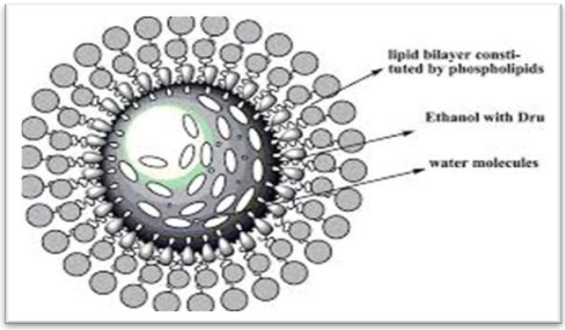

Fig. 5 Structure of Ethosomes [32]

They are mostly utilised for medication administration via the transdermal method. Drugs can be entrapped in ethosomes with varying physicochemical properties, such as hydrophilic, lipophilic, or amphiphilic. [33-34].

Ethosomes are soft, flexible vesicles that are used for drug distribution to the deep skin layers and/or the systemic circulation. Ethosomes are liposomes that have been modified to contain a high ethanol concentration. The ethosomal system is made up of phospholipids (phosphatidylcholine, phosphatidylserine, and phosphatidic acid), a high concentration of alcohol (ethanol and isopropyl alcohol), and water. Ethosomes are distinguished by their high ethanol concentration because ethanol disrupts the skin's lipid bilayer architecture and, as a result, when mixed into a permeate the stratum corneum. [35]

Advantages [36]

1. Its formulation contains non-toxic raw materials.
2. Large molecules (peptides, protein molecules) can be delivered.
3. Improved drug penetration through skin for transdermal drug delivery
4. High patient compliance: Because the ethosomal medication is administered in semisolid form (gel or cream), it has a high patient compliance rate.
5. In comparison to Iontophoresis, Phonophoresis, and other sophisticated drug delivery systems, this method is simple.

Disadvantages [37-38]

vesicle membrane, it enhances the vesicles' ability to

1. Ethosomes with weak shells may clump together, resulting in precipitation.
2. Excipients and enhancers of medication delivery systems cause skin irritation or dermatitis.
3. The transfer of ethosomes from the organic to the aqueous layer results in product loss.

CHRONOLOGICAL ADVANCEMENT OF VESICULAR SYSTEMS

1. Shahiwala et al., 2002 developed a topical application of nimesulide containing niosomally. The lipid film hydration method was used to create niosomes from tweens and spans. The prepared niosomes were then mixed with 1% carbopol gel basis. The prepared formulation was tested for drug entrapment and retention. The in vitro permeability and in vivo evaluation of niosomal gel were thoroughly investigated. They also compared niosomal nimesulide gel to plain drug gel and other commercially available products and discovered an

improvement in drug delivery mechanism and sustained drug release. [39].

2. Lakshmi et al., 2007 developed Niosomal methotrexate gel for the treatment of psoriasis. Methotrexate-containing niosomes were created using the lipid layer hydration approach. The niosomes were combined with chitosan gel, which has previously been tested in human volunteers for skin irritation and sensitivity. Clinical techniques for the Phase I and Phase II studies were carried out in a hospital. The formulations demonstrated greater clinical efficacy and tolerance than other current marketed Methotrexate gels, resulting in high patient compliance. A study found that methotrexate can be used topically to treat psoriasis. [40].

3. Modi et al., 2012 created a niosomal gel for topical administration of a BCS Class-III anti-viral medication with increased efficacy for the treatment of herpes. Thin film layer hydration was used to create ACV niosomes. Centrifuged niosome vesicles were separated for encapsulated drug and later integrated with carbopol-971 gel base. The prepared niosomal gel was then analysed further for its shape, stability investigations, skin retention qualities, and in-vitro diffusion studies with the formulations. Niosomal ACV compositions are available at the site of affected skin for an extended period of time. [41].

4. Shirsand et al., 2013 developed Ketoconazole niosomal gel for medication delivery. A thin lipid film hydration approach was used to create varied ratios of surfactants (Spans and Tween) with cholesterol. The size, shape, entrapment effectiveness, and in vitro drug release profile of the prepared niosomes were all analysed. In order to make it isotonic with blood, PBS (pH 7.4) is added. A medication release study in vitro was performed. The successful development of a niosomal gel formulation containing ketoconazole demonstrated sustained action as well as increased antifungal efficacy. [42].

5. Abhishek Budhiraja et al., 2015 developed ROA-loaded niosomes and tested them in vitro against P. acnes and S. aureus. This effort also involves the creation of a rosmarinic acid niosomal gel for prolonged administration to bacteria-infected cells. Rosmarinic acid niosomes were created utilising a reverse phase evaporation process and varying ratios of span 85 and cholesterol. It was clear that niosomes are an unique transporter for naturally existing antibacterial compounds in deeper skin tissues. The results demonstrated that drug-loaded niosomes dispersed in a gelling agent are an effective delivery strategy for acne vulgaris treatment. [43].

6. Mohamed Shafik El-Ridy et al., 2018 developed Niosomal Gel for Enhanced Transdermal Lornoxicam Delivery in order to increase Lornoxicam penetration and anti-inflammatory action (LX). The dorsal area of wistar rats was subjected to an ex vivo skin permeation test. Skin irritation tests and anti-inflammatory activity experiments were conducted in vivo. These findings suggested that LX-loaded niosomal gels could be used as a transdermal medication delivery system. [44].

7. Saurabh Satija et al., 2020 reported that theranostic pharmacological treatments using chloroquine efficiently suppressed the 2019 new coronavirus in vitro. Wang et al colleagues investigated the virus inhibition potential with penciclovir, a well-known theranostic antiviral drug with potent antiviral activity. These discoveries have bolstered and encouraged the need for the development of emerging technologies such as theranostics. Chen et al. performed a study incorporating a quick, responsive lateral flow immunoassay to detect anti-SRV-CoV-2 IgG in human serum using lanthanide-doped polysterene nanoparticles, which could be useful in following the progression of COVID-19. [50].

EXPERT OPINION

Vesicular drug delivery methods are currently used in a wide range of scientific fields. These systems have recently become one of the most prevalent and crucial delivery methods due to their effective features and functionalities such as selective targeting. However, drug pharmacokinetics is being researched in order to improve the efficacy of various drug delivery systems. The mechanism of action of this system is likewise nearing its conclusion. [45].

Loxapine succinate is an anti-psychotic medication that is taken on a daily basis. Capsules, pills, and injectable dosage forms are currently available on the market. However, these dose forms are tough for my psychotic patient to take on a daily basis, and they sometimes refuse to cooperate with administration. The first disadvantage of Loxapine is that it is only available in capsule form, which makes it difficult to divide into smaller doses. Second, the drug's oral side

effects are significant, such as restlessness with inability to sit still, painful urination, and a lack of granulocytes, a type of WBC.

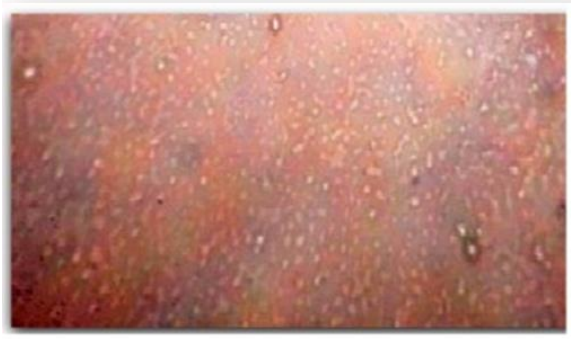

Fig. 6. Niosomes under Optical Microscope (45X).

RECENT APPLICATIONS IN THE PHARMACEUTICAL SCIENCE

Vesicular drug delivery systems have various advantages over traditional dose forms and extended-release dosage forms. [46-48]:

- Effective permeation of drugs into cells
- Prolongation of existence of drugs in systemic circulation.
- As selective uptake is taken place so reduces toxicity.
- Reduces the cost of therapy.
- Improves bioavailability.
- Hydrophilic-Lipophilic drugs can be incorporated.
- Sustained-release system function.
- Delayed elimination of rapidly metabolized drugs.
- Overcomes the problems of the drug insolubility, instability,

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1. Drug penetration into cells that is effective
2. Extending the life of medications in systemic circulation.
3. Because selective absorption occurs, toxicity is reduced.
4. Lowers the expense of therapy.
5. Increases bioavailability.
6. Hydrophilic and lipophilic medicines can be combined.
7. The function of the sustained release system.
8. Delayed elimination of medicines that are rapidly digested.
9. Overcomes drug solubility, instability, and fast degradation issues.

ADVANCEMENT IN VESICULAR SYSTEMS

Nanoparticle-based vesicular drug delivery platforms, for example, have enhanced various aspects such as drug bioavailability, solubility, stability, and controlled release features. Applications of vesicular-delivery systems in the medical sector will be very promising, particularly in the development of new treatment and diagnostic approaches to COVID-19. [49]. Theranostics using vesicular-delivery systems may also provide novel remedies to future coronavirus outbreaks. There are currently no particular antiviral therapies available for COVID-19. However, already discovered treatments for treating other viral diseases, as well as various anti-malarial therapies, are being investigated for efficacy against the COVID-19 virus. [50]. As previously noted, clinical trials are currently underway to investigate the efficacy and safety of numerous medications, including chloroquine, arbidol, remdesivir, and favipiravir [51]. In the future, these medications could be used with vesicular-delivery devices as part of a theranostic strategy to produce innovative COVID-19 treatment regimens.

CONCLUSION

According to the findings of the study, topical niosomal formulations can offer constant and sustained release of loxapine succinate. It will result in sustained activation of the entrapped medicine,

reducing the side effects associated with frequent oral delivery of the drug. It is possible that Loxapine succinate could be used topically. It demonstrates that topical niosomal gel base drug delivery systems may be a promising carrier for loxapine succinate delivery.

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