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ASPASOMES: AN INNOVATIVE APPROACH FOR TARGETED DRUG DELIVERY

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ABSTRACT

Novel drug delivery system can significantly improve the performance of bioactive in terms of patient compliance, safety, efficacy and novelty. Aspasomes is a novel carrier for drug delivery; it is an Ascorbyl palmitate vesicle with their own biological activity. Ascorbyl palmitate is explored as bilayer vesicle forming material for Aspasomes. Ascorbyl palmitate forms vesicles in combination with cholesterol and a negatively charged lipid (dicetyl phosphate). Aspasomes are capable to suppress pigmentation of the skin and decomposition of melanin; it also improves elasticity of the skin by promoting the formation of collagen. Ascorbyl palmitate is more stable than ascorbic acid and its lipophilic character is beneficial for its skin penetration**.** Aspasomes are prepared by film hydration method. The potential of Aspasomes vesicles to overcome biological barriers, enhance drug bioavailability, and minimize systemic side effects is underscored, along with recent advances and future prospects in this rapidly evolving field. This review article provides a thorough examination of the design principles, formulation strategies, classifications, mechanism of action, evaluation parameters and therapeutic applications of aspasomes vesicular drug delivery systems.

KEYWORDS: Aspasomes, Vesicular drug delivery, Thin film Hydration, Ascorbyl palmitate, Pigmentation.

INTRODUCTION

Novel drug delivery system promotes the ease and convenience of administration, deliverance of accurate dose as well as to prolong residence time of drug in contact with skin membrane.[1]

Vesicular drug delivery systems have emerged as a valuable approach for administering pharmaceutical compounds, particularly for topical disorders. Lipid vesicles, including liposomes and their derivatives like niosomes, transferosomes, aspasomes and ethosomes, have shown effectiveness in treating various topical condition.[2]

Ascorbyl palmitate vesicles, known as Aspasomes, are bilayer vesicles formed using Ascorbyl palmitate (ASP) in combination with cholesterol and a negatively charged lipid like dicetyl phosphate. These vesicles have shown potential applications in various fields due to their unique properties.[3,4]

HISTORY OF ASPASOME

The first mention of aspasomes was found in a study published in 2004 by Gopinath et al. from the University of Mumbai, India. The study explored Ascorbyl palmitate (ASP) as a bilayer vesicle-forming material and found that it formed stable vesicles (Aspasomes) in combination with cholesterol and a negatively charged lipid, dicetyl phosphate. The authors noted that while other studies had explored amphiphilic ascorbic acid esters/ethers, none had attempted to convert them into bilayered vesicles (liposome-like structures). The study found that the thin film of Ascorbyl palmitate on hydration did not form vesicles, but in the presence of cholesterol and dicetyl phosphate, stable vesicles were formed. These vesicles are considered safe and efficient in enhancing the delivery of both lipophilic and hydrophilic drug.

CHARACTERISTICS OF ASPASOME

Formation and Composition

- Aspasomes are formed by combining Ascorbyl palmitate with cholesterol and a negatively charged lipid like dicetyl phosphate.
- These vesicles have a bilayer structure composed of Ascorbyl palmitate, cholesterol, and dicetyl phosphate, confirmed through differential scanning calorimetric data.

Pharmaceutical Properties

- Aspasomes demonstrate stability for up to 18hours, indicating their potential for sustained drug release.
- They exhibit antioxidant activity, with studies showing that the antioxidant potency of the Ascorbyl moiety is retained even after conversion to Ascorbyl palmitate.

Drug delivery efficiency

- Aspasomes have shown enhanced transdermal permeation compared to other preparations, highlighting their ability to improve drug delivery across the skin.
- The release rate of drugs from aspasomes can be influenced by varying the proportion of cholesterol in their composition.

Pharmaceutical Formulation

- The size, charge, storage stability, skin deposition ability, and antioxidant properties of prepared aspasomes are crucial pharmaceutical characteristics that are assessed during their formulation.
- Techniques like thin film hydration are commonly used to prepare aspasomes, allowing for the encapsulation of active ingredients like quercetin within these vesicles.

ADVANTAGES

1. Improved Antioxidant Activity: Aspasomes exhibit better antioxidant activity compared to ascorbic acid, which can be beneficial in protecting drugs from degradation and enhancing their stability.
2. Enhanced Skin Permeation: Ascorbyl palmitate vesicles have shown improved skin penetration due to their lipophilic character, making them effective for transdermal drug delivery.
3. Versatile Drug Encapsulation: Aspasomes can encapsulate both hydrophilic and hydrophobic drugs, making them versatile carriers for a wide range of therapeutic molecules.
4. Therapeutic Efficacy Enhancement: Aspasomes have been demonstrated to enhance the therapeutic efficacy of drugs like tizanidine by improving their bioavailability and reducing skin irritancy, leading to better treatment outcomes
5. Stable Vesicle Formation: Aspasomes formed with ascorbyl palmitate, cholesterol, and dicetyl phosphate are stable vesicles, ensuring the integrity of the drug delivery system.
6. Transdermal Delivery Improvement: Aspasomes have been used to enhance the transdermal delivery of drugs like Azidothymidine(AZT), showing a significant increase in drug flux compared to unformulated drugs.
7. Potential Anti-Inflammatory Effects: Multidrug aspasomes loaded with idebenone and naproxen have demonstrated significant anti-inflammatory effects, suggesting their potential for treating cutaneous inflammation.[5,6]

DISADVANTAGES

1. Instability: Ascorbyl palmitate vesicles (aspasomes) formed without cholesterol or other lipids were found to be very unstable. The presence of cholesterol was necessary for the formation of stable vesicles, indicating that the absence of cholesterol can lead to instability.
2. Limited Shelf Life: Aqueous suspensions of niosomes, which are related to aspasomes, may have a limited shelf life due to issues like fusion, aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs. This limitation can affect the storage and usability of the formulations
3. Complex Preparation: The preparation of aspasomes involves specific methods like film hydration under nitrogen atmosphere, which can be time-consuming and require specialize.[7,8]

CLASSIFICATION

Multi-Lamellar Vesicles (MLVs): Are defined by their arrangement of multiple concentric bilayer membranes. These vesicles have a nested spherical shape. The size of MLVs ranges from 1-5 micrometer in diameter.

It is commonly employed, simple to produce, and maintains stability throughout extended periods of storage.

Large Unilamellar Vesicles (LUVs): Ranging in size between 100 nm to 250 nm.

Small Unilamellar Vesicles (SUV): These are ranged from 20 nm to 100 nm.

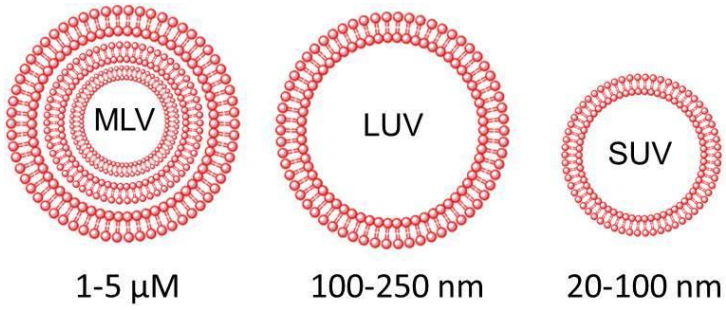

Fig. 1: Classification of Aspasomes.

STRUCTURE AND COMPOSITION

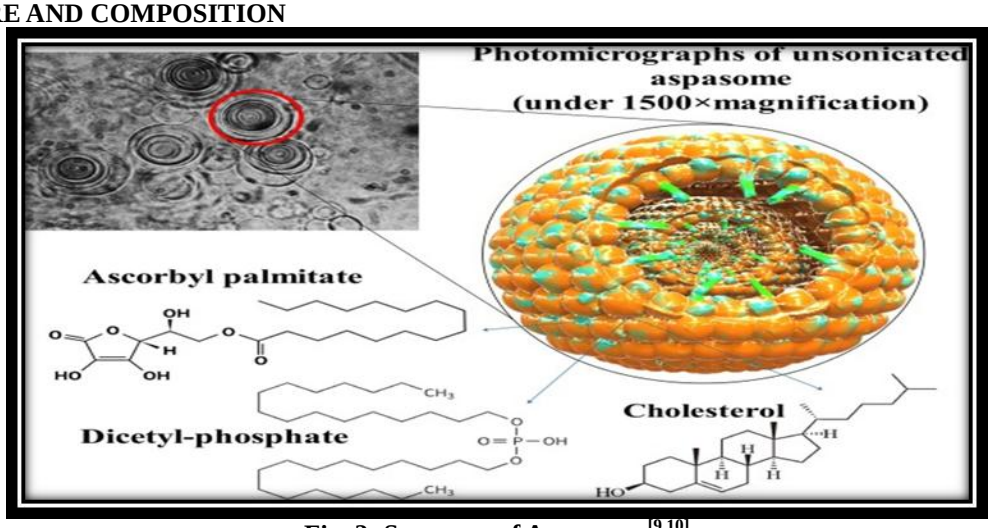

Fig. 2: Structure of Aspasome.[9,10]

The composition of Aspasome typically includes Ascorbyl palmitate as the primary lipid component, cholesterol to enhance stability, and dicetyl phosphate as a charge inducer to facilitate the formation of stable vesicles. The molar ratio of these components may vary depending on the specific formulation and intended application.

Ascorbyl palmitate: Ascorbyl palmitate (ASP) is a lipophilic form of vitamin C that has been explored for its ability to form vesicles (Aspasomes) in combination with cholesterol and negatively charged lipids such as dicetyl phosphate. The Aspasomes have shown potential as a drug delivery system for disorders implicated with reactive oxygen species due to their antioxidant potency, which is superior to that of ascorbic acid. Ascorbyl palmitate (AP) is a fat-soluble form of vitamin C that is composed of ascorbic acid and palmitic acid, a naturally occurring fatty acid. It is used in skincare products due to its antioxidant properties, which can help protect the skin from damage caused by free radicals. However, it can produce excess reactive oxygen species that can interfere with cellular signalling, cause mutations, lead to cell death, and may be implicated in cardiovascular disease. It is also suspected to be an environmental toxin.[11]

Cholesterol: Cholesterol is a sterol that is often added to Ascorbyl palmitate (AP) to strengthen the bilayer of the vesicles formed, called aspasomes. The presence of cholesterol in the aspasome dispersion has been shown to stabilize the bilayers and decrease their permeability, leading to a stable aspasome with retarded Azidothymidine (AZT) permeability at certain concentrations of cholesterol. The addition of cholesterol to AP in the presence of a negatively charged lipid, dicetyl phosphate, forms stable vesicles called aspasomes, which have been shown to enhance the transdermal permeation of AZT and have antioxidant properties that are superior to those of ascorbic acid. The liquid crystalline state is a prerequisite for the formation of bilayered vesicles, and there is evidence for the formation of liquid crystals with ascorbyl palmitate, cholesterol, and dicetyl phosphate anhydrous mixture based on DSC study. The heat of transition of aspasome dispersion decreases with an increase in cholesterol concentration, indicating a stable bilayer configuration. The thin film of ascorbyl palmitate on hydration does not form vesicles, but in the presence of cholesterol, vesicles form, but are very unstable. However, in the presence of cholesterol and dicetyl phosphate, stable vesicles form, indicating the importance of cholesterol in the formation and stability of aspasomes.

Dicetyl phosphate: Dicetyl phosphate (DCP) is a negatively charged lipid that is used in the formation of aspasomes, a type of vesicle formed by ascorbyl palmitate (AP) and cholesterol. DCP is added to the AP and cholesterol mixture to stabilize the suspension and enhance the formation of stable vesicles. The presence of DCP in the aspasome dispersion has been shown to stabilize the bilayers and decrease their permeability, leading to a stable aspasome with retarded AZT permeability at certain concentrations of DCP. The addition of DCP to AP and cholesterol forms stable vesicles, indicating the importance of DCP in the formation and stability of aspasomes. DCP is also used in other vesicular drug delivery systems, such as niosomes, to provide a negative charge and enhance stability.[12]

METHOD OF PREPARATION

The aspasomes are prepared by using **Thin film hydration** method.[13,14,15]

Ascorbyl Palmitate, Dicetyl phosphate and Cholesterol are dissolved in chloroform: methanol (9:1)

The solution is dried under rotary evaporator by applying vacuum

Ten milliliter warm solution of drug in phosphate-buffered saline (pH 7.4) is added to hydrate the formed film and the mixture is allowed to cool at room temperature Left overnight at 4°C and centrifuge at 1500rpm.

The separated residue is washed with phosphate-buffered saline (pH 7.4). The supernatant is subjected to ultracentrifugation to collect suspended aspasomes.

EVALUATION PARAMETERS

1. Particle size Analysis
2. Zeta potential
3. Surface morphology
4. Entrapment efficiency
5. Drug content
6. Number of vesicles per cubic millimetre
7. *In vitro* release studies
8. Stability study.

1. Particle size Analysis

Particle size and Shape of empty aspasome formulation and drug loaded aspasomal formulation is determined by optical microscopy and Transmission Electron Microscopy (TEM).[16,17]

2. Zeta potential

The Zeta potential may be used to get a rough idea of the surface charge of a vesicle by measuring the electrophoretic mobility of its particles using Zeta sizer.[18,19]

3. Surface Morphology

The morphology of the Aspasomes are determined by transmission electron microscope (TEM).[20,21]

4. Entrapment Efficiency

The entrapment efficiency of Aspasomal formulation is studied using ultracentrifugation method. Prepared formulation is centrifuged at 15000 rpm, 4°C for 60 mins. This leads to the separation of free drug (appearing as supernatant) from drug loaded vesicles (settled at bottom). The supernatant is taken and diluted with methanol. The amount of drug present in the supernatant is determined by ultraviolet (UV) spectrophotometrically. The amount of free drug in the supernatant is then subtracted from the total amount of drug added during the preparation of Aspasomes. All the prepared formulations are characterized for percent entrapment efficiency (%EE), using the formula.[22,23]

$$\%EE = \frac{Total\ amount\ of\ drug - Free\ drug\ in\ supernant}{Total\ amount\ of\ drug} \times 100$$

5. Number of vesicles per cubic millimetre

This is measure by using Hemocytometer which is used to count the number of vesicles per cubic millimeter. The vesicles are diluted with water and vesicles in 80 tiny squares are counted.[24]

6. Drug Content

To evaluate the total drug content, which is encapsulated, 0.2 mL of an aspasome dispersion is dissolved in 25 mL of methanol and stirred on a magnetic stirrer to disrupt the vesicle and drug content is measured spectrophotometrically.[25]

7. *In Vitro* Release

In vitro drug release from prepared Aspasomes formulation is evaluated by dialysis bag membrane diffusion technique. The formulation will be added to the dialysis bag immersed in phosphate buffer pH 7.4 solution maintained at 37°C. Suitable volumes of the sample is withdrawn at regular time intervals and equivalent volume will be replaced with phosphate buffer solution to maintain sink condition. The samples will be analyzed spectrophotometrically using UV-Visible Spectroscopy to determine amount of drug released over a period of time.[26]

8. Stability Study

The Aspasomal gel is prepared in triplicates and kept for three months at 25±2°C/65±5%RH and 40±2°C/75±5%RH. Samples will be withdrawn after specific time intervals and visually examined for any physical changes in the formulation.[27,28]

APPLICATION

Aspasomes are lipid-based vesicular systems that have found various applications in pharmaceuticals, particularly in drug delivery. Here are some notable applications of aspasomes.

Topical Drug Delivery: Aspasomes can encapsulate drugs for topical delivery, enhancing drug penetration through the skin. This is particularly useful in dermatological conditions where targeted delivery to the skin layers is necessary.

Transdermal Drug Delivery: Aspasomes can deliver drugs through the skin for systemic effects. They can improve the bioavailability and sustained release of drugs, making them suitable for transdermal patches.

Targeted Drug Delivery: Aspasomes can be modified to target specific cells or tissues, thereby reducing systemic toxicity and improving the therapeutic index of drugs. Surface modification with ligands facilitates targeted delivery to specific receptors or sites of action.

Vaccine Delivery: Aspasomes have been investigated for the delivery of vaccines. They can encapsulate antigens and adjuvants, protecting them from degradation and enhancing their immunogenicity. This application is particularly promising for the development of novel vaccine formulations.

Gene Delivery: Aspasomes can also be utilized for the delivery of genetic material, such as DNA or RNA, for gene therapy applications. They can protect nucleic acids from enzymatic degradation and facilitate their uptake by target cells.

Cosmeceuticals: Aspasomes are being explored in the cosmetic industry for the delivery of active ingredients like vitamins, antioxidants, and skin-whitening agents. They can improve the stability and efficacy of these compounds, leading to enhanced skincare products.

Nutraceuticals: Aspasomes can encapsulate bioactive compounds in nutraceuticals, such as vitamins, minerals, and polyphenols, improving their bioavailability and stability. This application is relevant in the development of functional foods and dietary supplements.

Diagnostic Imaging: Aspasomes can encapsulate imaging agents for various diagnostic imaging modalities, including magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound. They can improve the contrast and specificity of imaging, aiding in the diagnosis and monitoring of diseases.[29,30]

CONCLUSION

Aspasomes represent a versatile and promising class of lipid-based vesicular systems with numerous applications in pharmaceuticals and biomedicine. Their ability to encapsulate a wide range of drugs, bioactive compounds, and imaging agents, coupled with their biocompatibility and potential for targeted delivery, makes them highly valuable in various fields. From topical and transdermal drug delivery to vaccine development, gene therapy, cosmeceuticals, and nutraceuticals, aspasomes offer solutions for enhancing drug efficacy, improving bioavailability, and reducing systemic toxicity. Further research and development in the formulation and functionalization of aspasomes hold great potential for advancing drug delivery technology and addressing challenges in healthcare and biomedical research.

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