

Ufasomes: A Potential Vesicular Carrier System

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Abstract

Vesicular drug delivery system consists of one or more concentric bilayers made up of amphiphilic molecules surrounding an aqueous compartment. Their ability to localize the activity of drug at the site or organ of action makes it an important delivery system for the targeted delivery of drugs. Vesicular drug delivery system sustains the drug action at a predetermined rate. Thus it maintains an efficient drug level in the body, and simultaneously minimizes the undesirable side effects. Ufasomes are unsaturated fatty acid vesicles. They are suspensions of closed lipid bilayers that are composed of fatty acids and their ionized species (soap) which are restricted to narrow pH range from 7 to 9. Lipid film hydration method is used commonly for the preparation of fatty acid vesicles. Oleic acid is the most common fatty acid used as the major component for the preparation of ufasomes. This article describes method of ufasome preparation, advantages, disadvantages, future progress and characterization of ufasomes. [3, 7]

Keywords: Fatty Acid Vesicles, Lipid film hydration, Oleic acid, Ufasome, Vesicular Drug Delivery System

INTRODUCTION

Ufasomes are vesicles of long chain unsaturated fatty acids obtained as a result of mechanical agitation of evaporated film in the presence of buffer solution. The fatty acid vesicles are colloidal suspension consisting of fatty acids and their ionized species. It provides an efficient method for delivery to the site of infection, leading to reduced drug toxicity with less adverse effects.

To localize the drug at the site of action and enhance the permeation of the biologically active moiety into the skin, a number of approaches have been explored including development of vesicular systems such as liposome. In liposomes, phospholipids are used as the major component. Natural phospholipids are chemically heterogeneous and pure synthetic phospholipids are not yet available in reasonable quantities. The ready availability of fatty acids is the major advantage of ufasomes over liposomes. The fatty acid vesicles can be formed not only from unsaturated fatty acids such as oleic acid, linoleic acid, but also from saturated fatty acid such as octanoic acid and decanoic acid.

Skin is known to be an important route for the localized delivery of certain bioactive molecules. But the permeation of the drugs through this route becomes difficult since it acts as a physical protective barrier to the body against the external environment. The upper most layers of the skin, consisting of corneocytes surrounded by lipid regions, i.e. stratum corneum acts as the main physical barrier. A number of penetration enhancers can be used for the successful and effective topical delivery of the drugs. The primary purpose of applying drugs onto the skin is to induce local effects at or close to the site of application for the treatment of skin diseases. The conventional formulations like creams, gels, and ointments suffer from the predicament of dermatopharmacotherapy (limited local activity). To enhance the penetration of bioactive moiety into the skin and further to localize the drug at the site of action; a number of approaches have been explored including development of vesicular systems such as liposomes, niosomes and ufasomes.

Ufasome is the new approach to enhance drug permeation through the skin. Unsaturated fatty acids like linoleic acid

and oleic acids are used as natural permeation enhancers in the preparation of ufasomes. Surfactant is also used in combination with fatty acid which enhances the flexibility of skin and improves the passage of drug via skin membrane. Ufasomes enhanced the drug retention properties of drugs within the cell of the skin membrane for long period of time. [7, 10]

ADVANTAGES

- Prolong the existence of the drug in systemic circulation and reduces the toxicity.
- Selective uptake of the drug can be achieved due to the delivery of drug directly to the site.
- Improves the bioavailability especially in case of poorly soluble drugs.
- Both hydrophilic and lipophilic drugs can be incorporated in ufasomes.
- Delays the elimination of rapidly metabolizable drugs and thus function as sustained release systems.
- The drug can penetrate easily in case of topical application.
- Due to the easy availability of fatty acids, ufasomes are cost effective compared to liposomes and niosomes.
- Entrapment efficiency of the drug is appreciable. [8]

STRUCTURE OF UFASOMES

ufasome

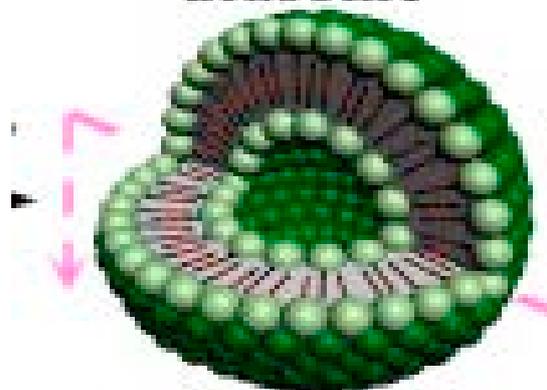


FIG. 1: STRUCTURE OF UFASOME

Ufasomes are basically fatty acid vesicles. The membrane fatty acids are oriented in a bilayer form in which the hydrocarbon tails of the fatty acids are arranged towards the membrane interior and the carboxyl groups are in contact with water. Ufasomes are suspensions of closed lipid bilayers mainly composed of fatty acids, and their soap. They are usually restricted to a narrow pH range from 7 to 9. [3]

METHODS OF PREPARATION

• Thin Film Hydration Method

In this method, vesicle formation occurs in a narrow pH range. It involves the addition of fatty acid in an organic solvent in a round bottom flask. This method requires a very high concentration of the fatty acid. Evaporation of the mixture is carried out until the organic solvent evaporates completely. At the end, a thin film of fatty acid is formed which is hydrated with buffer of appropriate pH.

• By Addition Of Alcohol

In this method, formation of fatty acid vesicles is by the addition of alcohol having the same chain length as that of fatty acid. The main advantage of this method is that the fatty acid vesicles show good stability over a wide pH range. The rate of vesicle formation can be triggered in the presence of pre-added fatty acid vesicles and liposomes in the system. This avoids the time consumption, as this method is very time consuming.

• Autopoetic Process

Fatty acid vesicles are formed when aqueous solution of fatty acid is added to water-buffered solution because of the spontaneous pH change. There is a tendency of formation of vesicles when half of the carboxylic acids present in the fatty acid ionize. The hydrocarbon chain encloses into a bilayer structure opposite to the aqueous compartment which decreases the interaction between hydrocarbon chain and water. [5]

CHARACTERIZATION OF UFASOME

• Particle Size And Size Distribution

90 Plus particle size analyzer is used at a fixed angle of 90° and at 25°C to determine the average diameter and size distribution of ufasome suspensions using Photon Correlation Spectroscopy (PCS). The suspensions were diluted with phosphate buffer (pH 7.4) and filtered through a polycarbonate membrane. This is to minimize interference particulate matter before sizing. Each measurement was done in triplicate. [4]

• Shape And Surface Morphology

Morphological parameters like sphericity and aggregation of selected drug loaded ufasomal dispersion can be examined using Transmission Electron Microscopy (TEM). It can be examined by placing one drop of the selected ufasomal dispersion on a carbon film-covered copper grid which is negatively stained with 1% phosphotungstic acid. Then it is allowed to dry at room temperature for 10 min for investigation by TEM.

• Differential Scanning Colorimetry

The physical state of the drug inside the oleic acid vesicles is investigated by Differential Scanning Calorimetry (DSC). The vesicles are placed in the conventional

aluminum pan, and a scan speed of 2°C/min was employed. [2]

• Entrapment Efficiency

The entrapment efficiency of the drug can be determined by ultracentrifugation at 25000 rpm for 3 h at 4°C. The entrapment efficiency can be calculated using the supernatant by UV spectroscopy. The amount of entrapped drug can be determined as a percentage from the following equation:-

$$\text{Entrapment efficiency (\%)} = (A-B)/A \times 100$$

Where:

A=Amount of drug added initially;

B=Amount of drug determined in the filtrate spectrophotometrically;

A-B=Represents the amount of drug entrapped in the formulation. [1]

• In Vitro Drug Release

This study is conducted to evaluate the release rate/kinetics of the drug from ufasomes. This can be done by using Franz diffusion cells. The Franz diffusion cell consists of two compartments, i.e. donor and receptor compartment. A polycarbonate membrane (pore size: 50 nm) is clamped between these two compartments. The donor compartment contained 1 ml of ufasomal dispersion, whereas the receptor compartment contained phosphate buffered saline (PBS), pH 7.4, which is stirred with the help of a magnetic stirrer at a constant speed and the temperature was maintained at 37°C. Aliquots of samples are withdrawn at specified time intervals and replaced with equal volumes of fresh PBS (pH 7.4). [6]

• pH Dependent Stability

By incubating optimized vesicular dispersion with buffers of pH 8.5, 7.4, 6.5, and 5.5, The effect of pH on the stability and on the drug release behavior was monitored. The samples are withdrawn at pre-determined time intervals and centrifuged at 14,000 rpm for 30 min. Free drug released can be analyzed using the supernatant. The amount of drug leached can be calculated by the formula:

$$\% \text{ Drug diffused} = \frac{\text{Amount of free drug}}{\text{Total drug}} \times 100$$

The incubated vesicles are also observed for any change in morphology and size of the vesicles using an optical microscope. [4]

RECENT INNOVATIONS IN CONVENTIONAL UFASOMES

Applications of ufasomes within the field of drug delivery are largely unexplored, which is due to the concerns regarding the colloidal stability of carboxylic acid vesicles. However, there are some recent studies which uses either new types of fatty acids or mixed systems with other surfactants, which might be beneficial in drug delivery.

New Type of Fatty Acids

Between pH 8.5 and 9, the fatty acid cis- 4, 7, 10, 13, 16, 19 docosahexaenoic acid (DHA) was reported to self-assemble into vesicles.

Extension of The pH Range

Narrow pH range are generally suitable for the formation of fatty acid vesicles due to the requirement that

approximately half of the carboxylic acid must be ionized. The pH range can, however, be extended by using the following novel approaches.

a) Addition of amphiphilic additives such as linear alcohols or a surfactant with a sulfate or the sulfonate head group:

For example, vesicles are formed between pH 6.4 and pH 7.8 using mixtures of decanoic acid and decanoate form, but by adding sodium dodecylbenzenesulfonate (SDBS), the pH for vesicle formation can be lowered to at least 4.3.

b) Synthetically modify the size of the hydrophilic head group of fatty acids:

Fatty acid with an oligo (ethylene oxide) unit intercalated between the hydrocarbon chain and the carboxylate head group is found to enhance the stability of the vesicles at lower pH. The presence of very bulky polar group has two effects, a lowering of the phase transition temperature and a lowering of the pH region for vesicle formation.

Insensitivity Toward Divalent Cation

Precipitation of vesicles are caused due to divalent cations such as Mg^{2+} , Ca^{2+} even at low concentrations. Fatty acid glycerol esters can be added to stabilize the fatty acid vesicles in the presence of ionic solutes

Enhancement Of Stability By Crosslinking Fatty Acid Molecules By Chemical Bonds

Fatty acid (soap) with a polymerizable moiety (e.g., sodium 11-acrylamidoundecanoate: SAU) can be used to enhance the stability. The vesicles from polymeric SAU were found to self-assemble into vesicular aggregates and also they were stable at elevated temperatures.

Mixture Of Fatty Acid Vesicle And Surfactant-Based Vesicles

A model system of mixed vesicles would be mixtures of tetradecyltrimethylammonium hydroxide (TTAOH) and fatty acids. It has been found that, if approximately the same concentration of TTAOH and fatty acid were mixed, unilamellar and multilamellar vesicles were formed. [9]

APPLICATION OF UFASOMES

Drug loaded ufasomes can be used for the transdermal delivery of various therapeutic agents. Various category of drugs such as anti-inflammatory, antifungal, antiosteoarthritic, anticancer etc. loaded in ufasomes have been used for transdermal delivery.

• Antifungal Drugs

To minimize the drawbacks of the conventional formulations such as allergic reactions and less penetration power, novel formulations like niosomes, liposomes, ethosomes, microemulsions, and micelles have been developed for transdermal delivery of these drugs. Ufasomes are more advanced systems developed for this purpose. In-vitro drug release study showed sustained release of drug from the ufasomal dispersion. In-vivo study confirmed prolonged release of drug from ufasomes up to five days. This indicates its usefulness for long-term therapy compared with other marketed formulations.

• Anticancer Drugs

5 Fluorouracil (5-FU) has been approved by US-FDA for topical treatment of basal cell carcinoma (BCC). The marketed formulation shows various side effects such as

itching, eczema, redness, and poor penetration into the skin. Ufasomes are used to reduce side effects since the drug is encapsulated inside the vesicles. They can enhance the penetration of the drug and sustain the release of the drugs. The fatty acid vesicles were fairly stable at refrigerated conditions. Ex-vivo skin permeation studies confirmed that the fatty acid vesicles penetrated the stratum corneum and retained the drug in the epidermal part of the skin.

• Antiinflammatory Drugs

The preliminary treatment of rheumatoid arthritis (RA) involves the use of nonsteroidal antiinflammatory drug (NSAID). The use of slow-acting disease modifying antirheumatic drugs (DMARDs) has been currently suggested for the early treatment of RA to prevent or reduce joint damage. The amount of drug permeated through rat skin was found to be three to 4-fold higher using fatty vesicles compared with that of plain drug solution or carbopol gel. Skin permeation assay shows that up to 50% of the administered dose was present in the skin when fatty acid vesicles are used. Thus, the inflammation in RA could be reduced by using this system. The transdermal permeation of fatty acid vesicular gel was found to be about 4.7 times higher when compared to that of plain drug gel. Significant reduction of edema was also observed in case of fatty acid vesicular gel compared with the same amount of the commercial product. So, fatty acid vesicles-based gel of drugs could be more effective to treat inflammation compared to that of the marketed gel.

• Antiosteoarthritic drugs

Components in the human body such as collagen and proteoglycans are vital for the joint rebuilding and the formation of synovial fluid which lubricates the joints. Their synthesis in the body is promoted by glucosamine supplementation. So, in the treatment of osteoarthritis glucosamine has been always suggested. Therefore, fatty vesicles of glucosamine sulfate are prepared and then dispersed them in carbopol gel for topical delivery to treat osteoarthritis. Muscular concentration of the drug for vesicle-based gel on rats was found to be 6-fold higher compared to the plain carbopol gel. The gel loaded with fatty acid vesicles also showed sustained release of the drug. Therefore, this formulation could act as an effective depot formulation for the treatment of osteoarthritis. [5]

CONCLUSION

Ufasomes are suspensions of closed lipid bilayers which are composed of fatty acids, and their soap which are restricted to narrow pH range. In ufasomes, the hydrocarbon tails of the fatty acid molecules are arranged towards the membrane interior and the carboxyl groups of the fatty acids are in contact with water. The proper selection of fatty acid, amount of cholesterol, buffer, pH range, etc are some of the factors that determine the stability of ufasome formulation. Ufasomes are highly potential therapeutically and can be used for the treatment of various skin disorders. The drug is released in a controlled or sustained manner, thus the side effects of drugs such as burning, itching, and other allergic reactions on the skin can be minimized. Fatty acid vesicles are also

found to be highly beneficial to treat the skin disorders in conditions like AIDS, because they do not activate the immune system due to controlled release of the drug. Ufasome is considered as a better alternative to liposomes for topical delivery of the drugs because of their cheaper cost, high penetration power, and good entrapment efficiency.

REFERENCES

1. Meraz CA, Rodriguez VA. Clotrimazole Loaded Ufosomes for Topical Delivery: Formulation Development and In-Vitro Studies. *Molecules*. 2019; 1-15.
2. Kumar P, Singh SK. Oleic acid nanovesicles of minoxidil for enhanced follicular delivery. *Medicines*. 2018; 1-16.
3. Patel DM, Jani RH, Patel CN. Ufasomes: A Vesicular Drug Delivery. *Systematic Reviews in Pharmacy*. 2011; 2(2): 72-78.
4. Kaur N, Garg R. Optimization and evaluation of oleic acid based unsaturated fatty acid liposomes gel. *Journal of Bioequivalence and Bioavailability*. 2017; 9(3): 424-9.
5. Kumar L, Verma S. Fatty acid vesicles acting as expanding horizon for transdermal delivery. *Artificial Cells, Nanomedicine, and Biotechnology*. 2016: 1-10.
6. Salama AH, Aburahma MH. Ufasomes nano-vesicles-based lyophilized platforms for intranasal delivery of cinnarizine: preparation, optimization, ex-vivo histopathological safety assessment and mucosal confocal imaging. *Pharm Dev Technol*. 2015. 1-10.
7. George A, Nair SC. Ufasome: A potential phospholipid as a novel pharmaceutical formulation. *Int. Res. J. Pharm*. 2014. 5(4): 250-253.
8. Jain S, Mahajan SC. Lipid based vesicular drug delivery system. *Advances in Pharmaceutics*. 2014: 1-12.
9. Patel SA. Review on ufasomes and vesicular drug delivery system. *The Pharma Research*. 2013; 9(01): 32-43.
10. Verma S, Bhardwaj A. Oleic acid vesicles: a new approach for topical delivery of antifungal agent. *Artificial Cells, Nanomedicine, and Biotechnology*. 2013: 1-7.