UFASOMES: A Potential Vesicular Drug Delivery System

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Abstract **- Many Novel Vesicular Delivery systems have been discovered to administer drugs for controlled and targeted delivery. These vesicular systems include liposomes, niosomes, transferosomes, ethosomes, ufasomes, etc. Ufasomes are unsaturated fatty acid vesicles. They are suspensions of fatty acid and their ionized species(soap) which are arranged as closed lipid bilayers that are restricted to narrow pH range from 7 to 9. They are obtained from unsaturated fatty acids such as oleic acid, arachidonic acid, linoleic acid etc. The fatty acid molecules in the ufasomes are arranged in such a manner that the hydrocarbon tails is faced inwards while the carboxyl groups are in contact with aqueous media. The study focuses on the advantages and disadvantages, method of preparation and characterization of ufasomes.**

Index Terms **- Liposomes, niosomes, transferosomes, ufasomes.**

INTRODUCTION

Drug delivery can be defined as the process of administering a pharmaceutical compound to achieve therapeutic benefits in humans or animals. The method by which a drug is delivered can have a significant impact on its efficacy. Most drugs have an optimum concentration range within which maximum benefit is derived. Concentrations above or below this range can cause toxic effect or show no therapeutic benefit at all. For this reason, new strategies called novel drug delivery systems (DDS), which are based on interdisciplinary approaches that combine polymer science, pharmaceutics, chemistry, and molecular biology, are being investigated (1). The two requirements for a system to be novel are:

- The drug is delivered at a rate directed by the needs of the body for pre-determined span of time;
- Carries the active entity to the target site.

Vesicular structure is one such novel drug delivery system which helps in improving the bioavailability of the drug, prolonging the existence of drug in the body and controlled release of drug (2). Vesicular systems can be defined as highly ordered structures consisting of one or more concentric bilayers formed as a result of self-assembly of amphiphilic building blocks in the presence of aqueous media (3). The first lipid based vesicles was reported in 1965 by Bingham. Later various types of vesicular systems like liposome, noisome, and pharmacosome, came into existence. Some of the recent advances in vesicle research are listed in Table 1.

Type	Description	Application
Aquasomes	Three layered self-assembled nanoparticulate carrier system comprising of central solid nanocrystalline core coated with oligomeric film onto which biomolecular active molecules adsorb.	Specific targeting
Discosomes	Giant niosomes containing poly-24 oxyethylene cholesteryl ether (known as solulan 24).	Ligand mediated drug delivery. Ophthalmic drug carrier
Emulsomes	Lipoidal vesicular system with an internal solid fat core surrounded by a phospholipid bilayer.	Parentral administration of hydrophilic compound.

Ethosomes	Soft malleable vesicles composed of phospholipids, high concentration of ethanol and water.	Targeted Delivery through skin.
Virosomes	Reconstituted liposomes containing viral glycoproteins in the liposomal membrane.	Delivery of immunological products like influenza vaccine.
Invasomes	Invasomes are the liposomal vesicles consisting of small amounts of ethanol and terpenes or terpene mixtures.	Transdermal Drug Delivery
Ufasomes	Unsaturated fatty acid vesicles	Targeted drug delivery system with high stability and enhanced drug entrapment.

Table 1: List of Recent Vesicular Structures

UFASOMES:

Ufosomal preparation was first reported in 1973 by Gibicki and Hicks (4). Ufasomes are vesicles enclosed by long chain fatty acids. They are colloidal suspensions of closed bilipid layers comprising of fatty acids and their ionic species (Figure 1) which are restricted to a narrow pH range of 7-9. They contain two types amphiphiless, non- ionized neutral forms and ionized negatively charged forms (5).

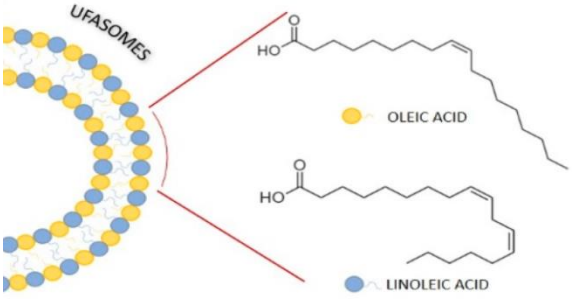

Figure 1: Structure of Ufasomes

Ufasomes are generally prepared from unsaturated fatty acids like linoleic acid or oleic acid. The membrane fatty acids are oriented in a bilayer form such that the hydrocarbon tails of the fatty acids are arranged towards the membrane interior and the carboxyl groups are in contact with water.

ADVANTAGES:

1. Enhanced penetration of drug in case of topical application.
2. High drug entrapment.
3. Due to easy availability of fatty acids they are cost effective compared to liposomes and niosomes.
4. Improves bioavailability of poorly soluble drugs.

DISADVANTAGES:

1. Undergoes oxidation easily and may result in toxicity
2. May cause atherosclerosis.

KEY ISSUES IN MANUFACTURING:

The stability of these vesicles depends on the ratio of non- ionized form and ionized form, selection of fatty acid, amount of cholesterol and pH range, amount of lipoxygenase and presence of divalent cations (6).

1. Selection of Fatty Acid:

Fatty acids with 18 carbons showed great promise. Studies showed that only oleic acid and linoleic acid formed membranes for ufasomes.

2. Amount of cholesterol:

Cholesterol maintains the membrane fluidity and rigidity by filling the gaps caused by imperfect packing of lipid species. Higher concentrations of cholesterol reduces thee vesicle's ability to hold solute. Hicks et.al. studied that there is leakage of glucose when 17% of cholesterol is incorporated in the formulation.

NAME	CHEMICAL STRUCTURE
Myristoleic acid	$CH_3(CH_2)_3CH=CH(CH_2)_7COOH$
Palmitoleic acid	$CH_3(CH_2)_5CH=CH(CH_2)_7COOH$
Sapienic acid	$CH_3(CH_2)_8CH=CH(CH_2)_4COOH$
Oleic acid	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$
Linoleic acid	$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_3$ COOH
Arachidonic acid	$CH_3(CH_2)_4CH=CHCH_2CH=CHCH_2CH$ $=CHCH_2CH=CH(CH_2)_3COOH$
Erucic acid	$CH_3(CH_2)_3CH=CH(CH_2)_{11}COOH$

Table 2: List of unsaturated fatty acids

3. pH:

A narrow range of pH 7-9 is required for ufasomes where approximately half of carboxylic acids are ionized. Below this range the fatty acids form unstructured precipitates while above this range they

are too soluble. Micelles are formed at high pH while at low pH oil droplets are observed. The concentration just above the concentration at which vesicles are formed is called "Critical Vesiculation Concentration". At critical vesicular concentration self assembly into bilayer structures takes place and forms colloidal suspension of vesicles.

4.Selection of buffer:
Selection of buffer depends on the solute to be entrapped. Tris hydroxymethyl aminomethane is most used for the preparation of ufasomes. Other buffers like borate, glycine- hydroxide and biocarbonate solutions can also be used.
For example, glucose entrapped ufasomes prepared in biocarbonate solution did not hold glucose while borate solution lead to the formation of glucose buffer complex.

5. Peroxidation:
Peroxidation disturbs the bilayer arrangements of fatty acids. When a bulky hydrophilic group is introduced to the hydrophobic bilayer it distorts and allows easy passage of water soluble molecules. Hicks et.al. used soya bean lipoxygenase for release of glucose from linoleic vesicles. Lipoxygenase induces release of drug from the bilayer membrane by forming peroxides. The rate of release is proportional to the concentration of lipoxygenase. But lipoxygenase fails to form peroxides with monoenoic fatty acids.

METHOD OF PREPARATION

- Vortex Mixing: In this method 10% of oleic acid and linoleic acid in chloroform are prepared as stock and stored at 200c. 0.2ml of this stock solution is taken in a test tube and placed on a water pump for the solution to evaporate which is followed by drying with a stream of nitrogen to obtain a film. The resultant fatty acid film is broken completely on addition of 0.2ml of 0.1M Tris- hydroxymethyl aminomethane buffer of pH8-9 by vortex mixing to form a suspension of ufasomes (7).
- Thin Film Hydration: In a clean and round bottom flask, accurately weighed oleic acid, span 80, and drug were dissolved in a suitable solvent like methanol followed by solvent evaporation using rotary evaporator under reduced pressure at 400c to form a dried film. The dried film is then hydrated with 7.4 pH phosphate buffer for 1hr followed by sonication to obtain uniform size vesicles.
- By Addition of Alcohol: Ufasomes(fatty acid vesicles) can be formed by the addition of alcohols having the same chain length as that of the fatty acid (8). The rate of vesicle formation can be increased in the presence of pre- added vesicles. The main advantage of the method is that vesicles prepared are stable over a wide pH.
- By Autopoetic Process: 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 (9).

CHARACTERIZATION OF UFASOMES

Vesicle Shape and Surface Morphology:
Fatty acid vesicles are visualized by using TEM with an accelerating voltage of 100 kV. A drop of the ufasomal preparation is placed onto a carbon-coated copper grid which is negatively stained with 1%phosphotungstic acid (PTA). The grid is then air-dried thoroughly and the samples are viewed on a transmission electron microscope.

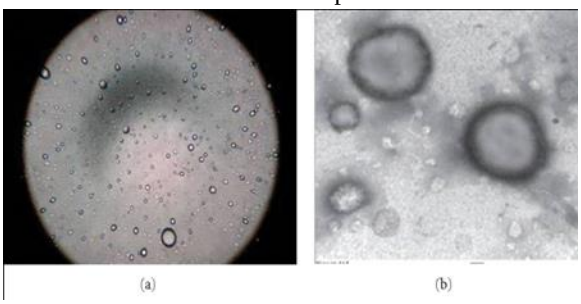

Figure 2: a) Optical microscope observation; b) Transmisiion electron microscope observation.

Vesicles can also be visualized under optical microscope by spreading a thin film of the preparation onto a slide covered with a cover slip

Particle Size Distribution
Average diameter and particle size distribution are determined by Photon Correlation Spectroscopy using 90 plus particle size analyzer at a fixed angle of 900 and temperature of 250c. The suspension is first diluted with phosphate buffer of pH7.4 and filtered

through a 1m polycarbonate membrane to minimize interferences by any particulate matter.

Entrapment Efficiency:
Entrapment efficiency (EE%) is defined as the portion of the applied drug which is entrapped by the ufasomes. Unencapsulated free drug can be removed from the suspension using ultracentrifugation or dialysis. The supernant is observed under UV spectroscopy. The amount of entrapped drug can be determined as a percentage from the following equation:

$$\text{Entrapment efficiency} = \frac{\text{Amount entrapped}}{\text{total amount}} \times 100$$

Bilayer Characterization:
Bilayer characteristics have an importance on drug entrapment efficiency. For multilamellar vesicles, the number of lamellae can be determined by Atomic Force Microscopy (AFM), NMR, and small angle X-ray scattering (SAXS) Membrane rigidity can be measured by means of the mobility of the fluorescence probe as a function of temperature. DPH (1,6 diphenyl-1,3,5-hexatriene) is one of the most used fluorescent probe. The bilayer thickness can also be characterized using in situ energy-dispersive X-ray diffraction (EDXD).

Zeta Potential:
The zeta potential of the ufasomal preparation is determined using a Zetasizer. The vesicular suspension is mixed with an appropriate medium(like ethanol) and measurements are to be conducted in triplicate.

In-vitro Drug Release Studies:
The study is conducted using Franz Diffusion Cell. It consists of two compartments, a donor compartment and an receptor compartment partitioned by a membrane. The ufasomal preparation is placed in the donor compartment while the receptor compartment consists of phosphate buffer which is stirred with magnetic stirrer at constant speed at 370c. Samples are withdrawn at specified intervals and observed under UV- spectrometer.

pH Dependant Stability:
The effect of pH on stability and drug release was studied by incubating the vesicular dispersion with buffers of 5.5, 6.5, 7.4 and 8.5. Samples are withdrawn at specific time intervals and centrifuged at 14,00rpm for 30min. the supernant was analyzed for free drug. The incubated vesicles were also observed under optical microscope for any change in size and morphology.

APPLICATIONS

1.Anti-cancer:
5-Flurouracil is a topical treatment for basal cell carcinoma (10). Ufasomes of 5-flurouracil reduce the side effects like eczema, itching and redness since the drug is encapsulated inside the vesicles. 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.

2.Anti-Inflammatory:
Rajkamal et.al. prepared Dexamethasone loaded ufasomes (11). Significant reduction in edema was observed when compared to conventional formulation. Hence oleic acid vesicles were used as an alternative for topical delivery.
Arvind Sharma et.al. prepared Methotrexate loaded ufasomes for treating Psoriasis (12). Permeation of fatty acid vesicles through rat skin was threefold higher than drug solution. Skin permeation assay of the vesicles showed 50% of administered drug in the rat skin. Therefore, oleic acid vesicles may be of value for administering methotrexate.

3.Anti- Fungal:
Sankha Bhattacharya et.al. prepared glyceryl oleate ufasomes of Terbinafine hydrochloride to treat fungal infection caused by Candida albicans (13). The fatty acid vesicles showed enhanced penetration and higher systemic absorption than the conventional formulations like creams and gels.
Kaur et.al. formulated Oxiconazole loaded ufasomes to treat Candida alibican infection (14). The optimized ufasomal formulation showed higher zone of inhibition than the marketed formulation.

4.Anti-Osteoarthritic:
A.Sharama et.al. formulated glycosamine sulfate ufasomes for the treatment of osteoarthritis (15). Entrapment efficiency was found to be greater than 60% and the in- vitro release tests showed sustained

release thus proving fatty acid vesicles can be used as an alternative to topical delivery.

5.Other applications:

Minoxidil ufasomes were used for the treatment of hair loss(16).

Neutraceutical product Oleuropein obtained from olives used for its antioxidant property was also formulated as fatty acid vesicles called ufasomes (17).

RECENT INNOVATIONS

1. Cis- 4, 7, 10, 13, 16, 19-docosahexaenoic acid (DHA) was reported to self-assemble into vesicles between pH 8.5 and 9.
2. Addition of amphiphilic additives such as surfactant with a sulfate or linear alcohols can vary the pH range at which vesicles are formed.
3. Example: mixture of decanoic acid and decanoate can form vesicles at pH 4.3 by the addition of sodium dodecylbenzene.
4. Enhancement of stability: By cross linking fatty acid molecules with the addition of polymerizable moiety like sodium 11-acrylamidoun decanoate.
5. Mixture of fatty acid vesicle and cationic surfactant-based vesicles: Mixtures of tetradecyltrimethyl ammonium hydroxide (TTAOH) and fatty acids were investigated as a model system of mixed vesicles. Unilamellar and multilamellar vesicles were reported to form, if aproximately the same concentration of TTAOH and fatty acid were mixed.

CONCLUSION

Ufasomes are suspensions of closed lipid bilayers which consisting of fatty acids, and their soap which are restricted to narrow pH range. The stability of the formulation depends on the selection of fatty acid, amount of cholesterol, pH range, presence of divalent cations and peroxidation. Ufasomes are potential alternative to topical delivery for the treatment of various skin disorders. The drug can be released in sustained or controlled order thus reducing side effects. Further research may provide opportunities to formulate ufasomes with tailorable features like insensitivity to divalent cations and broadening of pH range.

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