# UFASOMES: A PROMISING VESICULAR SYSTEM FOR ENHANCED DRUG DELIVERY

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**Abstract-** Ufasomes, vesicles containing unsaturated fatty acids, are a new and hopeful method for delivering drugs. These vesicular systems made of lipids provide various benefits such as enhanced drug solubility, stability, and controlled release properties. In contrast to conventional liposomes, ufasomes are created using readily available single-chain amphiphiles, which makes them affordable and easy to formulate. They have demonstrated promise in improving the administration of different medications, such as those for cancer, inflammation, fungi, and osteoarthritis. The distinctive qualities of ufasomes, including improved penetration and long-lasting release, are beneficial in pharmaceutical formulas. This review examines the latest developments, techniques for preparation, and various uses of ufasomes, showcasing their ability to enhance the effectiveness and safety of drug delivery systems.

**Keywords:** Ufasomes, Drug Delivery, Unsaturated Fatty Acids, Controlled Release, Pharmaceutical Formulations.

## INTRODUCTION

Lipid vesicles are valuable in various fields such as immunology, membrane biology, diagnostics, and genetic engineering. It is possible for them to simulate biological membranes, transport active substances, and extend drug circulation time while reducing toxicity. Drug-loaded vesicles delivered through phagocytic absorption target infection sites effectively, reducing drug toxicity and therapy costs. These systems increase drug bioavailability, particularly for poorly soluble drugs, and can include both hydrophilic and lipophilic drugs. Vesicular drug delivery systems offer sustained release, solving issues of drug insolubility, instability, and quick degradation. The biological origin of vesicles was discovered in 1965 by Bingham, leading to advancements in drug targeting and regulated drug release, improving therapeutic efficacy [1-3]. There are advantages of vesicular delivery system in selective absorption achieved through direct delivery to infection site can prolong drug circulation and minimize toxicity. Enhanced bioavailability for drugs with low solubility. Both hydrophilic and lipophilic medications can be included. Sustained release system for delaying elimination of quickly metabolized drugs.

Following are some recent developments in the field of vesicle research

**Table 1**

| Type | Description | Application |
|---|---|---|
| Aquasomes | Three-layered self-assembled nanoparticulate carrier systems with an oligomeric film-coated solid nanocrystalline core in the center that bio molecularly active molecules adsorb onto. | Precise aiming |
| Discosomes | Giant liposomes contain poly-24 oxyethylene cholesteryl ether. | Drug delivery mediated by ligands. Drug carrier for the eyes. |
| Emulsomes | Phospholipid bilayer around an internal solid fat core in a lipoidal vesicular system. | Administering a hydrophilic substance parenterally |
| Ethosomes | Phospholipid-based soft, malleable vesicles with a high ethanol and water content. | Targeted administration by Skin Contact. |
| Virosomes | Viral glycoproteins in the liposomal membrane of reconstituted liposomes. | Distribution of vaccinations against infections, such as the influenza vaccine. |
| Invasomes | Terpenes or terpene mixtures with trace amounts of ethanol are combined to form liposomal vesicles called invasomes | Drug delivery through transdermal application |
| Ufasomes | Vesicles containing unsaturated fats | Improved drug entrapment and high stability in a targeted medication delivery system. |

## COMPARISON OF UFASOMES WITH OTHER VESICULAR SYSTEMS

Ufasomes have superior penetration compared to liposomes [(4)].Ethosomes may agglomerate and self-destruct upon transitioning into water, resulting in product loss during the conversion from organic to aqueous environments. Conversely, the components of ufasomes are readily accessible and exhibit stability in their natural environment [(5)]. In comparison to ufasomes, they are expensive to produce, and the substance is difficult to store due to stability concerns [(6)] .The components utilized possess a longer shelf life than the requisite instructions. Conversely, ufasomes, including unsaturated fatty acid surfactants like oleic acid and its sodium counterpart, sodium oleate, are non-toxic and function as an exceptional penetration enhancer. Due to the absence of ester linkage, enzymatic degradation does not occur [(7)]. The formulation cost of sphingosomes exceeds that of niosomes; nevertheless, their drug leakage and trapping efficiency are inferior compared to other vesicular structures. Conversely, ufasomes are readily available and the formulation cost is lower [(6)].

## FORMATION OF UFASOMES

Ufasomes are bilayered, closed lipid suspensions. They are made of soap, which is an ionized form of unsaturated fats. In fatty acid vesicles, there are two primary forms of the ionised amphiphiles, negatively charged soap shape and the neutral, non-ionic shape. The pH range of unsaturated fatty acid vesicles, or ufasomes, is 7 to 9. The basis for the determination of vesicle stability is the ratio of neutral forms that are ionic to non-ionic [(8)]. Fatty acid vesicle formation was first documented for oleic and linoleic acid by Gebicki and Hicks in 1973 and was later reported for both acids in later years. Initially, the vesicle formation was called ufasomes. However, subsequent studies showed that saturated and unsaturated fatty acids, which resemble fatty acid vesicles can also be formed by octanoic

and decanoic acid [9,10]. Among the main features of ufasomes is that they consist of single chain amphiphiles and readily accessible fatty acids.

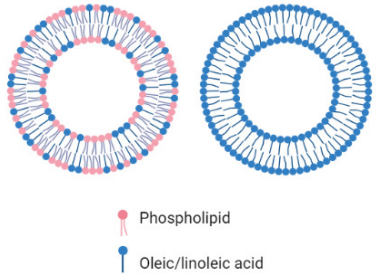


**FIGURE 1. STRUCTURE OF UFASOMES**

## Advantages

- Hydrophilic and hydrophobic drugs are more effectively entrapped by ufasomes.
- Ufasomes are cost effective.
- It's simple to prepare.
- Medicinal feasibility.
- Fatty acids for ufasomal composition are readily available.
- Less absorbable medications can be taken orally.
- Reliability-wise, ufasomes outperform liposomes.
- Ufasomes have enduring effects when applied topically because they have better drug retention and sustained release in the dermal layer.

## Disadvantages

- Ufasomes oxidize easily, fatty drug products may experience stability issues.
- Ufasomes utilisation in food additives and medicine administration is impacted by their colloidal instability.
- Atherosclerosis risk [11].

## UFASOMES METHODS OF PREPARATION

Various methods have been reported to formulate ufasomes, which are mentioned below,

A. The Rotary film evaporation technique
B. The Modified handshaking technique
C. The Vortexing Sonication technique
D. The Reverse phase evaporation technique
E. The Ether injection technique
F. The Film dispersion technique [12,13]

## A. The Rotary film evaporation technique:

The combination of unsaturated fatty acid and surfactant, which form vesicles, is dissolved in a volatile organic solvent (ethanol: methanol) to create a thin film. A rotary evaporator is employed to evaporate an organic solvent at a temperature higher than the lipid transition temperature. Overnight, the last remnants of solvent were extracted using a vacuum. A prepared thin film is rotated for one hour at the correct temperature while spinning at 60 rpm to hydrate it with buffer (pH 7.4). The resulting vesicles inflated for two hours at room temperature. Using a bath sonicator or a probe that was sonicated for 30 minutes at 4°C, small vesicles were created by sonicating the resulting vesicles for 30 minutes at room temperature or 50°C. The sonicated vesicles were homogenised by ten hand extrusions across a sandwich of 200 and 100 nm polycarbonate membranes.

### B. Modified handshaking method:

A mixture of ethanol and methanol (1:1) was used to dissolve the medication, lecithin (PC), and edge activator. When handshaking above the temperature of the lipid transition (43°C), evaporation was utilised to remove the organic solvent. A thin lipid coating formed within the flask wall as the flask rotated. To enable the solvent to totally evaporate, the thin film was left overnight. Subsequently, the film was hydrated using phosphate buffer (pH 7.4) and moderate shaking for 15 minutes at the proper temperature. The Ufasomes suspension was further hydrated for a maximum of one hour at 2–8°C.

### C. Vertexing sonication technique:

To create a milky suspension, mixed lipids (such as oleic acid, surfactant, and the therapeutic agent) are mixed together in phosphate buffer and vortexed. This technique is known as vortexing sonication. The suspension is sonicated and then extruded via polycarbonate membranes. This process, which entails combining cationic lipids with PBS to reach a 10 mg/ml concentration and then counting sodium deoxycholate (SDC), has also been used to set cationic Ufasomes. The mixture is then extruded through a polycarbonate (100 nm) filter after being vortexed and sonicated.

### D. Reverse phase evaporation technique:

A 50 ml round-bottom flask with a long extension neck is filled with lipid, and a rotary evaporator is used to remove the solvent under low pressure. injects nitrogen into the to resolving lipids in the organic phase, like trifluoro trichloroethane, halothane, Isopropyl and diethyl ether, and to prevent the lipid mixtures from degrading. Using ether, chloroform, or methanol, increase the solubility of lipids as well. Aqueous phase should be added, and the system should always be running on nitrogen. Use a bath-style sonicator to sonicate the resultant two-phase system for a short period of time (two to five minutes) until the mixture transforms into a homogeneous opalescent dispersion or a transparent one-phase dispersion. The mixture needs to be put on the rotating evaporator. At 20 to 25°C, remove the organic solvent while applying less pressure while rotating at a speed of about 200 rpm. An aqueous suspension will be formed as a viscous gel. To get rid of any remaining solvent, add extra water or buffer and let the suspension evaporate for a further 15 min at 20°C. Centrifuge the mixture after diluting it and running it through a Sepharose 4B column.

### E. Ether injection technique:

By gradually adding oleic acid and cholesterol that had been dissolved in diethyl ether combined with two milliliters of methanol that had previously contained a weighed amount of medication, this technique allowed for the creation of ufasomes. The resultant solution was kept at 60–65°C while being gradually injected with a magnetic stirrer with a micro syringe into 10 ml of hydrating phosphate buffer at a rate of 1 ml/min. Subsequently, the lipid solution was slowly injected into the aqueous phase. Ufasomal vesicles were formed as a result of the rapid vapourization of ether caused by temperature differences between the phases.

### F. Film dispersion technique:

Lipids dissolved in chloroform are usually added to a glass flask or tube at a level between 10 to 25 mg/ml. To evaporate the solvent, argon gas is passed over the mixture in a stream. Lipids accumulate in a film on the tube walls. Under vacuum, residual solvent is extracted (for example, by actively pumping for a few hours at 5–15 m bar). You can also use a rotary evaporator, sometimes referred to as a "rotavap." The desired aqueous buffer or buffer plus additives (for example, in encapsulation experiments) are then combined with the lipid film, and the mixture is vortexed until the film is entirely removed from the

vessel walls. This usually leads to the spontaneous formation of MLVs (multilamellar vesicles) and LUVs (large unilamellar vesicles) when working with phospholipids. If small unilamellar vesicles (SUVs) are needed, this process should be expanded with an extrusion step. If necessary, size exclusion chromatography should be performed after to obtain more homogeneous size distributions.

• **By Addition of Alcohol:** To make fatty acid vesicles, or Ufasomes, add alcohols that have the same chain length as the fatty acid. Vesicles with pre-added material may quicken the vesicle formation process. The principal advantage of the methodology is the stability of the resultant vesicles over an extensive pH range [(14)].

• **By Autopoietic Process:** Vesicles form when an aqueous fatty acid solution is added to a water-buffered solution due to the spontaneous pH change. Vesicles are more likely to form when half of the fatty acids carboxylic acids ionise [(15)].

## FORMULATION ASPECTS OF UFASOMES

### The selection to use of fatty acid

Examination of phospholipids in natural membranes and data from measuring surface film pressure in the fatty acid region indicate that fatty acids with 12-22 carbons are suitable for creating stable Ufasomes. Because C-18 acids demonstrated the highest potential in initial tests, they were the main focus of the study. Ufasomes can fulfill these criteria as membranes can only be formed by two acids: oleic acid (cis-9-octadecenoic acid) and linoleic acid (cis-9,12-octadecenoic acid). Palmitic acid can endure 33% of its weight in an oleic acid membrane, while stearic acid can endure 5%. The charged membranes with traces of oleic, linoleic, or stearic acid amides had no major impact on the preparations. In stability tests, it was found that linoleic acid showed peroxide formation in 2–3 weeks, whereas oleic acid remained peroxide-free for a minimum of 6 weeks.

### Addition of cholesterol

Cholesterol has a unique ability to regulate the permeability, flexibility, and fluidity of membranes in lipid vesicles. It fills in the empty spaces caused by the imperfect arrangement of other lipid molecules. Increased levels of cholesterol result in a quick decrease in the ability of vesicles to hold solutes. Moreover, membrane permeability does not increase with any level of cholesterol content. The release of glucose from Ufasomes with 17% cholesterol was compared to release from spheres with the same cholesterol content. Their results showed that the leakage of glucose from vesicles with 17% more cholesterol was greater compared to the leakage from cholesterol-free oleic and linoleic acid Ufasomes.

### pH

Fatty acid vesicles can form within a certain pH range (7–9) when approximately half of the carboxylic groups are ionized. Fatty acids are very soluble beyond this range and create disordered precipitates under it. At 80 mM concentration, the titration curve for the oleic acid/oleate technique will identify three different regions for the formation of micelles, vesicles, and oil droplets. At elevated pH levels, micelles are the dominant aggregation species characterized by a greater proportion of ionized to protonated molecules, while oil droplets are predominant at lower pH levels. Fatty acid vesicle systems are easier to recognize at concentrations slightly higher than the critical vesiculation concentration, CVC, where vesicle production is visible. The required concentration of vesiculation results in the formation of colloidal vesicle suspensions in a bilayer structure via the combination of monomers and non-vesicular aggregates. When a

fatty acid micellar solution is diluted to a neutral pH, vesicles of various sizes are formed in a random manner, which should be emphasized.

## Selection of buffer

Tris hydroxymethyl aminomethane is a popular buffer utilized in Ufasomes preparation. On the other hand, spheres are created by solutions of borates, glycine-hydroxide, and bicarbonate. The choice of buffer is determined by the type of solute that needs to be included. For example, Ufasomes formed using bicarbonate could not hold onto glucose within vesicles, and preparations containing borate could not be examined for retention as a glucose buffer complex was created. Creating Ufasomes from 1 mg of fatty acid requires 0.1 ml of Tris at 0.1 M concentration with a pH of 8.

## Electrolyte

The majority of electrolytes prevent the formation of Ufasomes. The spheres can be immersed in phosphate or chloride solutions while preserving the enclosed glucose, once they have been stabilized in the correct buffer.

## Peroxidation

Ufasome membranes are significantly impacted by peroxidation, which causes fatty acid molecules' typical bilayer structure to break down. The oxidation of a bulky hydrophilic moiety will distort the interior of the hydrophobic membrane, facilitating the movement of water-soluble molecules. The amount of fatty acid peroxidation may vary significantly depending on the preparation method used. In the brief period needed for manual vortexing, peroxidation did not occur. In a higher intensity ultrasonic resuspension, linoleic acid was subjected to 30-W irradiations, resulting in oxidation at a speed of 0.1% per minute in air-saturated buffers. Despite being exposed for up to 3 minutes, this technique couldn't effectively oxidize the easily oxidizable linoleic acid. Hicks and Gebicki found that nitroxide radicals, butylated hydroxytoluene, and α-tocopherol showed resistance to linoleic acid membrane peroxidation.

## Divalent cations

Lipid peroxidation (LPO) involves both enzymatic and nonenzymatic catalytic processes. Transition metal ions are a crucial element in non-enzymatic lipid peroxidation. Only a few metals have the ability to quickly induce peroxidation in unsaturated lipids by altering their oxidation state through a single electron transfer. Non-variable valence state metals like calcium, magnesium, and zinc have been found to affect lipid peroxidation. These metals cannot carry out redox-coupled homolysis. Calcium ions have a dual effect on LPO, being able to either stimulate or inhibit it due to their biphasic nature. The scientists studied how calcium works in two different stages in Ufasomes (derived from methyl linoleate and linoleic acid) and liposomes (derived from egg yolk lecithin). LPO was triggered in liposomes and Ufasomes with the addition of Fe along with either hydroperoxide or ascorbate. Through its interaction with the negatively charged lipid groups, including the carboxyl groups of linolenic acid and the phosphate groups of lecithin, calcium induced lipid peroxidation by displacing iron ions that were already bound. Free Fe ions play a direct role in LPO catalysis at low concentrations. Ca's ability to inhibit relies on its interaction with superoxide anion radicals at elevated levels. This dual impact on LPO can also be seen with other cations besides Ca ions, which can release Fe ions bound to negatively charged lipids and interact with superoxide radicals. When there were no Ca ions present, activation of LPO occurred by introducing La ions to linolenic acid Ufasomes at a concentration matching that of Fe ions. Preventing linolenic acid peroxidation was influenced by the combined effect of equimolar amounts of Ca and La, with their overall concentration higher than that of Fe [(17)].

### A novel form of fatty acids found in Ufasomes formulation

1. Cis-4, 7, 10, 13, 16, and 19-docosahexaenoic acid (DHA) was found to form vesicles on its own within the pH range of 8.5 to 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. Improvement of stability: Through linking fatty acid molecules by incorporating a polymerizable group such as sodium 11-acrylamidoundecanoate.
5. Combining fatty acid vesicles with cationic surfactant-based vesicles: The study focused on mixtures of tetradecyl trimethyl ammonium hydroxide (TTAOH) and fatty acids as a representative model of mixed vesicles. It was observed that both single-layered and multiple-layered vesicles could be created by mixing a similar amount of TTAOH and fatty acid [(18)].

## CHARACTERISATION OF DRUG-LOADED UFASOMES

### Particle size

Particle size and Polydispersity index (PDI) were measured using a dynamic light scattering method and a particle size analyzer (Horiba Scientific® SZ-100).

### Zeta potential:

The stability of the nanoparticles was estimated using zeta potential analysis. An indicator of the impact of electrostatic charges is the zeta potential. This is the fundamental force that makes neighbouring particles repel one another. The net effect is either attraction or repulsion, depending on how strong both forces are. The relationship between the nanoparticles' zeta potential determination responses is described by the thumb rule.

### Surface Morphology

One of the most popular methods for examining the surface morphology of nanoparticles and other small particles is scanning electron microscopy (SEM). While DLS provides the particles' hydrodynamic radius, this method uses an electron beam as a probe to obtain high-resolution images of the particles. When comparing the sizes of the vesicles obtained from DLS, the sizes seen with SEM were larger. The vesicles' collapse and fusion due to water loss during the air-drying process may be the cause of the size differences [(19)].

### (%) Entrapment efficiency

The proportion of formulated media with entrapment efficiency. By employing the ultra-centrifugation technique, the Ufasomes formulation was distinguished from the free drug. The Ufasomes dispersion was spun in a Remi cooling centrifuge located in Mumbai, India, for a duration of 90 minutes. Following appropriate dilution of the transparent liquid layer of the solution with water, an ultraviolet spectrophotometer (Shimadzu 1800) was employed for analysis.

The EE% was calculated from the below Equation.

**E% = [(W initial drug – w free drug)/W initial drug] *100**

The mass of the initial drug used for the assay is denoted as 'W initial drug', while the mass of free drug detected in the supernatant after centrifugation of the aqueous dispersion is denoted as 'W free drug'[(20)].

### *In vitro* drug release and Kinetics

The in vitro drug release studies are assessed at $37^0$C through in vitro diffusion cell (Franz diffusion cell) or by using dialysis bag. The diffusion membrane or bag must be wet through receptor medium containing pH 7.4 buffer with constant stirring under sink

conditions, which mimics the in vivo conditions. At regular time intervals, the required volume of the medium was collected, and the concentration was determined by using HPLC and UV–Visible spectrophotometry, and at the same time equal volume of fresh medium was added to receptor media[21].

There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and reference dissolution profiles. Various mathematical models are used to describe drug release kinetics from vesicular system including ufasomes. Generally, zero order permeation profile is expected with vesicular system. The fatty acid concentration in Ufasomal formulations will affect the release of water-soluble drugs, and as the concentration of fatty acid increases, it enhances the release rate of the drug. Drug release kinetics depends upon the thickness of the vesicle and nature of the fatty acid used hydrophilic and lipophilic nature of the drug also influence the mechanism of drug release and kinetics.

## Dynamic properties of Ufasomes

Since unsaturated fat vesicles consist of amphiphiles with one chain, they display dynamic characteristics. The unsaturated fat acid vesicles move dynamically within single-chained surfactants forming micelles and double-chained amphiphiles forming conventional vesicles. Simply altering the ratio of ionization or protonation of the terminal carboxylic acid can give rise to different forms of fatty acid aggregates. The process of analyzing the formation speed of vesicles and micelles from either a saturated fat solution or soap monomer solution was done by passing the soap monomers or saturated fatty acids through a membrane made of cellulose acetate. The speed at which equilibrium is achieved is calculated by beginning with an uneven spread of soap monomers or fatty acids between two chambers separated by a dialysis membrane. One chamber holds aggregates such as vesicles or micelles, while the other chamber holds only a buffer solution. Due to the presence of the micellar system, a state of equilibrium was rapidly attained. Yet, vesicles greatly impeded the attainment of the equilibrium state (the concentration in the diffusate chamber slowly rose as the solution became saturated with monomers). Vesicles have a much greater amount of amphiphiles compared to micelles. The findings from the dialysis study show that creating fatty acid vesicles requires a much greater energy barrier compared to producing fatty acid monomers (soap). Adding alkaline soap solution to a buffer solution with a moderate pH level is an effective method for generating fatty acid vesicles. For example, consider a buffer solution with a pH of 8.5 and introduce a concentrated sodium oleate micelle solution into it. This occurs spontaneously due to the pH dropping between 10.5 and 8.5, leading to the partial protonation of the oleic acid molecules. Both the vesicles produced vary in both size and lamellarity [22].

## Recent innovations in conventional Ufasomes

Fatty acid vesicles have not been widely utilized in drug delivery and food additives due to concerns about their colloidal stability (sensitivity to pH and divalent cations). Nonetheless, recent research employing novel fatty acid types or blended systems with additional surfactants could potentially alter the landscape in the future.

### APPLICATION OF UFASOMES

Ufasomes loaded with drugs can be utilized to deliver various medicinal drugs through the skin. Ufasomes have been utilized for delivering anti-inflammatory, anti-fungal, anti-osteoarthritic, anti-cancer, and various other drugs through transdermal distribution.

### 1.Anti-cancer:
5-Flurouracil is a topical treatment for basal cell carcinoma [23]. Ufasomes of 5-flurouracil reduce the side effects like eczema, itching and redness because the medication is enclosed within the vesicles. Experiments on skin permeation outside the body verified that the fatty acid vesicles entered the outermost layer of skin and kept the medication in the skin's upper layer.

### 2.Anti-Inflammatory:
Significant reduction in edema was observed when compared to conventional formulation. Hence oleic acid vesicles were used as an alternative for topical delivery. 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 [24].

### 3.Anti- Fungal:
The fatty acid vesicles showed enhanced penetration and higher systemic absorption than the conventional formulations like creams and gels [25]. The optimized Ufasomal formulation showed higher zone of inhibition than the marketed formulation [26].

### 4.Anti-Osteoarthritic:
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 [27].

### 5.Other applications:
Minoxidil ufasomes were used for the treatment of hair loss [28]. Nutraceutical product Oleuropein obtained from olives used for its antioxidant property was also formulated as fatty acid vesicles called Ufasomes [29].

## CONCLUSION
Ufasomes is a novel and exciting drug delivery technique. Benefits from their lipid-based vesicular structure include enhanced stability, controlled release properties, and drug solubility. Ufasomes are useful in pharmaceutical formulations because they have demonstrated the ability to improve the delivery of a variety of medications. Ufasomes have the potential to significantly enhance the safety and efficacy of drug delivery systems with additional study and development, which would ultimately benefit patients by bringing more potent treatments to them.

## CONFLICTS OF INTEREST
There is no declaration of a conflict of interest.

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