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Ufasomes: A New Frontier in Vesicular Drug Delivery

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ABSTRACT

Innovative and advanced drug delivery systems provide greater precision in targeting and control than conventional methods. Vesicular drug delivery approaches allow for accurate regulation of drug release and the specific site of action, resulting in enhanced effectiveness and better patient adherence. These vesicular systems consist of multiple layers of amphiphilic molecules surrounding a water-filled core. Their capability to direct drugs to particular organs or tissues makes them suitable for targeted drug delivery. Such systems can sustain drug release at a steady rate, keeping therapeutic levels while minimizing adverse effects. Ufasomes are vesicles created from unsaturated fatty acids. These lipid bilayer structures are composed of soaps and fatty acids and maintain stability within a small range of pH from 7 to 9. The lipid film hydration method is typically employed to manufacture ufasomes, with fatty acid serving as a key ingredient. This article covers the preparation process, benefits, drawbacks, potential advancements, and description of ufasomes.

Keywords: Oleic acid, ufasomes, lipid film hydration, fatty acid vesicles, and vesicular drug delivery systems.

INTRODUCTION [1]

When layers of fatty acids are mixed with a buffer solution, they produce ufasomes—vesicles made up of long-chain unsaturated fatty acids. These structures are similar to liposomes, which are composed of phospholipids. Ufasomes represent a promising approach for drug delivery as they can effectively transport medications to the site of infection, minimizing opioid toxicity and associated side effects. In contrast to liposomes, which depend on phospholipids, ufasomes can be constructed from various fatty acids, including saturated ones like oleate, linolic acid, as well as unsaturated fatty acids such as octanoic acid and decanoic acid. This adaptability allows ufasomes to be more versatile and accessible for drug delivery purposes.

The skin is a recognized pathway in addition to a medication delivery barrier, with the stratum corneum presenting particular challenges for penetration. Although penetration enhancers can facilitate the passage of drugs through the skin, conventional formulations such as creams and ointments often have restricted local efficacy. To enhance drug delivery and site-specific action, researchers are investigating vesicular systems like niosomes, liposomes, and ufasomes. These systems can improve drug penetration through the skin and better target specific areas for treatment.

Ufasome is an innovative approach for improving the absorption of opioids through the skin. The production of ufasome incorporates surfactants and unsaturated fatty acids. Natural permeation enhancers, such as oleic and linoleic acids, are categorized as unsaturated fatty acids. Surfactants and unsaturated fatty acids contribute to better skin flexibility and enhance the absorption of medication through the epidermal barrier. Research has shown that ufasomes facilitate the retention of medication within skin cells. Ufasomes are small vesicles composed of fatty acids, featuring a bilayer structure with carboxyl groups oriented towards water and fatty acid tails directed inward. These soapy solutions based on lipid bilayers are typically found within a pH range of 7 and 9.

COMPONENTS OF UFASOMES

Solvent: Organic solvents like mixtures of chloroform and methanol are frequently employed to spread lipid layers and isolate key proteins and subcellular constituents. These solvents generate mixed micelles that incorporate fragments from the lipid layer along with the detergent. The success of these methods depends on chloroform and methanol creating a unified solvent system that can

effectively extract and degrade lipids. The selected solvents must be able to dissolve the desired components, allowing for precise control over the procedure.

Surfactant: When added to a liquid, a surfactant also referred to as a surface-active agent decreases surface tension, improving the liquid's capacity to spread and moisten surfaces. Fatty acid vesicles are formed from colloidal suspensions of closed lipid bilayers created from trans fats and their ionized versions (soaps), functioning as surfactants. These vesicles develop rapidly when soluble micelles are integrated with buffered vesicles. Oleic acid, which features a double bond in its hydrophobic oleyl tail, is one surfactant that has shown a notable capacity to lower the surface tension of an aqueous solution.

Cholesterol: Cholesterol has a complex role in modulating the fluidity of membranes. When temperatures are high, it stabilizes the lipid bilayer by raising its melting point. In contrast, at low temperatures, cholesterol integrates itself among the phospholipids, inhibiting their aggregation and solidification. From a biophysical standpoint, cholesterol improves the order of lipid packing, decreases membrane permeability, and sustains membrane fluidity by creating fluid-ordered lipid rafts. It acts as a fluidity regulator in extreme temperatures, helping our membranes to keep an ideal level of fluidity. In cold environments, cholesterol enhances fluidity to prevent the membrane from freezing, while in warmer environments, it reduces fluidity.

ADVANTAGES [2]

1] Prolonged circulation and reduced toxicity: Ufasomes have the potential to prolong the duration a medication remains in the bloodstream, which helps to minimize adverse effects.

2] Targeted delivery: Ufasomes can enhance drug absorption and minimize waste by administering drugs directly at the target location.

3] Enhanced bioavailability: Ufasomes have the potential to enhance the absorption of drugs that are poorly soluble.

4] Versatility: Ufasomes have the ability to encapsulate drugs that are either water-soluble or fat-soluble.

5] Sustained release: Ufasomes have the ability to slow down the degradation of quickly metabolized medications, allowing for a more prolonged release.

6] Rapid absorption: When used on the skin, ufasomes can swiftly absorb through the surface.

7] Cost-effective: Ufasomes tend to be less costly than liposomes and niosomes due to the easier availability of fatty acids.

8] Effective drug encapsulation: Ufasomes have the capability to capture and transport medications.

DISADVANTAGES

Oxidation: Ufasomes have a tendency to oxidize, resulting in instability in fatty drug formulations.

Drug Leakage: Drugs often tend to escape from ufasomes.

High Production Costs: Fatty acids are generally inexpensive, but the formulation of ufasomes entails specific conditions and ingredients, making the overall process costly.
Entrapment effectiveness: While ufasomes can capture both hydrophilic and lipophilic drugs, their effectiveness in entrapment is often less than that of alternative vesicular systems like liposomes.
Potential for Skin Irritation: In some cases, the fatty acids present in ufasome formulations can cause skin irritation.

BROAD WAY OF FORMATION [3]

Only materials that have not undergone oxidation are utilized in the creation of ufasomes. Stock solutions of linoleic acid and oleic acid are prepared in chloroform and left at room temperature. A small portion of the stock solution is dried and evaporated using nitrogen. The fatty acid layer is then dispersed in a buffer solution with the help of an ultrasonic generator or vortex blender. During the ultrasonic treatment, nitrogen gas is employed to remove air from the buffer, while an ice-water bath is used to maintain a consistent temperature. The ufasome suspensions that result from this process remain stable for at least twenty-four hours.

APPROACHES TO PREPARATION [4]

Method of Thin Film Hydration

Fatty acids and an organic solvent are mixed in a container to create ufasomes. The solvent is subsequently evaporated, resulting in a thin film of fatty acids. This film is then hydrated with a buffer solution at a designated pH to create the ufasomes. This process necessitates a high concentration of fatty acids.

By Addition of Alcohol

To generate fatty acid vesicles, an alcohol that matches the fatty acid's chain length is incorporated. This technique results in vesicles that maintain stability across various pH levels. The inclusion of pre-formed vesicles can accelerate the process. Nonetheless, this method can ultimately be quite time-consuming.

Autopoetic Method

When an aqueous solution of fatty acids is mixed with a buffered water solution, the resulting change in pH can trigger the formation of fatty acid vesicles. Vesicles can develop when approximately half of the carboxylic acid groups in the fatty acids become ionized. The HC- chains of the fatty acids organize themselves into a bilayer formation, minimizing their contact with water.

ESSENTIAL PROBLEMS WITH UFASOME MANUFACTURING [5]

fatty acid selection

Research indicates that fatty acids containing between 12 and 22 carbon atoms are the most effective for producing stable ufasomes, as shown in studies of natural membrane phospholipids and fatty acid surface films. Although C-18 acids showed great potential in initial experiments. Incorporating palmitic acid into an oleic acid membrane was feasible at levels up to 33% without compromising its stability, whereas stearic acid could only be included at a maximum of 5%. Adding small amounts of oleic, linoleic, or stearic acid amides did not improve the formulations. Oleic acid demonstrated stability for For a minimum of six weeks, but linoleic acid began forming peroxides in two to three weeks. Additionally, cholesterol was included in the formulations.

Cholesterol addition

The research indicated that cholesterol is essential for managing the elasticity, fluidity, as well as permeability of lipid vesicles. It occupies the spaces between other lipid molecules, but higher cholesterol levels can impair the vesicles' capacity to retain solutes. Nevertheless, cholesterol does not enhance the impermeability of membranes. In their comparison of glucose leakage, researchers observed that ufasomes containing 17% cholesterol exhibited greater glucose leakage than spheres with the same cholesterol content, as well as than cholesterol-free oleic along with linoleic acid ufasomes.

pH

According to the research, fatty acid vesicles can only develop when approximately half of the carboxylic groups are ionized, which happens within a pH range of 7 to 9. When the pH drops below this range, fatty acids form unorganized precipitates, while at higher pH levels, they dissolve more readily. A titration curve based on the oleate method identifies three distinct phases: micelle formation, vesicle development, and oil droplet creation at a total concentration of 80 mM. Micelles dominate at higher pH values, while reduced pH results in the generation of oil droplets. Fatty acid vesicle systems become more apparent when the concentration surpasses the critical vesiculation concentration (CVC), allowing monomers and non-vesicular aggregates to arrange into bilayer formations. If a micellar solution of fatty acids is diluted to a neutral pH, it may spontaneously produce vesicles of different sizes.

Choice of buffer

The study showed that tromethamine is commonly utilized as a buffer for producing ufasomes, while spheres are formed using solutions made of borax/borates, glycine, and bicarbonate. The choice of buffer depends on the solute involved. For example, ufasomes made with bicarbonate were unable to maintain glucose stability, while those prepared with borate could not be evaluated for glucose retention because a glucose buffer complex was formed. To produce ufasomes from one milligram of fatty acid, one millilitre of 0.1 M tris at pH 8 is required.

Electrolyte

The research revealed that the majority of electrolytes inhibit the development of ufasomes. Nevertheless, after the spheres have been stabilized in the suitable buffer, they can be introduced to phosphate or chloride solutions without influencing the trapped glucose.

Peroxidation

According to the study, peroxidation can alter fatty acid molecules' bilayer structure, which has an impact on ufasome membranes. When a large hydrophilic group is peroxidised, the interior of the hydrophobic barrier is deformed, making it easier for molecules which is water-soluble to flow through. The degree of peroxidation may vary depending on the preparation technique. Short-term hand vortexing did not result in peroxidation; nevertheless, linoleic acid oxidised at a rate of 0.1% per minute after 30 minutes of ultrasonic resuspension in air-saturated buffers. Despite the highest exposure of 3 minutes, this technique did not significantly oxidise oxidation-sensitive linoleic acid.

Divalent cations

The study found that lipid peroxidation (LPO) is catalyzed by both enzymatic and non-enzymatic mechanisms. Transition metal ions have an impact on non-enzymatic LPO; metals capable of undergoing valency changes catalyse the fast peroxidation of unsaturated lipids. Metals, such as zinc, magnesium, and calcium, can affect LPO even if they are unable to take part in redox-coupled homolysis. LPO is affected by calcium ions in two phases: at low quantities, it is activated, and at high concentrations, it is inhibited. By interacting with negatively charged lipid groups and dislodging bound Fe2+ ions, calcium ions can cause LPO, according to research on this action in liposomes and ufasomes. Calcium ions' ability to inhibit is dependent on their interaction with superoxide anion radicals.

CHARACTERIZATION OF UFASOME [6]

Particle Size and Size Distribution

The average diameter and size distribution of ufasome suspensions at a fixed angle of 90°and 25° Celsius are measured using a particle size analyser in conjunction with photon correlation spectroscopy. The solution suspension were dilute using a pH 7.4 phosphate buffer and passed through a polycarbonate membrane before sizing in order to reduce particulate matter interference.

Morphology of The Surface and Shape

TEM is used to examine the morphological characteristics of sphericity and drug-loaded ufasomal dispersal accumulation. The chosen ufasomal dispersion was applied as a drop on a copper grid coated with carbon film and negatively stained with 1% phosphotungstic acid. Prior to TEM examination, the sample was let to dry at ambient temperature for 10 min.

(DSC)Differential Scanning Calorimetry

To ascertain the material's physical condition within the oleic acid vesicles, differential scanning calorimetry was used. Using a conventional aluminium pan, the vesicles were scanned at a rate of 2°C per minute.

(EE)Entrapment Efficiency

The percentage of entrapped drug was calculated using the following equation: Entrapment efficiency (%) = (Amount of drug added initially - Amount of drug determined in the filtrate spectrophotometrically) / Amount of drug added initially × 100. Using ultracentrifugation at 25,000 rpm for three hours at 4°C, the drug's entrapment efficiency was assessed, and UV spectroscopy was used to analyse the supernatant.

***In-Vitro* Drug Release**

The purpose of the study was to use Franz diffusion cells to examine the kinetics and rate of drug release from ufasomes. A 50-nanometer-pore polycarbonate membrane divides the two compartments of these cells. Phosphate-buffered saline (PBS) at pH 7.4 was kept at 37°C and continuously stirred in the receptor compartment, while 1 ml of ufasomal dispersion was present in the donor compartment. To track the drug release, samples were periodically removed from the receptor compartment and replaced with new PBS.

pH-Dependent Stability

In order to examine how pH affects ufasome stabilisation and drug release activity, optimised vesicular dispersions were incubated in buffers with pH values of 8.5, 7.4, 6.5, and 5.5. To extract the free medication from the supernatant, samples were taken at predetermined intervals and centrifuged. The following formula was used to determine the proportion of drug diffused: **Drug Diffusion Percentage** = Free Drug Amount / Total Drug × 100

Dynamic Charater of Ufasomes [7]

Compared to conventional vesicles made from double-chain amphiphiles and micelles made from single-chain surfactants, fatty acid vesicles made of single-chain amphiphiles have special dynamic features. The dynamics of ufasome production have been studied by researchers. An unequal distribution of fatty acid molecules across two chambers—one containing aggregate and the other containing simply buffer solution separated by the dialysis membrane was used to gauge the pace of equilibrium attainment. The concentration in the diffusate increased gradually after the solution became saturated with monomers, indicating that equilibrium was considerably delayed in the case of vesicles. Amphiphiles are often far more prevalent in vesicles than in micelles. According to the dialysis research, the energy barrier needed to generate fatty acid vesicles is much greater than that needed to form fatty acid (soap) micelles. Upon adding a concentrated solution of sodium oleate micelles to a buffered solution at pH 8.5, oleic acid/sodium oleate vesicles spontaneously develop due to the partial protonation of the oleate molecules produced by the pH reduction from about 10.5 to 8.5. The resultant vesicles exhibit lamellarity and size polydispersity. Adding alkaline micelles to buffered vesicles also causes fatty acid vesicles to develop on their own.

Taking Stability Into Account When Formulating Ufasome [8]

The fatty acid-water system's free energy must be decreased for ufasome membranes to remain stable throughout time. The creation of a distinct phase at pH 8 prevents the membrane from forming spontaneously. When circumstances are right, bilayer formation can be aided by mild mechanical agitation. Since the aligned hydrocarbon chains interact hydrophobically, the increased entropy of water is responsible for a large amount of the energy generated during this process. The attractive contact in the bilayer is offset by the repulsive contacts with the ionized carboxylic head groups. Electrolytic dissociation, which can lead to membrane rupture, decreases the durability of fatty acid films. By reducing the degree of head group dissociation or creating stable complexes among protonated and ionized carboxyl head groups, screening counter ions lessen charge repulsion. Any of these mechanisms can enhance ufasome membrane stability. Lowering the pH at the particle surface reduces lateral charge repulsions, contributing to membrane stability. In the first place, anions are more soluble in water than protonated molecules. Second, removing the second charge from a tightly packed headgroup reduces lateral headgroup repulsion by halving Coulombic repulsions by increasing the mean distance among charges. Third, anions and molecules of protonated acids create close-knit complexes, usually 1:1 complexes. Hydrophobic contact-induced free energy changes, the entropy of demixing linked to dimer formation, and a free energy decrease from the formation of hydrogen bonds between protonated and ionized carboxyl groups make up the binding energy. According to research on dicarboxylic acids, the existence of a negative charge close to the hydrogen forming the link causes the -COOH and COO-groups to create very strong hydrogen bonds. Ufasome membrane stability is ascribed to the hydration of dissociated carboxyl groups, complex formation between charged and neutral acid molecules, and headgroup hydrogen bonding with water.

MICROSCOPIC STUDIES [9]

Through electron microscopy of sliced vesicular structures, the organization of biological membrane components like phospholipids and fatty acids was revealed. But the strong chemicals used for the required staining and fixing frequently distorted these delicate structures, causing artefacts and a loss of clarity. These problems were also addressed using less forceful techniques. The freeze-fracture method worked well for analysing natural elements. Even more tactful was the finding of birefringence. Negatively stained specimens used to investigate the structure of ufasomes were shown to be incapable of withstanding the preparation procedure by

electron microscopy. Ufasomes were stained with neutralized potassium phosphotungstate for electron microscopy, however the results showed no internal structure.

Freeze fracturing and etching

After 10 minutes of equilibration with 17% glycerol, the ufasome suspension is quickly frozen in a copper helmet filled with Freon and then kept in liquid nitrogen for storage. After fracturing in a Balzers microtome at -110°C and 2 × 10-6 Torr pressure, etching is done for one minute at -100°C. On the fracture face, a three nanometer layer of carbon and platinum is applied at a 45° angle. After removing the metal helmet, the replicas are cleaned by floating them in water and mixing it with methanol until the mixture contains 80% alcohol. Within half an hour, the fatty acid indicators vanished. After then, a Hitachi HS8 electron microscope was used to inspect the replicas. The researchers found that ufasomes made from oleic and linoleic acids had the same look. A significant portion of the uneven, freeze-fractured surface was composed of ice due to the high water content of ufasome preparations. The ice and particle surface were clearly separated by etching the surface, particularly if the ufasomes had been previously equilibrated in glycerol. Additionally, there was roughness between the membranes, indicating that it had been flooded before.

Double Refraction/Birefringence

The various inter-membrane lengths commonly observed in ufasomes may account for the variability in birefringent particle frequency. In multi-lamellar particles, the different forms of birefringence usually have either positive or negative signs. Lipid molecules arranged perpendicular to the membrane surface contribute to a positive sign, whereas adjacent membranes arranged parallel to one another contribute to a negative "form" component. As the distance between neighbouring membranes grows, birefringence diminishes. Preparations of freeze-etched ufasomes revealed that huge water-filled spheres or irregular multi-membrane particles were more prevalent than symmetrical particles.

NEW DEVELOPMENTS IN TRADITIONAL UFASOMES [10]

Owing to worries regarding their stability, ufasomes are still being developed for medication delivery. According to recent studies, medication dispersion may be enhanced by mixing several surfactants or employing various fatty acid types.

Fatty Acid New Type

The fatty acid cis-4,7,10,13,16,19-docosahexaenoic acid (DHA) self-assembles to create vesicles at pH values between 8.5 and 9.

Expansion of the pH Spectrum

As the formation of fatty acid vesicles requires the carboxylic acid to be ionized, this procedure works best within a certain pH range. A greater range of pH levels could be possible with new methods.

a) Chemicals that are amphiphilic, such as linear alcohols or surfactants with a sulphate or sulfonate head group.

The pH range for vesicles made of decanoic acid and decanoate mixes is 6.4 to 7.8. It is possible to lower the pH to as low as 4.3 by adding sodium dodecylbenzene sulfonate (SDBS).

b) Synthetically change the magnitude of the hydrophilic head group of fatty acids.

At lower pH levels, fatty acids that include an oligo (ethylene oxide) unit between the carboxylate head group and the hydrocarbon chain can increase vesicle stability. A big polar group can increase the pH range for vesicle production and decrease the phase transfer temperature.

c) Insensitivity toward Divalent Cation.

Vesicle precipitation can be induced by divalent cations such as calcium and magnesium, even at low concentrations. When fatty acid vesicles include ionic solutes, they can be stabilized by adding fatty acid glycerol esters.

d) Improvement in stability by the use of chemical bonds to cross-link fatty acid molecules.

Vesicles can be made more stable by adding a polymerizable fatty acid, like sodium 11-acrylamidoundecanoate (SAU). Polymeric SAU vesicles were shown to be stable at high temperatures and to form aggregates.

e) Combination of Vesicles Based on Surfactants and Fatty Acids

A model system for mixed vesicles is made up of fatty acids and tetradecyltrimethylammonium hydroxide (TTAOH). Unilamellar and multilamellar vesicles are produced when TTAOH and fatty acid are combined in roughly equal proportions.

APPLICATIONS OF UFASOMES [11]

Numerous medications can be administered transdermally using ufasomes. Ufasomes with anti-inflammatory, anti-fungal, anti-osteoarthritic, anti-cancer, and other medications have been distributed transdermally.

Anti-fungal Drugs

For transdermal drug delivery, new formulations including niosomes, liposomes, ethosomes, microemulsions, and micelles have been developed. administration in order to overcome the drawbacks of conventional formulations, including limited penetration and allergic responses. A more sophisticated kind of carrier made especially for this use is called a ufasome. Drug release from ufasomal dispersion was maintained, according to an in vitro investigation. Comparing ufasomes to other commercially available formulations, in-vivo testing demonstrated a five-day drug release, indicating their potential for long-term therapy.

Anti-cancer Drugs

The topical therapy of basal cell carcinoma with 5-fluorouracil (5-FU) has been approved by the US Food and Drug Administration (BCC). Redness, eczema, itching, and poor skin penetration have all been connected to the commercial formulation. Ufasomes are utilized to lessen side effects since the drug is contained within the vesicles. In addition to delaying the administration of medications, they may increase the penetration of opioids. The refrigeration kept the fatty acid vesicles largely intact. Ex-vivo skin penetration studies showed that the fatty acid vesicles penetrated the stratum corneum and then stored the material in the epidermal layer.

Anti-inflammatory Drugs

Rheumatoid arthritis (RA) is frequently treated with non-steroidal anti-inflammatory medications (NSAIDs). To avoid or lessen joint deterioration, slow-acting disease-modifying antirheumatic medications (DMARDs) are currently advised for early therapy. Compared to simple liquids or gels, studies have demonstrated that the amount of medication that enters the skin may be greatly increased by employing fatty vesicles for drug administration. This enhanced penetration of the skin may lessen RA-related inflammation. Research has demonstrated that fatty acid vesicles (gels based) are more successful than commercial gels at lowering inflammation.

Anti-osteoarthritic drugs

The human body contains collagen and proteoglycans, which are essential for joint healing and the lubricating creation of synovial fluid. Supplementing with glucosamine can increase the body's synthesis of these compounds. Due to this, glucosamine has been used majorly to treat osteoarthritis. Encapsulated glucosamine sulphate fatty vesicles are used topically in Carbopol gel to treat osteoarthritis. Mouse experiments showed that the vesicle-based gel had a much higher drug concentration than the conventional Carbopol gel. Furthermore, the fatty acid vesicle gel consistently released the medication. This implies that the formulation might be used as a depot formulation for the treatment of osteoarthritis.

CONCLUSION

Ufasomes are suspensions of closed lipid bilayers composed of fatty acids that are limited to a certain pH range. Fatty acid molecules in ufasomes have their carboxyl groups towards the aqueous environment and their hydrocarbon tails pointing inward. The stability of ufasome formulations is affected by many of factors, involving buffer, pH change, cholesterol level, and fatty acid selection. Numerous skin problems can be treated using ufasomes, which offer a great deal of therapeutic potential. Ufasomes can help lessen negative skin effects including swelling, itching, and allergic responses by releasing medicine in extended or controlled manner. It has been shown that fatty acid vesicles are really beneficial for skin disorders in illnesses like AIDS because of their regulated release. Because ufasomes are less expensive, penetrate more quickly, and have greater drug trapping properties than liposomes, they are thought to be a better choice for topical medication administration.

CONFLICTS OF INTEREST

There is no stated conflict of interest.

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