THE TRUTH ABOUT UFASOMES: A CRITICAL REVIEW

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ABSTRACT

Several forms of vesicular systems for drug delivery have been created including liposomes, niosomes, ufasomes etc. Unsaturated fat fatty acid vesicles, or ufasomes. A pH level in the range of 7 to 9 is preserved by these solutions of closed lipid bilayers made up of fatty acids and their ionization species. Oleic acid is the most important fatty acid that serves as a vital component in the ufasome synthesis procedure. Recent research may make it possible to make ufasomes with customizable qualities such increased stability, insensitivity to divalent cations, and greater pH range. The aim of this current research is to examine the possibility for employing fatty acid vesicles for topical delivery of medication. In earlier times, ufasomes were believed to be the initial representations of compartments for cells. These days, ufasomes have been found to act as carriers for the vertical transfer of changed genes from plants to the environment or soil microorganisms. The features, production process, application, composition, rapid growth, microscopic investigations of ufasomes, stability considerations, and current advancements in ufasomes are all explored in this piece of literature.

Keywords: fatty acid vesicles, Linoleic acid, Solvents, Birefringence, Amphiphiles

INTRODUCTION

Ufasomes are nanovesicular structures composed of polyunsaturated fatty acids, including linoleic and lanoleic acid, and conjugated fatty acids with surfactants in more recent years. Either unilamellar and multilamellar kinds of ufasomes have been shown to occur, with particle sizes ranging from micro through submicron. In comparison to liposomes, these are less costly and have greater stability and entrapment efficiency. They have less entrapment efficiency for hydrophilic medicines and skin toxicity as a side effect.[1]Fatty acids are amphiphilic compounds made up of a final carboxyl unit functioning as an ionic element with a series comprising atoms of carbon acting as a neutral element.[2] The bioactive's passage through the outermost layer of skin is made possible by free fatty acids.[3] Fatty acid vesicles are composed of single-chain amphiphiles, which gives them a variety of intriguing properties, one of which is their dynamic nature. The fluid properties of fatty acid vesicles place them between micelles formed of single-chain surfactants and regular vesicles composed of double-chain amphiphiles. [4] Even though encapsulation yields can occasionally be a little low, the process of encapsulating substances that dissolve in water into oil-soluble particles provides a means of locating molecules. It is potential to directly contain smaller molecules like tints and macromolecules like RNA but creating fatty acid vesicles.[5] Further to these benefits, oxidation of these supramolecular aggregates is inexpensive.[6]

The medication will accumulate more readily in the dermis. The medicine will be administered gradually to prevent skin side effects. NSAIDs and antifungal medications are injected transdermally via ufasomes.[7] Ufasome is a new method for improving the skin's ability to absorb opioids. When ufasomes are forming, naturally occurring acid lipid such as oleic and linoleic oils are used as organic permeability promoters. Fatty acids or lubricants are frequently utilized to increase skin suppleness and facilitate drug absorption through the epidermal barrier. Ufasome enhanced the skin barrier cells' ability to hold onto medications for a considerable amount of time.[8]

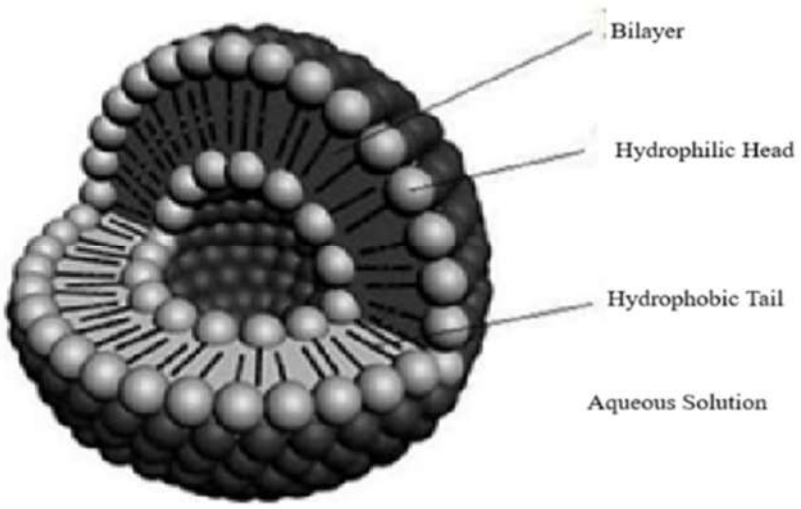

Fig 1: Structure Of Ufasome

Since they originate from the lipid layer and penetrate the outer barrier, they are regarded as promising candidates for local medication release. They are more affordable than liposomes and have stability advantages over liposomes.[10] At pH > 7.0, combines of fully charged and unionized fatty acids are thought to produce ufasomes as an effect of associative contact.[11] Both the horizontal transfer of plant genes and the oral delivery of poorly absorbed medications may be facilitated by ufasomes.[12] Ufasomal topical gel contains a selection of medications, namely roxithromycin, a more recent antibiotic designed to treat acne, and etodolac, a non-steroidal anti-inflammatory medication that has a local pain-relieving effect on the targeted area of the body.[13, 14]

The proportion of ionic form to non-ionized neutral defines the fundamentals of vesicle stability.[15,16] But further studies showed that as an along with undivided lipids, saturated fats which mimic caprylic fatty acid and capric oil can also form lipid compartments. Two important features of ufasomes are the presence of lipids or their composition of single-chain amphiphiles.

.[17, 18]

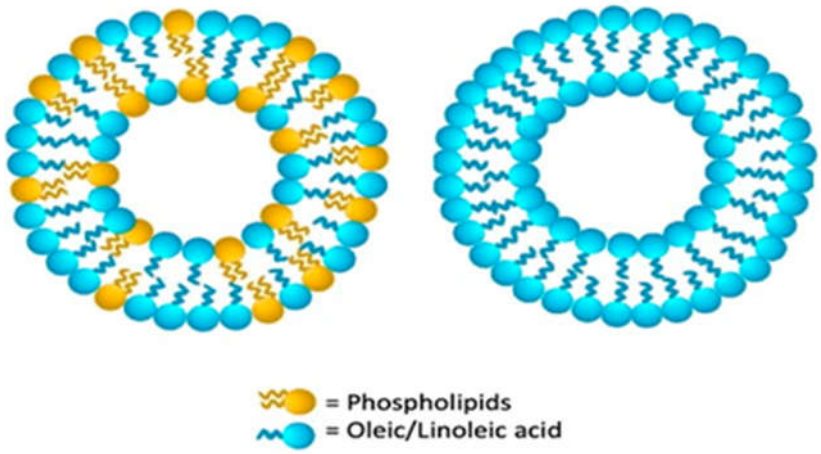

Fig: Schematic Structure Of Ufasomes Lipid Vesicular System

By spreading themselves among different nanotechnologies made up of single-chain surfactant micelles and double-chain amphiphiles, the main constituents of ufasomes, olive or fatty acids (cis, is-9,12-octadecadienoic acid), provide those tiny vessels with a greater versatile character that one of them Large Neutral Amino acid. Because of their manufacturing process, they are genuinely biodegradable and simple to assemble.[19]

ADVANTAGES

•Decreases toxicity and delays the drug's presence in the bloodstream.
•Increases bioavailability, particularly for medications that are poorly soluble.
•Ufasomes can contain both lipophilic and hydrophilic medications.
•Delays the elimination of drugs that are rapidly digested, serving as a prolonged release mechanism.
•When used topically, the medication penetrates the skin readily.
• Ufasomes are also less expensive than liposomes that and nucleic acids due to the easy access to lipids.
•The medication has a notable trapping efficiency. [20]
•More affordable than liposomes.
•Better capture of hydrophilic and hydrophobic medications.
• More stable compared to liposomes.

DISADVANTAGES

The drug level fluctuates.
Low bioavailability and poor penetration depth.[21]

THE PREPARATION METHOD

It is best to use only unoxidized components when making ufasome. Stock solutions containing 10% olive and linseed in CHCL3 are prepared and kept at 20°C. In conventional reservations, a nitrogen spray is used to dry 0.02 ml of the initial solution after it has been vaporized in a test container with a pump that circulates water. After that, the fatty acid layer is thoroughly broken up using a vortex mixer in 0.2 ml of 0.1 M tris-hydroxymethyl aminomethane buffer, pH 8–9. The resulting ufasome suspensions remain stable for a minimum of twenty-four hours. In certain tests, the particles are created using an ultrasonic generator equipped with a titanium

microtip. A stream of nitrogen first extracts air from the buffer, and the by a nitrogen stream, and during irradiation, the gas covers the suspension. An ice water bath keeps the temperature constant.[22]

Table 1: Additives for the Preparation of Ufasome

S. No.	Class	Example	Uses
1.	Solvents	1.Chloroform 2. Nitrogen discharge	1. To maintain the ability to leak of barriers 2. Preparation dehydrating
2.	Fatty Acids	10 % Oleic and linoleic acid	component that forms vesicle

Method of Thin Film Hydration : The procedure produces vesicles within a specific pH range. A cylindrical container with an elongated edge is filled with lipid and a natural solvent. A significant amount of lipids is necessary for this reaction. The natural solvent completely evaporates before the fluid does. Finally, fatty acids are hydrated and a thin layer is produced using a pH-appropriate buffer.

By Mixing Liquor : In this method, a solvent with the identical length of chain as the fatty acid is utilized to generate fatty acid vesicles. The stability of the fatty acid vesicles throughout a wide pH range is the primary advantage of this technique. The existence of previously hypothesized fatty acid vesicles and liposomes may encourage the formation of vesicles. Because this process requires several hours to complete, this saves time.

The Approach of Autopoetic :lipid particles are created when an aqueous fatty acid solution is mixed with a water-buffered solution due to an erratic the pH level shift. When 1⁄2 of the carboxylic acids in a fatty acid ionize, vesicles may form. By establishing a bilayer structure opposite the liquid compartment, the hydrocarbon chain reduces the quantity of liquid it's brought into contact with.[24]

APPLICATION

Gebicki and Hicks provided the first description in 1973. Whether in hydrophobic or hydrophillic pharmaceuticals, ufasomes exhibit excellent entrapment efficiency and produce vesicles with sizes ranging from nano to submicron. Ufasomes play an important part in topical delivery systems as well.[25, 26] It has improved drug entrapment and great stability.[27]

1. Antifungal medications

Regarding the transdermal administration of these drugs, new formulations including nuclei, liposomes, ethosomes, tiny emulsion or tiny particles have been developed to overcome the drawbacks of traditional compositions, such as minimal absorption potential severe adverse effects. For this purpose, higher-tech instruments known as ufasomes were created. The drug that was administered from the ufasomal dispersion was found to be retained in an in-vitro drug

release study. In-vivo tests confirmed the five-day medication release via ufasomes. This indicates that, unlike other commercially available formulations, it is suitable for long-term therapy.

2. Cancer-fighting drugs

The drug 5-FU has been approved by the Food and Drug Administration of the United States to be used externally for the treatment of carcinoma of the basal cells (BCC). The commercialized formulation has been linked to redness, acne, itching, & poor skin permeation. Ufasomes are utilized to lessen negative consequences because the medication is contained within the vesicles. These can boost the ingestion of opioids and postpone the release of medications. In the fridge, the lipid particles fared well. According to ex-vivo skin penetration tests, the lipid vesicles made it to the stratum corneum and deposited the material in the dermal portion of the skin.

3. Drugs that prevent arthritis

Hip regeneration and the production of synovial fluid, a fluid which moisturizes the joints, depend on gelatin and peptide g Glucosamine-containing supplements stimulate the body to make them. Because of that, chondroitin has been used for years as a rheumatism treatment. Thus, chondroitin sulfate lipid particles are packed and distributed in carbopol gel for topical therapy of osteoarthritis. Rats' drug concentrations in the vesicle-based gel were six times higher than those in the conventional the substance gel. Additionally, an acidic vesicle buffer was frequently used for printing the medication. This combination could therefore be used as a storage to treat rheumatism.[28]

Characterization

Size Distribution and Particle Size Water-based solution:A particle size analyzer is used to determine the standard deviation as well as size distribution in ufasome solutions at twenty-five degrees Celsius along with an angle set of ninety degrees using Photon Correlation Spectroscopy. A polypropylene screen with a pH of 7.4 was used to filter the suspensions after they had been diluted with phosphate buffer. This is done in order to reduce the particle's interference till sizing.

Transmission electron microscopy: One drop of the chosen ufasomal dispersion can be evaluated using a grid of brass grid covered in charcoal paper then adversely colored by one percent phosphotungstic acid. The material is allowed to dry at room temperature for ten minutes before being examined using a TEM.

Differentially Examining Calorimetry, as Imaging using Asymmetric Style: Calorimetry is used to examine the material's state of being inside the fatty acid particles. In a standard aluminum pan, vesicles of various sizes were imaged as an average speed of 2°C/min.

The effectiveness of trapping : Ultracentrifugation at 25,000 rpm for three hours at 4°C can be used to assess how well the medication is entrapped. The effectiveness of the supernatant's entrapment can be evaluated using UV spectroscopy.

Drug Release in Vitro Assessing the drug's ufasome release rate and kinetics is the aim of this investigation. Franz diffusion cells may be used for this. A donor compartment and a receptor compartment make up the Franz diffusion cell. A polycarbonate membrane with a 50 nm pore size separates these two sections. The recipient section contained one milliliter of ufasomal

dispersion, and the recipient section contained 37°C PBS (pH 7.4) that was continuously swirled using a magnetic stirrer. Aliquots of samples are taken at regular intervals and swapped out for equal amounts of brand-new PBS (pH 7.4).[29]

COMPOSITION

The fatty acid microspheres known as ufasomes are enclosed phospholipid Dimodel solutions composed of unsaturated lipids to its cationic constituent (soap) that have a pH between 7 and 9. Fatty acid vesicles frequently contain two amphiphile forms: a nonionic neutral form plus an energized version (soapy water that is adversely attracted). Vesicle stability is primarily determined by nonionic neutral ratios and ionic form ratios. Gebicki and Hicks were the first to describe the fatty acid microspheres in 1973; electoral and linoleic acids were added to the list in subsequent years. The vesicles were once referred to as ufasomes. Nevertheless, later research revealed that saturated fatty acids that resemble decanoic and octanoic acids also produce fatty acids in addition to unsaturated fatty acids.[30]

Microscopic Research

Divided vesicles were examined using electron microscopy, which revealed the arrangement of phospholipids and fatty acids, two components of membranes in living things. However, it was widely held that the required staining and fixing required strong chemicals, which may distort these delicate structures and cause objects to be manufactured and lose their definition. Such concerns could be alleviated using less harsh methods. One of the best techniques for working with natural components is Cryopreparation. Finding refraction is a lot nicer approach. Negatively tagged samples utilised to analyze the internal makeup of the ufasome struggled to survive the preparation stages, according to electron microscopy. Neither attempt to use diluted potash phosphotungstate to pigment ufasomes for electron microscopy
produced samples with any internal organization.[31]

Birefringence

The variance in the frequency of birefringent particles can be explained by the wide range on inter-membrane lengths commonly observed in ufasomes. The several types of refraction observed in multilamellar molecules usually have a natural element that is both beneficial and detrimental in sign. The adverse "structure" portion is generated by the alternating layout of adjacent pores, whereas the plus (+) component is produced by the slanting arrangement of lipid molecules with the cell interface. As the distance between adjacent membranes increases, the birefringence's amplitude decreases. Large water-filled spherical with irregular multimembrane aggregates have become considerably more common 5Than symmetrical fragments, which should lead to high birefringence, as was clearly shown by the preparation of freeze-etched ufasomes.[32, 33]

Eaching and freeze fracturing

A ufasome solution is first adjusted using 17% glycerin over 10 minutes before freezing.
The ufasome suspensions are stored in liquid nitrogen after having rapidly froze onto copper helmets with Freon. With the Balzers microscope, fracturing is carried out around 110 degrees Celsius with 2×106 Mmhg stress. To etch, the pH level is increased above 100 degrees Celsius for one minute at a time. After cutting, the damaged surface is covered with a 3 nm thick layer of palladium and graphite over a 45° angle. The best way to clean the copies is to float them from the steel hat onto liquid that has methanol added gradually till 80% of the mixture is methanol. It takes 30 minutes to remove all fatty acid residues. The replicas are then studied with a Hitachi high school8 electron microscope.[34, 35]Hicks and Gebicki found that there

was no difference in the appearance of ufasomes made from oleic and linoleic acids.[36] Due to the high water content in ufasome preparations, a sizable portion of the freeze-fractured face was composed of ice, which often had a very uneven surface.
When the particle surface was etched, there was a discernible difference in appearance between it and the ice, especially when the ufasomes were already previously balanced with glycerin. The visible exterior or interior fatty acids faces are effortless, but the surrounding ice is typically grainy. Furthermore, the roughness of the space between the membranes suggests that water has filled it.[37, 38]

CHANGING NATURE

among the finest characteristics of fatty acid packets is their complicated existence, which is a result of their composition of single-chain amphibians. Fatty acid packets differ from ordinary particles made of double-chain amphibians with tiny particles made of single-chain mediators due to their dynamical properties. Being able to alter the protonation/ionization ratio of the terminal carboxylic acid in order to produce various fatty acid aggregates. The dynamics of ufasome formation are being studied by researchers. Researchers used a cellulose acetate (CAT) barrier to dilute fatty acid/soap monomers in order to examine the process of micelle and vesicle production using a heavy lipid acid/soap monomer solution.

An uneven arrangement of lipid acid/soap particles across two spaces divided through a filtration membrane—one holding agglomeration (tiny particles or spheres) or one holding simply a buffer solution—was used to test the rate at which equilibrium was established. Micelles developed within the diffusate space, and the quantities of fatty acids plus soap were identical in both chambers. However, as the mixture filled up by the monomers, the number of molecules that could diffusate expanded gradually, making it very challenging to achieve equilibrium in the case of vesicles.Compared to micelles, vesicles often contain a significantly greater number of amphiphiles. The results of dialysis study utilizing fatty acid vesicles show that the energy barrier for creating fatty acid vesicles is much higher than that for making fatty acid (soap) micelles. Making fatty acid vesicles is as easy as combining a neutral detergent solution with a neutral acidity solution of buffers. If a concentrated suspension of sodium oleate micelles is introduced to a balanced condition with a pH of 8.5, linoleic acid/sodium oleate particles are created spontaneously. The oleate molecules get largely protonated when the pH falls from about 10.5 to 8.5. The resultant vesicles exhibit lamellarity in addition to diversity. When buffered vesicles are exposed to alkaline micelles, lipid particles spontaneously develop.[39]

IMPORTANT MANUFACTURING ISSUES

Choosing a fatty acid The fatty acid

Research based on surface films and information studies suggests that Twelve - Twenty two carbon lipids will be appropriate for the creation of permanent ufasomes. Few tests were conducted since C's-18 fatty acids demonstrated the highest level of assurance in the initial testing. Only membranes made of linoleic conjugated lipids (cis, cis-9, 12-octadecadienoic acid) and olive conjugated lipid acids (cis-9-octadecenoic acid) are preferred when making ufasomes. Ufasome production is not aided by charging the membrane with trace amounts of olive, the lino, and acidic substances. Oleic acid remains uncontaminated for at least six weeks, however significant peroxides appeared after two to three weeks and were assessed using equilibrium testing.[40]

Adding cholesterol

In lipid-based vesicles, cholesterol plays a unique role by controlling the membrane's permeability, elasticity, and fluidity. Spaces are filled with lipoprotein when other lipid species are not properly packed. However, the vesicle's capacity to hold solute quickly declines as cholesterol levels rise. Furthermore, at all sterol concentrations, barrier impregnability does not improve. Hick et al. used spherical that contained 17% by weight of cholesterol to assess the glucose leakage from oily and linoleic acids ufasomes. The findings suggested that spherical with seventeen per cent cholesterol on bulk leaked more glucose than ufasomes made of olive and acid linoleic. [41]

Range of pH

When the acidity of the lipid membrane is kept within the very narrow range of 7 to 9, fifty percent of its carboxylic acids are typically charged. The acidity range of unsaturated fatty acids is 7. Furthermore, it is highly soluble above this range, but only frames unstructured precipitates below it. Droplets of oil form at lower pH levels, but tiny particles are the main aggregating species at higher pH values. "Critical vesiculation quantities" (CVS) are values for fatty acid vesicle systems that are slightly higher than the levels at which vesicle formation takes place. A colloidal suspension of vesicles is produced at CVS, where monomers and non-vesicular clusters come together to generate a double-layered pattern.[42, 43]

Choosing a buffer

Trishydroxymethyl aminomethane is the most widely utilized buffer when manufacturing ufasomes. Solutions of glycine-hydroxide, borate, and bicarbonate can also form spheres. The solute that needs to be integrated determines which buffers are used. The formation of a sugar-buffer combination prevented cylindrical sucrose entrapment-ufasomes prepared in carbonates from retaining sucrose or bromo setup, making retention testing unfeasible.

The electrolyte

Electrolytes mainly prevent ufasomes from forming. The balls are put through a chloride or phosphate buffer solution once they have solidified completely in the appropriate buffers and still contain the occluded glucose.[44]

Peroxidation

When a large hydrophilic group is added by peroxidation, the hydrophobic membrane's interior is distorted, making it easier for water-soluble molecules to get through. Peroxidation primarily affects the ufasome membrane by breaking the fatty acid molecule's normal multilayer structure. The degree of fatty acid oxidation may vary depending on the processing method. The short times needed for manual swirling did not result in oxidation. After being exposed to 30-W radiation, oleic acid oxidizes at a rate of 0.1% per m in air-saturated buffers under more severe supersonic resuscitation. Because the maximum exposure time of 3 ms was used, even the oxidation-sensitive linoleic acid did not experience substantial oxidation utilizing this method. Hicks and Gebicki, however, found that α-tocopherol, butylated hydroxytoluene, and nitroxide ions can all significantly reduce the oxidation process of the oily walls. Lipoxygenase cannot peroxidize monoenoic fatty acids since the enzyme's activity had no ability to induce leakage from ufasomes formed of oleic acid.[45,46]

There are also enzymatic and non-enzymatic catalytic processes involved in the oxidation of lipids (LPO). Change elements are essential components in Inorganic substances peroxidation of lipids.[47, 48] The fast rate of peroxidation in the unsaturated lipids can only be triggered by a limited number of elements that experience a single electron transfer and valency change. Lipid peroxidation is also impacted by redox-coupled homolysis, which is inaccessible to materials with non-variable valency, which includes zinc, calcium, and magnesium.[49] calcium dioxide has been demonstrated to induce peroxidation of lipids at tiny amounts (~10-6–10-5) due to its ability to interact with negatively charged lipid groups (such as lecithinphosphate and linolenic acid-carboxyl groups). By releasing the bound Fe2+ ions that directly contribute to the catalysis of lipid peroxidation, this raised the amount of unbound Fe2+ particles. The way that calcium interacts with superoxide anion radicals determines its inhibitory effect at significant levels (-10-3). Moreover, it is shown that biphasic action on lipid peroxidation is not exclusive to calcium ions because other cations with greater charges are just as successful in generating Fe2+ ions linked with the negative charged class of lipids while binding to oxidant free radicals as well. Even without Ca2+, it was shown that lipid peroxidation was enhanced when La3+ ions were introduced to linolenic acid ufasomes at a concentration equivalent to that of iron dioxide ions. About the combined impact of Ca2+ and La3+ ions Recent developments in traditional ufasomes have shown that linolenic acid inhibits peroxidation at equimolar doses (where the total amount exceeds Fe3+).[50]

NEW DEVELOPMENTS

There aren't many applications for fatty acid bubbles in the fields of meals enhancers and drug delivery because of concerns over their hydrodynamic equilibrium, which is sensitive to acidity and divalent cations. However, recent studies that employ new fatty acid types or combinations with additional surfactants may alter the situation in the future. [51]

A novel fatty acid family utilized in the production of ufasomes : Around a pH of 8.5 and pH 9, it has been seen that the do acid (DHA) forms cis-4, seven, ten, thirteen, sixteen, and 19-a can self-assemble to osomes. [52]

Growth of the pH scale : The pH range that is typically suitable for the formation of lipid packets is constrained because about fifty percent of the carboxylic acid must be ionization. Nonetheless, the pH range can be expanded using the following creative techniques.

The inclusion of amphiphilic chemicals : Sodium dodecylbenzenesulphonate (SDBS) can be added to lower the pH to about 4.3, where a vesicle can form, however a mixture of the acid decanoic decanoate will create a vesicle between pH 6.4 and 7.8. [53]

Via altering the fatty acids hydrophilic group's size : It has been discovered that a fatty acid with an oligo unit intercalated between the carboxylate head group and the hydrocarbon chain improves the stability of the resultant vesicle at low ph. Bulky polar groups lower the phase transition temperature and pH for vesicle formation.[54]

The intensity of the divalent cation : Divalent cations like Mg2+, Ca2+, etc. induce the vesicles to precipitate even at this low concentration and little amount. The fatty acid vesicles were shown to stabilize when fatty acid glycerol esters were added when ionic solutes were present.[55]

CONCLUSION

A viable platform for improving drug delivery in a variety of applications is provided by ufasomes, a novel vesicular drug delivery system made of unsaturated fatty acids such as oleic and linoleic acids. They are better than conventional vesicular systems like liposomes in various ways due to their distinct dynamic nature, affordability, and stability. In topical, transdermal, and controlled drug administration, ufasomes have shown great promise, especially for antifungal, anticancer, anti-inflammatory, and anti-osteoarthritic medications. Their versatility is demonstrated by their capacity to encapsulate both hydrophilic and lipophilic medications, as well as by their enhanced bioavailability and prolonged release characteristics. To optimize their effectiveness, however, issues like limited bioavailability, inadequate deeper penetration, and oxidation susceptibility must be resolved. Their stability and functionality have been increased by recent developments, such as the use of saturated fatty acids and improvements in preparation techniques. Their importance is further increased by their potential for gene transfer and other biomedical uses. Ufasomes' true potential will probably be unlocked by more research on their kinetics, stability, and applications, opening the door for broad therapeutic use.

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