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REVIEW ARTICLE

Ufasomes: Potential Vesicular Systems for Transdermal Delivery of Drug Molecules

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ABSTACT
Unsaturated fatty acid vesicles called ufasomes are mostly made up of a long chain of fatty acids (oleic acid, linoleic acid) and their ionised soap (surfactant). The hydrocarbon tails of fatty acid molecules are pointed towards the inside of the membrane, while the carboxyl groups are in contact with water. These are colloidal suspensions of closed lipid bilayers that are confined to a small pH range of 7-9 because fatty acids become excessively soluble at pH levels above and below this range, respectively, and precipitate out in an unstructured manner at pH levels in between. Oleic acid is employed as a key ingredient since it is typically found in raw materials like sunflower seeds, olive oil, almond oil, and coconut oil, all of which are also quite cheap. The lipid film hydration method is frequently used to create fatty acid vesicles. The most important fatty acid used as a key ingredient in the formation of ufasomes is oleic acid and various surfactant cholesterol concentrations as well as unsaturated fatty acids in high quantities. Significant developments in ufasomes, as well as their dynamicity, stability, and microscopic characterisation. A vesicular drug delivery device encloses an aqueous compartment in one or more concentric bilayers comprised of amphiphilic molecules. They are a crucial delivery mechanism for the targeted distribution of medications due to their capacity to localise the activity of drugs at the location or organ of action.
Keywords: *Ufasomes, Oleic acid, Vesicular drug delivery system, Unsaturated fatty acid*

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INTRODUCTION

Innovative and effective treatments such as nanotechnology have created a new way to transport drug molecules to the desired site. Formulations based on nanotechnology, or "nano formulations," are customizable systems with a wide range of uses and improved therapeutic results.[1] Transdermal preparations are designed to decrease a drug's retention and absorption in the skin while increasing the drug's instability once it crosses the skin and enters the bloodstream. The main goal of the transdermal drug delivery method is to get around the challenges presented by the oral route. Improved bioavailability with controlled drug release, fewer adverse effects, and prevention of first-pass metabolism are the main benefits of TDDS.[2] The main challenge in creating TDDS is to overcome the skin's inbuilt transport barrier. The liposomes' potential utility for topical treatment was initially mentioned by Mezei and Gulasekharam in 1980. Since then, scientists have worked to create lipid vesicles that can carry drugs into the skin. The use of vesicular drug delivery systems has a number of benefits over traditional dose formulations and extended release formulatios.[3] To improve the penetration of medications via the skin, vesicular systems like liposomes can be used. Recently, liposomes have been investigated as transdermal drug delivery systems because of their biocompatibility and ability to contain both hydrophilic and lipophilic medicines.[4] Due to their large minimum size, the utilisation of liposomes, albeit intriguing, is currently unknown. Although there is still discussion over whether delivering liposomes can pass through or into intact skin, the majority of specialists agree that most liposomes do not penetrate far into intact skin.[5] The phospholipid bilayer that forms when the phospholipids are dispersed in water forms the boundary of the aqueous internal environment of liposomes, which are vesicular systems.[6] A drawback of liposomes is that drugs do not effectively

penetrate into the deeper layers of epidermal tissue. In order to bypass the stratum corneum barrier and enable medication administration, a novel drug delivery mechanism must be developed.[7] These lipid vesicles have the capacity to get over the stratum corneum's threshold and remain in the stratum corneum's deepest layers, where they release their drugs.[8] Vesicular systems, which are highly ordered assemblies of one or more contiguous lipid bilayers, are produced when amphiphillic building blocks and water are combined. Both hydrophilic and lipophilic drugs can be transported by vesicular drug delivery systems. They extend the time of drug residence in the systemic circulation, delay the clearance of quickly metabolizable drugs, and increase the bioavailability of poorly soluble drugs. There are several different vesicular drug delivery systems that have been created, including liposomes, sphingosomes, pharmacosomes, niosomes, ethosomes, ufasomes, virosomes, and transferosomes.[6] Different traditional enhancement techniques have been created employing chemical enhancers (such organic solvents and surfactants), physical enhancers (like iontophoresis, sonophoresis, micro needles, and electroporation), and altering drug-vehicle interactions.[7]

Vesicular drug delivery:

The three structurally independent skin layers are stratum corneum (SC), viable epidermis (consisting of the granulosum, spinosum, and basale layers), and dermis. Although the skin is a primary area for the non-invasive delivery of therapeutic agents, due to its impermeability, most drugs cannot enter or pass through this organ.[9] There are two paths across the epidermis: intercellular and transcellular (between corneocytes and the lipid matrix) (across the lipid domains between the corneocytes). It is widely understood that the intercellular pathway serves as the main pathway for a significant proportion of medications to enter cells.[10] Vesicles are potential drug delivery routes for topical use. Vesicles can have certain benefits over conventional topical dose forms when it comes to delivering drugs to the skin. Vesicles' ability to serve as transdermal or dermal delivery mechanisms is unclear. Dermal delivery should only be used to specify targeting to skin locations with limited systemic absorption, whereas transdermal delivery happens when a molecule diffuses through the skin layers and into the bloodstream.[11]

NOVEL VESICULAR SYSTEM - MODIFICATIONS TO LIPOSOMES

Gebicki and Hicks' innovative research, unsaturated fatty acid vesicles, or ufasomes, are another name for vesicles. Dispersed closed lipid bilayers compose their structure. (fatty acids) that are only capable of forming soap in the pH range of 7-9, and their ionised species (the membrane's inside containing hydrocarbon tails and water-contacting carboxyl groups).Fatty acid vesicles are capable of independently forming in alkaline micelles that are linked to buffer vesicles.[12] In order to increase drug molecule penetration into the stratum corneum while reducing toxicity, fatty acids are regarded to be particularly useful transporters. The cost of fatty acid vesicles is lower, and making them is very simple.[13] Unsaturated fatty acids like oleic acid and linoleic acid are the building blocks of ufasomes, which are fatty acid vesicles. Ufasomal suspension has a pH range of 7 to 9.3 those have several benefits when used and are unsaturated fatty acids. The ufasomes' dynamic character makes them unique from traditional nano systems built of double-chain amphiphiles and micelles made of single-chain surfactants due to the inclusion of single-chain amphiphiles in their structure, making them more versatile than their better-known precursor liposomes.[14] They exhibit enhanced versatility when sandwiched between classic double-chain amphiphiles.[15] Ufasomes include fatty acid molecules that have hydrocarbon chains that are orientated towards the interior of the vesicle while carboxyl groups are oriented towards the outside watery core.[16] Oleic acid and other unsaturated fatty acids enhanced the transdermal transport of bioactive through the SC. As a result of lowering the lipids' viscosity in the SC's outermost layers and causing phase separation, oleic acid led to lipid disturbance. Oleic acid produces a distinct liquid domain to solubilize the SC lipids, which causes phase separation.[17] Oleic and linoleic acid (cis, is-9,12-octadecadienoic acid), the principal components of ufasomes, provide these nanovesicles a more versatile character than that of the other LNV by putting them amid other nanosystems created from double-chain amphiphiles and from single-chain surfactant micelles. They are simple to build and really biocompatible due to their biological nature.[18] Fatty acids are thought to be particularly effective carriers that reduce toxicity while enhancing drugs component diffusion into the stratum corneum. The cost of fatty acid vesicles is lower, and making them is very simple.[13] Numerous investigations supported oleic acid's capacity to create ufasomes, which can encapsulate drug molecules and improve their skin absorption.[19] Topical medication appears to be the most advantageous mode of administration because it carries a decreased risk of systemic side effects, even if the stratum corneum prevents medication penetration into healthy skin.[20] These vesicles have several benefits over liposomes, such as being less expensive, more effective at loading and entrapping molecules, and having superior stability.[21]

ADVANTAGES

- They can function as a reservoir for formulation to slowly release the medicine they contain.
- Decreases the toxicity and prolongs the drug's time in the bloodstream.
- The drug is delivered directly to the site, selective drug absorption can be achieved.
- Enhances bioavailability, particularly for drugs that are poorly soluble.
- Hydrophilic, hydrophobic, and amphiphilic drugs can easily be encapsulated into ufasomes.
- Act as sustained release mechanisms by postponing the elimination of medicines with rapid metabolization.
- When used topically, the drug can easily permeate.
- Why because fatty acids are so widely available, ufasomes are cheaper than liposomes and niosomes.
- The drug's trapping effectiveness is astounding.
- Since the lipids used in the formulation of ufasomes are biodegradable in nature, ufasomes are biodegradable.
- Additionally, they have fewer double bonds than lecithin, making them less susceptible to rancidity.
- Ufasomes are cheaper than liposomes.
- They do not require any particular handling or storage specifications.[22]

METHOD OF PREPARATIONS

Generalized Method Of Formation

To formulate ufasomes, only non-oxidized components are used. The 10% oleic and linoleic acid stock solutions in chloroform are made and processed there at a temperature of 20 °C. Utilizing a water pump and 0.02 ml, the stock solvent is normally evaporated in a test tube, which is then dried with a nitrogen spray. The fatty acid layer is thoroughly disseminated in 0.2 ml of 0.1 M tris-hydroxymethyl amino methane buffer, pH 8–9, after rapid rotating on a vortex blender. Ufasome suspensions made with this method last for at least 24 hours. In a number of studies, particles are produced utilising an ultrasonic generator with a titanium micro tip. Air is removed from the buffer during irradiation using a stream of nitrogen, an ice bath aids in maintaining a steady temperature.[23]

Rotary film evaporation method is employed for the preparation of ufasomes which comprised three steps:

- A thin film is prepared from the mixture of vesicles forming ingredients that is unsaturated fatty acid and surfactant by dissolving in a volatile organic solvent (ethanol-methanol). Organic solvent is then evaporated above the lipid transition temperature using rotary evaporator. Final traces of solvent were removed under vacuum for overnight.
- A prepared thin film is hydrated with buffer (pH 7.4) by rotation at 60 rpm for 1 h at the corresponding temperature. The resulting vesicles were swollen for 2 h at room temperature.
- To prepare small vesicles, resulting vesicles were sonicated at room temperature or 50°C for 30 min using a bath sonicator or probe sonicated at 4°C for 30 min. The sonicated vesicles were homogenized by manual extrusion 10 times through a sandwich of 200 and 100 nm polycarbonate membranes.

Modified handshaking method, lipid film hydration technique is also founded forthe preparation of transfersomes which comprised following steps:

- Drug, Lipid, and edge activator were dissolved in ethanol: methanol (1:1) mixture Organic solvent was removed by evaporation while handshaking above lipid transition temperature (43°C). A thin lipid film was formed inside the flask wall with rotation. The thin film was kept overnight for complete evaporation of solvent.The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 min at corresponding temperature. The ufasome suspension further hydrated up to1 h at 2-8°C.

Vertexing sonication method:

- In the vortexing sonication method, mixed lipids (i.e. oleic acid, surfactant and the therapeutic agent) are blended in a phosphate buffer and vortexed to attaina milky suspension.
- The suspension is sonicated, followed by extrusion through polycarbonate membranes.
- Cationic ufasomes have also been set by this method, which involves mixing cationic lipids, with PBS to attain a concentration of 10 mg/ml followed by a count of sodium deoxycholate (SDC).
- The blend is vortexed and sonicated, followed by extrusion through a polycarbonate(100 nm) filter

Co-acervation phase separation method:

This is the generally used method to prepare ufasomal gel. Drug, lipid, and surfactant dosages are measured. In a dry, wide-mouthed glass beaker, add the following: is a solvent. The ingredients are

thoroughly combined and heated. Until the surfactant mixture dissolves, 60–70 C water bath completely. Care must be taken during the process to prevent any solvent loss as a result of evaporation. In the end, the aqueous phase is included and heated in a water bath. The resulting solution is cooled overnight to obtain ufasomal gel.

By Addition of Alcohol:

When an alcohol with the same chain length as the fatty acid is introduced, this reaction leads to the creation of fatty acid vesicles. The main benefit of this technique is that it over a wide pH range, fatty acid vesicles remain stable. Vesicle development could be accelerated by the presence of liposomes and vesicles with additional fatty acids. Because of this saves time because the method is time-consuming.

A fresh approach to preparing was developed at the University "Magna Graecia" of Catanzaro's Advanced Drug Delivery Lab:

Using an Ultra-Turrax T25 equipped with an S25 N-8G homogenising probe, the lipid mixture was suspended in distilled water and homogenised for 20 minutes at 15,000 rpm. (IKA-WERKE). Three cycles of homogenization were performed, followed by five minute breaks. While carrying out the preparation stage, the sample was kept in an ice bath. Add the appropriate amount of drug in the lipid mixture to the above-mentioned mixture. The formulations were then stabilised for 20 minutes while being continuously agitated.[25]

The Conjugated Linoleic Acid Ufasome with Self-crosslinking:

Safflower oil was saponified to produce linoleic acid, which was then enhanced with the addition of urea. Typically, 400 mL of sodium hydroxide solution (4 weight percent in ethanol) was applied dropwise over the course of four hours to a flask holding 100 g of safflower oil. The reaction mixture was stirred at 60C for another 2 h, and then cooled to room temperature. Filter was used to retrieve the sodium soap made from the fatty acid combination, and the filter solution's unreacted components were eliminated. The filtrate was repeatedly rinsed with distilled water and saturated saline before being acidified with 10 weight percent HCl to pH 2. The resulting combination of fatty acids was then dried over Na2SO4. Then, 75 g of urea and 240 mL of 95% v/v ethanol were combined, and this combination was refluxed for an additional 30 minutes after being added dropwise over the course of two hours. The reaction mixture was kept at -18C for 12 hours, and after filtering, the crystal that resulted was recovered. It was then acidified one more to pH 2 using 10 10 wt % hydrochloric acid. With anhydrous diethyl ether, the mixture that had been acidified was extracted. After the ether was removed, the ether phase was repeatedly alternately washed with distilled water and saturated salt water, and ultimately dried over Na2SO4 to produce pure LA.[26]

Crucial aspects in the production of UFASOMES

Choosing of fatty acid

The creation of stable ufasomes seems to require 12 to 22 carbon fatty acids, according to research on natural membrane phospholipids and data from the pressure region. Fatty acid measurements on surface coatings. Actually, the majority of the research was focused on C-18 acids since they were the ones that originally showed the greatest promise. Only the presence of membrane-forming oleic (cis-9-octadecenoic acid) and linoleic (cis-9, 12-octadecenoic acid) acids allowed ufasomes to satisfy these conditions. Palmitic acid can be tolerated in an oleic acid membrane up to 33% by weight, however stearic acid can only be tolerated up to 5% by weight. Small doses of oleic, linoleic, or stearic acid amides showed no impact on the preparations when applied to the membrane. Oleic acid had not been contaminated by peroxide.[27]

Incorporation of cholesterol

Cholesterol has the unique ability to modify the membrane's fluidity, flexibility, and permeability in vesicles comprised of lipid. It symbolically fills in the gaps created by other lipid molecules that were not correctly packed. The ability of the vesicle to hold solute quickly decreases in the presence of elevated cholesterol concentrations. Additionally, a lack of cholesterol makes membranes more impermeable. Given the chemical composition of these phytosterols, all of the analogues have at least one more carbon atom in the C24 aliphatic chain compared to cholesterol, which likely disrupts lipid packing. According to the proposed cryo-EM classification, Sito, Camp, and Stig have saturated aliphatic tails with half as many carbon atoms as cholesterol. Fuco, in contrast, has a double bond and two extra carbon atoms.The fact that Stig has a completely saturated stanol core in addition to significant differences from other analogues must be recognised. According to a prior study by Iwahashi et al., cholestanol has a lower enthalpy of fusion than cholesterol, demonstrating that the double bond in the sterol core lowers bond strain in comparison to the stanol core and enhances lipid packing. Compared the glucose leakage from spheres with 17% integrated cholesterol by weight to that from ufasomes composed of oleic and linoleic acid.

Vesicles with 17% integrated cholesterol leaked more glucose than oleic and linoleic acid ufasomes that did not include cholesterol.[28]

CHARACTERIZATION OF UFASOME

Entrapment efficacy

The effectiveness of the drug's entrapment was assessed using centrifugation at 4500 rpm for three hours at room temperature. The drug quantity was determined using the supernatant after the supernatant had been separated and by measuring the entrapment efficiency using UV spectroscopy. The following equation was used to estimate how much entrapment drug there is as a percentage:

Entrapment efficiency (%) = (Amount of drug added initially - Amount of drug determined in the filtrate spectrophotometrically) / Amount of drug added initially × 100

Shape and Surface Morphology

SEM was used to examine the morphological properties of a selected ufasomal dispersion, such as sphericity and aggregation (SEM). In order to image the samples, they were first dissolved in methanol. The resultant slurry was then drop cast onto a silicon wafer and taped with double-sided conductive tape. Furthermore, samples were dried by air before being covered with gold plating. High quality images of the ufosomes were captured using a strong vacuum and an accelerated voltage of 20 keV.

Particle Size (PS), Zeta Potential (ZP), and Polydispersity Index (PDI)

The average PS, ZP, and PDI were evaluated using Zetasizer Nano 7.11 (Malvern Instruments, Malvern, UK) using the dynamic light-scattering technique at 25 °C and a 90 ° incident beam angle To ensure the intensity of light scattering was within the sensitivity range of the instrument, 0.1 mL of each dispersion were diluted in 10 mL of deionized water before the experiments. The average results obtained after performing each measurement three times were recorded.

The creation of PRO-UFAs

Techniques for thin-film hydration were used to produce PRO-UFAs. In brief, a combination of 10 mL chloroform: methanol (2:1 v/v) and 10 mg of PRO were measured, and precise concentrations of oleic acid, span, and cholesterol were dissolved rotary evaporator (Heidolph Laborota 4000 Series, Heizbad, Germany), operating at 60 rpm and 60 C in vacuum, was used to produce a thin, dry layer on the flask wall After that, a phosphate buffer saline solution (10 mL, pH 7.4) was used to hydrate the lipid film by rotating the flask in a water bath for 30 minutes at 60 degrees Celsius. By sonicating the resulting vesicles in a bath sonicator for 10 minutes, the size of the vesicles was changed.

Transmission electron microscopy

Formulations were examined using transmission electron microscopy to determine their morphological traits (JEM-1400, Jeol, and Tokyo, Japan). A copper grid was coated with a drop of each dispersion, and any extra was removed with filter paper. Similarly, the excess of the negative-staining aqueous phosphotungstic acid solution (2 percent w/v) was removed. In the end, samples that had been air-dried were looked at using TEM at 80 kV.

In-vitro drug release

In-vitro dialysation of ufasomes was performed using 10 mm flat-diameter cellulose membrane dialysis tubing. (0.4 in). In a conical flask, 5 mL of ufasomes were added to 50 mL of a pH 7.4 phosphate buffer solution that included 0.01% sodium lauryl sulphate. The dialysis tube was then stitched together using nylon thread at both ends. The conical flask was then incubated for a further 15 minutes in an incubator shaker at 37 °C and 60 rpm. A 5 mL sample was withdrawn from the bottle and added to the conical flask along with 5 mL of fresh buffer. The withheld sample was filtered before being analysed spectrophotometrically.

In vitro skin permeation study for ufasomes

Skin permeation investigation for ufasomes using Sing Franz diffusion cells in vitro (Dolphin Pharmacy Instruments Private Limited, India). The 4.5 cm2 Franz diffusion cell, which had a 60mL volume retention, was used. The 47 mm 60/pk Strat-M® membrane [27] (Millipore, Canada), a synthetic non-animal model that is particularly made to resemble human skin, was used for the penetration research. The most notable benefits of this synthetic skin are its extended self-life and lack of storage requirements, its lack of an animal model, its low human to animal skin variability alternative (CV = 8%), and its almost 1.38 correlation to human skin. The disc-shaped Strat-M® membrane was taken out with forceps and put in a Petri dish with 10 mL of saline water. Using forceps, the Strat-M® membrane was also inserted into the Donner compartment of the Franz diffusion cell, maintaining a temperature of 35–37 °C. Using digital micropipettes, samples were removed from the acceptor compartments for various time options containing 30% w/w optimised ufasomes in less than 0.5 mL. (Thermo Fisher Scientific India Private Limited, Mumbai, India). The same quantity of buffer solutions was introduced to the acceptor

compartment's sustained sink state. The samples that have been filtered were examined using a UV-1280-UV-VIS Spectrophotometer. (Shimadzu Life Science, Japan).

Differential Scanning Calorimetry (DSC)

Before entering the samples for analysis, the heat flow scale for evaluating the thermal behaviour of ufasomes was calibrated using TA Q100 DSC Instruments. All substances were weighed. (Pure drug, PL90G, and lyophilized MXD-OAVs. In pans made of aluminum, which was then crimped after being reduced in size. (5 mg). With nitrogen gas flowing at a rate of 20 millilitres per minute and the temperature being heated up at a rate of 10 degrees per minute, the thermogram was taken between 20 and 240 degrees Celsius.

Storage Stability Studies

The formulation's stability was tested for 30 days at three different temperatures 40°, 30°, and 5°C in a glass container. A spectrophotometric approach was used to determine the drug concentration of the formulations, with phosphate buffer acting as a reference. The formulations were also tested for physical changes in appearance.

Determination of Particle Size and Polydispersity Index

Using a zetasizer (Nano ZS-90 apparatus, Malvern Panalytical Ltd., London, UK), particle size (PS) and polydispersity index were determined for ufasome formulations. (PDI). The zetasizer measures size using the light scattering techniqueWith 0.1 mL of each product diluted to 10 mL with distilled water using the zetasizer, each measurement was carried out three times at 25 °C.

Zeta Potential

The zeta potential of the ufasomes was utilised to compute the total charges in the vesicles, and the stability of colloidal dispersions may be evaluated using this knowledge. Zetasizer measurements were made following dilutions of the formulation samples in distilled water ranging from 0.1 mL to 10 ml. At 25 °C, a 90° scattering angle, a 0.89 cp dispersant viscosity, and a 78.5 cp dielectric constant were used for each test, which was carried out in triplicate. The samples were presumptively the same viscosity as water.

X-ray Diffraction Study

In order to investigate the drug's crystalline state in both its pure form and its lyophilized, optimised formulation, X-ray diffraction analysis (XRD) was performed using an X-ray diffractometer (Bruker D8 advance diffractometer, Bruker Corporation, Billerica, MA, USA, Berlin, Germany). Selected drug-loaded ufasomes that had been lyophilized were subjected to an XRD examination against the pure drug. Using a thin spatula, the tested sample was placed on top of the sample holder. The sample holder was then covered with double-sided adhesive tape. In the 2 range between 10° and 70°, the intensity of the diffracted beam was next examined.

Vesicular drug delivery system classification (VDDS)

According to their composition, the vesicles are categorised.

1. Lipoidal Biocarriers
2. Nonlipoidal Biocarriers.

Lipoidal biocarriers as VDDS

Liposomes

Self-assembled closed vesicles known as liposomes have a phospholipid bilayer structure that keeps them isolated from the surrounding aqueous environment. Their bilayers are made up of amphiphilic lipids, which contain two hydrophobic tails and a hydrophilic head. Phospholipids are composed of two fatty acid chains with a total of 10–24 carbon atoms and 0–6 double bonds in each chain, with phosphoric acid attached to a water-soluble molecule at the head. Possesses a special ability to transport hydrophobic and hydrophilic compounds.[28]

Emulsomes

Emulsomes are a new type of colloidal carrier system made up of a triglyceride-based solid lipid core that is supported by a phospholipid bilayer envelop made up of one or more layers. Emulsomes provide increased lipophilic drug loading by combining the properties of emulsomes and emulsion. [29]

Ethosomes

Drug distribution is made possible through vesicular structures called phasomes, which are made of phospholipids like PC, ethanol (20–45%), and water (20–45%). Ethanol's presence enhances the loading of poorly soluble compounds into the well-known liposomes. Indeed, on the one side, ethanol renders vesicle softer withrespect to liposome, and on the opposite side ethanol and phosphoripids enhance permiation. Indeed, Ethosomes are phospholipid-based vesicle systems such as Phospholipids like phosphatidylcholine, phosphatidic acid, alcohol like isopropyl alcohol, and water make up ethosomes. Ethosomes can penetrate the skin more easily when the ethanol is strong. Ethosomes are utilised to

administer a broader class of medications, such as NSAIDs and antifungal medicines. The systemically administered of medications through the skin for topically applied and dermal transfer is an obvious advantage of ethosomes. [30]

Transferosomes

Owing to the incredible permeability and deformation qualities that transferosomes, which are ultra-elastic phospo vesicles, provide to the bilayer of normal bubbles owing to the presence of edge activators like Tween® 80, Span® 80, and sodium cholate, have been employed for transdermal administration. Currently, transferosomes are being employed to enhance the stratum corneum's permeability to various substances. Transferosomes' capacity to deform after passing through holes that are substantially smaller than them and the osmotic gradient between the exterior and interior skin layers have both been suggested as reasons for their success as a transdermal delivery system.[31]

Sphingosomes

Sphingosomes are colloidal, phospholipid bilayer vesicles that mostly consist of sphingolipids, whether they are produced naturally or artificially. There are several ways to administer them, including pills, intravenous fluids, intra-arterial, intradermal, and intramuscular injections.

Pharmacosomes

Pharmacosomes, which are colloidal dispersions, are pharmaceuticals that are covalently attached to lipids. They occur as micelles, hexagonal, and ultrafine vesicular aggregates in accordance with the chemical composition of the drug lipid complex. These prodrugs behave amphiphilically and self-assemble into a single layer or many layers.[32]

Enzymosomes

If an enzyme is covalently attached to the wall of a liposome or lipid vesicle, enzymemosomes are being created. The methods utilised to connect enzymes include arylation, direct conjugation, physical adsorption, and entrapment.

Non-lipoidal biocarriers as VDDS

Aquasome

An aquasome is a self-assembling nanosized carrier system. It is constituted of a ceramic core encapsulated in polyhydroxyl oligomer, to which surface-active molecules are added by co-polymerization, diffusion, or adsorption techniques. Because of their ideal biocompatibility, biodegradability, lack of toxicity, and stability due to the presence of calcium phosphate, bones are a good material for use as a drug carrier. Hydroxyapatite and calcium phosphate are the ceramic building blocks of aquasomes. Aquasomes are typically constructed using non-covalent bonds, ionic bonds, and Van der Waals forces. Carbohydrate coating forms a glassy molecular layer that adsorbs curative proteins or tiny molecules in three-dimensional conformations without modification. Cancer cells absorbed more sugars when they were added on top of a ceramic core.[33]

Niosomes

Niosomes, a type of nonionic surfactant vesicle capable of encasing a range of drugs, have been investigated as an alternative to liposomes. They are produced by the self-assembly of hydrated synthetic nonionic surfactant monomers.

Nonionic surfactants can be used to create unilamellar and multilamellar vesicles, which are considerably less costly drug delivery systems that share physical characteristics with liposomes. Drug molecules that are soluble in water are found in the aqueous compartments between the bilayers of niosomes, whereas those that are insoluble are confined inside the bilayer matrix. When niosomes are used for drug delivery, the biodistribution may be changed, allowing for more precise targeting of the medication to specific tissues, prolonged release, and modified pharmacokinetics.[34]

Bilosomes

Bile salts are integrated into the membrane of niosomes by use of bilosomes, one of the most cutting-edge vesicular nanocarriers. Compared to previous nano-vesicular carrier systems, They are more stretchy, flexible, and ultra-deformable. Traditional nano-vesicular carriers, such as lipid nanoparticles and nanoparticles, can protect drugs from enzymatic degradation in the intestinal system (GIT), but intestinal bile salt, which is available in the GIT, limits these carriers' abilities by provoking membrane deformation and lysis, which results in imminent release target. the entrapped molecule before it reaches the target Bile salt stabilised nanovesicular systems, or bilosomes, are created by incorporating bile salts into the lipid bilayers of the nanovesicles in order to overcome problems with traditional nano-vesicular carrier systems.[35]

UFASOMES

Ufasomes (UFM) are formed by physically agitating evaporated film in the presence of a buffer solution. They are fatty acid-enclosed vesicles. As everyone is aware, fatty acid vesicles are closed lipid bilayer

colloidal suspensions that were restricted to a certain pH range from 7 to 9 together with their ionised species (soap). The non-ionic neutral and ionised versions of the fatty acids (the negatively charged soap) are both kinds of amphiphiles, and the hydrocarbon tails of the fatty acids that contain carboxyl groups are orientated towards the lower membrane. Unsaturated fatty acids like linoleic acid and oleic acid, among others, are the building blocks of ufasomes. Further investigation, however, has shown that it might also be made from saturated fatty acids like octanoic and decanoic acid. [36]

The initial assertion on the origin of ufasomes was given in 1973 by Gibicki and Hicks. Additional factors affecting the stability of ufasome formulation include the ratio of non-ionized form, proper fatty acid selection, amount of cholesterol, buffer pH range, amount of lipoxygenase, and the presence of divalent cations. There aren't enough pure synthesised phospholipids, nor are there enough of the other essential components needed to create liposomes, which are chemically heterogeneous even in their natural condition. The fast availability of fatty acids in ufasomes over liposomes is one of their key benefits.[37]

Types and unique features of nonlipoidal bio carriers are shown in table no.1

Table no 1: List of non lipoidal bio carriers and their features

S.N	Carrier	Constituents	Entrapped drugs	Unique features	References
1	Aquasome	bovine serum albumin, Cellobiose, Calcium nitrate, sodium chloride, potassium dihydrogen phosphate, ammonia solution	Antibiotics, antineoplastic agents, antitubercular drugs	Ceramic nanoparticles are a cutting-edge drug delivery method that may improve oral medication absorption and lessen systemic adverse effects related to traditional treatment.	38-39
2	Niosomes	sorbitan monopalmitate, sorbitan stearate, sorbitol, palmitic acid Nhydroxysuccinimide, cholesterol and glucosamine	NSAIDs, anesthetics, steroidal hormones, anti-cancer, antibacterial	Increases in HLB of the surfactant were observed to increase drug entrapment. This sample shown both a high level of biocompatibility and regulated drug release.	40-41
3	Bilosomes	span 60, Formic acid, Cholesterol, Sodium deoxycholate	Antifungal agent, antiviral agent, antikeratinizing agent, NSAIDs	Enhanced ability and solubilizing and permeation-enhancing properties are provided by elastic Nano-scale vesicles. Poorly soluble medicines' bioavailability and drug permeability without irritation may be improved.	42-43
4	Ufasomes	Oleic acid, Tween 80,Span 80, Cholesterol, linoleic acid	Antihistaminic activity, Hypertension Antioxidant, Antifungal.	It offers a practical method of delivering medication to the infection site, which lessens drug toxicity and side effects, improves drug penetration, disrupts tight junctions, reduces mucous layer viscosity, improves membrane fluidity, and increases the ability of medications to be retained by skin membrane cells for a long time.	44,11,2

Table no 2: list of work on ufasomes

Drug	Experiment	Reference
Terbinafine hydrochloride	Topical fungal infections may respond quite well to treatment with ufasomes of glyceryl oleate. Higher drug entrapment effectiveness (52.45 0.56%), steady anionic zeta potential (33.37 0.231 mV), and desirable globular size were found to be produced by the UF3 formulation. (376.5 0.42 nm), Following effective formulation optimisation employing thin-film hydration and a 3:7 drug-to-glyceryl oleate ratio, and decent polydispersity index (0.348 0.0345). Terbinafine hydrochloride glyceryl oleate ufasomes may be an effective way to treat superficial fungal infections since the enhanced batch had a diffusion-controlled and zero-order sustained	[12]

	release profile.	
Etodolac	Topical ufasomal gel was made by hydrating lipid films with oleic acid as the primary component. Fatty acids in the gel act as a permeation enhancer to improve the drug's penetration. Topical ufasomal gel formulations from all batches were evaluated quantitatively for their physical characteristics, yield rate, drug content, and entrapment. The study found that the presence of fatty acids, which act as a permeation enhancer, in the topical ufasomal gel of etodolac effectively increases the drug's penetration through skin while reducing its toxicity.	[2]
Minoxidil	For improved physical stability and a longer period of contact with the scalp, the nanovesicles were added to the emugel Sepineo® P 600 (2% w/v). Using vesicular gel and PDI analyses, MXD was assessed for in vitro drug release, ex vivo drug permeation, and drug deposition investigations. Overall, the results show that oleic acid vesicles have potential. The goal of this work was to create an MXD formulation with improved follicular delivery and fewer adverse effects.	[11]
oleuropein	Oleic and linoleic acids are the main components of ufasomes, which are unsaturated fatty acid liposomes. Olives and olive oil include a phenolic molecule called oleuropein, which has a number of biological features, including antioxidant action. Antioxidant substances should be able to consistently and successfully cross cell membranes to increase their biological activity.	[45]
Propranolol hydrochloride	Chitosan-ufasomes (CTS-UFAs) are a good option for creating innovative transdermal delivery systems for neurological regeneration since they have biomimetic properties. When NCIS platin-induced sciatic nerve injury in rats was being studied, propranolol HCl was being employed as a model medication to enhance sciatica. The effectiveness of PRO-CTS - UFA and PRO-UFA transdermal hydrogels was examined in-vitro and ex-vivo studies on rats with asciatic nerve damage. Investigations were done to determine the best formulation choice and how formulation parameters affected the physicochemical properties of UFAs.	[15]
cinnarizine	Intranasal gels containing cinnarizine (CN) and encapsulated in unsaturated fatty acid liposomes (ufasomes) were created from oleic acid to overcome the poor and unpredictable absorption of cinnarizine when administered orally. The 14% cholesterol-containing optimised ufasomes had an entrapment effectiveness of 80.49% and a spherical shape with an average size of 788 nm. Reconstituted ufasomal lyophilized gel is characterised rheologically. The predicted next step in this investigation is to examine the systemic medication absorption following intranasal injection of the ufasomes to determine the therapeutic application of this potential vesicular carrier.	[46]
Dexamethasone	Transmission electron microscopy revealed the ufasomal gel vesicles to be round and multilamellar. The optimised formulation's permeation was found to be around 4.7 times greater than that of the basic drug gel. For further assessment, an optimised formulation (UF-2) with a drug to oleic acid molar ratio of 8:2 was produced.	[47]
Methotrexate	Oleic acid vesicles may be useful when applying methotrexate (MTX) topically to treat psoriasis. MTX is required to treat rheumatoid arthritis because it localises in the synovial joint. Oleic acids increased the quantity of MTX that penetrated through rat skin by three to four times compared to plain drug solution or carbopol gel.	[48]
Itraconazole	Ufasomes are a potential medication delivery strategy for fungal infections since they encapsulate ITZ to increase its penetration power and are made of oleic acid. It was	[49]

	discovered that the chosen formula's lowest inhibitory concentration for Candida albicans was 0.0625 ng/mL. Drug availability, which has poor penetration, and resistance.	
Albendazole	Albendazole (ABZ), which possesses a wide range of therapeutic effects including anticancer and anti-psoriasis capabilities, has recently attracted a lot of media interest. Its limited clinical application results from its poor water solubility. The current study's goal was to make ABZ-loaded ufasomes ready for topical application. When multiple mathematical models were used to analyse an in vitro drug release investigation, the optimised ABZ-UG displayed a zero-order release pattern with a 99.86% cumulative ABZ release after 24 hours. Overall, the research demonstrated that ABZ may provide promise as a carrier for the treatment of skin conditions. Particle size, polydispersity index (PDI), zeta potential, and entrapment effectiveness of optimised ABZ-U were all measured.	[50]

Table 3: Unsaturated fatty acids

NAME	CHEMICAL FORMULA	C:1
Oleic acid	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	18:1
Linoleic acid	$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$	18:2
Elaidic acid	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	18:1
Arachidonic acid	$CH_3(CH_2)_4CH=CHCH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_3COOH$	20:4
Erucic acid	$CH_3(CH_2)_7CH=CH(CH_2)_{11}COOH$	22:1
Myristoleic acid	$CH_3(CH_2)_3CH=CH(CH_2)_7COOH$	14:1
Sapienic acid	$CH_3(CH_2)_8CH=CH(CH_2)_4COOH$	16:1
Palmitoleic acid	$CH_3(CH_2)_5CH=CH(CH_2)_7COOH$	16:1

Recent Innovations in Conventional Ufasomes Extension of pH range

Restrictive pH ranges are frequently appropriate since only about half of the carboxylic acid has to be ionised in order for fatty acid vesicles to form. The following state-of-the-art methods can be used to widen the pH range:

a) Comprised of a linear alcohol or surfactant, such as amphiphilic additives containing a sulphate or sulfonate head group: Decanoate, a part of decanoic acid, for example, produces vesicles between a pH range of 6.4 and 7.8. Vesicles are also produced below pH 6.8 when equimolar quantities of dodecylbenzenesulfonate and decanoic acid are combined. Sodium dodecylbenzene sulfonate can be used to slightly lower the pH for vesicle formation at a pH of. (SDBS).[14]

b) Using fatty acids with an oligo unit (ethylene oxide) inserted between the carboxyl head group and the hydrocarbon chain was shown to increase the hydrophilicity of the synthetic fatty acid head group, which in turn increased the stability of vesicles at lower pH levels. The extremely polar bulky group has two impacts on vesicle formation, namely a decrease in the pH range and a reduction in the phase transition temperature (around Kraft point).[51]

Insensitivity toward divalent cation

Mag2+ and Ca2+ Vesicles can develop from fatty acid molecules that include a chemical connection that increases their stability, such a divalent cation, even at low concentrations. Fatty acid vesicles stabilise when glycerol esters of fatty acids are introduced in the presence of an ionic solution. The generation of unilamellar and multilamellar vesicles from a monoolein and sodium oleate combination was also demonstrated by a study of ternary monoolein mixed sodium oleate water system using cryogenic transmission electron microscopy. Additionally, the stable vesicle was maintained alive for a very long time (more than a year).[52]

Enhancement of stability by crosslinking fatty acid molecules by chemical bond

Vesicles with a carboxyl head group are produced by an anionic gemini surfactant in this instance. Another example is the use of sodium-11-acrylamidoundecanoate (SAU), a polimerizable moiety, with fatty acids (soap). According to one study, polymeric vesicles made of sodium-11-acrylamidoundecanoate (SAU) are stable at high temperatures and may self-assemble into vesicular aggregates.[53]

Mixture of fatty acid/soap vesicle and cationic surfactant-based vesicles

Mixtures of fatty acids and tetradecyltrimethylammonium (TTAOH) were investigated as a model system for mixed vesicles. Unilamellar and multilamellar vesicles were found to form when fatty acids and TTAOH were combined in about equivalent proportions. Didodecyldimethyl ammonium bromide (DDAB)

and anionic fatty acid vesicles work together to form a significant link (23% of vesicles with opposing charge). The formation of a reactive intermediate by the connection of vesicles with opposing charges led to the formation of a larger single vesicle that included the solutes that were previously present in disassociated vesicles as well as a mixed membrane. (Comprising of lipids of both cations and anions).[54]

Dynamic nature of ufasomes

The single-chain amphiphiles that make up unsaturated fat vesicles give them their dynamic features. Unsaturated fatty acid vesicles were positioned in a dynamic environment between micelles, which are made up of single chain surfactants, and typical vesicles, which are made up of double chain amphiphiles. The terminal carboxylic acid has the ability to produce several fatty acid aggregates by just adjusting the ionisation or protonation ratio. Dialyzing the soap monomer solution or saturated fatty acid across a cellulose acetate membrane allowed researchers to study the kinetics of how vesicles and micelles develop from these substances. The rate at which equilibrium is reached is observed by beginning with an asymmetric distribution of fatty acids or soap monomers in the middle of two chambers that are divided by the dialysis membrane, with one chamber containing aggregates like vesicles or micelles and the other chamber containing only buffer solution. Micelles formed by the micellar system in the diffusate chamber quickly equalised the content of fatty acids or soap monomers in each chamber. Vesicles, on the other hand, made it far more difficult to achieve the equilibrium condition (the concentration in the diffusate chamber increased steadily after the solution's monomer saturation). In essence, vesicles contain considerably more amphiphiles than do micelles. The findings of the dialysis experiment show that synthesis of fatty acid monomers confronts a substantially lower energy barrier than that of fatty acid vesicles, which is a significant difference (soap). A practical approach for creating fatty acid vesicles can be achieved by adding alkaline soap solution to a buffer solution with an intermediate pH. For instance, when concentrated sodium oleate micelles solution is introduced to a buffer solution with a pH of 8.5, partial protonation occurs spontaneously.[55]

APPLICATION OF UFASOMES

Transdermal delivery of a variety of therapeutic drugs is possible using drug-loaded ufasomes. Drugs that are anti-inflammatory, antifungal, anti-arthritic, and others have all been administered by transdermal means.

ANTIFUNGAL DRUGS

For the transdermal distribution of these drugs, novel formulations have been created, including niosomes, liposomes, ethosomes, microemulsions, and micelles, in order to reduce the shortcomings of the conventional formulations, such as allergic responses and reduced penetrating ability. Ufasomes are more advanced tools created especially for this. The ufasomal dispersion's medication release was consistent, according to an in-vitro drug release investigation. Ufasomes may release drug over a five-day period, according to in vivo research. This demonstrates that, when compared to other commercial formulations, it is suitable for long-term therapy.

ANTICANCER DRUGS

The US-FDA has authorised the medication 5 Fluorouracil (5-FU) for the topical treatment of basal cell carcinoma (BCC). A number of negative side effects, including itchiness, eczema, redness, and inadequate skin penetration, are present in the commercial formulation. Because the medicine is confined within the vesicles, ufasomes are utilised to minimise adverse effects. They can increase the drug's penetration while preserving the drug's release. They can sustain the drug's release while increasing its absorption. Ex-vivo skin penetration studies revealed that the medication was maintained in the epidermal layer of the skin when the fatty acid vesicles entered the stratum corneum.

ANTIINFLAMMATORY DRUGS

Utilizing non-steroidal anti-inflammatory drugs (NSAIDs) is the initial step in treating rheumatoid arthritis (RA). For the initial stages of RA therapy, slow-acting disease-modifying anti-rheumatic medications (DMARDs) have been recommended to stop or slow down joint degradation. Comparing fatty vesicles to conventional drug solution or carbopol gel, it was shown that three to four times more medication went through the skin of rats utilising fatty vesicles. Skin penetration tests utilising fatty acid vesicles reveal that up to 50% of the injected dosage was present in the skin. Using this method might thus help to lessen the inflammation caused by RA. Transdermal penetration of fatty acid vesicular gel was demonstrated to be roughly 4.7 times more than that of standard pharmaceutical gel. The commercial product significantly reduced edoema as compared to fatty acid vesicular gel when used in

the same amount. Therefore, pharmaceutical gel based on fatty acid vesicles may be more efficient than commercial gel in treating inflammation.

ANTI-OSTEOARTHRITIC DRUGS

Collagen and proteoglycans, two biological substances, are required for joint healing and the production of synovial fluid, which lubricates joints. When glucosamine is used as a supplement, the body may generate these substances more readily. The use of glucosamine to treat osteoarthritis has long been recommended. To treat osteoarthritis topically, fatty glucosamine sulphate vesicles are created and mixed with carbopol gel. It was discovered that the vesicle-based gel had a six-fold greater drug concentration in rats' muscles compared to the conventional carbopol gel. Additionally, medication release from the gel containing fatty acid vesicles was delayed. To effectively treat osteoarthritis, this formulation may be utilised as a depot formulation.

CONCLUSION

Ufasomes, closed lipid bilayer solutions, are limited to a certain pH range. Soap and fatty acids make them up. The fatty acid molecules in ufasomes have their carboxyl groups in contact with water and their hydrocarbon tails positioned towards the inside of the membrane. There are several variables, including the best fatty acid, the amount of cholesterol, the buffer, and the pH range. Effect the stability of the formulation for the ufasome. Ufasomes have tremendous therapeutic promise and can be utilised to treat a variety of skin conditions. Negative side effects on the skin, such as burning, itching, and other allergic responses, can be minimised since the medication is supplied in a regulated or continuous manner. Since they are unable to stimulate the immune system, fatty acid vesicles have also been demonstrated to be immensely helpful in treating skin abnormalities in conditions like AIDS. Considering that the drug's distribution has been carefully monitored. For topical pharmaceutical administration, ufasomes are preferred over liposomes because they are less expensive, more able to penetrate skin, and more able to entrap drug molecules.

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