



Ufasomes: A comprehensive review on an emerging vesicular drug delivery system

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Abstract

Ufasomes are self-assembling vesicular systems made of unsaturated fatty acids and their ionized forms are a possible substitute for traditional lipid-based drug delivery techniques. These vesicles have special physicochemical characteristics, such as outstanding biocompatibility, structural flexibility and the capacity to encapsulate both hydrophilic and lipophilic medicinal molecules. Under carefully regulated pH conditions, they grow on their own. Over the past few decades, there has been a substantial advancement in our understanding of the mechanisms behind ufasome production, stability, membrane dynamics and permeability. Recent studies show their potential in transdermal, ocular, oral and targeted drug administration due to their improved penetration, higher drug bioavailability and decreased toxicity. However, challenges such oxidative degradation sensitivity, low long-term stability and scaling-up problems continue to restrict their clinical use.

This study highlights the growing importance of ufasomes as adaptable and efficient biocarriers in current pharmaceutical research by outlining their historical development, preparation methods, characterisation techniques, therapeutic applications and future prospects.

Keywords: Novel drug delivery system, vesicular drug delivery system, ufasomes, method of preparation, composition

Introduction

Drug delivery technology has advanced significantly in recent years, as seen by the emergence of novel drug delivery systems as practical tools for achieving targeted and regulated distribution of medicinal drugs. By delivering medications to particular tissues while limiting their exposure to non-target areas, targeted drug delivery improves therapeutic efficacy and lowers systemic side effects. Paul Ehrlich first put forth the basic idea of targeted delivery in 1909, envisioning the direct administration of medicinal compounds to damaged cells.

Several cutting-edge vesicular drug delivery systems that can release medications at a rate consistent with physiological requirements and therapeutic objectives have evolved throughout the years as a result of ongoing research. Because of their structural flexibility, biocompatibility and capacity to enhance medication stability and penetration, vesicle-based carriers have garnered significant attention among these. Bingham originally documented the biological genesis of these vesicular structures in 1965, referring to them as "Bingham bodies."

Ufasomes, which are lipid vesicles made of unsaturated fatty acids, have become a viable platform within this class of vesicular systems. They have become a major focus of current drug delivery research due to their special capacity to self-assemble in aqueous settings, encapsulate both hydrophilic and lipophilic medicines and improve transdermal and targeted distribution [1].

Novel Drug Delivery System

Over the past few decades, the development of new drug delivery systems (NDDS) has garnered substantial scientific attention due to their potential to solve the shortcomings of conventional dosage forms. A good NDDS must fulfill two primary requirements: it must effectively direct the therapeutic agent to the intended site of action and release the medication at a rate that aligns with physiological

demands during the course of treatment. Sustained-release or delayed-release drugs are examples of conventional formulations that occasionally fail to achieve both objectives simultaneously. Ongoing research has significantly narrowed the gap between theoretical predictions and practical applications, even though no system in use today functions perfectly.

Vesicular drug delivery systems in particular have demonstrated potential as carriers that may precisely transport active substances to their site of action while maintaining a controlled release profile. These techniques increase therapeutic efficacy, prolong drug residence duration and reduce systemic toxicity by encasing the drug within stable vesicular structures. Therefore, improving the effectiveness of both newly developed and existing drugs has required the creation of novel vesicle-based delivery systems.

Among these vesicular carriers, Ufasomes-self-assembling vesicles composed of unsaturated fatty acids-represent a major breakthrough. Ufasomes ability to encapsulate a range of therapeutic compounds, improve permeability and allow regulated and targeted drug administration makes them a viable technology for modern pharmaceutical applications [2].

Vesicular Drug Delivery System

Because of their adaptability and variety of biological uses, vesicular systems have become the preferred drug delivery vehicles in recent years. In immunology, membrane biology, diagnostics and more recently, genetic engineering, lipid-based vesicles have proven to be extremely useful. They are useful instruments for delivering and targeting medicinal medicines as well as modeling membrane processes because of their structural resemblance to biological membranes. When selective absorption is possible, encapsulating medications within vesicular structures can decrease drug-associated toxicity and extend the duration of systemic circulation. Additionally,

phagocytic cells absorption of drug-loaded vesicles minimizes systemic exposure while enabling localized delivery to infection or inflammatory locations.

By offering continuous release and shielding the medication from degradation, vesicular drug delivery devices also improve bioavailability, especially for poorly soluble or quickly degraded medicines. Their therapeutic possibilities are further expanded by their capacity to encapsulate both lipophilic and hydrophilic compounds. Amphiphilic molecules in aqueous fluids self-assemble to produce these vesicles, which are highly organized structures made up of one or more concentric lipid bilayers. Such vesicles can arise from a wide variety of amphiphilic components and the phrase "synthetic bilayer" emphasizes the possible non-biological origin of many vesiculogenic materials.

Bingham presented the first account of the biological origin of vesicular structures in 1965. These buildings were dubbed "Bingham bodies." Since then, vesicular drug delivery has advanced significantly, resulting in systems that can release drugs in a targeted, sustained and controlled manner. Vesicle design advancements have improved stability, decreased dosing frequency, eliminated dose-related side effects and increased the therapeutic efficacy of several medications^[3].

Classification of Vesicular Drug Delivery System (Vdds)

The vesicles are grouped on the basis of their composition⁴

- Lipoidal Biocarriers

- Nonlipoidal Biocarriers.

Lipoidal Biocarriers As Vesicular Drug Delivery System

- Liposomes
- Niosomes
- Ufasomes
- Transfersomes
- Phytosomes
- Nanoemulsions / Microemulsions
- Solid lipid nanoparticles (SLN)
- Nanostructured lipid carriers (NLC)

Nonlipoidal Biocarriers As Vesicular Drug Delivery System

a. Polymeric Carriers

- Nanoparticles (PLA, PLGA)
- Polymeric micelles
- Dendrimers

b. Natural Biopolymer Carriers

- Chitosan nanoparticles
- Alginate beads
- Gelatin nanoparticles

c. Inorganic Carriers

- Gold nanoparticles
- Silica nanoparticles
- Iron oxide nanoparticles

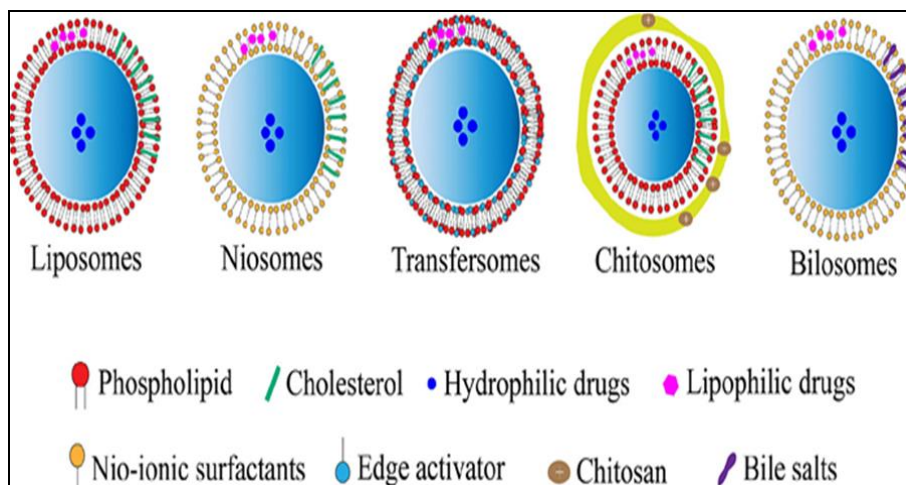


Fig 1: structure of a) liposomes, b) Niosomes, c) Transfersomes, d) Phytosomes, e) Bilosomes

Comparison Of Ufasomes With Other Carrier System^[5]

Table 1: comparission of ufasomes with other carriers

Feature	Ufasomes	Liposomes	Niosomes	Ethosomes
Composition	Unsaturated fatty acids	Phospholipids +/- cholesterol	Non-ionic surfactants + cholesterol	Phospholipids + high ethanol
Nature of vesicle	Fatty acid-based vesicles	Phospholipid bilayer vesicles	Surfactant-based vesicles	Soft, ethanol-rich lipid vesicles
Cost	Low	High	Moderate	High
Skin penetration	High	Moderate	Moderate	Very high
Colloidal stability	Moderate	High	High	Low
Ease of preparation	Simple	Moderate	Simple	Complex
Encapsulation	Both hydrophobic and hydrophilic drugs	Both hydrophobic and hydrophilic drugs	Both hydrophobic and hydrophilic drugs	Primarily hydrophilic drugs
Non-invasive delivery suitability	Highly suitable	Limited	Moderate	Mainly transdermal
Protection of proteins/peptides	Superior (fatty acid shielding)	Moderate	Moderate	Poor (ethanol denaturation)

Biocompatibility	excellent	Good	Good	Moderate
Route of delivery	Topical, transdermal, nasal	Oral, parental, topical	Oral, topical, transdermal	Mainly transdermal
Membrane fluidity	High (due to unsaturated fatty acids)	Moderate	Moderate	Very high (due to ethanol)
Applications	Drug delivery, gene therapy, vaccine delivery	Drug delivery, cosmetics, food	Drug delivery, cosmetics	Transdermal drug delivery

Ufasomes

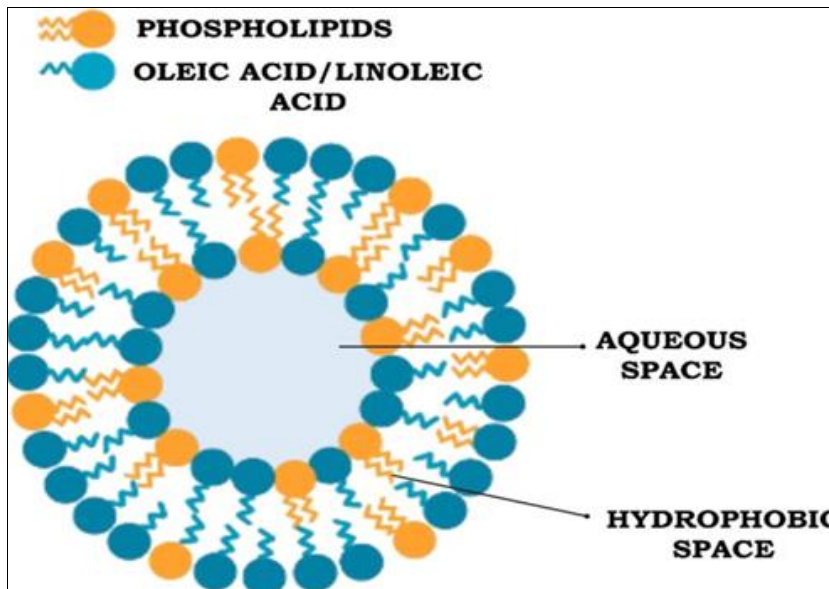


Fig 2: structure of ufasome

Unsaturated fatty acid vesicles, or usosomes, are a unique family of lipid-based carriers that self-assemble from naturally occurring unsaturated fatty acids like oleic acid. The creation of these nanoscale bilayered vesicles has made substantial use of oleic acid, a readily available monounsaturated fatty acid. To characterize these structures, the term "ufasomes" was coined, highlighting the fact that they are composed of unsaturated fatty acids arranged like liposomes.

Both ionized and unionized forms of fatty acids, which function as amphiphilic building blocks, interact associatively to produce ufasomes. In aquatic conditions, these molecules spontaneously form bilayer membranes, with the hydrophilic carboxyl groups facing the surrounding water and the hydrophobic hydrocarbon chains facing the membrane's core. Although this configuration resembles the structural arrangement of conventional phospholipid-based vesicles, the fatty acid makeup of ufasomes gives them distinct physicochemical properties.

The significant pH dependence of ufasome production is a crucial characteristic. A small pH window of 7–9, when about half of the carboxylic acid groups are ionized, is usually where stable ufasome vesicles form. Optimal packing and bilayer stability are encouraged by this partial ionization. Instead of forming organized vesicular structures, the fatty acids below this pH range prefer to cluster into oil droplets and stay mostly unionized. On the other hand, fatty acids are mostly ionized at pH levels higher than 9, resulting in the creation of soluble micelles rather than bilayer vesicles. Thus, stable ufasome assembly requires maintaining the proper pH environment.

Ufasomes have drawn a lot of interest as potential drug delivery vehicles because of their straightforward structure,

biocompatibility and capacity to encapsulate both hydrophilic and lipophilic substances. Their relevance in contemporary pharmaceutical research is further increased by their structural flexibility, ease of preparation and potential for controlled and targeted release. Ufasomes are therefore still being investigated as novel vesicular systems that can enhance therapeutic efficacy and get around the drawbacks of traditional delivery methods [6].

Mechanism of Drug Release from Ufasomes

1. Diffusion-Controlled Release

- The drug entrapment within the aqueous core or lipid bilayer diffuses slowly through the fatty acid membrane.
- This is the primary mechanism for hydrophilic drugs (core) and lipophilic drugs (bilayer).
- The compact bilayer structure provides sustained and controlled release.

2. Bilayer Fluidity and Permeability

- Unsaturated fatty acids contain double bonds, which increase membrane fluidity.
- Higher fluidity enhances controlled leakage of the drug.
- Release rate depends on:
 - a. Fatty acid chain length
 - b. Degree of unsaturation
 - c. Cholesterol or stabilizer content.

3. Ph-Dependent Release

- Ufasomes are stable at alkaline pH (8-9).
- At physiological or acidic pH:
 - a. Fatty acid becomes protonated
 - b. Vesicle structure destabilizes

- c. Drug is released more rapidly
- This property makes ufasomes suitable for site-specific and triggered release.

4. Vesicle Swelling and Erosion

- Upon contact with biological fluids:
 - a. Vesicles absorb water
 - b. Swelling occurs
 - c. Partial erosion or rupture of vesicle membrane releases the drug

5. Interaction with Biological Membranes

- Fatty acids can fuse with skin or cell membranes.
- This fusion enhances drug permeation and facilitates release at the target site.
- Especially important for topical and transdermal delivery.

Composition of Ufasome

There are two primary aggregates that make up the Ufasome^[1].

1. First, oleic acid (lipid) is an amphipathic component in which the aqueous solvents self-assemble form a lipid bilayer that closes into a straightforward lipid vesicle.
2. Second, a bilayer softening element that improves the flexibility and permeability of lipid bilayers, such as an amphiphile medication or biocompatible surfactant. As a result, by adjusting the local concentration of each bilayer component to the local stress it is under, the resulting and permeability-optimized ufasome vesicle can swiftly and easily change its structure. The ufasome is different from these more traditional vesicles in that it is a better adaptable artificial membrane.

Method of Preparation

With the increase in researches, many methods have been reported to formulate ufasomes which are mentioned below [7, 8],

1. Rotary film evaporation method
2. Modified handshaking method
3. Vortexing Sonication method
4. Reverse phase evaporation method
5. Ether injection method

The four forms of ufasome preparation techniques are film dispersion, reverse evaporation, high-pressure homogenization, and ultrasonic dispersion. One popular technique for preparing lipophilic drug ufasomes is the film dispersion method.

Three processes are involved in the preparation of ufasomes using the rotary film evaporation method:

- The mixture of unsaturated fatty acid and surfactant that form vesicles is dissolved in a volatile organic solvent (ethanol-methanol) to create a thin film. Next, a rotary evaporator is used to evaporate the organic solvent above the lipid transition temperature. The last residues of solvent were eliminated overnight under vacuum.
- To hydrate a produced thin film with buffer (pH 7.4), it is rotated at 60 rpm for an hour at the proper temperature. The resulting vesicles inflated for two hours at room temperature.
- To create tiny vesicles, the resulting vesicles were sonicated at room temperature or 50°C for 30 minutes using a bath sonicator or probe sonicated at 4°C for 30 minutes. The sonicated vesicles were homogenized by ten hand extrusions across a sandwich of 200 and 100 nm polycarbonate membranes.

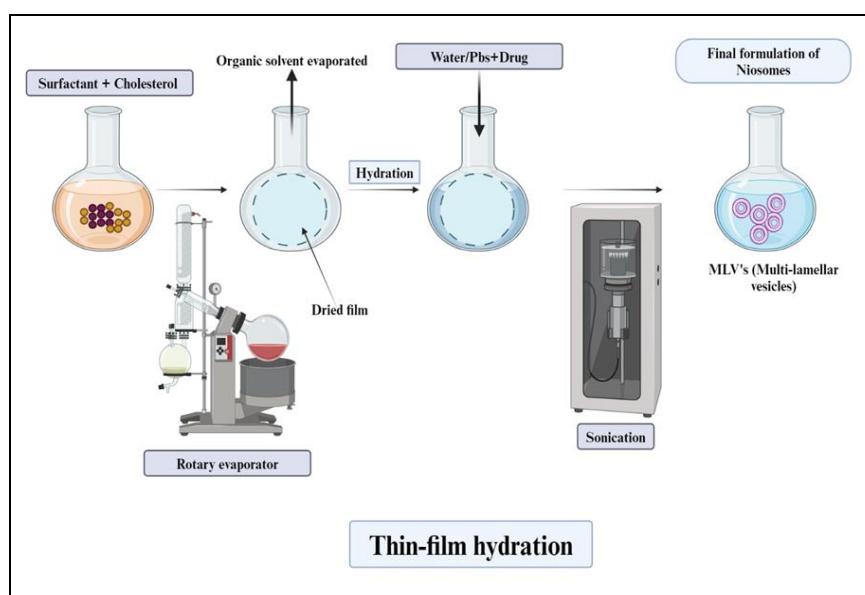


Fig 3: schematic representation of thin film hydration technique

- a. The preparation of ufasomes is likewise based on the modified handshaking method and the lipid film hydration methodology, which included the following steps:
 - The drug, edge activator, and lecithin (PC) were dissolved in a 1:1 ethanol to methanol combination. Shaking hands above the lipid transition temperature (43°C) allowed the organic solvent to evaporate.

With rotation, a thin lipid layer developed inside the flask wall. The thin coating was left overnight to allow the solvent to completely evaporate. After that, the film was hydrated for 15 minutes at the appropriate temperature using phosphate buffer (pH 7.4) and mild shaking. Up to one hour at 2–8°C, the ufasome suspension continued to hydrate.

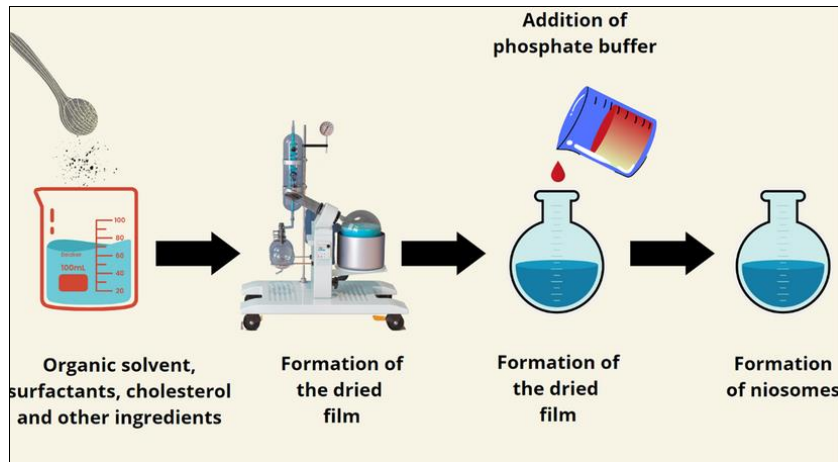


Fig 4: Hand Shaking Method

b. Vertxing sonication method: Using a phosphate buffer, mixed lipids (such as oleic acid, surfactant and the therapeutic agent) are blended and vortexed to create a milky suspension. The suspension is then sonicated and extruded through polycarbonate membranes. This technique, which entails combining cationic lipids with PBS to achieve a concentration of

10 mg/ml and counting sodium deoxycholate (SDC), has also been used to establish cationic ufasomes.

- After sonication and vortexing, the mixture is extruded through a polycarbonate (100 nm) filter.

c. Ether injection method

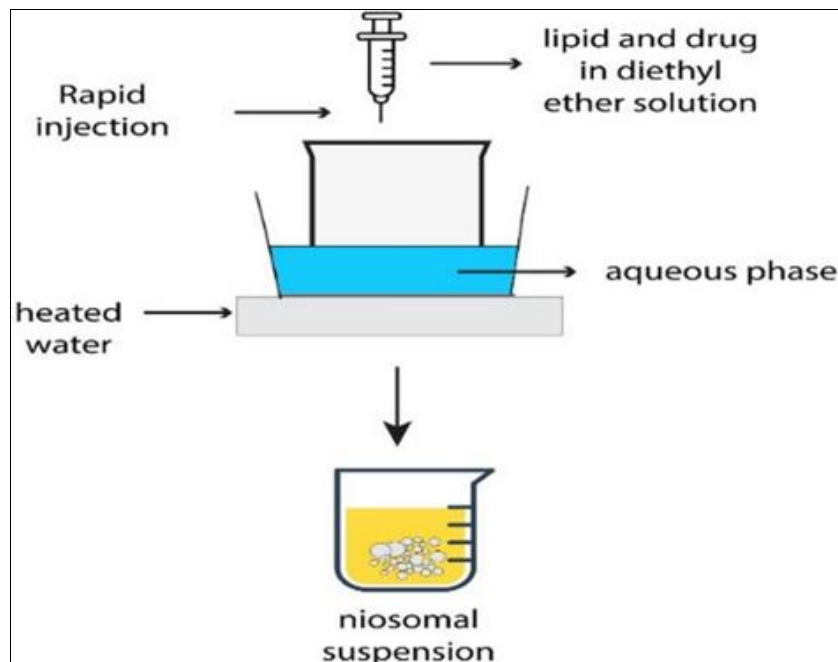


Fig 5: Ether injection method

Evaluation of Ufasomes

The evaluation parameters for ufasomes are as follows [7, 9],

▪ **Vesicle size distribution**

a. Purpose of vesicle size distribution evaluation

- To determine average vesicle size.
- To assess uniformity of vesicles.
- To predict stability and permeation behaviour.
- Smaller and uniformly distributed vesicles better skin penetration and stability.

b. Common methods used

- Dynamic light scattering (DLS)
- Laser diffraction
- Transmission electron microscopy (TEM)

c. Factors affecting vesicle size distribution

- Type and concentration of unsaturated fatty acid (oleic acid)
- Surfactant concentration
- Hydration medium and pH
- Sonication time and power

Zeta potential

Zeta potential measures the surface charge of ufasomal vesicles in dispersion. Vesicles with sufficient surface charge repel each other, preventing aggregation and thereby maintaining uniform vesicle distribution.

a. Method/Instrument

- Electrophoresis light scattering (ELS)
- Instrument: zetasizer

Vesicle morphology

a. Purpose of vesicle morphology study

- To confirm vesicle formation
- To determine shape (spherical/oval)
- To observe aggregation or deformation
- To correlate morphology with stability and drug delivery efficiency.

b. Common techniques used

- **Transmission electron microscopy (TEM):** Provides high resolution images, shows actual vesicle shape and size and confirms unilamellar or multilamellar structure
- **Scanning electron microscope:** Shows surface morphology, less accurate for internal structure and requires drying.
- **Atomic force microscopy (AFM):** Provides 3D surface topography, measures vesicle height and surface roughness and performed under near-physiological conditions.

Entrapment efficiency

Entrapment efficacy (EE%) is the fraction of total drug that is entrapped inside the ufasomal vesicles relative to the total amount of drug added during formulation.

a. Significance

- Higher EE% - better drug loading
- Indicates compatibility of drug with fatty acid vesicles
- Influences controlled release and therapeutic efficacy
- Reflects vesicle integrity and morphology

b. Method for determination

- Centrifugation method
- Dialysis method

c. Calculation formula

$$\text{Entrapment efficacy (EE\%)} = \frac{\text{total drug} - \text{diffused}}{\text{total drug}} \times 100$$

In vitro drug release

In-vitro drug release evaluates the rate and extent of drug released from ufasomal vesicles over time. It helps to predict controlled release behaviour, formulation performance and therapeutic effectiveness.

a. Calculation

$$\text{Cumulative \% drug released} = \frac{\text{amount of drug released at time } t}{\text{total drug entrapment}} \times 100$$

- Materials required: dialysis membrane, phosphate buffer pH 5.8 or 7.4, magnetic stirrer, water bath/dissolution apparatus and UV-Visible spectrophotometer.

Physical stability studies

Physical stability studies are carried out to evaluate the ability of ufasomal vesicles to retain their physicochemical properties during storage over time.

a. Objectives

- To assess stability of ufasomal dispersion
- To detect aggregation, leakage or degradation
- To evaluate effect of storage temperature
- To predict shelf life of formulation

b. Parameters evaluated

- **Visual appearance:** Color change, precipitation and phase separation.
- **Vesicle size and PDI:** Measured by DLS and increase indicated aggregation or fusion.
- **Zeta potential:** Reduction in magnitude indicated loss of stability
- **Entrapment efficacy (EE%):** decrease indicated drug leakage

Advantages of Ufasomes

- **Better Targeted Drug Delivery and Bioavailability:** These vesicles significantly boost the bioavailability of poorly soluble drugs by improving their solubility and absorption. Ufasomes are therefore particularly useful for drugs with low inherent solubility.
- **Effective Skin Penetration:** Ufasomes are especially useful in topical treatments due to their superior skin penetration qualities. For dermatological therapies that need for localized medication delivery, this feature is beneficial^[10].

Disadvantages of Ufasomes

- **Oxidation Susceptibility:** Ufasomes are particularly susceptible to oxidation, which compromises their stability and structural integrity, particularly in lipid-based formulations. This sensitivity results in their short shelf life and limited utility for long-term preservation and therapeutic applications^[11].
- **Colloidal Instability:** The vulnerability of ufasomes to colloidal instability may cause vesicle aggregation, fusion, or rupture. This instability may restrict their reliability in drug delivery and other biomedical applications, resulting in uneven drug release, reduced bioavailability and diminished efficacy^[12].

Application of Ufasomes

1. Delivery of Insulin

Mechanism of insulin delivery via ufasomes

a. Encapsulation

Insulin is entrapped within the aqueous core of ufasomal vesicles during permeation.

b. Vesicle-skin interaction

Unsaturated fatty acids interact with skin lipids, increasing skin fluidity and reducing barrier resistance

c. Enhanced permeation

Ufasomes act as penetration enhancers, facilitating insulin transport across the stratum corneum.

d. Controlled release

Vesicles provide sustained and controlled release of insulin, maintaining therapeutic levels for longer durations.

2. Delivery of Corticosteroids

Ufasomes are vesicular drug delivery systems composed of unsaturated fatty acid that enhance the topical and transdermal delivery of corticosteroids. Corticosteroids loaded into ufasomes show improved skin penetration due to the interaction of fatty acids with stratum corneum lipids, leading to increased membrane fluidity. Ufasomes protect

the drug, allow controlled and sustained release and reduce systemic absorption. This results in enhanced therapeutic efficacy, reduced dosing frequency and minimized side effects, making ufasomes a promising carrier for topical corticosteroid delivery.

3. Delivery of Proteins & Peptides

Ufasomes are vesicular carriers made from unsaturated fatty acids that improve the delivery of proteins and peptides by protecting them from enzymatic degradation. They enhance permeation across biological barriers by increasing membrane fluidity and enable controlled release of these macromolecules. Ufasomes are particularly useful for non-invasive routes such as transdermal and nasal delivery, improving bioavailability and patient compliance compared to conventional administration.

4. Delivery of Interferon

Ufasomes are fatty acid-based vesicular systems that enhance the delivery of interferon by protecting it from enzymatic degradation and improving its stability. The unsaturated fatty acids in ufasomes increase membrane permeability, facilitating better transdermal or nasal absorption. Ufasomes also provide controlled release, reduce dosing frequency and improve patient compliance, making them a promising carrier for interferon delivery.

5. Delivery of Anticancer Drugs

Ufasomes are vesicular carriers composed of unsaturated fatty acids that enhance the delivery of anticancer drugs by improving drug stability and cellular uptake. They increase membrane permeability, promote better penetration into tumor tissues and provide controlled and sustained drug release. Ufasomes can reduce systemic toxicity, enhance therapeutic efficacy and improve bioavailability, making them a promising system for targeted and topical anticancer drug delivery.

6. Delivery of Anesthetics

Ufasomes are unsaturated fatty acid-based vesicular systems that enhance the delivery of anesthetic drugs by improving skin permeation and prolonging drug action. They provide controlled and sustained release, reduce systemic absorption and increase local anesthetic efficacy. Ufasomes thus help achieve faster onset, longer duration of action and reduced dosing frequency in topical and transdermal anesthetic delivery.

7. Delivery of Non-Steroidal Anti-Inflammatory Drugs

Ufasomes are vesicular drug delivery systems composed of unsaturated fatty acids that enhance the topical and transdermal delivery of NSAIDs. They improve drug permeation through the skin by increasing membrane fluidity, provide controlled and sustained release and reduce gastrointestinal side effects associated with oral NSAIDs. Ufasomes enhance local anti-inflammatory action, improve bioavailability and increase patient compliance.

8. Delivery of Herbal Drugs

Ufasomes are fatty acid-based vesicular carriers that enhance the delivery of herbal drugs by improving their stability and skin permeation. They facilitate better penetration of phytoconstituents through biological membranes, protect them from degradation and provide

controlled release. Ufasomes improve bioavailability, therapeutic efficacy and patient compliance, making them suitable for topical and transdermal herbal drug delivery.

Future Prospective of Ufasomes

Ufasomes have strong future potential as novel vesicular drug delivery systems due to their biocompatibility and ability to enhance drug permeation. They may be widely used for non-invasive delivery of proteins, peptides, hormones, vaccines and anticancer agents through transdermal and nasal routes. Further advancements in formulation optimization, stability enhancement and large-scale production could improve their clinical applicability. Integration with nanotechnology and targeted delivery approaches may enhance therapeutic efficacy and safety. However, comprehensive *in vivo* and clinical studies are required to establish their long-term safety and effectiveness.

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