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Ufasomes: Unveiling the potential of vesicular drug delivery system

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ABSTRACT:
Several types of vesicular systems for drug delivery have been developed, each with its own set of advantages and applications. Among liposomes and niosomes, ufasomes stand out as versatile systems capable of encapsulating a wide range of therapeutic agents. Ufasomes, also known as unsaturated fatty acid vesicles are composed of closed lipid bilayers that are formed from fatty acids and their ionized species. These vesicles have a unique property of maintaining a pH range of 7 to 9, which allows them to function effectively in various physiological environments. Oleic acid, in particular, plays a crucial role as a key component in the synthesis of ufasomes, contributing to their stability and functionality. Recent research has highlighted the potential to develop ufasomes with customizable properties, such as enhanced stability, resistance to divalent cations, and an extended pH range, further improving their application in drug delivery systems. The primary aim of this review is to explore the potential of fatty acid vesicles for topical drug delivery. This paper provides a comprehensive review of ufasomes, covering various aspects such as their introduction, structure, and production methods. It also delves into the different applications of ufasomes, exploring their advantages and disadvantages in drug delivery. The composition and methods of preparation are discussed in detail, alongside the characterization techniques used to evaluate their properties. Additionally, the paper examines recent innovations in the field of ufasomes, emphasizing their growing importance in biomedical and environmental applications. Through this review, the potential of ufasomes as a versatile and effective delivery system is highlighted, offering new opportunities for therapeutic interventions and genetic applications.

Key words: Ufasomes, Unsaturated fatty acid vesicles, Amphiphiles, Autopoietic process

I. INTRODUCTION:

Transdermal drug delivery system is a painless way of systemic drug delivery by applying the medicated formulation to safe and intact skin. These dosage forms designed to deliver a therapeutically effective amount of drug across patient's skin. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through the skin at predetermined rate with minimal inter and intra patient variation. Transdermal dosage forms, are becoming more popular because of their exclusive advantages. Improved bioavailability, Controlled absorption, extra uniform plasma levels, painless and reduced side effects, easy application and flexibility of terminating drug administration by simply removing the patch from the skin. Being very promising route, it also has many challenges in delivering the drug through skin such as permeability issues. In order to overcome the challenges, researchers have found a system in which the drug encapsulated into the vesicle and these vesicles can penetrate deeper into the skin to hit the target site. Hence better skin permeation of bioactive agents can be achieved. These vesicular systems include liposomes, niosomes, transferosomes, ethosomes, and cubosomes, have the capacity to bypass the skin barriers, and increase drug permeability through the stratum corneum barrier[1].

There are significant problems in the general application of liposomes for drug delivery. In a dispersed aqueous system, liposomes have problems associated with degradation by hydrolysis or oxidation as well as sedimentation, aggregation, or fusion of liposomes during storage. Liposomes poses problem for transdermal delivery because they cannot reach the deeper layers of the skin as they are trapped in the superior layers of stratum corneum. Though vesicular systems assure targeted delivery, in most cases the liposomal or niosomal

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category vesicles do not achieve the desired transdermal penetration.

Since topical route of administration has lower risk of systemic side effects, topical treatment appears to be most favorable route of administration, although the stratum corneum restricts the penetration of drugs into viable skin[2].

UFASOMES:

In 1909, Paul Ehrlich introduced the target drug delivery approach, which involves administering drugs specifically to damaged cells[3]. Ufasomes are suspensions of closed lipid bilayers made up of ionized fatty acid species. With a pH range of 7-9, they are considered vesicles of unsaturated fatty acids[4]. Ufasomes have a lipid carrier that adheres to the skin's surface, helping lipids move more easily from the stratum corneum to the outermost layer of the skin[5]. Ufasomes can encapsulate both hydrophilic and hydrophobic drugs, making them an effective drug delivery system. Additionally, they are biocompatible and biodegradable[6]. In ufasomes, fatty acid molecules arrange themselves with their hydrocarbon tails facing inward toward the membrane, while their carboxyl groups stay in contact with the skin[7].

STRUCTURE OF UFASOMES:

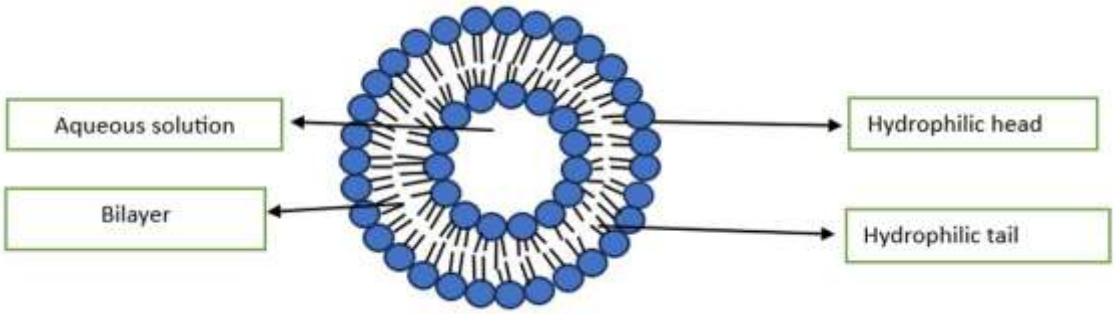

Fig-1: Structure of ufasomes

Since ufasomes originate from the lipid layer as shown in the Fig-1, and can penetrate the outer barrier, they are considered promising candidates for localized drug delivery. They are more cost-effective than liposomes and offer greater stability[8]. At pH levels above 7.0, ufasomes are believed to form due to associative interactions between fully charged and unionized fatty acids[9]. The stability of vesicles is primarily determined by the ratio of ionic forms to non-ionized neutral forms. Two key characteristics of ufasomes are the presence of lipids and their composition of single-chain amphiphiles[10]. By integrating into various nanotechnologies composed of single-chain surfactant micelles and double-chain amphiphiles, the primary components of ufasomes, such as oleic or fatty acids (cis, is-9,12-octadecadienoic acid), give these tiny vesicles enhanced versatility, surpassing that of large neutral amino acids[11].

SCHEMATIC STRUCTURE OF UFASOMES LIPID VESICULAR SYSTEM

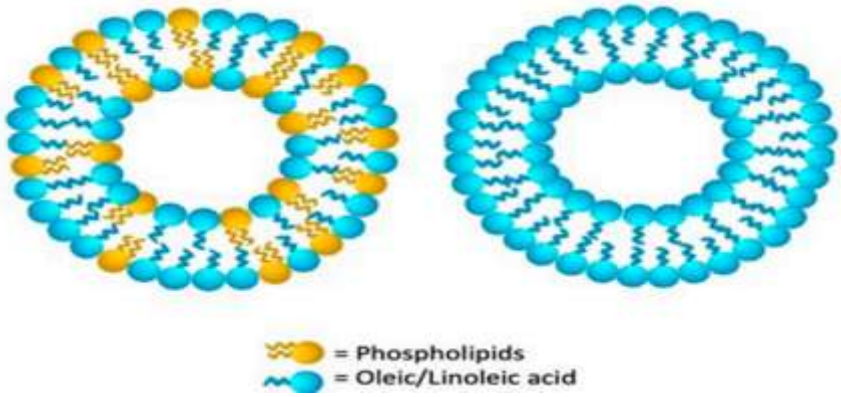

Fig-2: Schematic structure of Ufasomes Lipid Vesicular System

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COMPONENTS OF UFASOMES:

Fatty acid microspheres, known as ufasomes, are enclosed phospholipid dimodel solutions as mentioned in the Fig-2, composed of unsaturated lipids and their cationic (soap) components, with a pH range of 7 to 9. These vesicles typically consist of two forms of amphiphiles: a neutral, non-ionic form and an ionic form (soap) with a negative charge. The stability of these vesicles is mainly determined by the ratio of neutral to ionic forms. Initially described by Gebicki and Hicks in 1973, ufasomes were originally associated with unsaturated fatty acids like oleic and linoleic acids. However, later research showed that saturated fatty acids, such as decanoic and octanoic acids, can also form fatty acid vesicles, in addition to the unsaturated ones[12].

Table- 1: Components of Ufasomes

components	Function and description
Phospholipids	Lipid bilayer building components[13]
Unsaturated fatty acids	Ingredients for encapsulation that are active[14]
Cholesterol	Controls membrane fluidity[15]
Stabilizers	Improves stability[16]
Surfactants	Increases dispersibility and stability[17]
Polymers	Improves structural Integrity[18]
Solvents and excipients	Contributes to the production of Ufasomes[19]
Surface-modifying agents	Controls membrane fluidity[20]
Co-Solvents	Improves solubility[21]
Organic Solvents	Dissolve lipids and Ufasomes[22]
PEG (poly ethylene glycol)	Increase circulation time[23]
Buffer solutions	Controls pH
Ligands	Enable targeted delivery[24]
Anti-oxidants	Protects from oxidation[25]

ADVANTAGES:

- Prolongs the presence of the drug in systemic circulation while reducing toxicity. Selective uptake is achieved by delivering the drug directly to the target site.
- Enhances bioavailability, particularly for poorly soluble drugs.
- Both hydrophilic and lipophilic drugs can be incorporated into Ufasomes, delaying the elimination of rapidly metabolized drugs and functioning as a sustained release system.
- Facilitates easy drug penetration in topical applications.
- Entrapment efficiency of the drug is commendable[26].

DISADVANTAGES:

- Ufasomes are prone to oxidation, leading to stability issues in fatty drug formulations.
- Oxidation by-products may be potentially toxic.
- Colloidal instability of Ufasomes limits their effectiveness in food additives and drug delivery applications.
- There is a potential risk of atherosclerosis associated with their use[27].

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METHODS OF PREPARATION:

1) REVERSE PHASE EVAPORATION METHOD:

To prepare the oil phase, dissolve lipids and surfactants in an organic solvent. Next, create an aqueous phase containing the desired components. Mix the oil and aqueous phases to form an emulsion, then remove the solvent under low pressure to obtain water in oil emulsion[28]. To achieve a thick, gel like consistency, add a water solution and homogenize by vortexing[29]. Allow the system to stabilize for vesicle formation before proceeding with further steps, such as sonication or extrusion, to ensure uniform size and homogeneity.

2) THIN FILM HYDRATION METHOD:

In the Thin Film Hydration Method, the formation of ufasomes takes place within a specific pH range, which is crucial for the proper assembly of the vesicles. The process begins by dissolving fatty acids in an organic solvent within a round-bottom flask. A high concentration of fatty acids is essential for this method, as it ensures the formation of a sufficient amount of vesicles.

Once the fatty acids are dissolved, the solvent is gradually evaporated, typically under reduced pressure, leaving behind a thin film of fatty acid residue on the walls of the flask. The thin film of fatty acid serves as the precursor to the formation of the ufasomes.

Next, the film is hydrated by adding a buffer solution with an appropriate pH level, which is crucial for vesicle formation. The buffer facilitates the swelling and dispersion of the fatty acids, allowing them to spontaneously form vesicular structures. The hydration step is typically done under controlled conditions to ensure uniform vesicle formation and to prevent the disruption of the delicate structures.

This method is widely used for creating stable vesicles with controlled size and composition, making it a valuable technique for preparing ufasomes in drug delivery applications.

3) BY ADDITION OF ALCOHOL:

In this method, the addition of alcohol with a chain length similar to that of the fatty acids facilitates the formation of ufasomes. Alcohol acts as a solvent, helping to dissolve the fatty acids and promote the self-assembly of the molecules into vesicular structures. A significant advantage of this technique is that the resulting vesicles exhibit stability across a broad pH range, making them versatile for various applications.

The process of vesicle formation can be further accelerated by the inclusion of pre-existing fatty acid vesicles or liposomes. These pre-formed vesicles act as templates, enhancing the formation of new vesicles and reducing the time required for their formation. This can be especially beneficial in cases where the process is time-consuming, as it shortens the overall preparation time. The use of alcohol and pre-formed vesicles ensures that the vesicles are stable and have a controlled size distribution, which is essential for their effectiveness in drug delivery systems.

4) VORTEX MIXING

To prepare ufasomes using vortex mixing, a 10% stock solution of oleic and linoleic acid in chloroform is prepared at 200°C and stored fresh. A 0.2 mL portion of this stock solution is added to a test tube and dried under a nitrogen stream, forming a thin film after evaporation with a water pump. Next, 0.2 mL of 0.1 M Tris-hydroxymethyl aminomethane buffer (pH 8-9) is added to the test tube. The addition of the buffer dissolves the fatty acid film completely, resulting in a ufasome solution. The solution is then mixed using vortex mixing to ensure uniform vesicle formation.

5) AUTOPOIETIC PROCESS:

Ufasome formation occurs when an aqueous solution of fatty acids is added to a water-buffered solution, with random pH fluctuations driving the process. The vesicles form when about half of the carboxylic acid groups in the fatty acids become ionized. The ionized fatty acid molecules arrange themselves into a bilayer structure. In this structure, the hydrocarbon chains orient away from the aqueous environment, minimizing their interaction with water. This self-organizing process leads to the formation of vesicles, which are stable due to the hydrophobic interactions of the fatty acid chains[30].

CHARACTERIZATION OF UFASOMES:

1) PARTICLE SIZE AND SIZE DISTRIBUTION

The particle size and size distribution of ufasome suspensions were measured using a 90 Plus particle size analyzer with Photon Correlation Spectroscopy (PCS). The analyzer operated at a fixed angle of 90° and a temperature of 25°C. To prepare the sample, the suspensions were diluted with phosphate buffer (pH 7.4) and filtered through a polycarbonate membrane to eliminate particulate interference. This ensures accurate measurements

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of the average diameter and size distribution. Each measurement was performed in triplicate to ensure reproducibility and reliability of the results.

2) DIFFERENTIAL SCANNING CALORIMETRY (DSC)

Differential Scanning Calorimetry (DSC) was used to examine the physical state of the drug within oleic acid vesicles. The vesicles were placed in a standard aluminium pan, and the sample was sealed to prevent any loss during the analysis. The DSC instrument was set to heat the sample at a controlled rate of 2°C per minute.

This method records heat flow in response to temperature changes, identifying thermal events like melting or crystallization. By comparing the thermal behaviour of the drug-loaded vesicles with that of pure components, researchers can determine interactions, stability, and the encapsulation efficiency of the drug within the vesicular system[32].

3) EFFICIENCY

The entrapment efficiency of the drug is measured by ultracentrifugation at 25,000 rpm for 3 hours at 4°C. The supernatant is analysed using UV spectroscopy to calculate the entrapment efficiency. The percentage of the entrapped drug is determined using the following equation:

$$\text{Entrapment efficiency}(\%) = \frac{\text{Total drug - free drug}}{\text{Total drug}} \times 100$$

Where:

- **Total Drug** is the total amount of drug initially added to the ufasome formulation.
- **Free Drug** is the amount of drug that remains unencapsulated (free in the solution), typically measured from the supernatant after ultracentrifugation[33].

4) IN -VITRO DRUG RELEASE

This study aims to assess the release rate and kinetics of the drug from ufasomes, utilizing Franz diffusion cells. These cells consist of two compartments: the donor and receptor compartments. A polycarbonate membrane with a pore size of 50 nm is positioned between the two compartments. The donor compartment holds 1 ml of the ufasomal dispersion, while the receptor compartment contains phosphate-buffered saline (PBS) at pH 7.4. The solution is stirred continuously using a magnetic stirrer, with the temperature maintained at 37°C. At predetermined time intervals, aliquots of samples are taken and replaced with equal volumes of fresh PBS (pH 7.4)[34].

5) pH-DEPENDENT STABILITY

To assess the effect of pH on the stability and drug release behaviour, the optimized vesicular dispersion is incubated with buffers at pH 8.5, 7.4, 6.5, and 5.5. Samples are taken at pre-determined intervals and centrifuged at 14,000 rpm for 30 minutes. The free drug released is analysed from the supernatant, and the percentage of drug diffused is calculated using the following formula:

$$\text{Percentage of drug release}(\%) = \frac{\text{Amount of drug released}}{\text{Total drug encapsulated}} \times 100$$

The incubated vesicles are also examined for changes in morphology and size using an optical microscope[35].

PHARMACEUTICAL APPLICATIONS OF UFASOMES:

1) Anti-cancer

5-Fluorouracil (5-FU) is commonly used topically to treat basal cell carcinoma, but conventional formulations may cause side effects such as eczema and redness. By encapsulating 5-FU in ufasomes, or fatty acid vesicles, the drug can effectively penetrate the epidermal layer, reducing side effects and enhancing therapeutic efficacy[36]

2) Anti-inflammatory

Ufasomes, loaded with anti-inflammatory drugs like dexamethasone, have demonstrated potential in reducing inflammation, particularly in rheumatoid arthritis. They offer improved drug delivery compared to conventional formulations, which may enhance treatment strategies for inflammatory conditions such as psoriasis by increasing skin penetration and enabling more targeted administration.

3)Anti-fungal

Ufasomes loaded with antifungal drugs, such as terbinafine hydrochloride and oxiconazole, show improved skin penetration and systemic absorption compared to conventional creams and gels. This is especially important for treating deep fungal infections, including those caused by

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Candida albicans. Modified ufasomal formulations demonstrate greater efficacy, as evidenced by a larger zone of inhibition, underscoring their potential for more effective antifungal therapy[37]

Other Pharmaceutical Applications

Ufasomes are utilized in a wide range of medical and cosmetic applications, such as treating hair loss with minoxidil and boosting antioxidant properties in products like oleuropein. Their versatility highlights their effectiveness in addressing various medical and aesthetic conditions.

4) Transdermal hormone replacement

Ufasomes offer an efficient delivery system for transdermal hormone replacement therapy enabling the delivery of hormones like oestrogen and progesterone to postmenopausal women. This method ensures controlled hormone release through the skin eliminating the need for oral medication and reducing systemic side effects.

5) Pain management

Ufasomes, encapsulating analgesic drugs such as lidocaine and diclofenac, are transforming pain management. Lidocaine-loaded ufasomes effectively target localized pain, while diclofenac-loaded ufasomes provide targeted anti-inflammatory relief, reducing systemic side effects[3].

6) Vitamins and Anti-oxidants

Ufasomes infused with vitamins C and E enhance skincare formulations by delivering potent antioxidants and providing UV protection. Vitamin C ufasomes promote collagen production, reduce oxidative stress, and brighten the skin, while vitamin E ufasomes shield the skin from harmful UV rays and contribute to overall skin health[40].

7) Anti-viral medications

Ufasomes loaded with antiviral drugs, such as acyclovir, have shown promise in treating viral skin infections like herpes. This targeted delivery enhances efficacy and reduces systemic exposure, enabling effective management of herpes outbreaks through improved skin penetration[41].

8) Anti-wrinkle treatment

Ufasomes containing peptides and retinoids offer targeted anti-aging benefits in cosmetics, with retinoid-loaded ufasomes specifically addressing fine lines and wrinkles. The encapsulation ensures controlled release, enhancing their effectiveness in rejuvenating aging skin[42].

9) Acne Medications

Ufasomes facilitate the transdermal delivery of salicylic acid-based acne treatments, enhancing their effectiveness in managing acne. Salicylic acid-loaded ufasomes promote deeper skin penetration, effectively treating acne while reducing skin irritation[43].

RECENT INNOVATIONS IN CONVENTIONAL UFASOMES

The use of fatty acid vesicles in food additives and drug delivery remains largely unexplored, partly due to concerns about their colloidal stability, such as sensitivity to pH and divalent cations. However, recent studies involving novel types of fatty acids or mixed systems with other surfactants may lead to advancements in these applications in the future[44].

New type of fatty acids in ufasome preparation

A new type of fatty acid, cis-4, 7, 10, 13, 16, 19-docosahexaenoic acid (DHA), has been reported to self-assemble into vesicles at pH levels between 8.5 and 9[45].

Extension of pH Range

The pH range suitable for the formation of fatty acid vesicles is typically narrow, as about half of the carboxylic acid needs to be ionized. However, this range can be expanded through the use of the following innovative approaches

Addition of amphiphilic additives

Addition of amphiphilic additives such as linear alcohols or surfactants with sulphate or sulfonate head groups, can extend the pH range for vesicle formation. For example, mixtures of decanoic acid and decanoate form vesicles between pH 6.4 and 7.8, but the pH for vesicle formation can be lowered to at least 4.3 by adding sodium dodecylbenzenesulfonate (SDBS). When an equimolar amount of SDBS is combined with decanoic acid, vesicles also form at pH levels below 6.8[46].

Synthetically modify the size of the hydrophilic head group of fatty acids:

Synthetically modifying the size of the hydrophilic head group of fatty acids can improve vesicle stability at lower pH. For instance, incorporating an oligo (ethylene oxide) unit

International Journal of Pharmaceutical Research and Applications
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between the hydrocarbon chain and the carboxylate head group of a fatty acid has been shown to enhance stability. This bulky polar group has two effects: it lowers the phase transition temperature (near the Kraft point) and reduces the pH range required for vesicle formation.

Insensitivity to Divalent cations

Divalent cations such as Mg2+ and Ca2+ can cause vesicle precipitation even at low concentrations. However, the addition of fatty acid glycerol esters has been found to stabilize fatty acid vesicles in the presence of ionic solutes. Cryogenic transmission electron microscopy studies of the ternary monoolein–sodium oleate–water system have shown that uni and multilamellar vesicles formed from mixtures of monoolein and sodium oleate remain stable for extended periods, lasting over a year[47].

Enhancement of Stability through Crosslinking Fatty Acid Molecules with Chemical Bonds

One example of this approach is the formation of vesicles using anionic gemini surfactants with a carboxylic head group. Another example involves using a fatty acid (soap) that contains a polymerizable group, such as sodium 11-acrylamidoundecanoate (SAU). Both monomeric and polymerized SAU have been shown to self-assemble into vesicular aggregates, with vesicles formed from polymeric SAU remaining stable at elevated temperatures.

II. CONCLUSION:

Ufasomes, a novel vesicular drug delivery system composed of unsaturated fatty acids like oleic and linoleic acids, offer a promising platform for enhancing drug delivery in various applications. Compared to traditional vesicular systems like liposomes, ufasomes provide several advantages, including their unique dynamic properties, cost-effectiveness, and stability. They have shown significant potential in topical, transdermal, and controlled drug delivery, particularly for antifungal, anticancer, anti-inflammatory, and anti-osteoarthritic treatments. Their versatility is highlighted by their ability to encapsulate both hydrophilic and lipophilic drugs, along with improved bioavailability and extended-release profiles. However, challenges such as limited bioavailability, poor deep tissue penetration, and susceptibility to oxidation need to be addressed to optimize their efficacy. Recent advancements, including the incorporation of saturated fatty acids and refinements in preparation methods, have enhanced their stability and functionality. Their potential is further underscored by their applicability in gene delivery and other biomedical fields. Continued research into their kinetics, stability, and diverse applications is likely to unlock the full therapeutic potential of ufasomes.

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