Smart Stimuli-Responsive and Ligand-Mediated Ufasomes for Controlled and Targeted Transdermal Drug Delivery

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Abstract—**Improved skin penetration and site-specific activity, smart ufasomes have become cutting-edge vesicular carriers for targeted and regulated transdermal drug delivery (TDD). These vesicles, which are mostly made of unsaturated fatty acids like oleic acid, can be surface-functionalized with ligands to achieve precise drug targeting or can be designed to react to different physiological stimuli. By enabling regulated drug release in response to certain disease se**

I. INTRODUCTION

One of the most efficient ways to administer drugs is through cutaneous delivery. Because it offers a number of benefits over alternative drug administration methods, the transdermal drug delivery system (TDDS) is a cutting-edge method in the pharmaceutical industry. Larger dosages and longer regimens are needed to achieve therapeutic results with conventional drug delivery system formulations, and prolonged regimens may result in significant side effects and eventually low patient compliance [1]. Because of its many benefits, the oral route is typically the most appropriate, practical, and best way to administer drugs. Notwithstanding these benefits, this method of drug delivery has a number of drawbacks, such as gastrointestinal discomfort, enzymatic breakdown in the gastrointestinal system, poor absorption, low bioavailability, etc. Some medicines are dangerous to take this way as well. Needlestick fear is a frequent psychological issue that affects both adults and children when medications are supplied parenterally since there is a danger of infection during the administration of the drug [2]. TDDS is the best method for these medications to get over these obstacles.

An skin is thought to be its first line of defense, shielding it from environmental viruses, poisons, and hostile infections. The upper strata (15 μm) of the skin contain surrounded keratinocytes and many layers of lipid matrix that serve as a barrier. The primary barrier preventing the majority of medications from entering the body is the skin. To address the issues related to skin penetration, numerous permeation enhancers have been used. Several strategies have been developed in TDDS to improve medication penetration through the stratum corneum's skin layer through a variety of processes. The majority of molecules traverse the stratum corneum by both intracellular and intercellular pathways, whereas hydrophilic medications partition within the intracellular region and lipophilic pharmaceuticals travel through an intercellular pathway. Drug formulation activity can be influenced by a number of parameters, including drug solubility, dosage, polarity, and molecular weight. The physiochemical characteristics of the drug entity are crucial for the development of formulations that can reach the systemic circulation via the stratum corneum, since drug formulation is thought to be a significant factor in the production of the dose form that eventually reaches the target site.

A new technique for enhancing skin absorption is ufasome. Ufasomes are tiny vesicles of fatty acids. Ufasomes are colloidal suspensions of closed lipid bilayers composed of fatty acids and surfactant. Ufasomes have improved the retention properties of therapeutic drugs inside the skin cell membrane. In this review article we discussed about advantages and challenges of transdermal drug delivery system, ufasomes vesicular system , Ufasome formulation ,Characterization and Transdermal permeation, Mechanismof ufasome interaction with skin barrier, Stimuli-Responsive ufasomes for controlled transdermal drug delivery, Ligand-Mediated targeted transdermal drug delivery with ufasome, Importance of targeting in TDD, Targeting skin appendage (Hair

follicles and sebaceous glands), Combined and Hybrid systems, Challenges and future perspectives, conclusion.

1.1. Advantages and Challenges of Transdermal Drug Delivery system (TDDS):

Advantages of Transdermal Drug Delivery:

- ✓ Avoidance of First-Pass Metabolism: One of the biggest benefits is that the TDDS bypass the liver and gastrointestinal system, where it could be broken down and lose its potency before entering the bloodstream. Steady drug levels and enhanced bioavailability may result from this.
- ✓ Sustained and Controlled Release: Transdermal patches have the ability to deliver medication at a consistent rate for hours to days, which can result in more stable blood concentrations and less frequent dosage. This helps reduce drug level changes that frequently happen with oral drugs, which can result in better therapeutic outcomes and fewer adverse effects.
- ✓ Improved Patient Compliance: Transdermal patches are typically simple to apply and take off, they are a practical choice, particularly for patients who have trouble swallowing medications, experience nausea or vomiting, or need long-term treatment. Additionally, the decreased frequency of doses enhances compliance with treatment plans.
- ✓ Non-Invasive: Transdermal delivery eliminates pain, needle fear, and the danger of infection associated with parenteral methods, making it non-invasive as compared to injections.
  • Simple Termination Therapy : The patch can be removed to immediately interrupt drug delivery in the event of adverse events or if therapy needs to be discontinued.
  • Reduced Side Effects: Some gastrointestinal adverse effects linked to oral drugs can be prevented by avoiding the digestive tract.
- ✓ Suitable for Specific Drugs: It works especially well for medications that are heavily processed in the liver, have a short half-life, or are poorly absorbed orally.
- ✓ Self-Administration: Patients frequently apply and care for transdermal patches on their own, negating the need for help from medical professionals.
- ✓ Versatile Application: Transdermal devices can be used to treat a variety of ailments, such as motion sickness, hormone replacement, pain management, and quitting smoking.

Challenges of Transdermal Drug Delivery:

- ✓ Limitations of the Skin Barrier: The stratum corneum, the outermost layer of the skin, functions as a very strong barrier that prevents the majority of medications from penetrating. Effective skin penetration is limited to specific medications with particular physicochemical characteristics (e.g., low molecular weight, appropriate lipophilicity). The number of medications that can be administered transdermally is greatly limited as a result.
- ✓ Low Drug Doses: Because the skin can only absorb a certain quantity of medication at a time, transdermal delivery is typically not appropriate for medications that need high dosages.
- ✓ Variable Skin Permeability: Individuals, bodily parts, and variables such as age, race, and preexisting medical disorders can all affect skin permeability. Unpredictable therapeutic effects and uneven drug absorption may result from this variability.
- ✓ Skin Irritation and Sensitization: Extended exposure to the patch's ingredients (drug, adhesive, and excipients) may result in allergic reactions (contact dermatitis), localized skin irritation, redness, and itching. This may cause discomfort and force the treatment to be stopped.

Advantages of Vasicular System in TDDS

Vesicular systems play a key role in TDDS by enhancing the penetration and bioavailability of pharmaceuticals and overcoming the stratum corneum, the skin's natural barrier. They can encapsulate medications that are hydrophilic or lipophilic because to their special structure. They can transport medications to deeper layers of the skin and even into the bloodstream because of their deformability and capacity to fuse with skin lipids. Vesicles can release the encapsulated medication gradually, resulting in long-lasting therapeutic effects and a decrease in the frequency of doses. It lessens systemic exposure and related side effects by delivering controlled release or directing medications to certain areas. TDDS via vesicular systems may

provide a more efficient delivery method for medications with low oral bioavailability (for example, as a result of first-pass metabolism). The various vasicular system developed are liposomes, ethosomes, transferosomes, pharmacosomes, aquasomes, niosomes in which ufasomes offers advantages over other conventional vesicular systems include improved drug penetration, especially in topical applications, reduced cost because of easily accessible fatty acids, and versatility in drug loading for both hydrophilic and lipophilic substances. Additionally, they can increase the duration of drug circulation, which can result in a prolonged release profile and decreased drug toxicity, making them an economical and efficient drug delivery method.

1.3. Ufasomes: Ufasomes are vesicular structures made of unsaturated long-chain fatty acids that are created by mechanically agitating a non-lipoidal bilayer's evaporating thin film layer. Unsaturated fatty acid vesicles, or ufasomes, are closed lipid bilayered suspensions composed of unsaturated fats and their ionized species (surfactant), with a pH range of 7 to 9. There are typically two kinds of amphiphiles seen in fatty acid vesicles: non-im and ionized form (soap that is negatively charged). The ratio of non-ionic neutral to ionic form establishes the fundamentals of vesicle stability. Fatty acid and oleic and linoleic acid vesicles were first described by Gebicki and Hicks in 1973. In the years that followed, the vesicles were also identified as ufasomes. However, subsequent research revealed that saturated fatty acids that resemble octanoic and decanoic acids can also form fatty acid vesicles in addition to unsaturated fatty acids. The availability of fatty acids and their composition of single-chain amphiphiles are two significant characteristics of ufasomes. Although phospholipids are utilized in the production of liposomes, there is a shortage of pure synthetic phospholipids in sufficient quantities, and natural phospholipids are chemically diverse.

II. FORMULATION, CHARACTERIZATION AND TRANSDERMAL PERMEATION

2.1 Ufasomes Preparation Methods:

Thin Film Hydration Method:

In this mechanism, vesicle formation happens across a narrow pH range. In a flask with a circular rim, fatty acid is combined with an organic solvent. A high fatty acid concentration is required for this technique. Before the organic solvent has completely evaporated, the liquid is vaporised. Finally, a thin fatty acid layer is created and hydrated using a pH-appropriate buffer

By Addition of Alcohol:

Fatty acid vesicles are formed in this method by adding an alcohol with the same chain length as the fatty acid. The primary advantage of this method is that the fatty acid vesicles are stable over a wide pH range. Vesicle formation may be increased in the presence of pre-added fatty acid vesicles and liposomes. Because this procedure takes a long time to perform, this method saves time.

Autopoetic Process

When an aqueous fatty acid solution is introduced to a water-buffered solution, fatty acid vesicles form as a result of the random pH change. It is possible for vesicles to form when half of the carboxylic acids in a fatty acid ionise. The hydrocarbon chain creates a bilayer arrangement opposing the aqueous compartment, decreasing water interaction.

CHARACTERIZATION OF UFASOMES

Vesicle Charge and Size Every formulation requires vesicle size and charge in order to be trapped or regulated. The size, shape, and other characteristics of a vesicle, such as stability, are characterized using a zeta analyzer. The charge of the molecule is ascertained using a zeta potential analyzer; the lower the charge, the more stable the molecule will be. Therefore, we take into consideration excipients and surfactants with lower zeta potential for high stability. Using an optical magnifying lens that has been adjusted (by ocular and stage micrometer), the optical microscopy technique determines the size of the vesicles. The repulsive forces that operate between the bilayers9 largely determine the size.

Photo microscopy: Photograph microscopy for vesicle organization and morphology was used to illustrate vesicle scattering. Using a fitted camera and an optical magnifying lens, ufasomal suspension was examined and recorded at 40–100X amplification.

Efficiency of entrapment
A few factors, such as the addition of cholesterol, the surfactant's structure, and the preparation method, were examined and improved in order to achieve the maximum entrapment productivity. Centrifugation, gel filtration, and other techniques are used to compare the entrapped and unentrapped medication in order to assess the entrapment efficiency.

Differential Scanning Calorimetry:
Scanning Differentially The physical state of the substance inside the oleic acid vesicles is assessed using calorimetry. The vesicles were filtered at a rate of 2°C/min8 in a conventional aluminum pan. The DSC curve shows the compatibility of the entrapped medication with its excipients and allows us to analyze the enthalpy and melting behavior of oleic acid and other excipients that make up the vesicles.

Zeta Potential-Charge Repulsion Measurement:
The strength Repulsiof the charge or electrostatic repulsion or attraction between particles is measured by the zeta potential. Both the liquid's and the particles' characteristics affect the zeta potential. It is crucial in establishing the solution's or emulsion's aggregative stability.

In-Vitro Drug Release:
This study aims to determine the release kinetics and the speed at which a medicine is delivered from ufasomes. The Franz diffusion cell is used for this. The donor and the receptor are the two compartments that make up the Franz diffusion cell. These two compartments are separated by a 50 nanometer-pore-size polycarbonate film. While the receptor compartment had phosphate buffer saline (PBS) at a pH of 7.4, which was maintained at 37°C and continuously swirled with a magnetic stirrer, the donor compartment held 1 milliliter of Ufasomal dispersion. Test aliquots are taken out and swapped out for.

Ufasomes Transdermal permeation
Unsaturated fatty acid-based vesicles called ufasomes are a promising transdermal medication delivery method. They may improve the efficacy of drugs given topically by increasing drug penetration through the skin. This is made possible by ufasomes' special structure, which enables them to merge with the lipid bilayers of the skin and release their pharmacological payload.

Ufasomes enhance transdermal permeation :
The primary mechanism by which ufasomes enhance transdermal permeation involves their ability to fuse with the stratum corneum, the outermost layer of the skin. The stratum corneum is a major barrier to drug penetration due to its lipid-rich structure. Ufasomes, with their fatty acid composition, can integrate into this lipid barrier, disrupting it and allowing the encapsulated drug to pass through more easily.

2.3 Mechanisms of Ufasome Interaction with the Skin Barrier:
Unsaturated fatty acids, such as oleic acid, and their salts, such as sodium oleate, make up the majority of ufasomes, which are vesicular drug delivery vehicles. Their ability to effectively distribute drugs transdermally (TDD) depends on how well they interact with the skin barrier, particularly the stratum corneum (SC), which is the skin's outermost layer. The main ways that ufasomes engage with and pass through the epidermal barrier are as follows:

1. Lipid Bilayer Fusion:Ufasomes resemble skin lipids in their bilayer structure.
Their tight structure may be disrupted if they combine with SC lipids.
This improves drug penetration by lowering the skin's barrier resistance.

2. The stratum corneum's fluidization: Oleic acid and other unsaturated fatty acids have the ability to break apart the SC's dense lipid packing.

3. Enhancement of Intercellular Pathways :
Ufasomes mostly travel through the lipid-rich intercellular gaps between corneocytes. These routes are widened by the permeability enhancer effect of fatty acid concentration.

4. Depot Formation: Ufasomes can function as a reservoir or depot once they are in the SC or upper viable epidermis, enabling gradual drug release.

5. Appendageal Routes of Penetration: Ufasomes can also enter through sweat glands and hair follicles, which is particularly advantageous for big or less

permeable molecules. A quicker initial penetration may be made possible by this appendageal channel.

6. Electrostatic and pH-Driven Interaction: Fatty acid salts are converted back to fatty acids by the skin's somewhat acidic pH (~5.5), which aids in membrane fusion and enhances skin penetration.

7. Permeation Dependent on Size :
Typically, ufasomes are 100–400 nm in size. While larger vesicles may stay in superficial layers and facilitate local delivery, smaller ones can penetrate deeper.

III. STIMULI RESPONSIVE UFASOMES FOR CONTROLLED TRANSDERMAL DRUG DELIVERY RELEASE

A promising development in regulated transdermal medication release is stimuli-responsive ufasomes. to recognize their potential. Stimuli-responsive ufasomes are designed to react to particular internal or external stimuli by releasing their encapsulated pharmacological payload. By enabling targeted and regulated drug release, this "smart" delivery maximizes therapeutic efficacy while reducing negative effects.The body uses these biochemical cues, which are frequently suggestive of a sick condition. Among the examples are:

3.1 PH Responsive Ufasomes: The pH of intracellular compartments, inflammatory tissues, and tumors is frequently lower than that of healthy tissues. In these acidic conditions, ufasomes can be engineered to destabilize and liberate their contents.

3.2 Redox potential Responsive Ufasomes: Drug release may be triggered by variations in the concentration of reducing agents, such as glutathione, between healthy and sick cells (such as tumor cells).

3.3 Enzyme-responsive ufasomes: By using the overexpression of particular enzymes at a disease location, certain bonds in the ufasome structure can be broken, releasing the medicine.

3.4 Thermo responsive temperature Ufasomes: It is possible to engineer ufasomes to go through a phase transition and release medications at slightly higher temperatures, which can be brought on by outside heat sources.

3.5 Photo-responsive light Ufasomes: Drug release can result from the breakdown or conformational alteration of specific light-sensitive ufasome components following exposure to light.

3.6Ultrasound Responsive Ufasomes: High-frequency sound waves have the ability to break down the integrity of ufasomes, which facilitates the release of drugs.

3.7 Ufasomes that are responsive to magnetic fields: When magnetic nanoparticles are integrated into ufasomes, they can react to external magnetic fields, enabling targeted delivery or controlled drug release.

IV. LIGAND- MEDIATED TARGETED TRANSDERMAL DRUG DELIVERY WITH UFASOMES

1. Targeted Drug Delivery Mediated by Ligands. The use of certain molecules (ligands) that attach to receptors on the surface of targeted cells or tissues is known as "ligand-mediated targeted drug delivery." By precisely delivering medications to targeted areas, this technique increases effectiveness and reduces unwanted effects.
• Ligands : That selectively identify and attach to receptors on cells or tissues can be peptides, antibodies, or tiny compounds. The medicine is directed to particular targets, including cancer cells or inflammatory tissue, by binding these ligands to drug carriers (such as nanoparticles, liposomes, or ufasomes).

2. Delivery of Drugs Transdermally.
Using the skin to distribute medication is known as transdermal drug administration. Although the skin serves as a barrier, it can be altered or circumvented to let specific molecules through. Transdermal medication delivery has the following benefits:
Combining Ligand-Mediated Targeting with Ufasomes for Transdermal Delivery
The goal of ligand-mediated targeted transdermal administration with ufasomes is to create ligand-decorated ufasomes that encapsulate the medication. To ensure that the medication is administered where

it is most required, these ligands would target particular receptors on the skin or deeper tissue layers (such as cancer cells, inflammatory cells, or others).

4.1 Importance of Targeting in TDD : Targeting in Transdermal Drug Delivery (TDD) refers to methods that minimize distribution to undesirable locations while precisely directing a drug to a desired target, such as local skin tissues or systemic circulation. This is particularly important for enhancing patient compliance, safety, and efficacy.

4.2 Strategies for Surface Functionalization of Ufasomes: One important strategy to improve ufasome performance for targeted drug administration, extended circulation, stimuli-responsiveness, and improved skin penetration is surface functionalization. The main tactics are listed below:

1. Ligand Conjugation:
2 .Charge Modification
3. Polymer Coating
4. Protein or Cell Membrane Camouflage
5. Experimental Techniques for Functionalization

4.3 Ligands for cell- Specific Targeting**:** Ligands for cell-specific targeting are substances that bind selectively to receptors or markers that are overexpressed on the surface of specific cell types in order to enable targeted medication administration, diagnostics, or imaging. Below is a list of commonly used ligands, their target receptors, and their applications:

1. Antibodies & Antibody Fragments
- Ligands: Monoclonal antibodies (mAbs), Fab fragments, scFv
- Targets:
  - HER2 (e.g., trastuzumab for breast cancer)
  - EGFR (e.g., cetuximab for colorectal cancer)
  - CD20 (e.g., rituximab for B-cell lymphoma)
- Advantages: High specificity and affinity
- Limitations: Large size, immunogenicity, complex production

2. Peptides:
- Ligands: Small peptide sequences that mimic natural ligands
- Common Peptides:
  - GE11 peptide – targets EGFR without triggering internalization
  - RGD peptide – binds to integrins ($\alpha v\beta 3$) overexpressed in tumor angiogenesis
  - TAT peptide – cell-penetrating peptide from HIV (non-specific)
- Advantages: Small, easy to synthesize, low immunogenicity
- Applications: Tumor targeting, intracellular delivery
- Limitations: Sensitive to nucleases unless chemically modified

3. Sugars & Carbohydrates:
- Ligands:
  - Mannose – targets mannose receptors (e.g., dendritic cells, macrophages)
  - Galactose/lactose – targets ASGPR on hepatocytes
  - Sialic acid derivatives – for targeting selectins
- Applications: Liver-targeted delivery, immune modulation

4. Natural or Synthetic Receptor Ligands:
- Transferrin: Targets transferrin receptor (highly expressed in many tumors)
- Hyaluronic acid: Targets CD44 (upregulated in cancer stem cells)
- EGF (epidermal growth factor): Targets EGFR

4.4 Targeting Skin Appendages (Hair Follicles, Sebaceous Glands):

Hair Follicles**:** The tube-like structure (pore) that envelops a hair's root and strand is called a hair follicle. Your skin's outermost two layers contain hair follicles. You have more than one million hair follicles on your head and more than five million on your body from birth. Hair emerges from your hair follicles as you mature. Your hair follicle is one of the few bodily structures that has the ability to degenerate and regenerate, or stop functioning and then start operating again. This technique aids in the growth of body hair.

Your skin has structures called hair follicles, which are responsible for hair growth. Millions of hair follicles are present in your skin from birth. The hair follicles cannot be removed. Hair loss or decreased hair growth is caused by damaged hair follicles.

Sebaceous Glands ;

Each hair follicle normally contains many sebaceous glands, which are a component of the pilosebaceous unit. With the exception of the palms, soles, lips, and tops of the feet, sebaceous glands are composed of lobules, ducts, and true exocrine glands that are present throughout the skin. Sebocytes, which make up the lobules, create sebum, a fatty substance with fungicidal and bactericidal qualities that lubricates hair. The entire sebocyte loses its cytoplasm and perishes during the excretory process as it releases its contents into the lumen of the gland, making these "oil glands" also classified as holocrine exocrine glands.

4.5. "Active" Permeation Enhancement through Receptor-Mediated Uptake:

A focused and energy-dependent method to enhance drug delivery across biological barriers (such as skin or mucosa), particularly in topical or transdermal drug delivery systems, is called "active" penetration enhancement through receptor-mediated uptake. In contrast to passive diffusion, this technique seeks to increase the absorption and penetration of drug-loaded carriers like ufasomes, liposomes, or nanoparticles by taking use of certain cell surface receptors.

1. Receptor-Mediated Uptake:

Involves ligands (affixed to drug carriers) attaching to certain target cell surface receptors. The vesicle can enter or pass through the cells as a result of this binding, which also causes endocytosis or transcytosis. Receptors that are frequently employed include EGFR, folate, transferrin, and lectin receptors.

2. Ligand Functionalization:

Antibodies, peptides, and sugars are ligands that bind selectively to receptors on the surface of drug carriers, such as ufasomes. increases bioavailability, reduces off-target effects, and guarantees cell-specific targeting.

3 Energy-Dependent Process:

Receptor-mediated uptake is temperature-sensitive and necessitates ATP, in contrast to passive diffusion. This pathway is pharmacologically modulable or inhibitable, and it is saturable (limited by the number of receptors).

4. Combined and Hybrid Smart Ufasome Systems:

Combining several functions to improve efficiency, targeting, responsiveness, and therapeutic results, combined and hybrid smart ufasome systems are a cutting-edge method of transdermal drug delivery. An organized summary of this idea that can be used in research papers, reviews, or thesis work is provided below:

V. CONCEPT OF COMBINED AND HYBRID SYSTEMS

Combined Systems: To enhance penetration, stability, or controlled release, ufasomes are combined with other delivery methods or technologies (such as microneedles, nanoparticles, or gels).

Hybrid Systems: Ufasomes that combine targeting and triggered release in a single system by incorporating ligand-functionalization and other stimuli-responsive components (such as pH, temperature, enzymes, and redox).

5.1. Multi-Stimuli Responsive Ufasomes:

A sophisticated family of vesicular drug delivery systems known as multi-stimuli responsive ufasomes is designed to react to two or more external (such as temperature, light, magnetic fields, or ultrasound) or internal (such as pH, redox potential, or enzymes) stimuli. These systems improve therapeutic efficacy and site-specific delivery, especially in illnesses like cancer, inflammation, and skin problems, by combining intelligent release mechanisms with the amphiphilic nature and strucstural benefits of ufasomes (unsaturated fatty acid vesicles).

5.2. Ligand-Targeted and Stimuli-Responsive Ufasomes:

Vesicular drug delivery systems known as ligand-targeted and stimuli-responsive ufasomes combine controlled release (via stimuli responsiveness) with active targeting (through ligands). These devices are very helpful in cancer treatment, topical medication delivery, and chronic inflammatory diseases. They also improve therapeutic precision and reduce off-target toxicity.

5.3. Ufasome-Integrated Microneedle Patches

Ufasome-Integrated Microneedle Patches are a cutting-edge hybrid drug delivery device that blends two potent technologies: microneedle patches and ufasomes, or unsaturated fatty acid vesicles.

Mechanism of Action:

1. Insertion

Without causing discomfort or bleeding, the microneedle patch is applied to the skin to create microchannels.

2. Transportation:

Deeper layers of skin are penetrated by ufasomes that are coated on or implanted in the microneedles. Drugs are released through:

propagation via the microchannels.

Microneedle dissolution when MNs are being dissolved.

Release from the ufasome vesicles under control.

3. Permeation: Ufasomes can improve drug penetration and retention by fusing with skin lipids or being absorbed by skin cells.

5.4. Ufasome-Based Theranostic Systems:

Based on Ufasomes A new family of vesicular nanocarriers known as "Theranostic Systems" combines therapeutic and diagnostic (theranostic) functions on a single platform. Ufasomes are unsaturated fatty acid vesicles that are perfect for theranostic applications, particularly in transdermal or localized administration systems, because of their benefits, which include biocompatibility, ease of manufacture, and improved skin penetration.

VI. CHALLENGES AND FUTURE PERSPECTIVES

6.1. Current Challenges:

Even though smart ufasome-based transdermal drug delivery systems have advanced significantly, a number of obstacles stand in the way of their widespread use and clinical translation:

1. Shelf life and stability

Vesicle fusion, drug leakage, and unsaturated fatty acid oxidation are among the physical and chemical instability issues that ufasomes are susceptible to. One major challenge is maintaining stability over the long term without sacrificing responsiveness or targeting capability.

2. Scalability and Reproducibility:

Methods such as sonication or thin-film hydration frequently result in batch-to-batch variability. Clinical and commercial viability depend on creating manufacturing methods that are scalable, repeatable, and GMP-compliant.

3. Controlled Responsiveness

Although stimuli-responsive systems (such as pH, temperature, enzymatic, and redox) provide regulated drug release, it is still difficult to fine-tune sensitivity to get exact spatiotemporal control in the dynamic skin environment.

4. Skin Barrier Complexity:

The stratum corneum serves as a strong defense. It is still challenging to consistently and sufficiently penetrate ufasomes via intact skin, even with targeted ligands and permeation enhancers.

5. Ligand Functionality and Target

The expression of particular receptors, which can differ between people or pathological conditions, is necessary for ligand-mediated targeting. Furthermore, ligand conjugation may change biodistribution or vesicle stability.

6. Potential Immunogenicity and Toxicity

Surface alterations (such as ligands or polymers) may cause local discomfort or immunological reactions. Thorough testing is required to determine whether using smart ufasomes repeatedly or over an extended period of time is safe.

7. Absence of Correlation in Vivo

Because of things like enzymatic breakdown, immunological clearance, or inadequate retention at the target site, in vivo efficacy frequently does not match with the optimistic outcomes of many in vitro trials.

8. Regulatory and Standardization Issues

Approval procedures for smart transdermal vesicular systems are unclear due to the lack of clear regulatory requirements. There are no standardized procedures for quality assurance and assessment.

6.2. Future Directions:
The following areas should be the focus of future research and development in order to fully utilize smart ufasomes in transdermal drug delivery.

1. Advanced Systems That Respond to Multiple Stimuli
Creating ufasomes that react to many stimuli (such as pH + temperature, redox + enzymatic) can improve site-specific delivery and offer more precise control over drug release in intricate physiological scenarios.

2. Accurate Ligand Design:
Targeting efficiency will be increased by creating ligands with high receptor affinity and selectivity for sick skin tissues (such as cancer, infections, or inflammation). Aptamers, antibody fragments, and peptide ligands all exhibit potential for improved specificity.

3. Composite and Nanohybrid Ufasomes :
The mechanical strength, penetrating ability, and responsiveness of ufasomes can be enhanced by combining them with polymers, inorganic nanoparticles (such as gold or silica), or microneedle platforms. This will improve the effectiveness of treatment.

4. Customized Transdermal Treatments:
Personalized medication delivery systems could result from using patient-specific biomarkers to adjust stimuli-responsiveness or ligand selection, which would be especially helpful for chronic or diverse skin disorders.

5. Theranostics and Real-Time Monitoring
Theranostic applications in dermatology and oncology may be made possible by integrating imaging agents or biosensors into ufasomes, which would allow for real-time monitoring of medication release and treatment response.

6. Sustainable and Expandable Production:
To support industrial translation, fabrication processes that are scalable, economical, and environmentally friendly—like continuous flow or microfluidics—are crucial.

7. Clinical Translation Using In Vivo Models:
To assess efficacy, penetration, and safety, more advanced preclinical models that replicate the physiology of human skin are required. In order to evaluate human applicability and obtain regulatory approval, early-phase clinical trials will be essential.

8. Development of Regulatory Frameworks
To create standardized procedures and safety standards unique to intelligent, responsivetransdermal systems, cooperation between academic institutions, business, and regulatory agencies is required.

VII. CONCLUSION

Because smart ufasomes combine ligand-mediated targeting techniques with stimuli-responsive mechanisms, they represent a substantial improvement in the field of transdermal drug delivery. Mostly made up of unsaturated fatty acids, these vesicular carriers have improved biocompatibility, flexibility, and the capacity to react to internal or external stimuli like light, pH, temperature, or enzymes. Additionally, targeted delivery to certain cell types or tissues is made possible by surface modification with particular ligands, increasing therapeutic efficacy while reducing systemic side effects.

REFERENCES

[1] Kaur, Jotinder, Jasmeen Kaur, Sandhya Jaiswal, and G. Gupta. "Recent advances in topical drug delivery system." *Pharmaceutical Research* 6, no. 07 (2016): 6353-6369.
[2] Jain, Shikha, Vikas Jain, and S. C. Mahajan. "Lipid based vesicular drug delivery systems." *Advances in Pharmaceutics* 2014, no. 1 (2014): 574673.
[3] Patel, D. M., R. H. Jani, and C. N. Patel. "Ufasomes: A vesicular drug delivery." *Systematic reviews in pharmacy* 2, no. 2 (2011).
[4] Nair, A. J., K. Aswathi, A. George, P. P. Athira, and S. C. Nair. "Ufasome: a potential phospholipid carrier as a novel pharmaceutical formulation." *International research journal of pharmacy* 5, no. 4 (2014): 250-253.
[5] Kaur, Loveleen Preet. "Topical gel: a recent approach for novel drug delivery." *Asian journal*

of biomedical and Pharmaceutical Sciences 3, no. 17 (2013): 1.

[6] Verma, Ashni, Sukhdev Singh, Rupinder Kaur, and Upendra K. Jain. "Topical gels as drug delivery systems: A review." *Int. J. Pharm. Sci. Rev. Res* 23, no. 2 (2013): 374-382.

[7] Rastogi, Vaibhav, and Pragya Yadav. "Transdermal drug delivery system: An overview." *Asian Journal of Pharmaceutics (AJP)* 6, no. 3 (2012).

[8] Pawar, P.M., Solanki, K.P. and Mandali, V.A., 2018. Recent advancements in transdermal drug delivery system. *Int J Pharm Clin Res*, *10*(3), pp.65-73.

[9] Kumar, L., Verma, S., Kumar, S., Prasad, D. N., & Jain, A. K. (2017). Fatty acid vesicles acting as expanding horizon for transdermal delivery. *Artificial cells, nanomedicine, and biotechnology*, *45*(2), 251-260.

[10] Madhavi, Nimmathota, Beeravelli Sudhakar, KV N. Suresh Reddy, and J. Vijaya Ratna. "Design by optimization and comparative evaluation of vesicular gels of etodolac for transdermal delivery." *Drug development and industrial pharmacy* 45, no. 4 (2019): 611-628.

[11] Shabbir, M., Ali, S., Shahid, N., Rehman, K., Amin, U., & Raza, M. (2014). Formulation considerations and factors affecting transdermal drug delivery system—A review. *Int. J. Pharm. Integr. Life Sci*, *2*, 20-35.

[12] Latheeshjlal, L., Phanitejaswini, P., Soujanya, Y., Swapna, U., Sarika, V., & Moulika, G. (2011). Transdermal drug delivery systems: an overview. *International Journal of PharmTech Research*, *3*(4), 2140-2148.

[13] Zaid Alkilani, Ahlam, Maelíosa TC McCrudden, and Ryan F. Donnelly. "Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum." *Pharmaceutics* 7, no. 4 (2015): 438-470.

[14] Tanwar, Himanshi, and Ruchika Sachdeva. "Transdermal drug delivery system: A review." *International journal of pharmaceutical sciences and research* 7, no. 6 (2016): 2274.

[15] Gebicki, J. M., and M. Hicks. "Preparation and properties of vesicles enclosed by fatty acid membranes." *Chemistry and physics of lipids* 16, no. 2 (1976): 142-160.

[16] Bolla, Pradeep Kumar, Carlos A. Meraz, Victor A. Rodriguez, Isaac Deaguero, Mahima Singh, Venkata Kashyap Yellepeddi, and Jwala Renukuntla. "Clotrimazole loaded ufosomes for topical delivery: formulation development and in-vitro studies." *Molecules* 24, no. 17 (2019): 3139.

[17] Kaur, N., and R. Garg. "Optimization and evaluation of oleic acid based unsaturated fatty acid liposomes gel." *J Bioequivalence Bioavailab* 9 (2017).

[18] Zakir, F., Vaidya, B., Goyal, A. K., Malik, B., & Vyas, S. P. (2010). Development and characterization of oleic acid vesicles for the topical delivery of fluconazole. *Drug delivery*, *17*(4), 238-248.

[19] Sharma, Arvind, and Sandeep Arora. "Formulation and in vitro evaluation of ufasomes for dermal administration of methotrexate." *International Scholarly Research Notices* 2012, no. 1 (2012): 873653.

[20] Mittal, Rajkamal, Arvind Sharma, and Sandeep Arora. "Ufasomes Mediated Cutaneous Delivery of Dexamethasone: Formulation and Evaluation of Anti-Inflammatory Activity by Carrageenin-Induced Rat Paw Edema Model." *Journal of pharmaceutics* 2013, no. 1 (2013): 680580.

[21] Bansal, Saurabh, Chandan Prasad Kashyap, Geeta Aggarwal, and S. L. Harikumar. "A comparative review on vesicular drug delivery system and stability issues." *Int J Res Pharm Chem* 2, no. 3 (2012): 704-713.

[22] Verma, S., Bhardwaj, A., Vij, M., Bajpai, P., Goutam, N., & Kumar, L. (2014). Oleic acid vesicles: a new approach for topical delivery of antifungal agent. *Artificial cells, nanomedicine, and biotechnology*, *42*(2), 95-101.

[23] Salama, Alaa Hamed, and Mona Hassan Aburahma. "Ufasomes nano-vesicles-based lyophilized platforms for intranasal delivery of cinnarizine: preparation, optimization, ex-vivo histopathological safety assessment and mucosal confocal imaging." *Pharmaceutical development and technology* 21, no. 6 (2016): 706-715.

[24] Li, Q. (Ed.). (2013). *Intelligent stimuli-responsive materials: from well-defined*

nanostructures to applications. John Wiley & Sons.

[25] Nagarkar, Sanjog S., Aamod V. Desai, and Sujit K. Ghosh. "Stimulus-responsive metal–Organic frameworks." *Chemistry–An Asian Journal* 9.9 (2014): 2358-2376.

[26] Jobbágy, Csaba, and Andrea Deák. "Stimuli-Responsive Dynamic Gold Complexes." *European Journal of Inorganic Chemistry* 2014.27 (2014): 4434-4449.

[27] Xu, Bingjia, et al. "A new ligand and its complex with multi-stimuli-responsive and aggregation-induced emission effects." *Chemical Communications* 47.39 (2011): 11080-11082.

[28] Mura, Simona, Julien Nicolas, and Patrick Couvreur. "Stimuli-responsive nanocarriers for drug delivery." *Nature materials* 12.11 (2013): 991-1003.

[29] Ding, Yue, et al. "Formation of stimuli-responsive supramolecular polymeric assemblies via orthogonal metal–ligand and host–guest interactions." *Chemical Communications* 49.53 (2013): 5951-5953.

[30] Dehaini, Diana, et al. "Ultra-small lipid–polymer hybrid nanoparticles for tumor-penetrating drug delivery." *Nanoscale* 8.30 (2016): 14411-14419.

[31] Zhu, Lin, and Vladimir P. Torchilin. "Stimulus-responsive nanopreparations for tumor targeting." *Integrative Biology* 5.1 (2013): 96-107.

[32] Torchilin V. Multifunctional and stimuli-sensitive pharmaceutical nanocarriers. Eur J Pharm Biopharm. 2009; 71:431–444. [PubMed: 18977297].

[33] Felber, Arnaud E., Marie-Hélène Dufresne, and Jean-Christophe Leroux. "pH-sensitive vesicles, polymeric micelles, and nanospheres prepared with polycarboxylates." *Advanced drug delivery reviews* 64.11 (2012): 979-992.

[34] Hu, Yun, et al. "In vitro controlled release of antigen in dendritic cells using pH-sensitive liposome-polymeric hybrid nanoparticles." *Polymer* 80 (2015): 171-179.

[35] Jaiswal, Manish K., et al. "Dual pH and temperature stimuli-responsive magnetic nanohydrogels for thermo-chemotherapy." *Journal of Nanoscience and Nanotechnology* 14.6 (2014): 4082-4089.

[36] Juluri, Abhishek, et al. "Minimally invasive transdermal delivery of iron–dextran." *Journal of pharmaceutical sciences* 102.3 (2013): 987-993.