IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Transferosomes: A Novel Vesicular Carrier For Skin Delivery System

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ABSTRACT

Transferosomes are elastic substances that can bend their structure and squeeze themselves through narrow pores smaller than their size, making them an effective drug delivery mechanism for poorly soluble medicines. They are ultra-deformable vesicles with a hydrophilic core in the center and a lipid bilayer around them. To address the challenges with conventional oral drug delivery, alternative formulations of transferosomes have been created employing non-ionic surfactants such Span 80, Span 20, soya lecithin, Carbopol 940, and Tween 80 by rotary film evaporation and Vortexing/sonication processes.This carrier system has piqued the interest of pharmaceutical researchers because it improves patient acceptability and reduces side effects associated with the traditional oral route by avoiding first-pass metabolism, thereby improving the physiological and pharmacological response through consistent drug levels. This review covers the structure, benefits and drawbacks of formulation materials, formulation procedures, evaluation techniques, and applications, as well as patents published in the literature.

KEYWORDS: Transferosomes, Lipophilic, Medication, Skin, Epidermis.

INTRODUCTION

Contrasting to traditional techniques like injection and oral delivery, topical drug delivery systems (TDDS) have several potential benefits [1]. The skin's permeability, which makes it highly impenetrable to hydrophilic and macromolecules and permeable to small molecules and lipophilic medicines, is the main drawback of TDDS. The stratum corneum (SC), the skin's outermost layer, serves as the primary barrier and rate-limiting step for drug diffusion over the skin [2].

Because it makes drug distribution simple, transdermal delivery is a desirable strategy. One of the main issues with dermal and transdermal drug delivery methods are the permeability of the stratum corneum. Made up of flattened, keratinized epidermal cells, the stratum corneum is the outermost layer of the epidermis. Chemical transfer is hampered by water-tight cells with a strong, flexible membrane, making this mode of administration inadequate for therapeutic use. Techniques including electrophoresis, sonophoresis, and iontophoresis have been researched and developed to address these problems. Colloidal carriers include non-ionic surfactant vesicles like proniosomes and niosomes [3].

The word "transferosomes" combines a Latin and Greek word. The Latin term "transfere" means "carry across," whereas the Greek word "soma" means "body." Therefore, "carrying body" is the meaning of the term "transferosomes."[4]. Phospholipids such as phosphatidylcholine, which self-assemble into a lipid bilayer in an aqueous environment and close to form a vesicle, make up the majority of these unique liposome

types [5]. By squeezing themselves, it gets past the skin layer's barrier to penetration. The vesicle is self-regulating and self-optimizing due to the interdependence of the bilayer's structure and local composition [6].
Both low and high molecular weight medications can be delivered transdermally using transferosomes [7]. Transferosomes are highly flexible, specially engineered lipid supra molecular aggregates that may pass through intact mammalian skin to serve as a drug carrier for targeted, non-invasive drug delivery and long-term release of medicinal substances [8]. Because "edge activators" are incorporated into the vesicular membrane, each transferosome has at least one inner aqueous compartment that is encircled by a lipid bilayer with unique characteristics. As edge activators, surfactants such sodium cholate, sodium deoxycholate, span 80, and Tween 80 have been employed [9].
Drugs applied topically, usually as patches or semisolids, are referred to as transdermal drug delivery systems. To transport the medication to the systemic circulation at a regulated rate, these formulations are applied to the skin that is still intact. Recent years have seen the emergence of a number of sophisticated Transdermal Drug distribution Systems (TDDS), which hold promise for the rate-controlled distribution of different medications [10].
These devices are made specially to guarantee a steady and regulated delivery of medications into the bloodstream through the skin. Through more accurate administration, the transdermal delivery method has the potential to improve medication safety and therapeutic efficacy [10].
Numerous illnesses, including those of the skin, eyes, brain, etc., have been treated by transferosomes [11]. For instance, according to published research, chemotherapy, which is often administered to address infections within cells, is less effective in treating cancer due to its incapacity to penetrate cells. As a result, new carriers that could enter cells deeply, such transferosomes, were developed [12].

Structure of transferosomes

A transferosome is a synthetic vesicle that mimics the properties of a cell vesicle or an exocytosing cell, making it appropriate for targeted and regulated drug delivery. Complex vesicles known as transferosomes feature a membrane that is incredibly flexible and self-regulating, allowing for deformation [13].

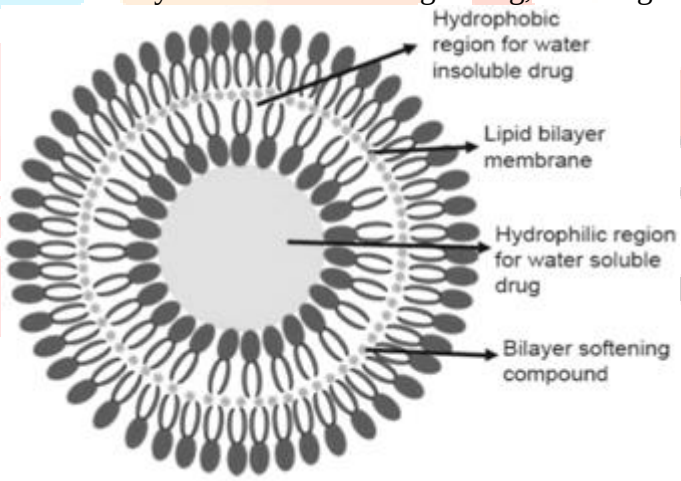

Figure1: Structure of Transferosomes

Composition of Transferosomes

Phospholipids such as phosphatidylcholine, which self-assemble into a lipid bilayer in an aqueous environment and form a vesicle, make up transferosomes. Additionally, it has an edge activator made of a single-chain surfactant that destabilizes the lipid bilayer, increasing its elasticity and fluidity as shown in Figure 1.
Sodium cholates, sodium deoxycholate, tweens, and spans {tween 20, tween 60, tween 80, span 60, span 65, span 80} dipotassium glycyrrhizinate are the most often utilized surfactants in transferosomes as shown in table no.1 [14]. The physicochemical characteristics of vesicles, such as their zeta potential, entrapment efficiency and vesicle size, are influenced by the kind and proportion of various edge activators [15].

Table No.1: Different types of additives used in the formulation of transferosomes [16,17]

CLASS	EXAMPLES	USES
Phospholipids	• Egg Phosphatidylcholine • Choline Soya Phosphatidylcholine • Dipalmitoyl phosphatidylcholine	Vesicles forming complex
Surfactants	• Sodium cholate • Sodium deoxycholate • Span 80 • Tween 80	Vesicles foaming components (edge activators)
Solvents	• Ethanol • Alcohol • Chloroform	Used as a solvent
Buffering agents	• Saline phosphate buffer (pH 6.4) • Phosphate buffer (pH 7.4)	Used as a hydrating medium
Dyes	• Rhodamine -123 Rhodamine DHPE • Nile red	For confocal scanning laser microscopy.

Mechanism of transferosomes

Another form of lipid-based vesicular system used for medication transport, especially percutaneous injection, is called a transferosome. They are made by hydrating a lipid film and then using high-speed homogenization procedures to produce stable nanoparticle dispersion [18].

Transferosomes carry drugs either intracellularly or transcellularly into the stratum corneum. The "osmotic gradient or transdermal gradient" is the main mechanism by which transferosomes penetrate the skin, where the colloidal particles that comprise the vesicles form an amphiphilic bilayer [21]. While hydrophobic pharmaceuticals are confined in the lipid bilayer, hydrophilic drugs are often transported by vesicular drug delivery mechanisms in the interior aqueous compartment as shown in Figure 2(A) [22].

However, because therapeutic agent carrier vesicles are more deformable and may attach to the tissue layer's flexibility and integrity, they make it easier for the transferosome to pass through the skin, which makes the transferosomes extremely flexible and self-optimizing [23].

The medication is integrated into the Transferosomes lipid matrix, which can enhance the drug's encapsulation, stability, and solubility [19]. The diffusion mechanism, which is controlled by the drug's concentration, the characteristics of the lipid matrix, and the external environment, controls the drug's release from the transferosomes [18].

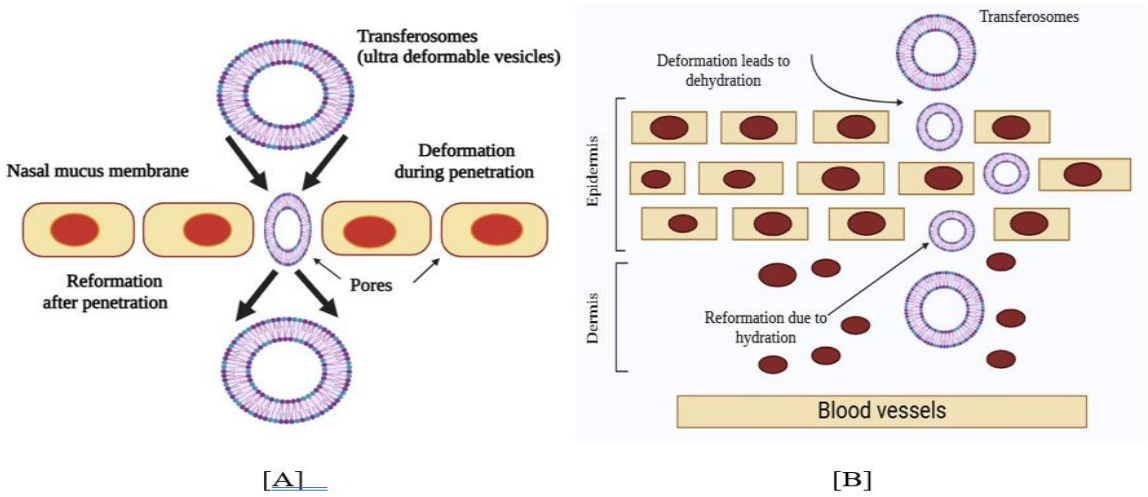

Figure 2: Mechanism of Transferosome's penetration includes A} deformation and subsequent reformation facilitating penetration and, B} tendency of transferosomes to seek moisture aiding their permeation

Transferosomes can improve drug absorption by profoundly penetrating mucosal layers. The transferosomes elastic and flexible membrane is thought to be the cause of this penetration [19].Drug distribution via transferosomes can occur both transdermally and dermally as shown in Figure 2 (B) The medicine may be able to pass through the skin more easily thanks to the interaction between the lipids in the transferosomes and the lipid layer of the skin [20].

Advantages of Transferosomes

- ❖ Drug molecules with a variety of solubilities can be accommodated by transferosomes because they hold a structure made up of hydrophilic and hydrophobic parts together. Transferosomes have the ability to distort or squeeze through small spaces five to ten times.
- ❖ This tailored drug delivery technology also allows for self-administration [26].
- ❖ Additionally, medicines with a limited therapeutic window can be employed with transferosomes [27].
- ❖ They need to make the bioavailability better.
- ❖ When it comes to lipophilic drugs, transferosomes have an entrapment efficiency of around 90% [28].

Disadvantages of Transferosomes

- ❖ Transferosomes are costly to create and chemically unstable due to their susceptibility to oxidative destruction [31].
- ❖ Another factor working against the use of transferosomes as drug delivery vehicles is the purity of natural phospholipids [32, 33].
- ❖ Transferosomes might not be appropriate for all drug kinds and might have a restricted capacity for drug loading [34].
- ❖ It provides hydrophilic skin structures with progressive therapeutic advantages [35].
- ❖ It is not suitable for high drug dosages and neither practical nor advantageous for less strong medications [36].
- ❖ The inability to get pure phospholipids and the high formulation costs brought on by the need for pricey raw materials and equipment [37].

Apply on skin

As phospholipid vesicles, transferosomes are useful for transdermal medication administration. Because of their incredibly flexible and self-optimized membrane properties, they can deliver the medication through or into the skin with high efficiency and repeatability, depending on the application or mode of administration.

The internal sealing lipid of the stratum corneum enables transferosomes to evade epidermal penetration barriers. Because of the high vesicle deformability that permits entry in response to external mechanical stress in a self-adapting way, these are typical of transferosomes.

The proper ratio of phospholipids to surface-active components regulates the flexibility of transferosome membranes. The flexibility of the transferosome membrane that results from non-occlusive application lessens the chance of a complete vesicle rupture in the skin and allows transferosomes to follow the natural water gradient across the epidermis [38].

Through two distinct internal lipid routes, each with distinct bi-layer properties, transferosomes can spontaneously penetrate the entire stratum corneum as shown in Figure 3 .Vesicular systems have garnered increasing attention since Bangham's discovery of liposomes in 1963. The low penetration value of conventional liposomes has lately come to light, nevertheless.

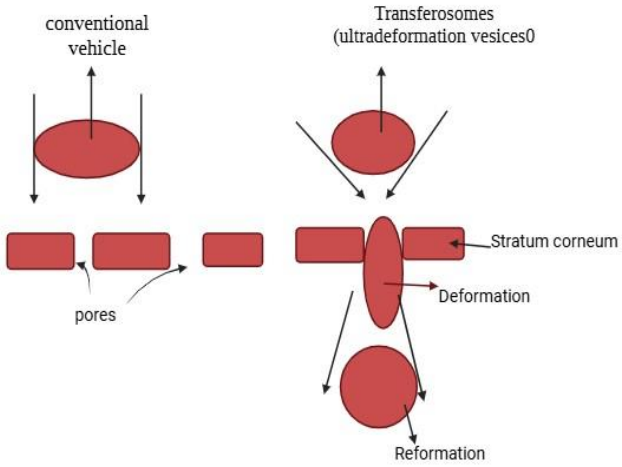

Figure 3: Distortion of Transferosomes into skin pores

Confocal microscopy research indicates that intact liposomes do not penetrate into the granular layer of the epidermis, but remain on the uppermost layer of the stratum corneum. Modifying the vesicular composition or surface properties can change the rate of drug release and its deposition at the target site [39].

Skin

The skin, the heaviest single organ of the body combines with the mucosal linings of the respiratory, digestive and urinogenital tracts to form a capsule which separates the internal body structures from the external environment. [Hofland H et al.2016] The skin is the largest organ in the human body. For the average adult human, the skin has a surface area of between 1.5-2.0 square metres. The thickness of the skin varies considerably over all parts of the body, and between men and women and the young and the old. An example is the skin on average 1.3 mm in the male and 1.26 mm in the female. The average square inch (6.5 cm^2) of skin holds 650 sweat glands, 20 blood vessels, 60,000 melanocytes, and more than 1,000 nerve endings. The average human skin cell is about 30 micrometers in diameter, but there are variants. A skin cell usually ranges from 25-40 micrometers (squared), depending on a variety of factors.

Microscopically, skin is multilayered organ composed of many histological layers. It is generally described in terms of three major layers – the epidermis, dermis and the hypodermis. Microscopic section of epidermis shows 5 parts- stratum corneum, stratum lucidum, stratum granulosum, stratumspinosum and stratum germinativm. [Tallau N et al., 2020]

STRUCTURE OF SKIN

Skin is composed of three primary layers:

- Epidermis,
- Dermis
- Hypodermis

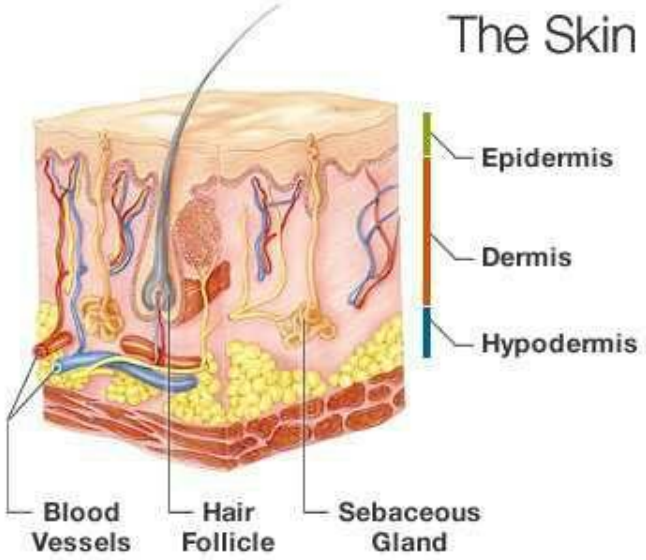

Figure 4: Structure of skin

Epidermis: The epidermis is the outermost layer of the skin. The average epidermal thickness is 0.1 millimeters, which is about the thickness of one sheet of paper. The epidermis acts as a protective shield for the body and totally renews itself approximately every 28 days.The epidermis contains no blood vessels, and cells in the deepest layers are nourished almost exclusively by diffused oxygen from the surrounding air and to a far lesser degree by blood capillaries extending to the outer approximately every 28 days.The epidermis contains no blood vessels, and cells in the deepest layers are nourished almost exclusively by diffused oxygen from the surrounding air and to a far lesser degree by blood capillaries extending to the outer layers of the dermis. The main type of cells which make up the epidermis are merkel cells, keratinocytes, with melanocytes and langerhanes cells also present. The epidermis can be further subdivided into the following strata (beginning with the outermost layer): corneum, lucidum (only in the palm of hands and bottoms of feet), granulosum, spinosum, basale.

Epidermis is divided into the following 5 sublayers or strata:

- Stratum corneum
- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum germinativum

Stratum Corneum. Composed of dead cells called keratinocytes, the stratum corneum is the outermost layer of skin, acting as a barrier to keep bacteria out and hold moisture in. As we age, this barrier deteriorates becoming crusty and flaky. Gentle exfoliants can help remove the outermost cells and help skin regain a youthful appearance while preserving this important layer of defense. The fifth layer, or horny layer, is called the stratum corneum. This is the top, outermost layer of the epidermis and is 25-30 layers of flattened, dead keratinocytes. This layer is the real protective layer of the skin. Keratinocytes in the stratum corneum are continuously shed by friction and replaced by the cells formed in the deeper sections of the epidermis. In between the keratinocytes in the stratum corneum are epidermal lipids (ceramides, fatty acids, and lipids) that act as a cement (or mortar) between the skin cells (bricks). This combination of keratinocytes with interspersed epidermal lipids (brick and mortar) forms a waterproof moisture barrier that minimizes

transepidermal water loss (TEWL) to keep moisture in the skin. This moisture barrier protects against invading microorganisms, chemical irritants, and allergens. If the integrity of the moisture barrier is compromised, the skin will become vulnerable to dryness, itching, redness, stinging, and other skin care concerns.

Dermis:

Dermis is the layer of skin beneath the epidermis that consists of epithelial tissue and cushions the body from stress and strain. The dermis is tightly connected to the epidermis by a basement membrane. It also harbors many nerve endings that provide the sense of touch and heat. It contains the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels. The blood vessels in the dermis provide nourishment and waste removal from its own cells as well as from the stratum basale of the epidermis.

Hypodermis

Hypodermis is not part of skin, and lies below the dermis. Its purpose is to attach the skin to underlying bone and muscle as well as supplying it with blood vessels and nerves. It consists of loose connective tissue, adipose tissue and elastin. The main cell types are fibroblasts, macrophages and adipocytes (hypodermis contains 50% of body fat). Fat serves as padding and insulation for the body.

TRANSFEROSOME PREPARATION TECHNIQUE

There are numerous published and patented methods for creating transferosomes. In ethanol, phosphatidylcholine is typically mixed with sodium cholate or another appropriate surfactant. Some of the most widely used methods are:

1. **Thin film hydration technique:** This process involves dissolving the medication, phospholipids, and surfactants in an organic solvent. Rotating evaporation is then used to evaporate the solvent at 40°C with reduced pressure. To get rid of any last traces of liquid, put this film under vacuum for the entire night [52]. After that, the lipid film is hydrated by centrifuging it with the appropriate buffer for an hour at room temperature at 60 rpm. At room temperature, the resultant vesicles will swell for two hours. Small lamellar lipid vesicles are created by further sonicating the multi-lamellar lipid vesicles that are created at room temperature [53] [54].
2. **Modified handshaking method:** This modified thin film uses the same basic idea as the rotary film evaporation process, but the solvent will be evaporated by hand shaking rather than a rotary evaporator. This technique entails filling a round-bottomed flask with organic solvents with a mixture of phospholipids, lipophilic medication, and edge activator (surfactant-non-Ionics/biosurfactants). Once a clear solution has formed, the organic solvent is evaporating by hand shaking. At the same time, the round-bottomed flask is placed on a water bath that is kept between 40 and 600 degrees Celsius. Thin film formation occurs overnight after the organic solvent has completely evaporated. At this stage, a hydrophilic medication can be incorporated. The buffer solution is then added, gently stirring, above the transition temperature as shown in Figure 4 [55].

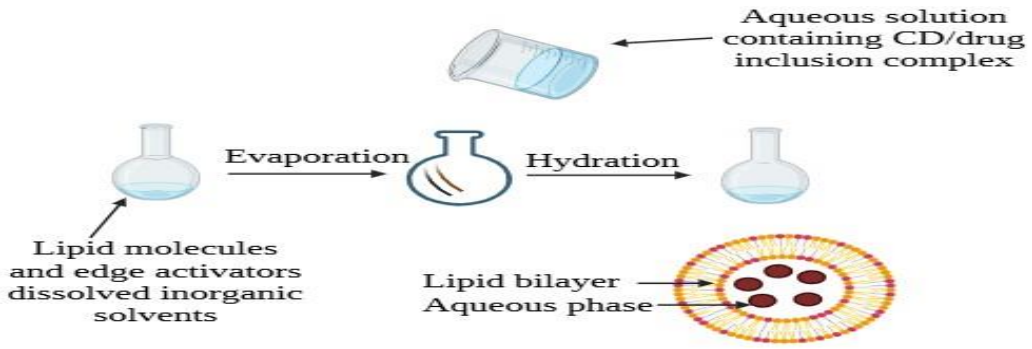

Figure 5: Modified handshaking method

3. **Suspension homogenization process:** An ethanol soybean phosphatidylcholine solution is combined with a suitable amount of an edge activator molecule, such as sodium cholate, to create a triethanolamine-HCL buffer, which in turn produces a total lipid concentration. The resulting suspension is then sonicated, frozen, and thawed two or three times [56].
4. **Vortexing or sonication method:** This method involves mixing the medication, surfactant, and PL in a phosphate buffer and Vortexing the mixture to create a milky suspension. Following the sonication procedure, the suspension is extruded using polycarbonate membranes [57]. To set cationic transferosomes, this process requires mixing cationic lipids, such as DOTMA, with PBS when the concentration reaches 10 mg/ml. Sodium deoxycholate is then counted [58]. Following sonication and Vortexing, the mixture is extruded through a polycarbonate (100 nm) filter [59,60,61].
5. **Centrifugation process:** The organic solvent dissolves the lipophilic medication, phospholipids, and edge activator. A rotary evaporator operating at the appropriate temperature and with reduced pressure is then used to extract the solvent. Under vacuum, the last parts of solvent are eliminated. Centrifuging at room temperature hydrates the formed lipid layer with the proper buffer solution. At this point, the hydrophilic medication can be incorporated. At normal temperature, the resultant vesicles swell. At ambient temperature, the resulting multilamellar lipid vesicles undergo further sonication [62].

6. **Ethanol injection method:** The method is widely employed in the production of elastic liposomes. The medicine is first dissolved in an aqueous medium, and then the contents are heated to a set temperature while being constantly stirred. The ethanol solution containing phospholipids and edge activator is then introduced into the aqueous media dropwise. Bilayer structures are created when the phospholipid and EA ethanolic solution is combined with the aqueous solution, causing the lipid molecules to precipitate [63]. The process in illustrated in figure 5.
7. **Reverse phase evaporation method:** Phospholipids, surfactants, and the medication are dissolved in alcohol to create transferosomes. Next, rotary evaporation is used to evaporate the organic solvent at 40–45 degrees Celsius with reduced pressure [64]. The last solvent remnant is eliminated under vacuum. The retainer lipid film is hydrated at room temperature by rotating it for an hour at 60 rpm with a different buffer [65]. At room temperature, the forming vesicles are overstated for two hours. After that, the multilamellar lipid vesicles undergo sonication. The sonication process can be replaced by extrusion, low shear blending, or high shear blending [66].

Transferosomes characterization parameters

To ensure transferosomes quality, stability, and efficacy as drug delivery vehicles, characterization is crucial. Transferosomes can be described using a variety of techniques that offer details on their size, shape, stability, stability, drug encapsulation effectiveness, and release kinetics. Here is a detailed list of some popular description techniques.

1. **Vesicle size distribution and zeta potential:** Malvern Zeta Seizer used the dynamiclight scattering (DLS) light method to assess the vesicle size, size distribution, and zeta potential. The sample is prepared using distilled water, and it is then thinned out or diluted with filter saline after passing through a 0.2 mm membrane filter [67].
2. **Entrapment efficiency:** Entrapment efficiency is typically represented as a percentage of drug entrapment or the amount of drug entrapped as a percentage of the additional amount. This technique uses the mini-column centrifugation method to release the medication that was entrapped.
3. **Vesicle morphology:** The dynamic light scattering (DLS) or photon correlation spectroscopy can be used to ascertain it.These samples were made in distilled water, filtered through a 0.2 mm (micro meter) membrane filter, and then diluted with filtered saline.
4. **Drug content:** Depending on the pharmacopoeia drug's analytical method, one of the instrumental analytical methods, such as a modified High-Performance Liquid Chromatography (HPLC) method with a UV detector (ultraviolet), column oven, pump, autosampler, and computerized analysis program, can be used to determine or express the drug's content [70].

- ***In-vitro* Release Kinetics:**
  a) **Dialysis Method:** The dialysis method, which involves immersing transferosomes in a release medium and placing them in a dialysis membrane, can be used to assess the release kinetics of medicines from transferosomes *in- vitro.* Analytical methods are used to test the drug's concentration at regular intervals over time [81].

  b) **Franz Diffusion Cell:** Franz diffusion cells are able to simulate the skin barrier and assess how well medications from transferosomes pass through animal or synthetic skin membranes. To evaluate release kinetics, the drug concentration that permeates the membrane is tracked over time. [82].

APPLICATION OF TRANSFEROSOMES

For topical drug administration, transferosomes are lipid-based Nano systems that provide benefits such improved permeability and solubility for medications with low bioavailability. They have been used in numerous trials to deliver a variety of medications, such as ferulic acid and antifungal medicines Among the noteworthy uses of transferosomes are:

1. Antifungal Agent Transferosomes:
2. Ferulic Acid Transferosomes:
3. Rotigotine HCL and Rasagiline Mesylate Transferosomes:
4. Anti-cancer drugs transferosomes:
5. Insulin transferosomes:
6. Proteins and peptides transferosomes:
7. Interferon transferosomes:
8. Anesthetic transferosomes:

CONCLUSION

Ultra-deformable vesicles called transferosomes address issues connected to transport, including Transdermal delivery of high molecular weight medicinal substances is not possible due to the barrier properties of the skin. Transferosomes' deformable particles can carry drugs through biological permeability barriers like the skin. These elastic vesicles distort so they can pass through holes into the skin. They are excellent at delivering proteins and peptides. These Transferosomes may adjust to environmental stress by forcing themselves through skin pores that are significantly smaller than usual, improving the transdermal flux of pharmaceuticals. The structure of transferosomes allows for a broad range of solubility by combining hydrophilic and hydrophobic molecules. Compared to other vesicular systems, transferosomes offer several benefits, including as deformability, systemic drug release, stability, and skin penetration.

ACKNOWLEDGEMENT

The author acknowledges the teacher’s staffs and friends for their kind support.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of the article.

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