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Review Article

Transferosomes: A Novel Topical Approach

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Abstract

Transdermal drug delivery technologies have gained attention in recent years due to their advantages over conventional drug delivery systems. Transdermal drug delivery is limited because the stratum corneum functions as a barrier. Transferosomes are ultradeformable vesicles consisting of a lipid bilayer with phospholipids and an edge activator. After topical treatment, transferosomes can deliver larger quantities of active ingredients to deeper skin layers than liposomes. Generally, molecules with a molecular weight of more than 500 Daltons cannot penetrate through skin. As a result, this route can only be used to give a few medications. Therefore, this issue can be solved by encapsulating the medicine in a transferosome. Drugs that are hydrophilic, lipophilic or amphiphilic can be enclosed in transferosomes, which have a bilayer structure and a higher penetration efficiency than traditional liposomes. The most prevalent lipid found in a cell membrane, phosphatidylcholine, is found in high concentrations in the majority of transferosomes. Surfactants including sodium deoxycholate, Tween 80, and span 80 are frequently utilized as edge activators since they increase skin tolerance and reduce the chance of unfavorable effects. Due to their elastic nature, transferosomes can bend and squeeze themselves as a complete vesicle through tiny pores that are much smaller than their size.

Keywords: Transferosomes, Transdermal drug delivery, stratum corneum

INTRODUCTION

In the last many decades, significant attention has been given on the development of topical delivery of medicines because of a number of advantages associated with this route. Skin covers an area of roughly 2m^2 and a total surface of 3kg, it receives about one-third of blood circulating among the body. A major drawback to cutaneous and transcutaneous drug delivery is the permeation characteristics of the stratum corneum, which restricts drug transport, making this route of administration deficient for medical use

SC (Stratum Corneum) is a superficial layer of the skin which comprises keratinized, flattened residues of dividing epidermal cells, impermeable to water and behaves as a tough flexible membrane. Many technologies have explored to avoid this barrier including electrophoresis, chemical permeation enhancers, iontophoresis, microemulsions and vesicular structures such as liposome, niosomes, Ethosomes, and transferosomes to formulate novel vesicular carriers for delivery of drug across the skin

Transferosomes show up promising among all these vesicular structures. The term transferosomes was presented by Gregor Cevc in 1991. Transferosome is enrolled as a logotype by the IDEA AG company located in Germany. The name means “carrying body” and is taken from the Latin word “transferred'' meaning “to carry across,” and the Greek word “soma,” implies a “body. There are some problems that come across with other vesicular structures like poor skin permeability, aggregation, leakage of the drug and breaking of vesicles

To overcome all these above issues, a modern sort of vesicular transporter has been created called “transferosome” which is able to deliver low molecular drugs in addition to the high molecular weight drugs. Transferosomes are vesicular carrier structures that are specifically laid down to have at least one internal aqueous compartment which is surrounded by a lipid bilayer, beside an edge activator

The aqueous core is surrounded by the lipid bilayer which makes ultra-deformable vesicles possessing regulating capabilities. Edge activator increases the vesicle membrane deformability and when blended in proper ratio with appropriate lipid proportion, it enables the transferosomes to become ultra-flexible, deformable with increased permeation capability.

The edge activators used facilitates the solubility of hydrophobic drugs thereby further increasing the entrapment efficiency of the drug [1]

The existence of lipophilic and hydrophilic moieties in the vesicle structure result in wide range of solubility of transferosomes, it has been distinguished that vesicle with size >600 nm penetrates deeper into skin layers, whereas <300 nm reach more profound into skin layers and vesicles with <70 nm shows a greatest deposition of contents in epidermal and dermal skin layers [2]

When liposomes, niosomes and nanoparticles are placed on the skin, usually they are able to reach only through the SC of the upper layer of skin, resulting in accumulation in the epidermal region but lacking to reach deeper skin areas such as the dermis or systemic levels.

The penetration capacity in niosomes has been related to reduced flux across the stratum corneum compared to liposomes in spite of the fact that they are more stable. transferosomes are indicated with better colloidal stability (without aggregation) compared to liposomes and niosomes in liquid medium for up to three months both at 4 ^{0} C and 25 ^{0} C

Transferosomes are hugely ultradeformable vesicles and are able to squash across the SC and they penetrate as intact vesicles through the skin when their estimate is under 300 nm. Hydrophilic drugs are encapsulated inside the aqueous middle cavity, whereas hydrophobic drugs are embedded inside the phospholipid bilayer. Transferosomes below 300 nm are more elastic and flexible compared to liposomes [3,4]

ADVANTAGES OF TRANSFERSOMES AS A CARRIER

1) Transferosomes improves bioavailability, patient compliance and reduces side effects [3]

2) High Entrapment Efficiency of about 90% lipophilic drugs can be achieved by transferosomes, In case of low entrapment efficiency; lipophilic encapsulation can be increased by including a surfactant with low HLB scale [4]

3) It releases the drug slowly and steadily and acts as a depot [5]

4) Transferosomes are made up of natural phospholipids similar to liposomes; hence they are biocompatible and biodegradable

5) Transferosomes are used for topical as well as systemic delivery of drugs.

6) Transferosomes do not involve lengthy procedures and unwanted use of pharmaceutical additives and easy to scale-up

7) They have high entrapment efficiency, especially in the case of lipophilic drugs, nearly 90%

8) They have elastic properties due to which they deform themselves and squeeze themselves across the skin barrier without wastage of drug.

9) It comprises of both lipophilic and lipophobic moieties due to which they can accommodate drug with large range of solubility [6]

10) They are used for the delivery of various compounds like protein, peptides, insulin, corticosteroids, NSAIDS, analgesics, anticancer drugs and anesthetics. [7]

DISADVANTAGES OF TRANSFERSOMES AS A CARRIER

1) One of the drawbacks in utilizing transferosomes is the difficulty to achieve the phospholipids purity, thus synthetic phospholipids can also be used as an alternative

2) Transferosomes are expensive to formulate because of the expensive equipment as well as raw materials used in lipid excipients.[3]

3) Barrier role of the skin changes with age and is different from person to person and from one site to another site of the skin on the same person.

4) Hypersensitivity directions and skin irritation may occur [5]

FACTORS AFFECTING TRANSDERMAL DELIVERY

The factors which affect transdermal delivery of drug are mainly two: biological factors and physicochemical factors

a) Biological factors

i) Skin age- Children are more sensitive to the absorption of toxins to skin; the young age of skin is more permeable than the old age skin

ii) Condition of skin-Skin condition is altered by the diseased state of the patient. Furthermore acids, alkalis, solvents like methanol and chloroform injures the skin cells and elevates penetration

iii) Metabolism of skin- Skin metabolizes drugs, hormones, steroids and some of the carcinogens. Thus, metabolism of the skin predicts the effectiveness of drug permeated into the skin

iv) Skin site- Nature of SC, thickness of skin, keratins and appendages vary from one site to another site

b) Physicochemical factors

i) Drug concentration- Flux is proportionate to the concentration gradient through the barrier. Thus, concentration gradient will be greater when the drug concentration is more across the barrier

ii) Skin hydration- Hydration is an important component in increasing the skin permeability. Permeability of the skin increases in contact with water. Hence, humectants are used in formulation of transdermal delivery

iii) Temperature and pH- The permeation of the drug increases with the variation in temperature. The temperature decreases as the diffusion coefficient decreases. The portion of unionized drug determines the drug concentration in skin

iv) Partition coefficient- For highly lipophilic molecules (log K > 3) and for the molecules with intermediate partition coefficient (log K 1 to 3) the intercellular route is the pathway and furthermore ability to partition out of the SC into aqueous region via epidermal tissues, hydrophilic molecules (log K < 1) the transcellular route are likely to dominate [6]

COMPOSITION OF TRANSFEROSOMES

Transferosomes consist of phospholipids like phosphatidylcholine which is an amphipathic component and a lipid bilayer constituent known as edge activator which leads to the arrangement of the vesicle.

Phospholipids

- The main ingredient in the vesicles are composed of phosphatidylcholine like soy phosphatidylcholine, egg phosphatidylcholine etc. are the vesicle forming elements that makes the lipid bilayer.
- 10-25% of surfactant and different solvents like methanol, ethanol comprising of saline phosphate buffer (pH 6.5 -7) and dyes like Nile red and Rhodamine are utilized for flexibility
- Phosphatidylcholine is a fatty composition which can be obtained from both human and vegetable origin, and is primarily an unsaturated fatty acid. These unsaturated fatty acids are mainly linoleic acid up to 70% of the total fatty acids.

Edge activators (EA)

- Edge activator is a biocompatible surfactant which is also known as “bilayer softening compound”. Edge activators increase lipid bilayer permeability and flexibility.
- Edge activator mainly consists of the nonionic nature of single chain surfactant which destabilizes the lipid bilayer. Therefore, increasing its flexibility and elasticity. By adding suitable surfactant in appropriate ratio, flexibility of transferosomes are modified.

- Surfactants such as Tweens like Tween 20, Tween 60, Tween 80

Spans like Span 60, Span 65 and Span 80, sodium cholates, sodium deoxy chocolate and dipotassium glycyrrhizinate are used to increase bilayer flexibility and permeability in transferosome preparations.

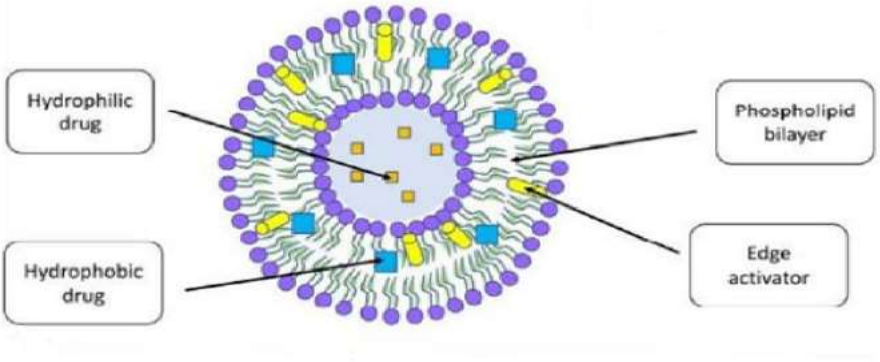

Figure-1 **Structure of transferosomes**

The total sum of surfactants and the right proportion of individual surfactants added to phospholipids are responsible for vesicle layer flexibility and permeability and further minimizes the risk of vesicle punctures in the skin. Hence the penetration increasing effect of these vesicles depends on size, shape, elasticity and the type of lipid and surfactants used. [3,7]

PREPARATION OF TRANSFEROSOMES

1. Rotary film evaporation method

Rotary film evaporation method is also known as hand shaking method which was first invented by Bagham. The amount needed of phospholipids and surfactants is essential to form a thin film and arrangement of phospholipids and surfactants are arranged in solvents of chloroform and methanol. This method is often employed in multilamellar vesicles. The produced solution is then transferred to the round bottomed flask and rotated at a constant temperature (above glass transition temperature)and reduced pressure further a layer of lipids and edge activators are found on the walls of the round bottomed flask. The formed film containing the drug is then hydrated with an aqueous media. This leads to swelling of lipids and form bilayer vesicles. Further desired vesicle size can be obtained by sonication or extrusion. [9,10]

2. Modified handshaking process

This process is also known as lipid film hydration technique. In this process drug, phosphatidylcholine and edge activators are dissolved in ethanol and methanol in a 1:1 ratio. While handshaking above lipid transition temperature (43°C) organic solvent is removed by evaporation. A thin film is formed inside the walls of the flask as a result of continuous rotation. The preparation is kept overnight to allow for the complete evaporation of solvent. After which the film is hydrated with a phosphate buffer of pH- 6.4 with gentle shaking for 15 minutes. The obtained transferosomes suspension is further hydrated for about 1 hr at 2-8°C. [10,11]

3. Thin film hydration technique / Rotary evaporation-sonication method

The phospholipids and edge activator are dissolved in a round-bottom flask using organic solvent mixture of chloroform and methanol in a suitable (v/v) ratio to form a thin film. The solvent is evaporated beyond lipid transition temperature using a rotary evaporator and the obtained film is hydrated with a phosphate buffer of pH-6.5 by rotation of 60 rpm for 1 hour. The obtained vesicles are swollen at room temperature or 50°C for 30 min. By manually extruding a sandwich of 200 and 100 nm polycarbonate membrane, the sonicated vesicles are homogenized. [3,7]

4. Ethanol injection method

Organic phase is formed by dissolving phospholipids, EA and active substances with magnetic stirring for a certain period, until a clear solution is formed. Meanwhile, water soluble substances are dissolved in a phosphate buffer to prepare aqueous phase. Both the solutions are heated up to 45°C-50°C. After which the phospholipids solution is drop-wise injected into aqueous solution with continuous stirring for some time. Ethanol removal is done by shifting the dispersion into a vacuum evaporator and then sonicating it for vesicle size reduction.[3,10]

5. Reverse phase evaporation method

Firstly, Lipids are dissolved in organic solvents placed in a round bottom flask.

An aqueous medium containing edge activators is introduced under nitrogen purging. The drug is added into a lipid or aqueous media based on its solubility characteristics. After which, the created system is sonicated until it becomes a homogenous dispersion, which should not be separated for at least 30 minutes. Under decreased pressure, the organic solvent is then extracted. The system will then transform into a thick gel, followed by the formation of vesicles. Centrifugation or dialysis method may be used to remove non-encapsulated material and residual solvents. [10]

6. Vortexing /Sonication method

The mixed lipids (edge activators, phosphatidylcholine, medicinal drugs) are all added in a phosphate buffer and are vortexed to create a milky suspension. After sonication, the suspension passes through a process of extrusion via polycarbonate membranes [10]

7. Suspension homogenization technique

Ethanolic phosphatidylcholine is combined with an appropriate quantity of edge activators like sodium cholate. This produced suspension is then combined with a Triethanolamine-HCl buffer solution to give a total lipid concentration and then sonicated, frozen, and thawed for twice or thrice times before being brought to the required size and is then quantified by photon correlation spectroscopy. Filtration of 0.2 µm micro porosity filter is used to sterilize the

water. The final vesicle size is confirmed using Dynamic Light Scattering (DLS). [5,7,10]

8. Centrifugation process

The phospholipids, EA and drug are dissolved in the organic solvent, Below reduced pressure and respective temperature, Using a rotary evaporator the solvent is removed ,the leftover residues of the solvent are removed under vacuum, the lipid film obtained is hydrated with a phosphate buffer by centrifugation at room temperature and drug incorporation is done at this stage and remaining vesicles are swollen at room temperature and resulting obtained multilamellar lipid vesicles are sonicated [3,7]

9. Freeze thaw process

The multilamellar vesicles are frozen at notable low temperatures and then heated to very high temperatures. The prepared suspension is then transferred to a tube for 30 seconds at 30°C, followed by which the tube is immersed in a nitrogen bath. After freezing, they are subjected to high temperatures in a water bath. This process is performed for eight to nine times [9,10]

10. High pressure homogenization technique

In this process phospholipids, edge activators and drugs are dissolved in distilled water followed by ultrasonic shaking and stirred vigorously**,** the mixture is subjected to ultrasonic shaking and then subjected to high pressure homogenization to be homogenized and finally obtained transferosomes should be properly stored. [3,7]

MECHANISM OF TRANSFEROSOMES

Transferosomes, when applied under appropriate conditions can transfer about 0.1 mg of lipid per hour and cm^2 area through the intact skin. This value is significantly higher than the ordinarily driven by the transdermal concentration gradient. The reason for this higher flux rate is actually "transdermal osmotic gradient". The skin penetration barrier prevents loss of water across the skin and maintains 75% of water content in epidermis and about completely dry Stratum corneum close to the skin surface of 15% of water content. Almost all polar lipids draw part of water due to the interaction between hydrophilic lipid remnants and their adjacent water.

When lipid transferosome suspension is put on the skin, it is partly dehydrated and vesicles of lipids sense this "osmotic gradient" and try to elude total drying by moving across this gradient. This can be accomplished if they are satisfactory for deformable to cross through the small pores of skin while transferosomes comprise of surfactant and hydration properties are capable for their significant deformability

When less deformable vesicles like liposomes are applied to the skin, they are totally dried out as they have penetration control less than transferosomes. Subsequently, transferosomes are optimized to achieve greatest flexibility therefore to take full convenience of transcutaneous osmotic gradient (water concentration gradient).

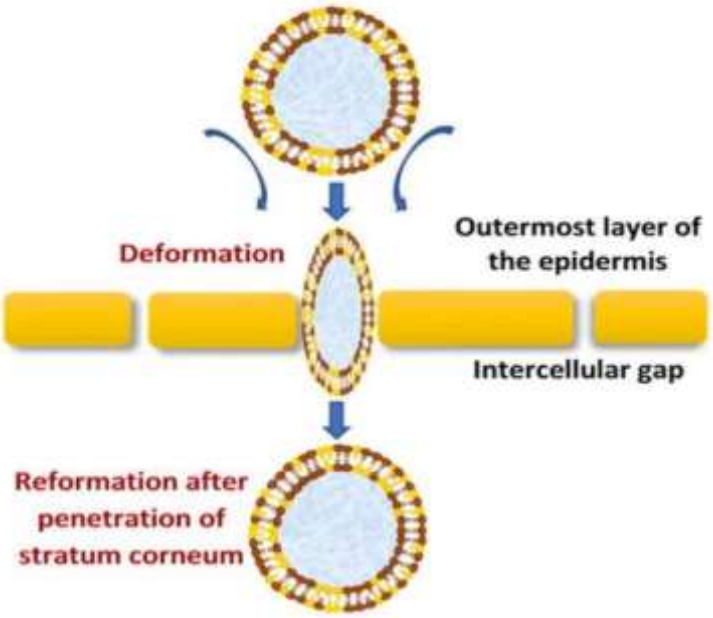

Figure-2 Mechanism of Transferosomes

Transferosomes overcome the difficulty of skin penetration by squashing themselves through the lipids of SC. Presently the mechanism to enhance the delivery of drug substances over the skin is not known. Two mechanisms have been suggested and are mentioned below:

1.Transferosomes function as drug vectors, by standing uninjured after penetrating the skin.

2.Transferosomes function as penetration enhancers, by disturbing the highly assembled intercellular lipids from SC, and therefore encouraging the movement of drug molecules throughout the stratum corneum [3,8]

CHARACTERIZATION OF TRANSFEROSOMES

1. Entrapment Efficacy

The amount of drug entrapped in the formulation is called percentage entrapment efficiency (%EE) The entrapment efficacy is determined by separating the unentrapped drug from the vesicles by minicolumn centrifugation in this process both direct and indirect methods are used to give EE. The direct approach is done after ultracentrifugation by removing the supernatant by disrupting the vesicles using 0.1 trion x-100 or n-propanol. To remove the impurities, the resulting solution is diluted and filtered using a syringe filter (0.22 –

0.45 µm) High-performance liquid chromatography (HPLC) or spectrophotometric method is used to determine the drug content. The %EE is calculated as

$$\%\text{Entrapment efficiency} = \frac{Amount\ of\ drug\ entrapped}{Total\ amount\ of\ drug\ added} \times 100$$

The indirect approach is characterized by diluting the supernatant using a suitable solvent and filtering it to remove the impurities. The supernatant in the concentration of the drug is determined as the free drug by analytical method, it is calculated as [3,10]

$$\%\text{Entrapment efficiency} = \frac{Total\ amount\ of\ drug\ added - Amount\ of\ free\ drug}{Total\ amount\ of\ drug\ added} \times 100$$

2. Vesicle size, morphology and zeta potential

The Dynamic Light Scattering (DLS) method can be used to determine the vesicle diameter. In this, vesicle suspension is mixed with an appropriate medium, and the vesicular size measurements can be obtained in triplicate or the sample can be prepared in distilled water and filtered through a 0.2mm membrane filter. In order to estimate the size of the vesicles by DLS, the filtered sample is diluted with saline and for the determination of the vesicle size and size distribution, Malvern Zeta Sizer is used, whereas the structural changes and visualization are observed by transmission electron microscopy (TEM). [3]

3. Number of vesicles per cubic mm

Unsonicated transferosomal formulations are diluted 5 times using 0.9% Nacl. A Hemocytometer along an optical microscope is used to study this sample by using an optical microscope, the transferosomes with vesicle sizes larger than 100nm can be seen. The number of transferosomes are counted in small squares and calculated as [3]

Total number of transferosomes per cubic mm =

$$\frac{Total\ number\ of\ transferosomes\ counted\ \ X\ dilution\ factor\ \ X\ 4000}{Total\ number\ of\ squares\ counted}$$

4. Drug content

The drug content can be determined using one of the instrumental analytical methods such as modified high performance liquid chromatography method (HPLC) using a UV detector, column oven, auto sample, pump, and computerized analysis program.[10]

5. Turbidity measurement

Turbidity of a drug in an aqueous solution is determined by using a nephelometer [10]

6. Degree of deformability / permeability measurement

Deformability test is determined using pure water as control. A vast number of microporous filters with pore diameters ranging from 50 to 400 nm are used to filter the preparation. The particle size, size distribution, are obtained after each pass using DLS measurements and is calculated by formula as

$$D = J(\frac{rv}{rp})$$

Where D = degree of deformability, J = amount of suspension extruded during 5 min, rv = size of the vesicle and rp = pore size of barrier [3,10]

7. Occlusion effect

For topical medicines, occlusion of the skin is thought to aid drug penetration. Elastic vesicles, on the other hand, suffer from the same problem. The hydrotaxis of water is the primary driving force behind vesicle penetration through the skin from its relatively dry surface to its water-rich deeper layers. Occlusion has an effect on hydration forces because it stops water from evaporating from the skin.[10]

8. Penetration ability, Surface charge and charge density

Fluorescence microscopy is used to assess the capacity of Transferosomes to penetrate and the surface charge and charge density of Transferosomes is determined by Zetasizer. [1,12]

9. In vitro drug release

In vitro drug release is determined by the Franz diffusion cell. The donor chamber is fitted to the receptor chamber by means of adhesive tape. The fluid in the receptor chamber is continuously mixed by a magnetic bar. At the proper intervals (such as 0, 0.5, 1, 2, 3, 4, and 6 h), aliquots of 1 ml of the receptor media are removed, and at the same time, the withdrawn medium is replaced with a comparable volume of new phosphate buffer to maintain the sink conditions. The collected samples may be examined using UV or HPLC analysis [3]

10. *In vitro* skin permeation studies:

This study is performed to decide the transport efficiencies and identify the factors that increase the transport flux, which is typically expressed in units of µg/cm2 /h the data from this study can be utilized to forecast in vivo behaviors from various transdermal delivery devices and to optimize the formulation before more costly in vivo experiments are carried out. It has been claimed that alternatives to human skin include monkey, porcine, rat, mouse, guinea pig, and snake skins.

The investigation on skin permeation uses Franz diffusion cell apparatus. The receptor compartment's capacity was 50 ml, and the effective permeation area between the donor and receptor compartments was 2.50 cm2. A magnetic bar was used to stir 50 ml of phosphate-buffered saline (pH 7.4) at 100 RPM in the receptor compartment. The top of the diffusion cell was covered and the formulation (equivalent to 10 mg of drug) was applied to the skin

To keep the sink conditions in place, aliquots of the receptor medium are taken out at the proper intervals and replenished at the same time with an equivalent volume of new phosphate buffer medium (pH-7.4). The collected samples may be examined using spectroscopic analysis or HPLC. [3,10]

11. Stability:

Transferosomal preparations are kept at various temperatures in airtight amber vials.

The general situation for the storage state is described as, for the long term, 25± 2℃/60% RH ±5% RH or 30 ±2 ℃/65% RH± 5% for 12 months, and, for accelerated testing, 40± 2 ℃/75% RH± 5% for six months, according to ICH (International Conference on Harmonization) rules. The recommended conditions for long-term storage and accelerated research for pharmaceutical items designated for refrigeration are 5 ±3 ℃ for 12 months and 25 ±2 ℃/60% RH ±5% RH for 6 months, respectively. Failure to achieve the requirements is seen as a significant change for the drug product.

samples from each ampoule were examined after 30 days to check for pharmaceutical leakage. The % drug loss was estimated by retaining the initial drug entrapment at 100%. [3, 10]

APPLICATIONS OF TRANSFEROSOMES [1,3]

S.No	Drug	Category	Results
1	Repaglinide	Anti- hypoglycemia drug	Improved site specificity and prolonged the release of the drug
2	Lidocaine	Local anesthetic	Improved skin permeation
3	Itraconazole	Antifungal drug	Prolonged release of the drug
4	Carvedilol	β- Blocker	Transferosomal vesicles were substantially more effective at delivering carvedilol through the nose with a bioavailability of 63.4%
5	Insulin	Anti-diabetic	prolonged hypoglycemic effect in diabetic rats over 24 h after transdermal administration
6	Mefenamic acid	NSAID	Better outcomes were obtained using the thin-film hydration technique, which had the maximum drug content, spread ability, and sustained drug release profile for 12 hours.
7	Sildenafil citrate	PhosphoDiesterase (PDE) Inhibitors	Improved transdermal permeation and bioavailability with reduced dose administration frequency
8	Tacrolimus	Immunosuppressants	Better antipsoriatic activities compared to liposomes due to better skin permeations

CONCLUSION

Enhancing the delivery of both small and large therapeutic substances into the skin is possible with transferosomes as Transferosomes can squeeze through skin pores that are numerous times smaller than usual in order to respond to environmental stress. Since the structure of transferosomes contains hydrophilic and hydrophobic molecules, a variety of solubilities are possible. Despite being 1500 times smaller than water, transferosomes can almost as easily pass-through pores as narrow as 100 mm. They are not as stiff as typical vesicles and are capable of carrying even big molecules. Because of this, transferosomes have a significant chance of solving existing issues that are faced by the conventional techniques. [6,7,12,13]

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