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Transferosome: A Novel Nano-Vesicular Technique for Transdermal Drug Delivery

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Nagma Fatima*, M Suresh Babu

Deccan School of Pharmacy, Dar-us Salam, Aghapura, Hyderabad-500001 India

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ABSTRACT

Novel drug delivery systems are now a day is creating a new interest in the development of drug deliveries. Vesicular drug delivery system is also a part of these novel drug delivery systems. They are non-invasive and self-administered delivery systems that can improve patient compliance and provide a controlled release of therapeutic agents. The greatest challenge of transdermal delivery systems is the barrier function of the skin's outermost layer. Molecules with molecular weights greater than 500 Da and ionized compounds generally do not pass through the skin. Therefore, only a limited number of drugs are capable of being administered by this route. They are biocompatible and biodegradable as they are made from natural phospholipids and have high entrapment efficiency. They have a bilayered structure that facilitates the encapsulation of lipophilic and hydrophilic, as well as amphiphilic, drugs with higher permeation efficiencies compared to conventional liposomes. The present review is made to describe the transferosomes, different methods of preparation, mechanism of action and characterization and their recent applications in the transdermal delivery of drugs.

1. INTRODUCTION

Since the last few years, the vesicular systems have been promoted as a means of sustained or controlled release of drugs. Transferosome is a trademark registered by the German company IDEA AG, which refers to its proprietary drug delivery technology. The name means "carrying body" and is derived from the Latin word 'transferre', meaning 'to carry across' and the Greek word 'soma', meaning 'a body'. A Transfersome carrier is an artificial vesicle designed to exhibit the characteristics of a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and potentially, targeted drug delivery. Transferosomes are vesicular carrier systems that are specially designed to have at least one inner aqueous compartment that is enclosed by a lipid bilayer, together with an edge activator (Figure 1) This aqueous core surrounded by a lipid bilayer makes ultra-deformable vesicles having both self-optimizing and self-regulating capabilities. In accordance with that, transfersomes are elastic in nature and can thereby deform and squeeze themselves as intact vesicles without a measurable loss through narrow pores or constrictions of the skin that are significantly smaller than the vesicle size. The presence of lipophilic and hydrophilic moieties in the vesicular structure result in a wide range of solubility of transfersomes [7,48,49]. It has been identified that vesicles with sizes ≥600 nm are unable to penetrate deeper skin layers, whereas ≤300 nm reach deeper into the skin [50,51]. However, those vesicles with ≤70 nm have exhibited a maximum deposition of the contents in both the viable epidermal as well as dermal layers of the skin. Furthermore, it has been reported that statistically enhanced skin penetration was exhibited by transfersomes with 120-nm sizes compared to larger ones.

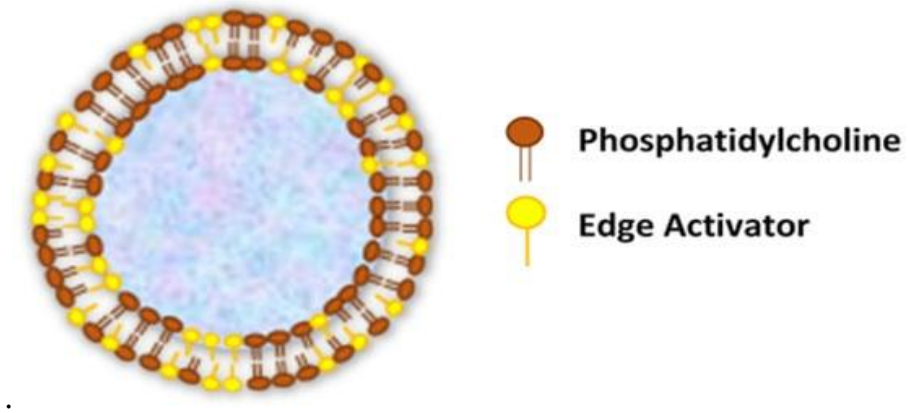

Figure 1. Structure of transfersomes

The system delivers the drug with high efficiency depending on the choice of administration or application. This system has several order magnitude of elasticity and flexibility over liposomal drug delivery which makes it favorable for efficient skin penetration and hence for the novel drug delivery system. They overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. With the application of mechanical stress, they can enter through stratum corneum in self adapting manner because of their high vesicle deformability. Flexibility or elasticity of transfersomes membrane is achieved by mixing suitable surface-active components (edge activator) in the proper ratios**.**

ADVANTAGES OF TRANSFEROSOME:

Transfersomes are able to squeeze themselves through constrictions of the skin barrier that are very narrow, such as 5 to 10 times less than the vesicle diameter, owing to their ultra-deformability and elastic properties.

Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result, can accommodate drug molecules with wide range of solubilities. They can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without significant loss.

Transdermal medication delivers a steady infusion of a drug over an extended period of time.

Avoiding the first-pass metabolism, which is a major drawback in oral drug administration, and results in optimized bioavailability of the drug.

Minimize the undesirable side effects of the drug, as well as protect the drug from metabolic degradation; moreover, the utility of short half-life drugs.

Self-administration is possible with these systems.

They are made up of natural phospholipids and EAs, therefore promisingly biocompatible and biodegradable.

Transfersomes can be used for the delivery of various active compounds, including proteins and peptides, insulin, corticosteroids, interferons, anesthetics, NSAIDs, anticancer drugs and herbal drugs.

Transfersomes are an obvious choice for achieving a sustained drug release, as well as a predictable and extended duration of activity.

LIMITATIONS:

Transfersomes are considered chemically unstable due to their tendency to oxidative degradation. The oxidation of transfersomes can be significantly decreased when the aqueous media is degassed and purged with inert gases, such as nitrogen and argon. Storage at a low temperature and protection from light will also reduce the chance of oxidation. Post-preparation processing, such as freeze-drying and spray-drying, can improve the storage stability of transfersomes.

Skin irritation and hypersensitivity reactions may occur.

Drugs that require high blood levels cannot be administered.

Purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles.

Not suitable for high drug doses.

MECHANISM OF ACTION:

Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of the stratum corneum. At present, the mechanism of enhancing the delivery of active substances in and across the skin is not very well known. Two mechanisms of action have been proposed.

- Transferosomes act as drug vectors, remaining intact after entering the skin.
- Transferosomes act as penetration enhancers, disrupting the highly organized intercellular lipids from the stratum corneum and therefore facilitating the drug molecules penetration in and across the stratum corneum.

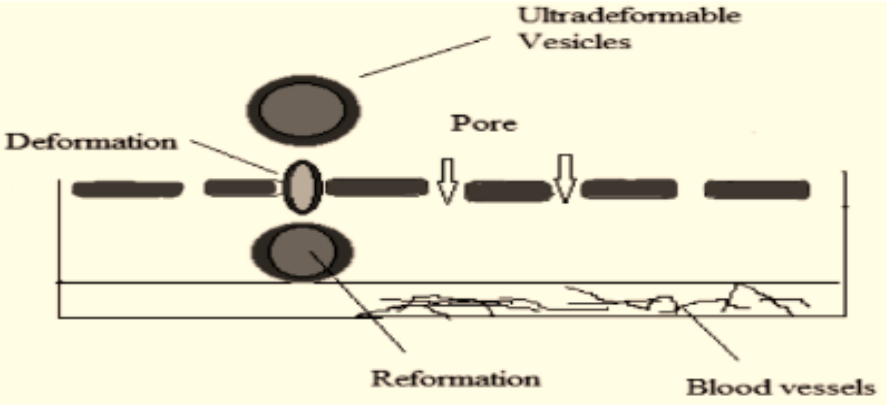

Figure 2: Penetration pathway of transfersomes

The mechanism for penetration includes the generation of "osmotic gradient" due to the evaporation of water while applying the transfersomes on the skin surface. The transport of these elastic vesicles is thus independent of concentration. This osmotic gradient is developed due to the skin penetration barrier, prevents water loss through the skin and maintains a water activity difference in the viable part of the epidermis. As the vesicles are elastic, they can squeeze through the pores in the stratum corneum (though these pores are less than one-tenth of the diameter of vesicles). Transfersomes by enforcing their own route induce hydration that widens the hydrophobic pores of skin, through the widen pores there is gradual release of drug occurs that binds to targeted organ. Transfersomes act as penetration enhancers that disrupt the intercellular lipids from stratum which ultimately widens the pores of skin and facilitates the molecular interaction and penetration of system across skin.

COMPOSITION OF TRANSFEROSOMES:

The transfersome is composed of two main aggregates namely,

1. Firstly, an amphipathic ingredient (phosphatidylcholine), in which the aqueous solvents self-assembleinto lipid bilayer that closes into a simple lipid vesicle.

2. Secondly, a bilayer softening component (such as a biocompatible surfactant oramphiphile drug) that increases lipid bilayer flexibility and permeability.

Materials commonly used in the preparation of Transfersomes;

S.NO.	**Class**	**Example**	**Use**
1.	Phospholipids	Soya phosphatidyl choline, Egg phosphatidylcholine, Dipalmitoylphosphatidyl choline	Vesicle forming component
2.	Surfactant	Sod.cholate,Sod.deoxycholate,Tween-80,Span-80,Tween-20	Vesicle forming component
3.	Solvents	Ethanol, Methanol, Isopropyl alcohol, Chloroform	As a solvent
4.	Buffering agent	Saline phosphate buffer(PH 6.4), Phosphate buffer PH 7.4	As a hydrating medium
5.	Dye	Rhodamine-123, Rhodamine-DHPE Fluorescein-DHPE Nile-red	For CSLM study

METHOD OF PREPARATION OF TRANSFEROSOMES:

1. Modified handshaking process

In this process, the transfersomes are prepared by modified hand shaking, 'lipid film hydration technique'. Drug, lecithin (PC) and edge activator were dissolved in ethanol: chloroform (1:1) mixture. Organic solvent was removed by evaporation while hand shaking above lipid transition temperature (43°C). A thin lipid film was formed inside the flask wall with rotation. The thin film was kept overnight for complete evaporation of solvent. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minute at corresponding temperature.

2. Vortexing-Sonication Method

The phospholipids, edge activator and drug are mixed in a phosphate buffer. The mixture is then vortexed until a milky transpersonal suspension is obtained. It is then sonicated, using a bath sonicator, for a respective time at room temperature and then extruded through polycarbonate membranes (example: 450 and 220 nm).

3. Suspension homogenization process

In this process, transfersomes are prepared by mixing an ethanolic soybean phosphatidylcholine solution with an appropriate amount of edge-active molecule, e.g. sodium cholate. This prepared suspension is subsequently mixed with Triethanolamine-HCl buffer to yield a total lipid concentration. The resulting suspension is sonicated, frozen, and thawed for 2 to 3 times.

4. Thin Film Hydration Technique/Rotary Evaporation-Sonication Method

The phospholipids and edge activator (vesicle-forming ingredients) are dissolved in a round-bottom flask using a volatile organic solvent mixture (for example: chloroform and methanol in a suitable (v/v) ratio). The lipophilic drug can be incorporated in this step. In order to form a thin film, the organic solvent is evaporated above the lipid transition temperature under reduced pressure using a rotary vacuum evaporator. Keep it under vacuum to remove the final traces of the solvent. The deposited thin film is then hydrated using a buffer solution with the appropriate pH (example: pH 7.4) by rotation for a respective time at the corresponding temperature. The hydrophilic drug incorporation can be done in this stage. The resulting vesicles are swollen at room temperature and sonicated in a bath or probe sonicator to obtain small vesicles. The sonicated vesicles are homogenized by extrusion through a sandwich of 200 nm to 100 nm polycarbonate membranes.

5. Centrifugation process

In this process, phospholipids, surfactants and the drug are dissolved in alcohol. Then the solvent is removed by rotary evaporation under reduced pressure at 40 °C. Final traces of solvent are removed under vacuum. Then the deposited lipid film is hydrated with the appropriate buffer by centrifuging at 60 rpm for 1 hour at room temperature. At room temperature, the resulting vesicles are swollen for 2 hours. The multi-lamellar lipid vesicles obtained which are further sonicated at room temperature.

CHARACTERIZATION OF TRANSFEROSOMES:

The characterization of transfersomes can be done by on following parameters:

1.Vesicle Morphology

(a) Vesicle Diameter: Determination of vesicle diameter can be done using photon correlation spectroscopy or dynamic light scattering (DLS) method. Samples are prepared in distilled water, filtered through a 0.2 mm membrane filter and diluted with filtered saline and then size measurement is done using photon correlation spectroscopy or dynamic light scattering (DLS) measurements. The stability of vesicles can be determined by assessing the size and structure of vesicles over time.

(b) Vesicle Shape and Type: The visualization of vesicle shape or its appearance can be carried out using TEM. They can also be visualized by phase contrast microscopy using the optical microscopy method, without sonication. Dynamic light scattering techniques can also be used.

(c) Vesicle Size, Size Distribution, and Zeta Potential: To study the vesicular shape, Transmission electron microscopic (TEM) studies are used. The size of the vesicle, size distribution and zeta potential are generally determined by the Dynamic Light Scattering Method (DLS) using a computerized inspection system by Malvern Zetasizer.

(d) No. of Vesicles per Cubic mm: For optimizing the composition and other process variables, number of vesicles per cubic mm is an important parameter. In this non-sonicated transfersome formulations are diluted five times with 0.9% sodium chloride solution. For further study, haemocytometer and optical microscope can then be used. The number of transfersomes in 80 small squares are counted and calculated using the following formula:

$$\text{Total number of transfersomes per cubic mm} = \frac{(\text{Total number of transfersomes counted} \times \text{dilution factor} \times 4000)}{\text{Total number of squares counted}}$$

2. Entrapment efficiency: Generally, expressed in terms of % drug entrapment. In this method, unentrapped drug first separated using mini column centrifugation method. After that, the vesicles were disrupted using 0.1% Triton X-100 or 50% n-propanol. The entrapment efficiency is expressed as:

Entrapment efficiency = (Amount entrapped/Total amount added) × 100

3. Determination of drug content: The drug content can be determined using one of the instrumental analytical methods such as modified high-performance liquid chromatography method (HPLC) method using a UV detector, column oven, auto sample, pump, and computerized analysis program depending upon the analytical method of the pharmacopoeial drug.

4. Turbidity measurement: The turbidity of drug in aqueous solution can be measured using nephelometer.

5. Surface charge and charge density: Zetasizer is used to determine surface charge and charge density of transferosomes. Surface charge and Charge density of transfersomes can be determined using Zetasizer.

6. Confocal scanning laser microscopy study: In this technique, lipophilic fluorescence markers are incorporated into the transfersomes and the light emitted by these markers used for following purpose:

a. Investigation of the mechanism of penetration of transfersomes across the skin.

b. Determination of histological organization of the skin, shapes and architecture of the skin penetration pathways.

c. Comparison and differentiation of the mechanism of penetration of transfersomes with liposomes, niosomes and micelles.

7. In-vitro drug release: In vitro drug release study is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from in vitro studies are used to optimize the formulation before more expensive in vivo studies are performed. For determining drug release, transfersomes suspension is incubated at 32°C and samples are taken at different times and the free drug is separated by minicolumn centrifugation. The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released).

8. In vitro skin permeation studies: Modified Franz diffusion cell with a receiver compartment volume of 50 ml and effective diffusion area of 2.50 cm2 was used for this

study. In vitro drug study was performed using goat skin in phosphate buffer solution (pH 7.4). Fresh abdominal skin of goat was collected from slaughterhouse and used in the permeation experiments. Abdominal skin hairs were removed, and the skin was hydrated in normal saline solution. The adipose tissue layer of the skin was removed by rubbing with a cotton swab. Skin was kept in isopropyl alcohol solution and stored at 0-40°C. To perform skin permeation study, treated skin was mounted horizontally on the receptor compartment with the stratum corneum side facing upward toward the donor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was 2.50 cm2 and capacity of receptor compartment was 50 ml. The receptor compartment was filled with 50 ml of phosphate buffer (pH 7.4) saline maintained at 37 ± 0.5°C and stirred by a magnetic bar at 100 rpm. Formulation (equivalent to 10 mg drug) was placed on the skin, and the top of the diffusion cell was covered. At appropriate time intervals, 1 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffers (pH 7.4) to maintain sink conditions. Correction factors for each aliquot were considered in the calculation of release profile. The samples were analyzed by any instrumental analytical technique.

9. Physical stability: The initial drug entrapped (percent) in the formulation was determined and was stored in sealed glass ampoules. The ampoules were placed at 4 ± 2°C (refrigeration), 25 ± 2°C (room temperature), and 37 ± 2°C (body temperature) for at least 3 months. Samples from each ampoule were analyzed after 30 days to determine drug leakage. Percent drug loss was calculated by keeping the initial entrapment of drug as 100%.

APPLICATIONS:

Delivery of Proteins and Peptides: For transportation of larger biogenic molecules of the body such as proteins and peptides, transfersomes are being widely used as a carrier otherwise given through oral routes such molecules get degraded in GIT. Because of this reason proteins and peptides still have to be introduced into the body through injections but now transfersomes have proven to be a suitable approach as they also provide bioavailability somewhat similar to subcutaneous injections of the same protein suspension.

Several proteins have been administered by preparing transfersomes e.g. bovine serum albumin, after repeated epicutaneous application, the transferosomal preparations induced

strong immune response. Gap junction proteins loaded in transfersomes also elicited antigen-specific antibody titer equivalent to subcutaneous route.

Delivery of corticosteroids: Problems arise with corticosteroids delivery is mask by incorporation it into transfersomes. Site specificity and overall drug of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose safety is achieved by transfersome encapsulation. The dose required for biological activity of corticosteroid is less by use of transfersomes technology.

Delivery of Anti-cancer Drugs: Transfersomes have also been tried for delivery of anti-cancer agents like methotrexate as they are especially suitable to be used as a carrier for treatment of skin cancer. The obtained results were favorable and this provided a new approach for treatment especially of skin cancer. Anti-breast cancer agent Tamoxifen (TAM) is delivered by transfersomes through the skin most efficiently and also accelerated the growth of murine uteri, where it act as an anti-oestrogen, even at low dose as 0.1-0.2 mg/kg/day.

Delivery of non-steroidal anti-inflammatory drugs (NSAIDs): Problems arise with most of NSAIDs are a number of GI side effects. This can be overcome by transdermal delivery using transfersome. Studies have been carried out on diclofenac and ketoprofen. Ketoprofen in a transfersome formulation gained marketing approval by the Swiss regulatory agency (Swissmedic) in 2007; the product is expected to be marketed under the trademark "Diractin." Further therapeutic products based on the transfersome technology, according to IDEAAG, are in clinical development.

Delivery of Insulin: Transfersomes have been used to deliver insulin to the systemic circulation in therapeutic amounts equivalent to subcutaneous injection. Cevc et al. reported about the study for insulin delivery from transfersomes composed of phosphatidylcholine incorporating sodium cholate and compared with conventional liposomes and mixed micelles applied to the skin of both mice and humans. There was a 30-minute lag time relative to a subcutaneous injection of the same formulation, but the overall efficacy of delivery was comparable.

Delivery of anesthetics: Transfersome based formulations of local anestheticslidocaine and tetracaine showed permeation equivalent to subcutaneous injections, with less than 10 min.

Maximum resulting pain insensitivity is nearly as strong (80%) as that of a comparable subcutaneous bolus injection, but the effect of transferosomal anesthetics last longer.

Delivery of Herbal Drugs: Due to the property of transfersome to supply nutrients locally by penetrating the stratum corneum, transfersomes of capsaicin have been prepared by Xiao-Ying et al., showing improved absorption through the topical route when compared to pure capsaicin.

Transfersomes are also used to increase the skin penetration of certain phytoconstituents like capsaicin and colchicine and along with these effects also increase the entrapment efficiency of certain phytoconstituents like vincristine.

CONCLUSION:

From the literature, it is evident that transferosomes being ultra-deformable vesicles can deliver both small as well large molecules efficiently by overcoming various problems of skin permeation. Transferosomes are specially designed vesicles capable of responding to external stress by squeezing themselves through skin pores that are many times narrower than they are leading to increased transdermal flux of therapeutic agents.

Transferosomes holds great prospects in delivery of a huge range of drug substances includes large molecules; proteins, peptides, antibiotics, etc. They not only assist in transportation of substances through the skin but can also be used for enhancing the solubility of poorly soluble drugs.Because of the neumerous functions , transferosomes are gaining potential in the market and ensuring promising transdermal delivery of drugs.

REFERENCES:

1. Honeywell-Nguyen PL, Bouwstra JA. Vesicles as a tool for transdermal and dermal delivery. Drug Discovery Today: Technologies. 2005; 2(1): 67-74.
2. Hofl HEJ, Bouwstra JA, Spies F, Gooris G, Nagelkerke JF. Interaction of liposomes and niosomes with human skin. J. Pharm. Sci. 1994; 83, 1192-1196.
3. Fang YP, Tsai YH, Wu PC, Huang YB. Comparison of 5- aminolevulinic acid-encapsulated liposome versus ethosome for skin delivery for photodynamic therapy. Int J Pharm. 2008; 356 (1-2): 44–52.
4. Prajapati ST, Patel CG, Patel CN. Transfersomes: A vesicular carrier system for transdermal drug delivery, Asian J Biochem Pharm Res. 2011; 2 (1), 507-524.
5. Kombath RV, Minumula SK, Sockalingam A, Subadhra S, Parre S, Reddy TR, David B. Critical issues related to transfersomes – novel Vesicular system", Acta Sci. Pol., Technol. Aliment. 2012; 11 (1), 67-82.
6.Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 2001;14:101-14.
7.Hamidi M, Azadi A, Rafiei P. Hydrogel nanoparticles in drug delivery. Adv Drug Deliv Rev 2008;60:1638-49.

8.Karande P, Mitragotri S. Enhancement of transdermal drug delivery via synergistic action of chemicals. Biochim Biophys Acta 2009;1788:2362-73.
9.Crommelin DJ, Eling WM, Steerenberg PA, Nässander UK, Storm G, De Jong WH, et al. Liposomes and immunoliposomes for controlled release or site specific delivery of anti-parasitic drugs and cytostatics. J Control Release 1991;16:147-54.
10.Yavlovich A, Singh A, Blumenthal R, Puri A. A novel class of photo-triggerable liposomes containing DPPC: DC8, 9PC as vehicles for delivery of doxorubcin to cells. Biochim Biophys Acta 2011;1808:117-26.
11. Gupta A., Aggarawal G., Singla S., Rora R., A, "Transfersomes: A Novel Vesicular Carrier for Enhanced Transdermal Delivery of Sertraline: Development, Characterization and performance Evaluation," Sci Pharm, 2012; 80: 1061-1080.
12. Wavle J.R BakliwalS.R, Rane B.R, Pawer S.P, "Transfersomes: A surrogated Carrier For Transdermal Drug Delivery System" International Journal of Applied Biology and Pharmaceutical Technology, Jan-Mar-2011; 2(1).
13. Kavitha K, Bharath N, Mani T T., "Physical Permeation Enhancers for Transdermal Drug Delivery "Research of Journal of Pharmaceutical, Biological and Chemical Sciences, October- December 2011; 2(4): 66.
14. Dave V., Kumar D., Lewis S., Paliwal S., "Ethosome for Enhanced Transdermal Drug Delivery of Aceclofenac" International Journal of Drug Delivery, 2010; 2: 81-92.
15. Kumar R., Philip A. "Modified Transdermal Technologies: Breaking the Barriers of Drug Permeation via the Skin" Page no.1-15.
16.Cevc, G.; Schatzlein, A.G.; Richardsen, H. Ultradeformable lipid vesicles can penetrate the skin and other semi-permeable barriers unfragmented. Evidence from double-label CLSM experiments and direct size measurements. Biochim. et Biophys. Acta (BBA)-Biomembr. 2002, 1564, 21–30.
17. Rajan, R.; Jose, S.; Mukund, V.P.B.; Vasudevan, D.T. Transferosomes—A vesicular transdermal delivery system for enhanced drug permeation. J. Adv. Pharm. Technol. Res. 2011, 2, 138–143.
18. Cevc, G. Lipid vesicles and other colloids as drug carriers on the skin. Adv. Drug Deliv. Rev. 2004, 56, 675–711.
19. Walve, J.R.; Bakliwal, S.R.; Rane, B.R.; Pawar, S.P. Transfersomes: A surrogated carrier for transdermal drug delivery system. Int. J. Appl. Biol. Pharm. Technol. 2011, 2, 204–213.
20. Sivannarayana, P.; Rani, A.P.; Saikishore, V.; VenuBabu, C.; SriRekha, V. Transfersomes: Ultra deformable vesicular carrier systems in transdermal drug delivery system. Res. J. Pharm. Dos. Forms Technol. 2012, 4, 243–255.
21. Sachan, R.; Parashar, T.; Soniya, S.V.; Singh, G.; Tyagi, S.; Patel, C.; Gupta, A. Drug carrier transfersomes: A novel tool for transdermal drug delivery system. Int. J. Res. Dev. Pharm. Life Sci. 2013, 2, 309–316.