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Review Article

Transfersomes: a novel technique for transdermal drug delivery

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ABSTRACT

Novel drug delivery systems are now a days is creating a new interest in development of drug deliveries. Vesicular drug delivery system is also a part of these novel drug delivery systems. TDDS is the permeability of the skin, it is permeable to small molecules, lipophilic drug and highly impermeable to the macromolecules and hydrophilic drugs. Recent approaches have resulted in design of two vesicular carriers, ethosomes and ultra flexible lipid based elastic vesicles, transferosomes. Transferosomes have recently been introduced, which are capable of transdermal delivery of low as well as high molecular weight drugs. This offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half life drugs, improving physiological and pharmacological response and have been applied to increases the efficiency of the material transfer across the intact skin, by the use of penetration enhancers, iontophoresis, sonophoresis and use of colloidal carriers such as lipid vesicles (liposomes & proliposomes) and non-ionic surfactant vesicles (niosomes & proniosomes). It is suitable for controlled and targeted drug delivery and it can accommodate drug molecules with wide range of solubility. Due to its high deformability it gives better penetration of intact vesicles. They are biocompatible and biodegradable as they are made from natural phospholipids and have high entrapment efficiency. The preparation variables are depending upon the procedure involved for manufacturing of formulation and the preparation procedure was accordingly optimized and validated. Characterization of transferosomes can be done to know the vesicle size, morphology, drug content, entrapment efficiency, penetration ability, occlusion effect, surface charge, in vitro drug release, in vitro skin penetration etc., It increases stability of labile drugs and provides control release. Transferosomes thus differs from such more conventional vesicles primarily by its softer, more deformable, better adjustable artificial membrane.

Keywords: Novel Drug Delivery System, Biocompatible, Characterization, Transferosomes.

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INTRODUCTION

In recent years, research scenario goes toward the development of new type of drug delivery system with the objective of high therapeutic activity along with patient compliance. Many drug delivery systems are developed with improved therapeutic activity, but some complications arise with some delivery systems are not as such overcomes.

Orally administered drugs experience a hostile environment in the gastrointestinal (GI) tract, where most drugs are degraded in variable pH conditions, or face solubility issues and most importantly first-pass metabolism. In case of parenteral preparation, disadvantages are a lack of drug reversal, hypersensitivity reaction, risk of infection, emboli and cost. Some drugs much bitter in taste, swallowing of such a bitter medication in oral delivery and pain associated due to needle in parenteral delivery make them less patient

compliance¹. From last few decades, considerable attention has been focused on the development of topical delivery of drugs because a number of advantages with this route. Skin in an average adult body covers a surface of approximately 2 m2 and total weight of 3 kg; it receives about one-third of the blood circulating among the body. Topical drug delivery means the application of drug to skin for localized effect and in transdermal drug delivery system (TDDS) skin is used as a potential route for the delivery of systemic action of drugs. TDDS is one of the systems with high patient compliance. Some potential advantages of transdermal route found over other conventional routes such as oral- and parenteral-like avoidance of first-pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter- and intra-patient variations

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and most importantly, it provides patients convenience^{2,3}. However, it also has some disadvantages such as possibility of local irritation effect, erythema, itching and low permeability in the stratum corneum. A major obstacle to dermal and transdermal drug delivery is the permeation characteristics of the stratum corneum, which limits drug transport, making this route of administration frequently insufficient for medical use⁴. Stratum corneum is the top layer of the epidermis consists of keratinized, flattened remnants of once actively dividing epidermal cells, impermeable to water and behaves as a tough flexible membrane. Many technologies and systems have been investigated to evade this barrier including electrophoresis, permeation iontophoresis, chemical enhancers. microemulsions, sonophoresis, as well as utilizing vesicular systems such as liposome, niosomes, ethosomes, and transfersomes, one of the most promising techniques is to formulate novel vesicular carriers for delivery through the skin as it delivered drug at sustained or controlled manner5-¹⁰. Among all these transfersomes appear promising. A new type of vesicular drug carrier system called transfersome. The term transfersomes (Fig 1) and the underlying concept were introduced in 1991 by Gregor Cevc. In broadest sense, a transfersomes is a highly adaptable and stress-responsive, complex aggregate possessing an aqueous core surrounded by a complex of lipid bilayer^{11,12}. Transfersome is a term registered as a trademark by the German Company IDEA AG and used by it to refer to its proprietary drug delivery technology. The name means carrying body and is derived from the Latin word transferred meaning to carry across and the Greek word soma for a body. A transfersome carrier is an artificial vesicle designed to be like a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and potentially targeted, drug delivery¹³. Most suitable form of transfersome is an ultra deformable vesicle possessing an aqueous core surrounded by the complex lipid bilayer. In terms of delivering of drugs through transdermal route, there are some problems encountered with some other vesicular systems such as poor skin permeability, breaking of vesicles, leakage of drug and aggregation and fusion of vesicles. To overcome all the above problems, a new type of vesicular carrier has been developed called transfersome which is capable of transdermal delivery of low as well as high molecular weight drugs. Transfersomes are artificial vesicles, and they are more deformable than standard liposomes. Transfersomes have been reported to enhance the transdermal delivery of drugs when applied onto the skin non occlusively^{12, 14-17}.



Figure 1: Deformable transfersomes vesicle

ADVANTAGES

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

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- ✓ An equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary.
- ✓ Self administration is possible with these systems.
- ✓ They are easily and rapidly identified in emergencies (e.g. unresponsive, unconscious or comatose patient) because of their physical presence, features and identifying markings.
- ✓ They can be used for drugs with narrow therapeutic window.
- Longer duration of action resulting in a reduction in dosing frequency.
- ✓ Increased convenience to administer drugs which would otherwise require frequent dosing.
- ✓ Improved bioavailability.
- More uniform plasma levels and maintain plasma concentration of potent drugs.
- Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
- Flexibility of terminating the drug administration by simply removing patch from the skin.
- ✓ Improved patient compliance and comfort via noninvasive, painless and simple application.
- ✓ Avoid inter and intra patient variation and enhance therapeutic efficacy.

DISADVANTAGES

- Many drugs especially drugs with hydrophilic structures permeate the skin too slowly to be of therapeutic benefit.
- ✓ The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.
- ✓ Drug molecule must be potent because patch size limits amount that can be delivered.
- ✓ Not suitable for high drug doses.
- ✓ Adhesion may vary with patch type and environmental conditions.
- ✓ Skin irritation and hypersensitivity reactions may occur.
- ✓ Drugs that require high blood levels cannot be administered.
- Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product.
- Transfersomes are chemically unstable because of oxidative degradation make its predisposition.
- ✓ Purity of natural phospholipids is another criterion for achieve for adoption of transfersomes as drug delivery vehicles¹⁸⁻²⁰.

WHY ONLY TRANSFERSOMES FOR SKIN

Transfersomes are advantageous as phospholipids vesicles for transdermal drug delivery. Because of their selfoptimized and ultra flexible membrane properties, they are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or

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application, with high efficiency. The vesicular transfersomes are more elastic than the standard liposomes and thus well suited for the skin penetration. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. These are characteristic with transfersomes, because of the high vesicle deformability which permits the entry due to the mechanical stress of surrounding, in a self-adapting manner. Flexibility of transfersomes membrane is governed by mixing suitable surface-active components in the proper ratios with phospholipids ²¹. The resulting flexibility of transfersome membrane minimizes the risk of complete vesicle rupture in the skin and allows transfersomes to follow the natural water gradient across the epidermis, when applied under non-occlusive condition. Transfersomes can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayers properties. Bangham discovered liposomes in 1963 and since then vesicular systems have attracted increasing attention. But recently it has become evident that classic liposomes are of minor values in terms of penetration. Confocal microscopic studies have shown that intact liposomes are not able to penetrate into granular layer of epidermis but, they rather remain on the upper layer of stratum corneum. The

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modification of the vesicular compositions or surface properties can adjust the drug release rate and the deposition to the target site ²²⁻²⁴.

COMPOSITION OF TRANSFERSOMES

The transfersome is composed of two main aggregates namely,

1. Firstly, an amphipathic ingredient (phosphatidylcholine), in which the aqueous solvents self-assemble into 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 permeability²⁵.

The resulting, flexibility and permeability optimized, transfersome vesicle can therefore adapt its shape easily and rapidly, by adjusting local concentration of each bilayer component to the local stress experienced by the bilayer. Therefore, the transfersome thus differs from such more conventional vesicle primarily by its "softer", more deformable, and better adjustable artificial membrane Table 1.

Table 1: Different additives used in formulation of transfersomes

S.No	Class	Example	Use
1	Phospholipids	Soya phosphatidyl choline, egg phosphatidyl choline,	Vesicles forming component
	0	dipalmitoylphosphatidyl choline	() .
2	Surfactants	Sod.cholate, Sod.deoxycholate, Tween-80, Span-80, Tween 20	Vesicles 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

METHODS FOR PREPARATION OF TRANSFERSOME

1. Vortexing-sonication method

In this method, mixed lipids (i.e. phospha-tidylcholine, EA and the therapeutic agent) are blended in a phosphate buffer and vortexed to attain a milky suspension. The suspension is sonicated, followed by extrusion through poly-carbonate membranes.

2. 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.

3. 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.

4. Aqueous lipid suspension process

In this process, Drug-to-lipid ratio in the vehicles is fixed between 1/4 and 1/9. Depending upon the particular formulation type, the composition is preferred. This would ensure the high flexibility of the vesicle membrane in comparison to the standard phosphatidylcholine vesicles in the fluid phase. Specifically, vesicles with the size ranging 100-200 are from nm prepared by using soyphosphatidylcholine with the standard deviation of size distribution (around 30%). This formulation could be prepared by suspending the lipids in an aqueous phase wherein the drug is dissolved.

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 40oC. 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 ²⁶⁻²⁸.

MECHANISM OF ACTION

Mechanism behind the penetration of transfersome is the development of osmotic gradient because while lipid suspension applies on skin surface water gets evaporated. Transfersomes have strong bilayer deformability and therefore they have increased affinity to bind and retain water. Dehydration is not happened in case an ultradeformable and highly hydrophilic vesicle; it is not identical to forward osmosis but may involve in transport process related to forward osmosis. Upon application on skin

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surface (non-occluded), it penetrates skin barrier and reaches at the deeper strata (water rich portion), where they get hydrated. Then, reach at deeper epidermal layer through dehydration of lipid vesicles within the stratum corneum by natural transepidermal activity (Fig 2). Therefore, transfersome uptake is a function of hydration gradient that exists across the epidermis, stratum corneum, and ambient atmosphere ^{29,30}.



Figure 2: Penetration pathway of transfersomes

OPTIMIZATION OF FORMULATION CONTAINING TRANSFERSOMES

There are some process variables such as lecithin, surfactant ratio, effect of various solvents, effect of various surfactants, and hydration medium. This could affect the preparation and properties of the transfersomes. Procedure for preparation of transfersomes will accordingly optimize and validate. The process variables depend on the procedure for manufacturing of formulation. Entrapment efficiency of drug is the tool used for optimization. Other variables were kept constant at the time of preparation of particular system³¹.

CHARACTERIZATION OF TRANSFERSOMES

The characterization of transfersomes is generally similar to liposomes, niosomes and micelles. The following characterization parameters have to be checked for transfersomes.

1. Vesicle size distribution and zeta potential

Dynamic light scattering method (DLS) using a computerized inspection system by Malvern Zetasizer used for determination of vesicle size, size distribution, and zeta potential.

2. Vesicle morphology

Photon correlation spectroscopy or DLS method generally used for vesicle diameter determination. Prepared sample in distilled water was filtered through 0.2 mm membrane filter and diluted with filtered saline and then size measurement done using photon correlation spectroscopy or DLS measurements. Transmission electron microscopy (TEM) and phase contrast microscopy can be commonly used for visualization of transfersomes vesicles. The stability of vesicle can be determined by assessing the size and structure of vesicles with respect to time. DLS and TEM used for mean size and structural changes, respectively.

3. Number of vesicles per cubic mm

This parameter is very important for optimization of composition and other process variables. Transfersome formulations which are unsonicated are diluted 5 times with 0.9% sodium chloride solution. Hemocytometer and optical microscope are used for further study.

The transfersomes in 80 small squares are counted and calculated using the following formula:

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Total number of transfersomes per cubic mm = (Total number of transfersomes counted × dilution factor × 4000)/total number of squares counted

4. Entrapment efficiency

Generally, expressed in terms of % drug entrapment. In this method, unentrapped drug first separated using minicolumn 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) \times 100

5. Drug content

The drug content is determined using one of the instrumental analytical methods such as a modified highperformance liquid chromatography method using an ultraviolet detector, column oven, auto sample, pump, and computerized analysis program depending on the analytical method of the pharmacopoeial drug.

6. Turbidity measurement

Nephelometer is one of the methods which generally used for turbidity measurement in aqueous solution.

7. Degree of deformability or permeability measurement

Permeability study is one of the important and unique parameters for characterization in case of transfersomes. The deformability study is done by taking pure water as standard. Transfersomes preparation is passed through a number of pores of known size (through a sandwich of different microporous filters, with pore diameter between 50 and 400 nm, depending on the starting transfersomes suspension). Particle size and size distributions are noted after each pass by DLS measurements.

8. Penetration ability

Fluorescence microscopy can generally use for evaluation of penetration ability of transfersomes.

9. Occlusion effect

Occlusion of skin is considered to be useful for permeation of drug in case of traditional topical preparations. However, the occlusion also proves to be harmful for elastic vesicles. Hydrotaxis is the major driving force for permeation of vesicles through the skin is hydrotaxis (movement in the direction) of water, from its relatively dry surface to water rich deeper regions. It affects hydration forces as it prevents evaporation of water from skin.

10. Surface charge and charge density

Surface charge and charge density of transfersomes can be determined using zetasizer.

11. 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).

12. 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.

13. Physical stability

The initial drug entrapped (percent) in the formulation was determined and was stored in sealed glass ampoules. The ampoules were placed at $4 \pm 2^{\circ}C$ (refrigeration), $25 \pm 2^{\circ}C$ (room temperature), and $37 \pm 2^{\circ}C$ (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% ³².

APPLICATION OF TRANSFERSOMES

1. Delivery of insulin

Transfersome is one of the successive ways to deliver such large molecular weight drugs on the skin. Insulin is generally administered by subcutaneous route that is inconvenient for patient. Encapsulation of insulin in transfersome (transfersulin) overcomes all problems arises with conventional insulin delivery. After application of transfersulin on the intact skin, therapeutic effect observed after 90-180 min, depending on the carrier composition.

2. 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. Dose required for biological activity of corticosteroid is less by use of transfersomes technology.

3. Delivery of proteins and peptides

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Transfersomes have been widely used as a carrier for the transport of proteins and peptides also safely given by means of transfersome technology. Proteins and peptide has problem is it is difficult to transfer into the body, are large biogenic molecules, GI tract degradation is problem arise when given orally. That's reasons why these peptides and proteins still given by means of injectables. A number of approaches have been developed to improve this condition. Transfersome is somewhat identical to that resulting from subcutaneous injection of protein suspension in terms of bioavailability. On repeated epicutaneous application, transfersome preparation of protein also induced a strong immune response. For example, the adjuvant immunogenic serum albumin in transfersomes, after several dermal challenges, is as active immunologically as is the corresponding injected proteo-transfersomes preparations.

4. Delivery of interferon (INF)

INF also delivered using transfersome as a carrier, for example, leukocyte-derived INF- α is a naturally occurring protein having antiviral, antiproliferative, and some immunomodulatory effects. Transfersomes as drug delivery systems have the potential for providing controlled release of the administered drug and increasing the stability of labile drugs. Hafer *et al.* studied the formulation of transfersome containing interleukin-2 (IL-2) and INF- α for potential transdermal application. They reported delivery of IL-2 and INF- α promising by transfersomes insufficient concentration for immunotherapy.

5. Delivery of anticancer drugs

Transfersome technology provides a new approach for cancer treatment, especially skin cancer. Result found to be favorable when methotrexate was tried for transdermal delivery using transfersome technology.

6. Delivery of anesthetics

Application of transfersome containing anesthetics induces a topical anesthesia, under suitable conditions, within 10 min. Effect when we said in case of pain in sensitivity is nearly as strong (80%) as of a comparable subcutaneous bolus injection, but transfersomal anesthetics preparation has last longer effect.

7. 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 IDEA AG, are in clinical development.

8. Delivery of herbal drugs

Herbal drug also delivered by transfersome approach. Xiao-Ying *et al.* who shows the better topical absorption of transfersomes of capsaicin in comparison to pure capsaicin³³⁻³⁹.

S.No	Name of drug	Inference	
1	Curcumin	Better permeation for anti-inflammatory activity	
2 3	Indinavir sulfate Ketoprofen	Improved influx for activity against acquired immune deficiency syndrome (AIDS) Improved penetration for anti-inflammatory activity	
4	Insulin	induce therapeutically significant hypoglycemia with good efficacy and reproducibility	
5	Capsaicin	Increase skin penetration	
6	Colchicine	Increase skin penetration	
7	Vincristine	Increase entrapment efficiency and skin permeation	
8	Interferon-α	Efficient delivery means (because delivery other route is difficult). Controlled release. Overcome stability problem.	
9	Norgesterol	Improved transdermal flux	
10	Tamoxifen	Improved transdermal flux	
11	Methotrexate	Improved transdermal flux	
12	Oestradiol	Improved transdermal flux	
13	Tetracaine, Lignocain	Suitable means for the noninvasive treatment of local pain on direct topical drug application.	
14	Corticosteroids	Improved site specificity and overall drug safety.	
15	Hydrocortisone	Biologically active at dose several times lower than currently used formulation.	
16	Triamcinolone acetonide	Used for both local and systemic delivery.	
17	Human serum albumin	Antibody titer is similar or even slightly higher than subcutaneous injection.	
18	Stavudine	Improved the in vitro skin delivery of Stavudine for antiretroviral activity	
19	Indinavir sulfate	Enhanced Transdermal delivery Indinavir sulphate for antiretroviral activity ⁴¹	
20	Tetanus toxoid	For transdermal immunization	

6.

CONCLUSION

Transdermal route of drug delivery does not allow transport of high mol.wt therapeutic agents and drugs because of the barrier properties of the stratum corneum layer of the skin. These 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 have beneficial advantages over other vesicular systems such as their high penetration power across skin, higher stability, systemic drug release possible and higher deformability than other vesicular systems such as niosomes, ethosomes etc., These will ensures reproducible and efficient transcutaneous carrier and drug transport. Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.

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