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TRANSFEROSOMES – A NOVEL TECHNIQUE: A REVIEW

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Abstract:

Novel Drug delivery System (NDDS) refers to the approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects. NDDS is a system for delivery of drug other than conventional drug delivery system. The aim of this chapter is to review the literature for SMART nanocarrier-based delivery systems and extended controlled release DDSs which maintain the concentration of the drug within the therapeutic window for a longer time, thereby lowering the frequency of administration. Also, microfluidics (MF), one of the most recent fabrication methods used to design and prepare NDDSs has been discussed. MF can be used to create innovative pharmaceutical formulations and can also be applied to other biological and diagnostic purposes. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility. The high and self-optimizing deformability of typical composite transfersomes membrane, which are adaptable to ambient tress allow the ultra-deformable transfersomes to change its membrane composition locally and reversibly, when it is pressed against or attracted into narrow pore. Transfersomes can deform and pass-through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. This high deformability gives better penetration of intact vesicles. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.

Keywords*: Transferosomes, Novel Drug Delivery System, Phospholipids, Sonification, Interferon.*

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INTRODUCTION:

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all [1]. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), which are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development [1]. Controlled and Novel Drug Delivery which was only a dream or at best a possibility is now a reality. During the last decade and half pharmaceutical and other scientists have carried out extensive and intensive investigations in this field of drug research.

Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable, natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release:

(i) Passive and;

(ii) Active targeting [1]

An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest.

FIGURE 1: TYPES OF DRUG DELIVERY

Any drug delivery system may be defined as a system comprising of:
a) Drug formulation
b) Medical device or dosage form/technology to carry the drug inside the body
c) Mechanism for the release

Conventional drug delivery involves the formulation of the drug into a suitable form, such as a compressed tablet for oral administration or a solution for intravenous administration. These dosage forms have been found to have serious limitations in terms of higher dosage required, lower effectiveness, toxicity and adverse side effects. New drug delivery systems have been developed or are being developed to overcome the limitation of the conventional drug delivery systems to meet the need of the healthcare profession.

These systems can be characterized as controlled drug release systems and targeted drug delivery systems.
The therapeutic benefits of these new systems include:

- Increased efficacy of the drug
- Site specific delivery
- Decreased toxicity/side effects
- Increased convenience
- Viable treatments for previously incurable diseases
- Potential for prophylactic applications
- Better patient compliance.

There is no uniform and established definition of drug delivery systems. It is assumed to be based on two basic parameters:

Route of entry (A) and Dosage form (B).
Any member of the cartesian product of (A X B) is defined as a drug delivery system.

Such a definition implies that there are a vast number of members in this group. Many of them may not even be feasible, while many others may not be relevant. So, the set of most relevant new drug delivery systems is deduced as follows:
Various Drug Delivery Systems:

Carrier based Drug Delivery System:
A) Liposomes
B) Nanoparticles
C) Microspheres
D) Monoclonal antibodies
E) Niosomes
F) Resealed erythrocytes as drug carriers
G) Transferosomes

Transdermal Drug Delivery Systems:
A) Sonophoresis

- Mucoadhesive delivery systems
- Supramolecular delivery systems
- Variable release delivery systems

B) Osmotic pump
C) Microencapsulation

Drug Delivery Carriers: Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity[2]. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties.

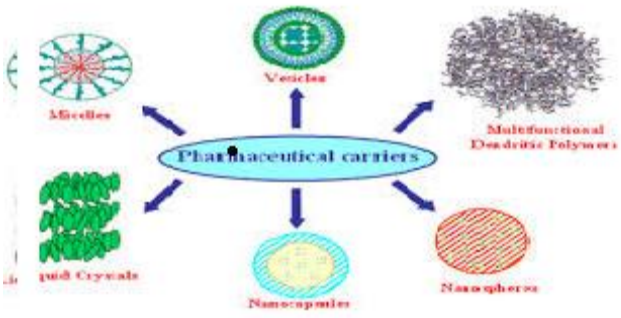

FIGURE 2: DIFFERENT PHARMACEUTICAL CARRIERS

Pharmaceutical Carriers: Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions are of great interest for drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water- solubility. Moreover, the hydrophilic blocks can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation. In addition,

the corona may prevent recognition by the reticuloendothelial system and therefore preliminary elimination of the micelles from the bloodstream.

A final feature that makes amphiphilic block copolymers attractive for drug delivery applications is the fact that their chemical composition, total molecular weight and block length ratios can be easily changed, which allows control of the size and morphology of the micelles. Functionalization of block copolymers with crosslinkable groups can increase the stability of the corresponding micelles and improve their temporal control. Substitution of block copolymer micelles with specific ligands is a very promising strategy to a broader range of sites of activity with a much higher selectivity [3].

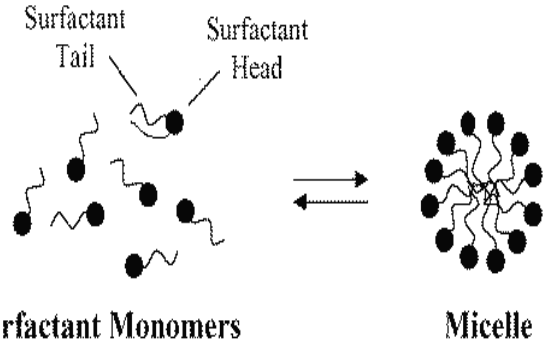

FIGURE 3: MECHANISM OF MICELLE FORMATION

TRANSFEROSOMES

Transfersome is a proprietary drug delivery technology, an artificial vesicle designed to exhibit the characteristics of a cell vesicle suitable for controlled and potentially targeted drug delivery. Transfersomes are elastic in nature, which can deform and squeeze themselves as an intact vesicle through narrow pores that are significantly smaller than its size. Encapsulating the drugs in transfersomes are one of the potential approaches to overcome the barrier function of the skin's outermost layer. They have a bilayered structure that facilitates the encapsulation of lipophilic and hydrophilic, as well as amphiphilic, drug with higher permeation efficiencies compared to conventional liposomes.

An efficacious, successful therapeutic treatment cannot be achieved in most cases, often due to many reasons, such as the occurrence of hepatic first-pass metabolism, adverse side effects, the rejection of invasive treatments and poor patient compliance[3]. Therefore, several drug delivery systems have been developed and studied over the past decades to overcome these problems. One promising approach is the use of transdermal delivery systems, as they are minimally invasive methods without first-pass effects. However, the barrier function of the skin that prevents or dampens the transdermal delivery of therapeutic agents has to be addressed[3].

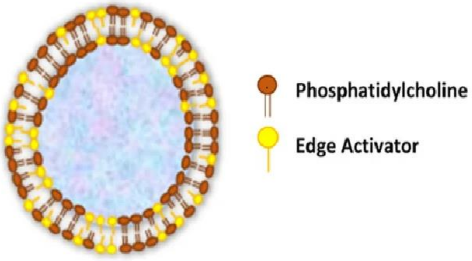

FIGURE 4: STRUCTURE OF TRANSFEROSOME

HISTORY OF TRANSFEROSOMES

A new type of carrier system-namely, Transfersomes-were introduced by Cevc et al. in the 1990s. Transfersomes are composed of Phospholipids and edge activator (EA), which is a membrane-softening agent (such as Tween 80, Span 80 and sodium cholate) that facilitates the ultra-deformable property of the Transfersomes. When Transfersomes reach the skin pores, they are capable of changing their membrane flexibility and passing through the skin pores spontaneously. This is the so-called self-optimizing deformability[4]. Moreover, transferomes are extremely deformable; therefore, they easily cross even the very narrow pores. These self-optimizing, highly deformable lipid aggregates were successfully used in extensive preclinical tests and diverse arrays of phase I and phase II clinical trials, as well as for the transcutaneous delivery of peptides and proteins and the sustain release of desired therapeutic agents. A number of transfersomes-based formulations are currently being assessed at different stages of clinical trials. For example, the study of the safety and efficacy of ketoprofen incorporated in transfersomes (Diractin®) for the treatment of osteoarthritis of the knees was carried out under a phase III clinical trial.

COMPOSITION OF TRANSFEROSOMES

A transferosome is a self-adaptable and optimized mixed lipid aggregate.

The surfactant molecules act as "edge activators", conferring ultra-deformability on the transferosomes, which reportedly allows them to squeeze through channels in the stratum corneum that are less than

one-tenth the diameter of the transferosome. According to their inventors, where liposomes are too large to pass through pores of less than 50 nm in size, transferosomes up to 500 nm can squeeze through to penetrate the stratum corneum barrier spontaneously[5]. They suggest that the driving force for penetration into the skin is the "transdermal gradient" caused by the difference in water content between the relatively dehydrated skin surface (approximately 20% water) and the aqueous viable epidermis (close to 100%).

Deformability of transferosomes is achieved by using surface active agent in the proper ratio. The concentration of surface active agent is crucial in the formulation of transferosomes because at sublytic concentration these agents provide flexibility to vesicle membranes and at higher concentration cause destruction of vesicles[5]. The resulting flexibility of transferosomal membrane minimizes the risk of complete vesicle rupture in the skin and allows the ultra deformable transferosomes to change their membrane composition locally and reversibly, when they are pressed against or attracted into a narrow pore. This dramatically lowers the energetic cost of membrane deformation and permits the resulting highly flexible particles first to enter and then pass through the pores rapidly and efficiently.

The carrier aggregate is composed of at least one amphiphat (such as phosphatidylcholine)[6] which in aqueous solvent self resembles into lipid bilayer that closes into a simple lipid vesicle. By addition of at least one bilayer softening component (such as a biocompatible surfactant or an amphiphilic drug), lipid bilayer flexibility and permeation are greatly increased. Thus, by optimizing the resulting flexibility and permeability, the transferosome vesicles can adapt to their ambient shape easily and rapidly. Thus, they can also adjust the local concentration of each bilayer component to the local stress experienced by the bilayer. The basic organization of these vesicles is broadly similar to liposomes.[6] But the transferosomes differ from the conventional vesicles primarily by their softer, more deformable, and better adjustable artificial membrane.

Another beneficial consequence of strong bilayer deformability is the increased transferosome ability to bind and retain water. An ultradeformable and highly hydrophilic vesicle always seeks to avoid dehydration; this may involve a transport process related to, but not identical with, forward osmosis. For example, a transferosome vesicle applied on an open biological surface, such as non-occluded skin, tends to penetrate its barrier and migrate into the water-rich deeper strata to secure its adequate hydration. Barrier penetration involves reversible bilayer deformation, but must not compromise unacceptably either the vesicle integrity or the barrier properties for the underlying hydration affinity and gradient to remain in place. Since it is too large to diffuse through the skin, the transferosome needs to find and enforce its own route through the organ. The transferosomes usage in drug delivery consequently relies on the carrier's ability to widen and overcome the hydrophilic pores in the skin or some other barrier. The subsequent, gradual agent release from the drug carrier allows the drug molecules to diffuse and finally bind to their target. Drug transport to an intracellular action site may also involve the carrier's lipid bilayer fusion with the cell membrane, unless the vesicle is taken up actively by the cell in the process called endocytosis.

MECHANISM OF TRANSFEROSOMES

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.

1. Transferosomes act as drug vectors, remaining intact after entering the skin.

2. Transferosomes act as penetration enhancers, disrupting the highly organized intercellular lipids from stratum corneum, and therefore facilitating the drug molecule penetration in and across the stratum corneum.

Cevc and coworkers proposed the first mechanism, suggesting that deformable liposomes penetrate the stratum corneum because of the transdermal hydration gradient normally existing in the skin, and then cross the epidermis, and enter the systemic circulation. The recent studies propose that the penetration and permeation of the vesicles across the skin are due to the combination of the two mechanisms. Depending on the nature of the active substance (lipophilic or hydrophilic) and the composition of the transferosomes, one of the two mechanisms prevails.[20]

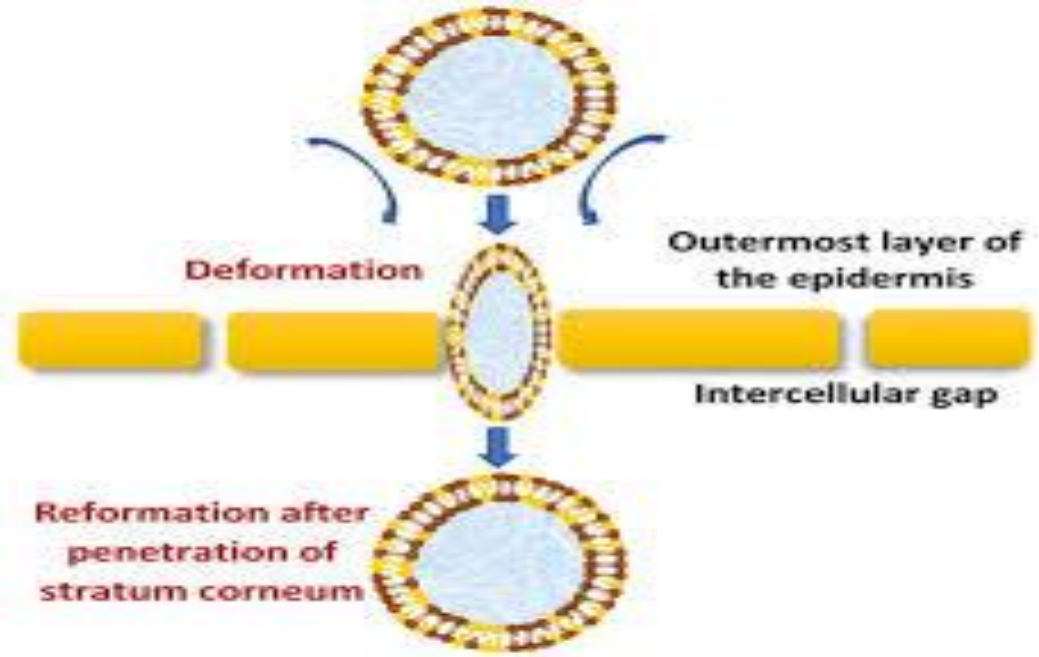

FIGURE5: MECHANISM OF TRANSFEROSOMES

MATERIALS AND METHODS:

Materials which are widely used in the formulation of transferosomes are various phospholipids, Surfactatnts, alcohol, dye, buffering agent etc, different addictives used in the formulation of transferosomes are summarized below[18, 20-23]

Material	Examples	Uses
Phospholipids	Soya phosphatidyl choline, egg phosphatidyl choline, dipalmitoyl phosphatidyl choline	Vesicles forming component
Surfactants	Sod.cholate, Sod.deoxycholate, Tween-80,Span-80, Tween 20	Vesicles forming Component
solvents	Ethanol, methanol, isopropyl alcohol, chloroform	As a solvent
Buffering agent	Saline phosphate buffer (pH 6.4), phosphate buffer pH 7.4	As a hydrating medium
Dye	Rhodamine-123 Rhodamine-DHPE Fluorescein-DHPE Nile-red	For CSLM study

Preparation of Transfersomes

A. **Thin film hydration technique is employed for the preparation of transfersomes which comprised of three steps:** [3 ,17, 25]

1. A thin film is prepared from the mixture of vesicles forming ingredients that is phospholipids and surfactant by dissolving in volatile organic solvent (chloroform-methanol). Organic solvent is then evaporated above the lipid transition temperature (room temp. for pure PC vesicles, or 50 ^{0}C for dipalmitoyl phosphatidyl choline) using rotary evaporator. Final traces of solvent were removed under vacuum for overnight.
2. A prepared thin film is hydrated with buffer (pH 6.5) by rotation at 60 rpm for 1 hr at the

corresponding temperature. The resulting vesicles were swollen for 2 hr at room temperature.

3. To prepare small vesicles, resulting vesicles were sonicated at room temperature or 50^0C for 30 min. using a bath sonicator or probe sonicated at 4^0C for 30 min. The sonicated vesicles were homogenized by manual extrusion 10 times through a sandwich of 200 and 100 nm polycarbonate membranes.

B. Modified hand shaking, lipid film hydration technique is also founded for the preparation of transfersomes which comprised following steps[23, 24, 25]

1. 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.
2. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minute at corresponding temperature. The transfersome suspension further hydrated up to 1 hour at 2-8^0C.

Advantages of Transferosomes

They have high entrapment efficiency, in case of lipophilic drug near to 90%.

1. This high deformability gives better penetration of intact vesicles.
2. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.
3. Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
4. They act as depot, releasing their contents slowly and gradually.
5. They can be used for both systemic as well as topical delivery of drug.
6. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
7. They protect the encapsulated drug from metabolic degradation.
8. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives [11,12,13].

Limitations of Transferosomes

1. Transferosomes are chemically unstable because of their predisposition to oxidative degradation.
2. Purity of natural phospholipids is another criterion militating against adoption of transferosomes as drug delivery vehicles.
3. Transferosomes formulations are expensive [10, 12,13].

Applications of Transferosomes [4,9]

Transferosomes as drug delivery systems have the potential for providing controlled release of the administered drug and increasing the stability of labile drugs.

Delivery of Insulin

Very large molecules incapable of diffusing into skin as such can be transported across the skin with the help of Transferosomes. For example, insulin, interferon can be delivered through mammalian skin. Delivery of insulin by Transferosomes is the successful means of noninvasive therapeutic use of such large molecular weight drugs on the skin. Insulin is generally administered by subcutaneous route that is inconvenient. Encapsulation of insulin into transferosomes (transferulin) overcomes the problems of inconvenience, larger size (making it unsuitable for transdermal delivery using conventional method) along with showing 50% response as compared to subcutaneous injection.

Carrier for Interferons & Interleukin:

Transferosomes have also been used as a carrier for interferons like leukocytic derived interferon-α (INF-α)) is a naturally occurring protein having antiviral, antiproliferative and some immune modulatory effects. Transferosomes as drug delivery systems have the potential for providing controlled release of the administered drug and increasing the stability of labile drugs. The formulation of interleukin-2 and interferone-α containing transferosomes for potential transdermal application. They reported delivery of IL-2 and INF- α trapped by Transferosomes in sufficient concentration for immunotherapy.

Carrier for Other Proteins & Peptides

Transferosomes have been widely used as a carrier for the transport of other proteins and peptides. Proteins and peptides are large biogenic molecules which are very difficult to transport into the body, when given orally they are completely degraded in the GI tract and transdermal delivery suffers because of their large size. These are the reasons why these peptides and proteins still have to be introduced into the body through injections. Various approaches have been developed to improve these situations. The bioavailability obtained from transferosomes is somewhat similar to that resulting from subcutaneous injection of the same protein suspension. Human serum albumin or gap junction protein was found to

be effective in producing the immune response when delivered by transdermal route encapsulated in Transferosomes. Transport of certain drug molecules that have physicochemical which otherwise prevent them from diffusing across stratum corneum can be transported.

Peripheral Drug Targeting

The ability of transferosomes to target peripheral subcutaneous tissues is due to minimum carrier associated drug clearance through blood vessels in the subcutaneous tissue. These blood vessels are non-fenestrated and also possess tight junctions between endothelial cells thus not allowing vesicles to enter directly into the blood stream. This automatically increases drug concentration locally along with the probability of drug to enter peripheral tissues.

Transdermal Immunization

Since ultra deformable vesicles have the capability of delivering the large molecules, they can be used to deliver vaccines topically. Transferosomes containing proteins like integral membrane protein, human serum albumin, gap junction protein are used for this purpose. Advantages of this approach are injecting the protein can be avoided and higher IgA levels are attained. Transcutaneous hepatitis-B vaccine has given good results. A 12 times higher AUC was obtained for zidovudine as compared to normal control administration. Selectivity in deposition in RES (which is the usual site for residence of HIV) was also increased.

Delivery of steroidal hormones and peptides

Transferosomes have also used for the delivery of corticosteroids. Transferosomes improves the site specificity and overall drug safety of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose. Transferosomes based corticosteroids are biologically active at dose several times lower than the currently used formulation for the treatment of skin diseases. Flexible vesicles of ethinyl estradiol showed significant anti-ovulatory effects as compared to plain drug given orally and traditional liposomes given topically. Extensive work has been done on other drugs like hormones and peptides viz Estradiol, low molecular-weight Heparin, Retinol, Melatonin, etc.

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 ensure 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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