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Transfersomes: A Peculiar and Promising 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. Transport of the drug through skin is best route of drug delivery because the skin is largest organ in human body. Drug carries which are used in transdermal drug delivery such as liposomes, niosomes, or micro emulsions pose a problem that they remains mostly confined to the skin surface and therefore do not transport drugs efficiently through the skin. Because of the deformable nature of transferosomes, it penetrates through the pores of stratum corneum which are smaller than its size and get into the underlying viable skin in intact form. The preparation variables are depending upon the procedure involved for manufacturing of formulation and the preparation procedure was accordingly optimized and validated. Vesicle shape and size, entrapment efficiency, degree of deformability, number of vesicles per cubic mm can be characterised by in-vitro studies. Thus, they act as a carrier for low as well as high molecular weight drugs e.g., analgesic, anaesthetic, corticosteroids, sex hormone, anticancer, insulin. Transferosomes thus differs from such more conventional vesicles primarily by its softer, more deformable, better adjustable artificial membrane.

Keywords: Novel drug delivery system, Transferosomes, Small Vesicles, Entrapment Efficiency

Introduction:

Drug Delivery via the transdermal route is an interesting option in this respect because a transdermal route is convenient and safe. They offers several advantages over conventional drug delivery system like avoidance of first pass metabolism, predictable and extended duration of action, 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, and most importantly, it provides patients convenience. Despite major research and development efforts in transdermal systems and the advantages of these routes, low stratum corneum permeability limits the usefulness of topical drug delivery[1]. These major obstacles have led to the discovery and development of other novel vesicles such as niosomes, sphingosomes, bilosomes, chitosomes, transferosomes, ethosomes and invasomes. They are identified as a better drug carrier system over liposomes due to considering factors such as a high chemical stability, high bioavailability, high entrapment efficiency and being inexpensive.

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According to the literature, niosomes tend to enhance the residence time of therapeutic drugs in the stratum corneum and epidermis, meanwhile reducing the systemic drug absorption and thereby improving the trapped drug penetration across the skin[2].When applied to the skin, the carrier searches and exploits hydrophilic pathways or 'pores' between the cells in the skin, which it opens wide enough to permit the entire vesicle to pass through together with its drug cargo, deforming itself extremely to accomplish this without losing its vesicular integrity. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-optimizing. This enables the Transferosomes to cross various transport barriers efficiently.

Transferosomes penetrate the stratum corneum by either intracellular route or the transcellular route[3].Each vesicular carrier overcomes the skin barrier spontaneously, to deposit the drug into deep tissues, as it is drawn from the dry surface to the water-rich region beneath the skin. The interest in designing Transdermal delivery systems was relaunched after the discovery of elastic vesicles like transferosomes, ethosomes, cubosomes, phytosomes, etc. The term Transfersomes concept was introduced in 1991 by Gregor Cevc. The name means ‘carrying body’ and is derived from the Latin word ‘transfere’ meaning ‘to carry across’ and the Greek word ‘soma’ for a ‘body’[4]. A new vesicular derivative, the “transferosomes”, has paved the way to decreases the defective Transdermal permeation of a number of low and high molecular weight drugs, which has been found to be one of the major improvements in vesicle research.

Advantages and Disadvantages:

Methods	Advantages	Disadvantages
Penetration Enhancers	Increase penetration through skin and give both local and systemic effect	Skin irritation Immunogenicity, only for low molecular weight drugs
Physical methods e.g., Iontophoresis	Increase penetration of intermediate size charged molecule	Only for charged drugs, Transfer efficiency is low (less than 10%)
Liposomes	Phospholipid vesicle, biocompatible, biodegradable	Less skin penetration, less stable
Proliposome	Phospholipid vesicle, more stable than liposomes	Less penetration, cause aggregation & fusion of vesicles
Niosomes	Non-ionic surfactants vesicles, greater stability,	Less skin penetration easy handling
Proniosomes	Will convert into niosomes in situ, stable	But will not reach upto deeper skin layer

Table 1: Advantages and disadvantages of different vesicular approaches[5]

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Salient Features:

- Transferosomes can deform and pass-through narrow constriction (from 5 to 10 times less than their own diameter) without significant loss.
- They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
- They have high entrapment efficiency, in case of lipophilic drug near to 90%.
- This high deformability gives better penetration of intact vesicles.
- They can be used for both systemic as well as topical delivery of drug[1].
- Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubilities[2].
- They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anaesthetic.
- They act as depot, releasing their contents slowly and gradually[6].
- They can be used for both systemic as well as topical delivery of drug.
- Easy to scale up, as procedure is simple, and avoid unnecessary use or pharmaceutically unacceptable additives.
- They can act as a carrier for low as well as high molecular weight drugs.
- They protect the encapsulated drug from metabolic degradation[2].
- They act as depot, releasing their contents slowly and gradually.

Novel Characteristics of Transferosomes:

- Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
- Transferosomes 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, anaesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
- They have high entrapment efficiency, in case of lipophilic drug near to 90%.
- They protect the encapsulated drug from metabolic degradation.
- They act as depot, releasing their contents slowly and gradually.
- They can be used for both systemic as well as topical delivery of drug.
- Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives[7].

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Why Only Transferosomes for Skin:

Transferosomes are advantageous as phospholipids vesicles for transdermal drug delivery. Because of their self optimized 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 application, with high efficiency. The vesicular transferosomes are more elastic than the standard liposomes and thus well suited for the skin penetration. Transferosomes overcome the skin penetration difficulty by squeezing themselves along the sealing lipid of the stratum corneum. These are characteristic with transferosomes, because of the high vesicle deformability which permits the entry due to the mechanical stress of surrounding, in a self-adapting manner. Flexibility of transferosomes membrane is governed by mixing suitable surface-active components in the proper ratios with phospholipids[8].

The resulting flexibility of transfersome membrane minimizes the risk of complete vesicle rupture in the skin and allows transferosomes to follow the natural water gradient across the epidermis, when applied under non-occlusive condition. Transferosomes can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayer's 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 modification of the vesicular compositions or surface properties can adjust the drug release rate and the deposition to the target site.[9-11]

Composition of Transferosomes: Transferosomes are generally composed of:

a. The main ingredient, an amphipathic ingredient (e.g., soy phosphatidylcholine, egg phosphatidylcholine, etc.) that can be a mixture of lipids, which are the vesicle-forming components that create the lipid bilayer [12, 13].
b. 10–25% surfactants/edge activators, the most commonly used edge activators in transfersome preparations are surfactants as sodium cholates, sodium deoxycholate, Tweens and Spans (Tween 20, Tween 60, Tween 80, Span 60, Span 65 and Span 80) and dipotassium glycyrrhizinate, which are biocompatible bilayer-softening compounds that increase the vesicles' bilayer flexibility and improve the permeability[14-17].
c. About 3–10% alcohol (ethanol or methanol), as the solvent and, finally, hydrating medium consist with either water or a saline phosphate buffer (pH 6.5–7) [18, 19].

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

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more conventional vesicle primarily by its "softer", more deformable, and better adjustable artificial membrane Table 2.

Sr. No.	Class	Examples	Use
1.	Phospholipids	Soya phosphatidyl choline, egg phosphatidyl choline, dipalmitoyl phosphatidyl choline	Vesicles forming component
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 agents	Saline phosphate buffer (pH 6.4), phosphate buffer pH 7.4	As a hydrating medium
5.	Dyes	Rhodamine-123 Rhodamine-DHPE Fluorescein-DHPE Nile-red	For CSLM study

Table 2: Different additives used in formulation of transferosomes

Mechanism of Action:

Vesicles are known as colloidal particles, which are an aqueous compartment enclosed by a concentric bilayer that is made-up of amphiphilic molecules. They are very useful as vesicular drug delivery systems, which transport hydrophilic drugs encapsulated in the inner aqueous compartment, whereas hydrophobic drugs are entrapped within the lipid bilayer[20]. With regard to transferosomes, they are highly deformable (ultra-flexible) and self-optimizing novel drug carrier vesicles, in which their passage across the skin is mainly associated with the transferosomes' membrane flexibility, hydrophilicity and the ability to maintain the vesicle's integrity[21,22]. They efficiently penetrate through the intact skin if applied under non occlusive conditions; this specific non occlusive state of the skin is required mainly to initiate a transepidermal osmotic gradient across the skin [23, 24].

The transdermal water activity difference, which originates due to the natural transdermal gradient, creates a significantly strong force that acts upon the skin through transferosomes vesicles, which enforce the widening of intercellular junctions with the lowest resistance and thereby generate transcutaneous channels 20–30 nm in width. These created channels allow the transfer of ultra-deformable, slimed transferosomes across the skin with respect to the hydration gradient[25, 26]. Moreover, the osmotic gradient develops as a result of evaporation of the skin surface water due to body heat, which exerts its action as the driving force to facilitate the flexible transport across the skin to deliver therapeutic agents from the site of application to the target area for local or systemic treatments in effective therapeutic concentrations and minimum systemic toxicity[27]. Transferosomes demonstrate a higher permeation efficiency (through small skin channels) compared to conventional liposomes but have a similar bilayered structure that facilitates the encapsulation of lipophilic and hydrophilic, as well as amphiphilic, drugs [28].

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Certain transferosomes have some amounts of alcohol (ethanol or propylene glycol) in their compositions as penetration enhancers and, also, used as cosolvents that have good solvating power. Ethanol has been proposed to induce modifications of the lipid bilayer polar head region[29]. Transferosomes can penetrate through the stratum corneum and reach the target sites, including the dermis and blood circulation. Their penetration ability depends on the deformability of the transfersomal membrane, which can be attributed to the vesicle compositions[30, 31].

Method of Preparation of Transferosomes:

1. Thin Film Hydration Technique or 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 (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 [32, 33].

2. Modified Handshaking Process:

The modified handshaking method has the same basic principle as the rotary evaporation-sonication method. In the modified handshaking process, the organic solvent, the lipophilic drug, the phospholipids and edge activator are added in a round-bottom flask. All the excipients should completely dissolve in the solvent and obtain a clear transparent solution. Then, the organic solvent is removed by evaporation while handshaking instead of using the rotary vacuum evaporator. In the meantime, the round-bottom flask is partially immersed in the water bath maintained at a high temperature (example: 40–60 ◦C). A thin lipid film is then formed inside the flask wall. The flask is kept overnight for complete evaporation of the solvent. The formed film is then hydrated with the appropriate buffer solution with gentle shaking at a temperature above its phase transition temperature. The hydrophilic drug incorporation can be done in this stage [33].

3. Vortex/Sonication Method:

In this method, phospholipids and edge activators are mixed by vigorous shaking and agitation in order to suspend them in phosphate buffer. The formed milky suspension is then sonicated using vortex or bath sonicator followed by extrusion through polycarbonate membranes.

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4. Ethanol Injection Method:

In this method, Drug along with aqueous solution is heated with continuous stirring at constant temperature. Ethanolic solution containing phospholipids and edge activators are injected into an aqueous solution drop wise. When the solution comes in contact with aqueous media the lipid molecules get precipitated and form bilayered structures. This method is more advantageous than other methods.

5. Freeze Thaw Method:

This method involves the exposure of prepared multi lamellar vesicles suspension to alternate cycles of very low temperature for freezing followed by exposure to very high temperature. The prepared suspension is transferred to a tube and dipped in a nitrogen bath (-30° C) for 30seconds. After freezing, it is exposed to high temperature in a water bath. This process is repeated for 8-9 times.

6. Reverse-Phase Evaporation Method:

The phospholipids and edge activator are added to a round-bottom flask and dissolved in the organic solvent mixture (example: diethyl ether and chloroform). The lipophilic drug can be incorporated in this step. Then, the solvent is evaporated using rotary evaporator to obtain the lipid films. The lipid films are redissolved in the organic phase mostly composed of isopropyl ether and/or diethyl ether. Subsequently, the aqueous phase is added to the organic phase, leading to a two-phase system. The hydrophilic drug incorporation can be done in this stage. This system is then subjected to sonication using a bath sonicator until a homogeneous w/o (water in oil) emulsion is formed. The organic solvent is slowly evaporated using rotary evaporator to form a viscous gel, which then becomes a vesicular suspension [34, 35].

Characterization of Transferosomes:

The characterization of transferosomes resembles that of other vesicles like liposomes, niosomes and micelles.

1. Vesicle Size, Zeta Potential and Morphology:

The vesicle size is one of the important parameters during transfersome preparation, batch-to-batch comparison and scale-up processes. During storage, the changing of the vesicle size is an important variable in terms of the physical stability of the formulation. Vesicles smaller than 40 nm are prone to fusion processes because of the high curvature state of their bilayer membranes, whereas much larger and electro neutral transferosomes are aggregated through van der Waals interactions due to relatively greater membrane contact areas. Vesicle size is a factor that influences the ability to encapsulate the drug compounds in transferosomes. For lipophilic and amphiphilic agents, a high lipid-to-core ratio is favored, while a larger aqueous core volume is preferred for the encapsulation of hydrophilic compounds. Generally, the

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dynamic light scattering (DLS) method or photon correlation spectroscopy (PCS) can be used to determine the vesicle diameter. The vesicle's suspension can be mixed with an appropriate medium, and the vesicular size measurements can be obtained in triplicate.

2. Number of Vesicles per cubic mm:

This parameter is important for the optimization of the composition of the transferosomes and other process variables. Unsonicated transfersomal formulations are diluted five times using 0.9% sodium chloride. A hemocytometer with an optical microscope is used to study this sample. The transferosomes with a vesicle size of more than 100 nm can be observed by optical microscope[36, 37]. The number of transferosomes in small squares is counted and calculated using the following formula:

Total number of transferosomes per cubic mm:

$$\frac{\text{Total number of transferosomes counted x Dilution factor x 4000}}{\text{Total number of squares counted}}$$

3. Entrapment Efficiency (%EE):

The entrapment efficiency (%EE) is the amount of drug entrapped in the formulation. The EE is determined by separating the un-entrapped drug from the vesicles using various techniques, such as mini-column centrifugation. In this process, direct or indirect methods can be used to determine the %EE. After ultracentrifugation, the direct approach would be removing the supernatant followed by disrupting the sedimented vesicles using a suitable solvent that is capable of lysing the sediment. Subsequently, the resulting solution can be diluted and filtered using a syringe filter (0.22–0.45 µm) to remove the impurities. The drug content is determined by employing analytical methods, such as modified high-performance liquid chromatography (HPLC) or spectrophotometrically, which depends on the analytical method of the active pharmaceutical ingredient (API) [38, 39]

The percentage drug entrapment (the entrapment efficiency) is expressed as:

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

4. Drug Content:

The drug content can be determined using a modified high performance liquid chromatography method (HPLC) method using a UV detector, column oven, auto sample, pump, and computerized analysis program.

5. Degree of Deformability:

This parameter is important, as it affects the permeation of the transfersomal formulation. This study is done using pure water as the standard. The preparation is passed through many

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micro porous filters of known pore sizes between 50 to 400 nm. The particle size, as well as the size distribution, is noted after each pass using DLS measurements. The degree of deformability is expressed as:

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

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

6. Turbidity Measurement:

Turbidity of drug in aqueous solution can be measured using Nephelometer.

7. Surface Charge and Charge Density:

Surface charge and Charge density of transferosomes can be determined using Zetasizer. Regarding the zeta potential measurements, all colloidal dispersions have a negative surface charge, containing Tween 80 which is a non-ionic surfactant. The reason for this result is that Tween 80 is a non-ionic surfactant while sodium cholate is anionic surfactant.

8. Penetration Ability:

Fluorescence microscopy is used to evaluate penetration ability of transferosomes.

9. Occlusion Effect:

Occlusion of skin is considered to be helpful for permeation of drug in case of traditional topical preparations. Occlusion affects hydration forces as it prevents evaporation of water from skin.

10. In-Vitro Drug Release:

The in vitro drug release profile can provide fundamental information on the formulation design and details on the release mechanism and kinetics, enabling a scientific approach to optimize the transfersomal formulation. The in vitro drug release of transferosomes is typically evaluated in comparison to the free drug or the reference product. Various research studies have evidently provided successful data related to the drug release profiles of developed transfersomes formulations[40]. In brief, Franz diffusion cells are employed in the in vitro drug release study. The donor chamber is fixed to the receptor chamber by means of adhesive tape. The fluid in the receptor chamber is constantly stirred by a magnetic bar. As normal skin surface temperature is approximately 32 ◦C [41, 42], therefore, in the release study, the temperature of the receptor fluid should be kept at the in vivo skin surface temperature of 32 ± 1 ◦C [43, 44]. A mixed cellulose ester membrane of an average pore size of 0.45 µm is used. The membranes are soaked in the release media (phosphate buffer) at room temperature overnight in order to allow the membrane pores to swell. The aliquots of 1 mL of the receptor medium are withdrawn at appropriate time intervals (such as 0, 0.5, 1, 2, 3, 4, 5 and 6 h), and

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simultaneously, the receptor medium is replaced by an equal volume of the fresh PBS to maintain the sink conditions. The obtained samples can be analyzed by using appropriate methods such as UV, HPLC and high-performance thin layer chromatography (HPTLC).

11. In-Vitro Skin Permeation Studies:

This study is performed to determine the transport efficiencies of the transdermal delivery systems and identify the factors that increase the transdermal flux of the drugs, which is typically expressed in units of µg/cm2 /h [45]. The information obtained from this study can also be used to predict in vivo behaviours from different transdermal delivery systems and used for the optimization of the formulation prior to performing more expensive in-vivo studies. Ideally, the human skin should be used for the evaluation of permeation properties of candidate formulations. However, the limited availability, ethical problems and religious restrictions of the human skin make it less attractive for the permeation study. Various animal models, such as primate, porcine, rat, mouse, guinea pig and snake skins, have been suggested as more accessible substitutes for human skin. However, it should be noted that percutaneous absorption through various animal skins may differ significantly from the results obtained with human skin models[46, 47].

Applications of Transferosomes:

1. 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 (transfersulin) overcomes these entire problems. After transfersulin application on the intact skin, the first sign of systemic hypoglycemia are observed after 90 to 180 min, depending on the specific carrier composition[48].

2. Delivery of Interferon: Transferosomes have the ability for providing controlled release for the drugs and increases the stability of labile drugs. They act as carriers for interferone (INF-α) which is a derivative of leukocyte exhibits antiviral, immunomodulatory effect. Transferosomes trap INF., provides controlled release of the active ingredient increase the stability of labile drugs and also provides immune therapy[49].

3. Delivery of Proteins and Peptides: Transferosomes have been used as a carrier for the transport of proteins and peptides. Proteins and peptide are large biogenic molecules which are very difficult to transport into the body, when given orally they are completely degraded in the GI tract. Peptides are not formulated as injections because they get degraded in the body. Various approaches have been developed to improve these situations. The bioavailability obtained from transferosomes is somewhat similar to that obtained from subcutaneous injection of the same protein suspension. The transferosomal preparations of this protein also induced strong immune response after the repeated application on skin, for

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example the adjuvant immunogenic serum albumin in transferosomes, after several dermal challenges is active immunologically as it is corresponding to transferosomes preparations[50].

4. Delivery of Anticancer Drugs: A research conducted by Jiang et al. in 2018 was associated with the topical chemotherapy of melanoma by transfersome-embedded oligopeptide hydrogels containing palcitaxel prepared by the thin-film dispersion method. Transferosomes composed of phosphatidylcholine, tween80 and sodium deoxycholate were shown to effectively penetrate into tumor tissues.

5. Delivery of Corticosteroids: The biological activity and characteristics of halogenated corticosteroid triamcinolone-acetonide-loaded transferosomes prepared by the conventional thin-film hydration technique were studied by Cevc and Blume in 2003 and 2004. The results showed that transferosomes had increased the biological potency and prolonged effect, as well as the reduced therapeutic dosage[51, 52].

6. Transdermal Immunization: Another most important application of transferosomes is transdermal immunization using transferosomes loaded with soluble protein like integral membrane protein, human serum albumin and gap junction protein. These approach offers at least two advantages, first they are applicable without injection and second, they give rise to rather high titer and possibly, to relatively high IgA levels. 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.

7. Delivery of NSAID: Anesthetics can be applicable in the form of suspensions through highly deformable vesicles known as transferosomes. They showed good effect as compared to subcutaneous administration within 10mts. The effect of anesthetics delivered through transferosomal suspensions last longer.

8. Delivery of Herbal Drugs: Herbal drug also delivered by transfersome approach. Xiao-Ying et al., who shows the better topical absorption of transferosomes of capsaicin in comparison to pure capsaicin.

9. **Delivery of Anesthetic:** Application of transferosome containing anesthetic 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.

Transferosomes Vs Other Carrier Systems:

1. Liposomes Vs Transferosomes: Structurally, Transferosomes are very similar to lipid bilayer vesicle, liposomes. However in functional terms, transferosomes differ vastly from commonly used liposomes in that they are much more flexible and adaptable because of edge

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activator. The extremely high flexibility of their membrane permits transferosomes to squeeze themselves even through pores much smaller than their own diameter. This is due to high flexibility of the transferosomes membrane and is achieved by judiciously combining at least two lipophilic/amphiphilic components (phospholipids plus bio surfactant) with sufficiently different packing characteristics into a single bilayer. The high resulting aggregate deformability permits transferosomes to penetrate the skin spontaneously. This tendency is supported by the high transferosomes surface hydrophilicity that enforces the search for surrounding of high-water activity.

2. Mixed Micelles Vs Transferosomes: It is almost certain that the high penetration potential of the transferosomes is not primarily a consequence of stratum corneum fluidization by the surfactant because micellar suspension contains much more surfactant than transferosomes (PC/Sodium cholate 65/35 w/w %, respectively). Thus, if the penetration enhancement via the solubilisation of the skin lipids was the reason for the superior penetration capability of transferosomes, one would expect an even better penetration performance of the micelles. In contrast to this postulate, the higher surfactant concentration in the mixed micelles does not improve the efficacy of material transport into the skin. On the contrary, mixed micelles stay confined to the topmost part of the stratum corneum even they are applied none occlusively. The reason for this is that mixed micelles are much less sensitive to the trans-epidermal water activity gradient than transferosomes.
Transferosomes differ in at least two basic features from the mixed micelles,

- A transferosomes is normally by one to two orders of magnitude (in size) greater than standard lipid micelles.
- Each vesicular transferosomes contains a water filled core whereas a micelle is just a simple fatty droplet. Transferosomes thus carry water as well as fat-soluble agent in comparison to micelles that can only incorporate lipoidal substances

Conclusion:

Transfersomes are ultra-deformable carriers that facilitate the delivery of a diverse array of drug molecules across the skin barrier with superior efficacy compared to the conventional vesicular systems. The osmotic gradient is the main driving force for the transport of transfersomes into the deeper skin layers. Importantly, transferosomes are specifically designed vesicular systems that need to be optimized in accordance with individual cases of drugs of interest to achieve the most effective formulations and ultimate pharmacological responses. Transferosomes are stable at low temperatures compared to high temperatures. Transferosomes are specially designed optimized particles or optimized vesicles, which generally respond to the external stress by shape transformations. These highly deformable particles can be used to bring drugs across the permeability barriers, such as skin. Transferosomes can pass through even tiny pores (100 mm) nearly as efficiently as water, which is 1500 times smaller when tested externally. Transfersomes, thus, hold a bright and promising future in transdermal drug delivery of drugs.

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