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AN OVERVIEW OF TRANSFERSOMAL DRUG DELIVERY

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ABSTRACT: Vesicular systems have gained immense importance in the last few years as a means for sustained and efficient drug delivery. This article was designed to review all aspects of a novel class of vesicles, transfersomes. Tranfersomes and the fundamental concept of transfersomes were launched by Gregor Cevc in the year 1991. It exists as an ultra-deformable complex having a hydrated core surrounded by a complex layer of lipid. The carrier aggregate is composed of at least one amphipathic molecule (like phospholipids) which when added to aqueous systems self-assemble into a bilayer of lipid which eventually closes into a lipid vesicle and one bilayer softening agent which is generally a surfactant which is responsible for the flexibility of the vesicle. Transfersomes provide the primary advantage of higher entrapment efficiency along with a depot formation which releases the contents slowly. The characterisation of transfersomes is similar to that of other vesicles like liposomes, niosomes and micelles. Transfersomes can be used for delivery of insulin, corticosteroids, proteins and peptides, interferons, anti-cancer drugs, anaesthetics, NSAIDs and herbal drugs. Certain disadvantages associated with transfersomes including deformation by a highly hydrophobic drug can be overcome by preparing transethosomes having characteristics of both transfersomes and ethosomes and has a mechanism of action that is a fusion of the mechanism of action of both. Deformability and penetration studies have proven that transethosomes provides a deeper penetration of the skin.

INTRODUCTION: There are several advantages of the transdermal route over the other traditional routes like preventing the metabolism in liver, alleviating the untoward side effects, predictability and extended duration of action, efficient delivery of drugs with a short half-life, improving the physiological as well as phamacological response, lesser fluctuation in blood levels of the drugs and last but the most important, improved patience compliance [1, 2].

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Vesicular systems have gained immense importance in the last few years as a means for sustained and efficient drug delivery. Vesicular drug delivery is preferred over other formulations due their definite characteristics of a better capacity of encapsulating hydrophillic and hydrophobic drugs, no toxicity, biodegradability, increased time of drug presence in the circulation due to encapsulation in the vesicular structure, ability to target different organs and tissues and an increased bioavailability. **Table 1** highlights the advantages and disadvantages of the vesicular systems.

The transdermal route for drug delivery is of great importance today because it overcomes the main problems associated with the oral drug delivery systems. There are many techniques which have come into light for enhancing the transdermal

delivery including electrophoresis, iontophoresis, microneedles, nanoneedles, sonophoresis and vesicles like liposome, ethosome, transfersome and cetosomes. Transfersomes provide a great scope for the delivery of active constituents. This carrier system is composed of phospholipids, surfactants and water [3, 4, 5].

Tranfersomes and the fundamental concept of transfersomes was launched by Gregor Cevc in the year 1991. In a broad sense, transferosome is a stress responsive, elastic and an extremely adaptable aggregate. It exists as an ultra-deformable complex having a hydrated core surrounded by a complex layer of lipid.

A self-optimizing and a self-regulatory property is incorporated in the vesicle due to the composition of the bilayer and the Interdependency of the local composition. This property helps the vesicle is traversing the different transport barriers effectively and helps the carrier in targeted and sustained delivery of active constituents in a non-invasive manner.

Transferosome is a trademarked technology of the German company IDEA AG. The name implies a "carrying body" in accordance with its parent Latin and Greek name "transferred" and "soma" respectively. Transferred literally means to carry across while "soma" means a body. An artificial vesicle is designed in such a way such that it acts like a cell involved in exocytosis which makes it appropriate for controlled and targeted drug delivery.

The carrier aggregate is composed of at least one amphipathic molecule (like phospholipids) which when added to aqueous systems self-assemble into a bilayer of lipid which eventually closes into a lipid vesicle. A bilayer softening agent is generally added (a biocompatible surfactant) to improve the bilayer flexibility and permeability. This vesicle can then adapt its shape easily and quickly, by adjusting the concentration at the local level of every bilayer component to the anxiety or stress experienced. Transfersomes differ from liposomes in that they are much softer than liposomes and are deformable to a higher extent. Therefore, are much adjustable an artificial membrane than liposomes.

Another advantage of this bilayer deformation is that it enhances the ability of the transferosome to absorb and retain water. This highly deformable and hydrophillic vesicle will steer clear of dehydration leading to a transport process much similar yet not completely identical to forward osmosis. For example, when a transferosomal preparation is applied to a non-occluded surface which is biological, it penetrates the skin barrier and moves into the aqueous layers and gets hydrated. The barrier penetration calls for reversible deformation of the bilayer but makes sure that there is no compromise on the integrity of the vesicle nor are the barrier properties affected.

TABLE 1: ADVANTAGES AND DISADVANTAGES OF VESICULAR SYSTEMS [14]

Methods	Advantages	Disadvantages
Liposomes	Phospholipid vesicle, biocompatible, biodegradable	Less skin penetration, less stable
Proliposome	Phospholipid vesicle, more stable than liposome	Less penetration, cause aggregation and fusion of vesicles
Niosomes	Non-ionic surfactant vesicles	Less skin penetration easy handling
Proniosommes	Convert to stable niosome in situ	Cannot reach in the deeper layers of the skin
Transfersomes and Protransfersomes	High deforming ability which ensures deeper penetration in skin layers	Very few disadvantages
Colloidosomes	Can withstand high mechanical load	Insufficient locking of drug can lead to coalescence
Cubosomes	Targeted and controlled release of materials in a biodegradable manner	No disadvantage as such is reported

Transfersomes for the Skin: Transfersomes ensure penetration through the skin by getting squeezed through the lipid present in the cells of the stratum corneum. This is possible due to the ability of the vesicle to deform to a great extent which provides the mechanical stress needed to enter the skin.

The main point to be kept in mind to have optimum flexibility of transfersomes is to have a suitable mix of surface active agents in proper ratios with phospholipids [6]. This flexibility minimises the possibility of complete rupture of the vesicle in the skin and helps the vesicles to follow a natural

aqueous gradient across the outer layer of non-occluded skin. There are two routes through which the transfersomes can penetrate the stratum corneum through the intracellular lipid and differ in the properties of the bilayer [5].

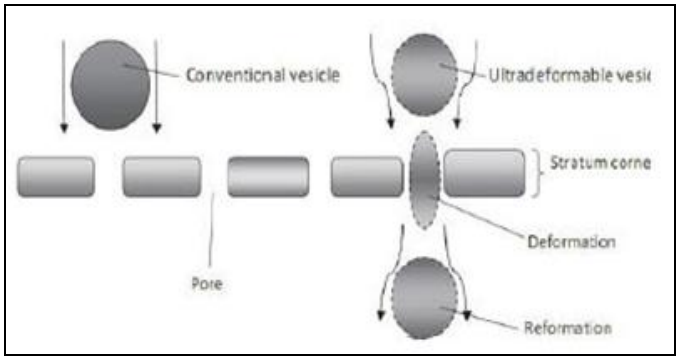

FIG. 1: DEFORMABILITY OF TRANSFERSOMES INTO SKIN PORES [8]

It has been proven through confocal microscopic studies that liposomes in the intact form cannot pass through the granular epidermis and remain as such on the upper layer of the stratum corneum. Changes in the composition of the vesicle and surface properties will make sure the appropriate rate of drug release and drug deposition [4]. Thus, transfersomes are ideal candidates for vesicular delivery of drugs and bioactives through the transdermal and topical delivery route.

Propensity of Penetration: Since transfersomes are too large to diffuse through the skin, they need to find their own route through the organ.

The magnitude of the driving force can then be calculated using the following formula:

Flow = Area × (Barrier) permeability × (Trans-barrier) force.

Hence flow of the lipid across the skin which is chemically driven, decreases drastically when the lipid in solution form is replaced by the same amount of suspension of lipid [7].

Prominent Features of Transfersome:

- They are able to accommodate drugs of varying solubility due to presence of hydrophillic and hydrophobic moieties in its infrastructure
- They are capable of deforming themselves and passing through narrow constrictions (5-10 times lesser than their diameter) without any significant losses.
- They can be a carrier for drugs of any molecular weight.
- They are made of natural phospholipids and are bio compatible.
- Entrapment efficiency of transfersomes is very high. Almost as much as 90% when it comes to hydrophillic drugs.
- They provide suitable protection to the encapsulated drug from degradation. This is specifically useful in case of proteins and peptides.
- They slowly release their contents, thereby acting as a depot [5].
- Useful for topical and systemic administration of drugs.
- No use of any pharmaceutically unacceptable additives.

Drawbacks of Transfersome:

- Susceptible to oxidative degradation which may render them unstable
- Purity of phospholipids poses problems in using transfersomes as drug delivery vehicles
- Manufacturing and processing is expensive [8, 9]

Composition of Transfersome: Two main aggregates make up the transferosome:

- Amphipathic molecule (*e.g.*: phosphatidyl choline) which is responsible for self-assembly
- Bilayer softening agent (*e.g.*: Surfactant) which is responsible for flexibility of the transfersome.

The main components of transfersome are phospholipids like soya phosphatidyl choline (Vesicle forming agent), surfactants like sodium cholate or spans and tweens and solvents like ethanol, methanol *etc*. [10, 11, 12, 13]

Method of Preparation: There are broadly two reported procedures for the transfersomes preparation.

Thin Film Hydration Technique: This method has three steps:

1. The first step involves dissolution of phospholipids along with surfactants in an organic solvent (Chloroform-methanol) to get thin film of vesicles. The mixture is then subjected to heat above the transition temperature of the lipid, in a rotary evaporator to free the mixture of the organic solvents. Any

remaining traces of the solvent are removed by placing over night in vacuum.

2. The formed film is then subjected to hydration with a suitable buffer at 60 rpm for 1 h. The vesicles formed are left for 2 h to swell at room temperature.
3. The small vesicles are then prepared by subjecting the prepared vesicles to sonication at room temperature or at 50°C for 30 min using a bath sonicator. In a probe sonicator, the vesicles are sonicated at 40 °C for 30 min. The desired vesicles are obtained by homogenizing the sonicated vesicles by manual extrusion 10 times through a sandwich layer of 200 and 100nm polycarbonate membranes yields [14, 15, 2].

Modified Hand Shaking Method:

1. Lecithin along with the edge activator (surfactant) and drug are dissolved in a mixture of chloroform and ethanol in the ratio 1:1. The mixture is subjected to evaporation to remove the organic solvent using temperature above the transition temperature of lipid by hand shaking. The thin lipid film is left overnight to ensure complete removal of the organic solvent.
2. The film which is formed, is then hydrated with buffer of choice along with gentle shaking for 15 minutes. The suspension formed is further hydrated at 80 °C for 1 - 2 h [16, 17, 18].

Variables which affect the process of preparation are:

- Lecithin: surfactant ratio
- Solvent used
- Surfactants used
- Hydration medium

The desired entrapment efficiency of drug is selected for optimization of the above parameters. All the other variables are kept constant while preparing a particular system [19, 20]. The edge activator that is used and the surface charge play a role in the development of these ultra-deformable vesicles for enhanced drug delivery.

Characterisation of Transfersomes: The characterisation of transfersomes resembles that of other vesicles like liposomes, niosomes and micelles [21].

Vesicle Size, Size Distribution and Vesicle Diameter: Transmission electron microscopic studies are used to study the vesicular shape. The size of the vesicle and size distribution is generally determined using light scattering technique. The diameter of the vesicle is determined by photon correlation spectroscopy or dynamic light scattering DLS method. The samples are prepared using distilled water, and diluted with filtered saline after passing through a membrane filter of 0.2 mm [11].

Vesicle Shape and Type: The visualization is carried out using TEM. Also, they can be visualized by phase contrast microscopy without sonication using optical microscopy method. Dynamic light scattering technique can also be used.

Number of Vesicle per cubic mm: This character is very important for not only for optimizing the composition of the system but also other process variables. The formulation is diluted five times with 0.9% sodium chloride solution, without sonication. This solution is then studied by using haemocytometer with optical microscope. The transfersomes in at least 80 small squares can be counted by application of the formula:

Total no. of Transfersomes per cubic mm = Total no. of Transfersomes counted X dilution factor X 4000/ Total no. of squares counted [22, 23]

Entrapment Efficiency: It is expressed as the amount of the drug entrapped in percent of that what is added. It is determined by separating the unentrapped drug by mini column centrifugation followed by disruption of the vesicles using 0.1% Triton X-100 or 50% n-propanol. The entrapment efficiency is expressed as:

Entrapment efficiency = (amount entrapped/ total amount added)*100 [24]

Drug Content: Instrumental analytical methods are used to determine the drug content like modified HPLC using a UV detector. The choice of the other parameters depends on the pharmacopoeial analytical method [20].

Confocal Scanning Laser Microscopy Study: Conventional methods of light microscopy and electron microscopy have problems when it comes to fixing, sectioning and staining the sample. There is an incompatibility generally observed between the sample and the processing techniques. The misinterpretations that arise from such studies can be corrected by using Confocal Scanning Laser

Microscopy (CSLM). This technique involves the use of lipophillic fluorescence markers and the light emitted by these markers is then used for:

- Understanding the mechanism by which the transfersomes penetrate the skin
- Determining the arrangement of the skin and the organization of the skin penetration pathway
- Understanding the similarities and dis-similarities in the mode of penetration of transfersomes with other vesicles like liposome, noisome, micelles *etc*.

The fluorescence markers that are generally used are:

- Fluorescein- DHPE (1, 2- dihexadecanoyl- sn-glycero- 3- phosphoethanolamine- N- (5fluore-sdenthiocarbamoyl), triethyl- ammonium salt)
- Rhodamine- DHPE (1, 2- dihexadecanoyl- sn-glycero- 3ogisogietgabikanube Lissamine Tmr hodamine-B- sulfonyl), triethanol- amine salt)
- NBD- PE (1, 2- dihexadecanoyl- sn-glycero- 3-phosphoethanolamine- N- (7-nitro- Benz- 2-xa- 1,3- diazol- 4- yl) triethanolamine salt)
- Nile red [25].

Turbidity Measurement: Turbidity of the drug is measured in the solution from using a nephelo-meter [2].

Surface Charge and Charge Density: A zeta sizer is used to determine the surface charge and charge density.

Penetration Ability: This is generally evaluated using fluorescence microscopy [15].

Occulsion Effect: It is considered to be helpful for permeation of topical preparations. Hydrotaxis appears to be the major driving force responsible for the permeation of transfersomes. Occlusion effect is important to study as it prevents evaporation of water from skin thus affecting hydration forces.

***In-vitro* Drug Release:** Determined by calculating the permeation rate. The formulation is incubated at 32 °C. The free drug from the samples which are drawn at regular intervals is obtained by mini column centrifugation. The calculation for amount of drug released is done indirectly from the amount of drug that was entrapped at zero time as 100% [2].

***In-vitro* Skin Permeation Studies:** Modified franz diffusion cell having a volume of 50 mL and receiver compartment which has an effective area of 2.50 cm^2 is generally used. Goat skin in phosphate buffer (pH 7.4) is used which is freshly collected from slaughter house. Hair is removed from the skin and the skin is allowed to hydrate in normal saline. The skin has to be cleaned of the adipose tissues using a cotton swab.

The skin can be stored in IPA at low temperatures. While mounting, the skin should be placed with the stratum corneum facing towards the donor compartment. The stirring is carried out at a rate of 100 rpm. Formulation equivalent to 10 mg of drug is used. At regular intervals 1 mL of aliquot is drawn and is replaced immediately with fresh phosphate buffer (pH 7.4). Analysis of samples is done using instrumental techniques after including the correction factors [18].

Skin Deposition Studies of Optimized Formu-lation: After the end of permeation study (at the end of 24 h), the goat skin surface is washed five times with a solution containing ethanol: PBS (pH 7.4) in the ratio 1:1 and the excess drug present on the surface should be removed by giving washings with water.

The skin is subjected to homo-genisation after it is cut into small pieces with the same ethanol and pH 7.4 buffer solution and is then left at room temperature for 6 h. After shaking it for 5min and centrifuging it for 5 min at 5000 rpm, the drug content is analysed using appropriate dilutions with phosphate buffer solution (pH 7.4). The result is compared, using a student's t test, with that of the control [2].

***In-vivo* Fate of Transfersomes and Kinetics of Transfersomes Penetration:** Upon transdermal delivery, transfersomes pass through the outer most layer of the skin and enter the blood circulation via the lymph and is eventually distributed throughout the body when applied under suitable conditions. Hence, transdermal transfersomes are capable of supplying to all the body tissues which are otherwise accessible to transfersomes that are sub cutaneously injected. The velocity of the carrier penetration and speed of distribution of drug after the passage are two important factors that

determine the kinetics of action of an epi-cutaneously applied agent. The main factors of this process are:

I. Carrier in-flow

II. Carrier accumulation at the targets site

III. Carrier elimination

The volume of the suspension medium that must evaporate from the skin surface determines the onset of penetration driving force.

Direct biological assays are considered as the best method to study the kinetics of transfersomes penetration as the drugs enclosed in a vesicle exert their action directly under the skin surface. Local anaesthetics generally used to determine the kinetics of penetration of transfersome. Vesicles loaded with lidocaine were left on intact skin and allowed to dry. A subcutaneous injection of lidocaine was used a control. The sensitivity of the animal to pain at the treated site after every application is assessed as a function of time. Standard liposome carrying drug applied dermally showed no analgesic effect. Such liposomal preparations are required to be injected to achieve a noteworthy suppression of pain.

However, lidocaine loaded transfersome showed active analgesic activity and the maximum effect was seen after 15 min of application. The kinetics of penetration of transfersomes and their reach are influenced by the interaction between the drug and carrier, the application condition, characteristics of the skin and dose applied. The penetration kinetics can be controlled to a major extent by fixing the physiochemical characteristics of transfersome suspension [26].

Stability Studies: Stability of the transfersomes is generally determined by TEM visualization at 4 °C and 37 °C. DLS size measurement can also be used at different time intervals (30, 45, and 60 days), following vesicles preparation. The initial entrapment is considered as 100 % and the percent drug loss is calculated. In a study conducted by K. Sudhakar *et al*., in which a comparison of various evaluating parameters was done of the three vesicular delivery systems of liposomes, ethosomes and transfersomes, transfersomes bearing lamivudine stood out as promising candidate. The entrapment efficiency of the three vesicles was reported as 49.76 ± 2.1%, 81.97 ± 1.5% and 83.81 ± 1.4% with the highest entrapment seen in transfersomes. The nanometric size range was 515 ± 4.6 nm, 374 ± 8.9nm and 315 ± 8.5 nm respectively.

Skin fluorescence studies also proved that the penetration depth and the intensity of fluoroscence of calcein was much higher in ethosomes and transfersomes as compared to liposomes. Vesicle particle size holds great importance in drug permeation. Smaller particle size ensures greater permeation rate of the drug due to larger surface area. Although the size of all the formulation was between 300-550 nm, yet liposomes were the largest vesicles. This shows the efficacy of trans-fersomes as a vesicular drug delivery system due to its ideal properties.

Applications of Transfersome:

Delivery of Insulin: Insulin is generally administered subcutaneously. However when Insulin is enclosed in a transfersome carrier and is administered by topical application on intact skin, the first signs of hyperglycemia are observed in 90 to 180 min of application which also depends on the composition of the carrier. Studies have also been done on preparation of other anti-diabetic drugs like repaglinide with improved skin permeation [27].

Malakar Jadupati *et al*., studied the delivery of insulin *via* transfersomal gel. The insulin permea-tion flux was altered by a number of factors like the ratio of lipids, ratio of lipids and surfactants and the ratio of surfactants. The *in-vitro* permeation flux for the optimized gel was 13.50 ± 0.22 μg/cm^2/h and was carried out using porcine ear skin with a small error value of 6.80 %.

It was also reported by Cevc *et al*., that the transdermal permeation of drug is generally 10 times greater than conventional vesicles. It has also been shown that the efficacy of transcutaneously delivered insulin remains unaffected by any previous therapy. The systemic normoglycaemia which lasts for a minimum of 16 h was achieved in a non-invasive administration of insulin [28].

Delivery of Corticosteroids: Transfersomes are used for delivery of corticosteroids due to site-specificity and over all drug safety when applied to

the skin by optimization of the administered dose. Steroids which are administered using transfersomes are biologically active at doses much lesser than the doses required in other conventional formulation techniques [14, 29].

Cevc *et al*., characterised two glucocorticosteroids, dexamethasone and hydrocortisone, for biological properties. The bioactivity indicator used was the minimum effective drug dose which is required to reduce arachidonic acid-induced murine ear oedema by 50 %. It was found that the minimum effective dose for hydrocortisone in deformable carriers was reduced to 2-3 μg cm^{-2} from the dose of 10 μg cm^{-2} as seen in cream and lotions. This enhancement in potency is accompanied by a corresponding >20% increase in absolute drug potency.

It was also observed that this mode of delivery prolongs the suppression of the oedema caused by the drug by nearly 2 folds. The effective dose of dexamethasone was reduced by 10 times as compared to lotion or cream based products. Also, duration of action of dexamethasone as transfersomes extended by four folds when compared to commercial cream products. Also, the abrasion properties of the drug were reduced. Thus, the use of transfersomes for delivery of corticosteroids leads to improved therapeutic risk-benefit ratio and better targeting.

Delivery of Proteins and Peptides: Proteins are biological molecules which are too large posing a difficulty in administering them into the body as they get degraded completely when given by the oral route. The bioavailability of proteins using transfersomes is almost similar to that of the bioavailability obtained after a subcutaneous injection of a suspension of proteins. The transfersome preparation also induced strong immune responses when repeatedly applied epicutaneously. An example of this is an adjuvant immunogenic serum albumin which in spite of several dermal challenges is active immunologically using transfersome carrier and also injected proteo-transfersome preparations [30, 31].

Delivery of Interferon: Another group of substances for whom transfersomes can be a carrier are interferons like the leukocytic derived interferon-α (INF-α) which is a natural protein with antiviral and anti-proliferative effects. Since transfersomes are capable of controlled release they improve the stability of such labile substances. A study conducted by Hafer *et al*., showed delivery of IL-2 and INF- α using transfersomes at a concentration, sufficient for immunotherapy [32].

Delivery of Anticancer Drugs: Anticancer drugs like methotrexate showed a promising future for application of transfersome technology, especially skin cancers [33]. Different formulations of transfersomes of 5 fluorouracil were prepared by Khan MA *et al*., using surfactants like tween 80 and span 80 as surfactants which were then compared for their particle size, particle shape, entrapment efficiency of the vesicles, deformability index and *in-vivo* skin permeation.

The optimized formulation was then incorporated into a gel made of 1% solution of carbopol 940. Transfersomes containing 5-Fu showed a particle size of 266.9 ± 2.04 nm with and entrapment efficiency of 69.2 ± 0.98 % and highest deformability index of 27.8 ± 1.08. They had the maximum skin deposition (81.3%) and a transdermal flux of 21.46 μg/cm^2/h. The transfersome-loaded gel showed even better skin penetration and deposition when compared to the marketed formulation. The transfersomal gel showed no signs of irritancy to the skin. Based on these studies, they had concluded that the transfersomal gel of flurouracil is a better treatment for skin cancer as it improves the absorption through the skin [34, 35].

Delivery of Anaesthetics: Transfersomes induce topical anaesthesia when applied under appropriate conditions in less than 10 min. The effect of transfersomal anaesthetic lasts longer than that of a comparable dose of subcutaneous bolus injection [1]. Planas, M. E. *et al*., conducted an experiment to study common and local analgesics for both duration of action and permeability when applied through transdermal transfersome in rats and humans. A comparison was done of the results obtained after application of analgesic transfersomes to that obtained from liposomes containing lidocaine. Subcutaneous solutions of 2% lidocaine or liposomal or transfersomal solution when injected in rats showed a strong analgesic effect initially which lasted for 6 - 7 min and the

withdrawal time was close to 30 s. The analgesic transfersomes that were applied dermally, increased the reaction to heat stimulus to >70 s, which was 130% longer than in controls that received a placebo or a standard aqueous lidocaine solution. It was concluded that the dermally applied transfersome was as effective as the SC injection containing same amount of the drug and that transfersomes stand out to be a very promising means for treatment of local pain noninvasively by topical application [35].

Delivery of NSAIDs: The typical problems associated with NSAIDs like GI irritation can be overcome by transdermal delivery using transfersomes. Some drugs like diclofenac and ketoprofen are already studied for their efficacy using tranfersomes and ketoprofen formulation is already approved by Swiss regulatory agency [36].

Delivery of Herbal Drugs: Transfersomes of capsaicin have been prepared by Xiao-Ying *et al*., showing improved absorption through the topical route when compared to pure capsaicin due to the property of transfersome to supply nutrients locally by penetrating through the stratum corneum due to the presence of the surface-active agent in their formulation [33].

Transfersomes of curcumin are used for their anti-inflammatory activity which also ensures better penetration of the drug. There was also an improved influx of indinavir sulfate for activity against the deadly acquired deficiency syndrome. Ketoprofen transfersomes ensure improved penetration of the drug due to the surfactant present in their composition which improved the anti-inflammatory activity of the same. Insulin transfersomes are used for inducing hypoglycemia which has therapeutical significance along with considerable efficacy and reproducibility.

Transfersomes are also used to increase the skin penetration of certain phyto-constituents like capsaicin and colchicine and along with these effects also increase the entrapment efficiency of certain phytoconstituents like vincristine. They have also made delivery of certain biotechnological products like Interferon-α easy, which are otherwise very difficult to deliver through other routes due to their short half-lives. A controlled release of interferon provided by transfersome can prevent the stability issues otherwise associated with them due to their short half-life.

Transfersomes also enhance the transdermal flux of drugs like norgesterol, tamoxifen, methotrexate and oestradiol. They provide a suitable means for treatment of local pain using tetracaine and lignocaine in a non-invasive manner on direct topical application. In corticosteroids, they improve the specificity of site and over all drug safety. Application of this technology to hydrocortisone produces a formulation that is active biologically at doses that are much lower than the currently used concentration. When applied to human serum albumin, this technology produced an antibody titer which is similar and in some cases even higher than that produced by sub cutaneous injection. It has also been reported that transfersomes tend to improvise the delivery of stavudine in the skin *in vitro*, for its antiretroviral activity. It has also been reported to be used for transdermal immunization of tetanus toxoid [37].

Transethosome: Though, transfersomes appear to be an important discovery for delivery of drugs which have poor absorption otherwise, they do pose a problem when trying to deliver a hydrophobic drug as they tend to lose their elasticity to a certain extent, although it has been proven that they are superior to other conventional vesicles like liposomes [38].

This problem associated with transfersomes can be overcome by using the properties of both transfersomes and ethosomes together in a vesicular drug delivery system called as transethosome. This novel vesicle was introduced by Song *et al*., in the year 2012 and is characterized by having a high content of ethanol (30%) and an edge activator. They have the advantages of both transfersomes and ethosomes and the mechanism of action is a fusion of mechanism of both [39].

A study conducted by Ascenso *et al*., showed the superiority of transethosomes over transfersomes. The study was mainly aimed to compare the effectiveness of the three vesicles *i.e* transfersomes, ethosomes and transethosomes and their influence on the skin delivery of caffeine and Vitamin E. The results proved that the transethosomes have greater advantages for deeper penetration of the skin in terms of deformability and permeation experiments[40].

CONCLUSION: Ultra-deformable vesicles like transfersomes are capable of providing an ideal solution to all transdermal delivery and transport related problems. They are especially useful for delivery of troublesome molecules likes peptides and proteins. The exceptional quality of transfersomes to deform themselves depending on the environmental stress due to the presence of surfactants, often referred to as "edge activators" makes them very flexible for delivery of a wide range of molecules also having a good scope for targeted delivery. Transfersomes, thus, hold a bright and promising future in transdermal drug delivery of drugs.

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REFERENCES:

1. Modi CD and Bharadia PD: Transfersomes: New dominants for transdermal drug delivery. American Journal of Pharmaceutical Technology 2012; 2(3): 71-91.
2. Prajapati ST, Patel CG and Patel CN: Transfersomes: A vesicular carrier system for transdermal drug delivery. Asian Journal of Biochemical and Pharmaceutical research 2011; 1(2): 507-24.
3. Kombath RV, Minumula SK, Sockalingam A, Subadhra S, Parre S, Reddy TR, *et al*., Critical issues related to transfersomes- novel vesicular system.Acta Scientiarum Polonorum Technologia Alimentaria 2012; 1(11): 67-82.
4. Swarnlata S, Gunjan J, Chanchal DK and Shailendra S: Development of novel herbal cosmetic cream with *Curcuma longa* extract loaded transfersome for anti-wrinkle effect.African Journal of Pharmacy and Pharmacology 2011; 5(8): 1054-62.
5. Schatzlein A and Cevc G: Skin penetration by phospholipid vesicles, Transfersomes as visualised by means of Confocal Scanning Laser Microscopy, in characterization, metabolism and novel biological applications. Champaign, American Oil Chemist's Society Press, 1995; 191-209.
6. Cevc G: Isothermal Lipid Phase Transitions Chemistry and Physics of Lipids 1991; 57: 293-99.
7. Jain S and Jain NK: Transfersomes: a novel carrier for effective transdermal drug delivery, advances in controlled and novel drug delivery, Ed., Prof. Jain NK, CBS publishers and Distributors, Chapter 18, 2001; 426-51.
8. Panchagnula R: Transdermal delivery of drugs. Indian Journal of Pharmacology1997; 29: 140-56.
9. Bain KR, Hadgkraft AJ, James WJ and Water KA: R. Prediction of percutaneous penetration Cardiff. STS Publishing, 1993; 3b: 226-34.
10. Cevc G, Blume G and Schazlein: Transfersomes mediates transepidermal delivery immproves the regiospecificity and biological activity of corticosteroids *in-vivo*.Journal of Controlled Release 1997; 45: 211-26.
11. Gamal M, EI Maghraby M, Williams AC and Barry BW: Skin delivery of oestrdiiol from deformable and traditional liposomes. Journal of Pharmacy and Pharmacology 1999; 51(10): 1123-34.
12. Planas ME, Gonzalez P, Rodriguez S, Sanchez G and Cevc G: Noninvasive percutaneous induction of topical analgesia by a new type of drug carrier, and prolongation of local pain insensitivity by anesthetic liposomes. Anesthesia and Analgesia 1992; 75(4): 615-21.
13. Schatzlein A and Cevc G: Non-uniform cellular packing of the stratum corneum and permeability barrier function of intact skin: a high-resolution confocal laser scanning microscopy study using highly deformable vesicles (Transfersomes). British Journal of Dermatology 1998; 138(4): 583-98.
14. Shashank J, Niketkumar P, Mansi KS, *et al*., Recent advances in lipid-based vesicles and particulate carriers for topical and transdermal application. J Pharm Sci. 2016; 116: 1-23.
15. Walve JR, Bakliwal SR, Rane BR and Pawar SP: Transfersomes: a surrogated carrier for transdermal drug delivery system. Internation Journal of Applied Biology and Pharmaceutical Technology 2011; 2(1): 204-13.
16. Jain CP, Vyas SP and Dixit VK: Niosomal system for delivery of rifampicin to lymphatics. International Journal of Pharmaceutics 2006; 68(5): 57-8.
17. Elsayed MMS, Abdallah OY and Nagar VF: Deformable liposomes and ethosomes: Mechanism of enhanced skin delivery. International Journal of Pharmaceutics 2006; 322(1-2): 60-6.
18. Patel R, Singh SK, Singh S, Sheth NR and Gendle R: Development and characterisation of curcumin loaded transfersome for enhanced skin delivery. Journal of Pharmaceutical Sciences and Research 2009; 1(4): 71-80.
19. Sheo DM, Shweta A, Vijay KT, Ram CD, Aklavya S and Ghansyam M: Enhanced transdermal delivery of indinavir sulfate *via* transfersomes. Pharmacie Globale: International Journal of Comprehensive Pharmacy2005; 5(9): 395.
20. Sheo DM, Shweta A, Ram CD, Ghanshyam M, Girish K and Sunil KP: Transfersomes- A novel vesicular carrier for enhanced transdermal delivery of stavudine: Development, characterization and performance evaluation. Journal of Scientific Speculations and Research 2010; 1(1): 30-6.
21. Charcosset C, Juban A, Valour J, *et al*., Preperation of liposomes at large scale using ethanol injection method: effect of scale up and injection devices. Chem Eng Res Des. 2015; 94: 508-515.
22. Berge vanden BAI, Wertz PW, Junginger HE and Bouwstra JA: Elasticity of vesicles assesed by electron spin resonance, electron microscopy and extrusion measurement. International Journal of Pharmaceutics 2001; 217(1-2): 13-24.
23. Kombath RV, Minumula SK, Sockalingam A, Subadhra S, Parre S, Reddy TR, *et al*., Critical issues related to transfersomes- novel vesicular system. Acta Scientiarum Polonorum Technologia Alimentaria 2012; 11(1): 67-82.
24. Gavali MS, Pacharane SS, Jadhav RK and Kadam JV: Transferosome: A new technique for transdermal drug delivery. International Journal of Research in Pharmacy and Chemistry2011; 1(3): 735-40.
25. Schatzlein A and Cevc G: Skin penetration by phospholipid vesicles. Transfersomes as visualized by means of the confocal scanning laser microscopy in characterisation, metabolism and novel biological appication. American Oil Chemist's Society Press 1995; 191-209.
26. Planas ME, Gonzalez P, Rodriguex S, Sanchez G and Cevc G: Non invasive Percutaneous induction of Topical

Analgesia by a new type of drug carrier, and prolongation of local pain insensitivity by anesthetic liposomes. Anesthesia and Analgesia 1992; 95: 615-21.
27. Laxmi MV and Zafaruddin MD: Design and characterization of transferosomal gel of repaglinide. Int Res J Pharm 2015; 6: 38-42.
28. Malakar J, Sen SO, Nayak AK and Sen KK: Formulation, optimization and evaluation of transfersomal gel for transdermal insulin delivery. Saudi Pharmaceutical Journal 2012; 20(4): 355-63.
29. Cevc G and Blume G: Hydrocortisone and dexamethasone in very deformable drug carriers have increased biological potency, prolongd effect and reduced therapeutic dosage. Biochimica et Biophysica Acta 2004; 1663(1-2): 61-73.
30. Maghraby EI, Williams GM and Barry BW: Skin delivery of oestradiol from lipid vesicles:importance of liposome structure. International Journal of Pharmaceutics; 204(1-2): 159-69.
31. Trotta M, Peira E, Carlotti ME and Gallarate M: Deformable liposomes for dermal administration of methotrexate. International Journal of Pharmaceutics 2004; 270: 119-25.
32. Hafer C, Goble R, Deering P, Lehmer A and Breut J: Formulation of interleukin-2 and interferon-alpha containing ultra-deformable carriers for potential transdermal application. Anticancer Research 1999; 19(2c): 1505-07.
33. Benson HA: Transfersomes for transdermal drug delivery. Expert opinion on Drug Delivery 2006; 3(6): 727-37.
34. Khan Ma, Pandit J, Sultana Y,Sultana S, Ali A, Aqil M and Chauhan M: Novel carbopol-based transfersomal gel of 5-fluorouracil for skin cancer treatment: *in-vitro* chracterisation and *in-vivo* study. Drug Delivery. 2015; 22(6): 795-802.
35. Planas ME, Gonzalez P, Rodriguez L, Samchez S, Cevc G: Non invasive percutaneous induction of topical analgesia by a new type of drug carrier and prolongation of local pain insensitivity by anaesthetic liposomes. Anesthesia Analgesia 1992; 75(4): 61-72.
36. Shaji J and Lal M: Preparation, optimization and evaluation of transferosomal formulation for enhanced transdermal delivery of a COX-2 inhibitor. Int J Pharm Pharm Sci 2014; 6: 467-77.
37. Nagaswamy D, Kalyani K, Tulasi K, Priyanka VS, Abid Ali SK and Kiran HC: Transfersomes: A novel technique for transdermal drug delivery.International Journal of Research in Pharmaceutical and Nano Sciences 2014; 3(4): 266-76.
38. Chen J, Lu WL, Lu SS, Chen ZP and Cai BC: Skin permeation of elastic liposomes:role of formulation ingredients. Expert Opinion on Drug Delivery 2013; 10(6): 845-56.
39. Song CK, balakrishnan P, Shim CK, Chung SJ, Chong S and Kim DD: A novel vesicular carrier, transethosome, for enhanced skin delivery of voriconazole: characterization and *in-vitro in-vivo* evaluation. Colloids and Surfaces B Biointerfaces 2012; 92: 299-304.
40. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, *et al*., Development, characterisation and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes and transethosomes. International Journal of Nanomedicine 2015; 10: 5837-51.

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