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ULTRADEFORMABLE SYSTEM: A CARRIER FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT: The delivery of therapeutic agents transdermally has received considerable interest because of the safety and convenience of drug administration via this route. Recently, various strategies have been used to augment the transdermal delivery of bioactives. A transfersome is an artificial vesicle designed to be like a cell vesicle, and used to deliver drugs or genetic material into a cell. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility. 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.

INTRODUCTION: Transdermal delivery of drugs through the skin is to the systematic circulation provides a convenient route of administration for a variety of clinical indication. The application of transdermal delivery to a wider range of drug is limited due to significant barrier to penetration across the skin which is associated primarily with outermost stratum corneum layer of epidermis [1]. To date many chemical and physical approaches have been applied to increase the efficacy of the material transfer across the intact skin, by use of the penetration enhancers, iontophoresis, sonophoresis and the use of colloidal carriers such as lipid vesicles (liposomes and proliposomes) and nonionic surfactant vesicles (niosomes and proniosomes) and elastic liposomes like ethosome and transferosomes [2].

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The term transferosomes and the underlying concept were introduced in 1991 by Gregor Cerc. Transfersome is a term registered as a trademark by the German company IDEA AG, and used by it to refer to its proprietary drug delivery technology. A novel vesicular drug carrier system called transferosomes consisting of phospholipids and an edge activator. An edge activator is often a single chain surfactant that destabilizes the lipid bilayer of the vesicles and increases the deformability of the bilayer by lowering its interfacial tension [3].

A Transfersome carrier is an artificial vesicle and resembles the natural cell vesicle. Later, a second generation of elastic vesicles was introduced consisting of mainly non-ionic surfactants. Not only have the physicochemical characteristics of the vesicles, but also the mode of application played a crucial role in the vesicles-skin interactions. Vesicles can be applied occlusively (covered by a patch to avoid water evaporation) or nonocclusively (exposed to the air, which results in evaporation of water). The difference in skin interaction between occlusive and non-occlusive application is of importance for deformable

vesicles [2]. Thus it is suitable for targeted and controlled drug delivery. In functional terms, it may be described as lipid droplet of such deformability that permits its easy penetration through the pores much smaller than the droplets size. 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. Transfersome penetrate the stratum corneum by either intracellular route or the transcellular route [3].

Mechanism of penetration of Transfersomes: The mechanism for penetration is the generation of "osmotic gradient" due to evaporation of water while applying the lipid suspension (Transfersomes) on the skin surface. The transport of these elastic vesicles is thus independent of concentration. The trans-epidermal hydration provides the driving force for the transport of the vesicles [4]. As the vesicles are elastic, they can squeeze through the pores in stratum corneum (though these pores are less than one-tenth of the diameter of vesicles) [5].

TABLE 1: DIFFERENT ADDITIVES USED IN FORMULATION OF TRANSFERSOME [6]

z	Example	Uses
Phospholipids	Soyaphosphatidylcholine, Dipalmitoyl, phosphatidylcholine	Vesicle Forming component
Surfactant	Sodium cholate, sodium deoxycholate, tween 80, span80	For providing flexibility
Alcohol	Ethanol, methanol	As solvent
Buffering	Phosphate For agents buffer pH(6.4)	Providing flexibility
Dyes	Rhodamine123, rhodamine DHPE, flouroesceins,OHPE Nile red	For CSLM Study

Characteristics of Transferosomes: Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.

- 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. 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].

Optimization of formulation containing Transfersomes: There are various process variables which could affect the preparation and properties of the transfersomes. The preparation procedure was accordingly optimized and validated. The process variables are depending upon the procedure involved for manufacturing of formulation. Preparation of transfersomes involves various process variables such as,

1. Lecithin: surfactant ratio
2. Effect of various solvents
3. Effect of various surfactants
4. Hydration medium

Optimization was done by selecting entrapment efficiency of drug. During the preparation of a particular system, the other variables were kept constant [8, 9].

Preparation of Transferosomes: To prepare vesicles capable of different shape adaptability, the relative concentration of surfactants, which act as membrane- softening and - destabilizing agents (such as cholate or polysorbate), is varied. Two techniques have been generally used to prepare transfersomes, with slight modifications used by individual researchers.

Vortexing-Sonication Method: In the vortexing-sonication method, mixed lipids (i.e. phosphatidylcholine, EA and the therapeutic agent) are blended in a phosphate buffer and vortexed to attain a milky suspension. The suspension is sonicated, followed by extrusion through polycarbonate membranes [10]. Cationic transfersomes have also been prepared by this method, which involves mixing cationic lipids, such as DOTMA, with PBS to obtain a concentration of 10 mg/ml followed by the addition of sodium deoxycholate (SDC). The blend is vortexed and sonicated, followed by extrusion through a polycarbonate (100-nm) filter [11].

Rotary Evaporation-Sonication Method: The rotary evaporation–sonication method involves dissolution of phosphatidylcholine and EA in a blend of chloroform and methanol (2:1, v/v), followed by the removal of organic solvent using rotary evaporation under reduced pressure at 4008C. The film deposited is hydrated with a solution of the therapeutic agent in a suitable aqueous phase while rotating the flask for one hour at room temperature. The vesicles produced are left to swell for two hours at room temperature, followed by 30 min of sonication in a bath sonicator so as to decrease their volume. Extrusion of vesicles then occurs through a sandwich of 450- and 220-nm polycarbonate membranes, with the resulting vesicles being stored at 408°C [10].

Characterization of Transferosomes:

1. **Vesicle size and shape:** Transferosomes vesicles can be visualized by TEM, with an accelerating voltage of 100 kV. Transferosomes vesicles can be visualized without Sonication by phase contrast microscopy by using an optical microscope [12].

2. **Vesicle Diameter:** Vesicle diameter can be determined using photon correlation spectroscopy or dynamic light scattering (DLS) method [13]. Samples were prepared in distilled water, filtered through a 0.2 mm membrane filter and diluted with filtered saline and then size measurement done by using photon correlation spectroscopy or dynamic light scattering measurements [14].

3. **Entrapment efficiency:** The entrapment efficiency is expressed as the percentage entrapment of the drug added. Entrapment efficiency was determined by first separation of the un-entrapped drug by use of mini-column centrifugation method. After centrifugation, the vesicles were disrupted using 0.1% Triton X-100 or 50% n-propanol [15]. The entrapment efficiency is expressed as:

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

4. **No. of vesicles per cubic mm:** This is an important parameter for optimizing the composition and other process variables. Non-sonicated transfersome formulations are diluted five times with 0.9% sodium chloride solution. Haemocytometer and optical microscope can then be used for further study [12]. The Transfersomes in 80 small squares are counted and calculated using the following formula:

Total number of Transfersomes per cubic mm = Total number of Transfersomes counted × dilution factor × 4000

5. **Degree of Deformability or Permeability Measurement:** Degree of deformability is an important and unique parameter of transfersomal formulations because it differentiates transfersomes from other vesicular carriers like liposomes that are unable to cross the stratum corneum intact. The deformability study is done against the pure water as standard.

   Transfersomes preparation is passed through a large number of pores of known size (through a sandwich of different microporous filters, with pore diameter between 50 nm and 400 nm, depending on the starting transfersomes suspension). Particle size and size distributions are noted after each pass by dynamic light scattering (DLS) measurements [16].

The degree of deformability was calculated by using the following formula:

$$D = J \times r_v / r_p$$

where, D = deformability of vesicle membrane, J = amount of suspension, which was extruded during 5 min, rv = size of vesicles (after passes), rp = pore size of the barrier

6. **Drug content:** The drug content can be determined using one of the instrumental analytical methods such as modified high performance liquid chromatography method (HPLC) method using a UV detector, column oven, auto sample, pump, and computerized analysis program depending upon the analytical method of the pharmacopoeial drug [17].

7. **Turbidity measurement:** Turbidity of drug in aqueous solution can be measured using nephelometer [18].

8. **Confocal Scanning Laser Microscopy study:** Conventional light microscopy and electron microscopy both face problem of fixation, sectioning and staining of the skin samples. Often the structures to be examined are actually incompatible with the corresponding processing techniques; these give rise to misinterpretation, but can be minimized by Confocal Scanning Laser Microscopy (CSLM). In this technique lipophilic fluorescence markers are incorporated into the transfersomes and the light emitted by these markers used for following purpose:

    - For investigating the mechanism of penetration of transfersomes across the skin,
    - For determining histological organization of the skin (epidermal columns, interdigitation), shapes and architecture of the skin penetration pathways [13].
    - For comparison and differentiation of the mechanism of penetration of transfersomes with liposomes, niosomes and micelles.

Different fluorescence markers used in CSLM study are as –

- Fluorescein- DHPE (1, 2- dihexadecanoyl- sn- glycero- 3- phosphoethanolamine- N- (5-fluoresdenthiocarbamoyl), triethyl- ammonium salt)
- Rhodamine- DHPE (1, 2- dihexadecanoyl- sn- glycero- 3ogisogietgabikanube- LissamineTmrhodamine-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)

9. **Penetration ability:** Penetration ability of Transfersomes can be evaluated using fluorescence microscopy [19].

10. **Occlusion effect:** Occlusion of skin is considered to be helpful for permeation of drug in case of traditional topical preparations. But the same proves to be detrimental for elastic vesicles. Hydrotaxis (movement in the direction) of water is the major driving force for permeation of vesicles through the skin, from its relatively dry surface to water rich deeper regions. Occlusion affects hydration forces as it prevents evaporation of water from skin [15].

11. ***In vitro* drug release:** *In vitro* drug release study is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from in-vitro studies are used to optimize the formulation before more expensive in vivo studies are performed. For determining drug release, transfersomes suspension is incubated at 320 ^{o}C and samples are taken at different times and the free drug is separated by mini column centrifugation [12]. The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released).

12. ***In-vitro* Skin permeation studies:** Modified Franz diffusion cell with a receiver compartment volume of 50ml and effective diffusion area of 2.50 cm2 was used for this study. In vitro drug study was performed by using goat skin in phosphate buffer solution (pH 7.4). Fresh Abdominal skin of goat were collected from slaughterhouse and used in the

permeation experiments. Abdominal skin hairs were removed and the skin was hydrated in normal saline solution. The adipose tissue layer of the skin was removed by rubbing with a cotton swab. Skin was kept in isopropyl alcohol solution and stored at 0-40˚C.

To perform skin permeation study, treated skin was mounted horizontally on the receptor compartment with the stratum corneum side facing upwards towards the donor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was 2.50cm^2 and capacity of receptor compartment was 50ml. The receptor compartment was filled with 50ml of phosphate buffer (pH 7.4) saline maintained at 37 ± 0.5˚C and stirred by a magnetic bar at 100RPM.

Formulation (equivalent to 10mg drug) was placed on the skin and the top of the diffusion cell was covered. At appropriate time intervals 1 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffers (pH 7.4) to maintain sink conditions. Correction factors for each aliquot were considered in calculation of release profile. The samples were analyzed by any instrumental analytical technique [8, 20].

13. **Physical stability:** The initial percentage of the drug entrapped in the formulation was determined and were stored in sealed glass ampoules. The ampoules were placed at 4 ± 20˚C (refrigeration), 25 ± 20˚C (room temp), and 37 ± 20˚C (body temp) for at least 3 months. Samples from each ampoule were analyzed after 30 days to determine drug leakage. Percent drug lose was calculated by keeping the initial entrapment of drug as 100% [9, 17].

Potential of transfersomes in drug delivery and therapeutics: Transferosomes with different composition and characteristics have been formulated and investigated for various therapeutic and pharmaceutical applications. Some important application of transferosomes are outlined below and summarized in table:

TABLE 2: IMPORTANT APPLICATION OF TRANSFEROSOMES IN DIFFERENT FIELD

Applications	Therapeutic agent	Additives	Purpose
NSAID therapy	Ketoprofen (IDEA-033)	PC and polysorbate soyaphosphatidycholine, Span 80 and tween 80 PC, cholesterol,	Low GI adverse effects and Improved penetration for anti-inflammatory activity [21].
	Ibuprofen	sodium cholate, sodium oleate and diacetyl-phosphate	Prolonged promising delivery system and good stability characteristics [22].
	Meloxicam	cholesterol & cationic surfactants	Higher skin permeation of MX than did liposomes because of greater disruption of stratum corneum [23].
	Meloxicam		Enhanced penetration mechanism for anti-inflammatory mechanism [24].
Antifungal activity	Terfinafine (TDT 067)	SPC, sodium cholate	Provide potent inhibitory and funcidicial activity [25].
	Amphotericin B (TF-3)	Sodium deoxycolate, SPC	Enhanced permaeation as compared to conventional [26].
	Ketoconazole	Eucalyptus oil, Peppermint oil, Turpentine oil	Compared to all oil eucalyptus oil enchanecd in vitro release and permaeation [27].
cancer therapy	Cisplatin	Soya lecithin, SDC	Tumour volumes decrease in size [28].
	Docetaxel (DTX)	PC, sodium cholate, trypan blue and Triton X-100	Enhance transdermal delivery of drug DTX without microneedle pretreatment [29].
Proteins and peptides delivery	Gap junction protein	SPC, Sodium cholate, sodium dodecyl sulphate, phosphate buffer pH 6.5	Increase the relative conc. Of Anti GJP IgA in serum [30].
	Insulin (Transferulin)	SPC	High encapsulation efficiency, increased permeation & induce therapeutically hypoglycemia with good efficacy [2].
	Stavudine	SDC, Tween 80, SPC, sodium cholate, span 80 and triton X-100	Improved in-vitro skin delivery for antiretroviral activity [17].
Antiviral therapy	Indinavir Sulfate	SPC, SDC, span 80, Tween 80, Triton	Improved influx for activity against AIDS [9]

		X-100	
Hypertension management	Telmistran	SPC, ethanol, Sodium cholate	Enhanced the skin absorption and prolonged release of drug [31].
	Diltiazem	Tween 80, sodium cholate , Soybean lecithin (PC)	Enhanced sustained effect, degradation independent of lipid composition [32].
Antiwrinkle effect	Curcuminods	Lecithin, Tween 20, surfactants	Improved elasticity, biological elasticity, recovered of deformed skin, firmness and reduction in fatigue [33].
Psoriasis	Methotrxate	soya lecithin (Epikuron 200) and hydrogenated lecithin (Phospholipon 100) as lipids and dipotassium glycyrrhizinate	Improved transdermal influx [34].
Antileishmansis	Paromamycin sulfate	SPC, sodium cholate, ethanol	Rate of penetration, retention and curable increased as compared to conventional [35].
Topical immunization	Tetanus toxoid	SPC	Elicit immune response [36].
	Hepatitis B	SPC,Span 80 & ethanol	Increased immune response [37].
Others	Quercetin	Tween 80 & Span 80	Improved its penetrability in a period of time [38].

CONCLUSION: Difficulty is associated with its topical application due to less permeability through skin. To alleviate this problem vesicular drug delivery system transfersomes is formulated to deliver drug across skin. Transfersomes are specially optimized particles or vesicles, which can respond to an external stress by rapid and energetically inexpensive, shape transformations. They are free from the rigid nature of conventional vesicles and can transport even the large molecules. Ultra-deformable vesicles hold great prospective in delivery of huge range of drug substances which includes large molecules like peptides, hormones and antibiotics, drugs with poor penetration due to unfavorable physicochemical characters, drugs for quicker and targeted action, etc. It is essential to explore new pharmaceutical excipients that can minimise the oxidative degradation of these vesicular systems and that are more consistent with regards to their purity, to realize completely the potential of these versatile systems in transdermal drug delivery.

Conflict of interest statement: I declare that I have no conflict of interest.

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