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TRANSFERSOMES - A BOON FOR TRANSDERMAL DELIVERY

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Abstract:
Transdermal drug delivery is in great demand and developing fast due to the various advantages over other conventional routes. Emerging as a safe, efficient transdermal drug delivery approach is the use of Transfersomes. These are hydrophilic lipid vesciles known to be ultra-deformable because of its ability to squeeze through the skin pores and penetrate the intact mammalian skin. Carrier systems like liposomes are unable to do this due to their larger size and inability of the vesicle walls to deform. This review describes the mechanism of transfersomal penetration through the stratum corneum, factors which influence these mechanism and formulation and evaluation of Transfersomes along with its scope in drug delivery. Transfersome consist of edge activators (mostly single chain surfactants) and phospholipids. Phospholipids form the outer rigid bilayer thus giving strength to the vesicles. The edge activators aid by weakning the lipid bilayer and increasing vesicle flexibility thus helping them penetrate through the stratum corneum. Thus selecting the optimum ratio of phospholipid and edge activator is very vital. Larger molecules can be easily administered by mere application onto the skin. It also reduces the dose required to show activity as it surpasses first pass metabolic pathway.

Keywords: *Transfersomes, Edge activators, Stratum corneum, Ultra-deformable, skin, transdermal delivery.*

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INTRODUCTION:

Topical drug delivery is considered as the most convenient route for transdermal drug delivery owing to the many advantages over conventional routes like surpassing first pass metabolism, longer duration of action, fewer side effects, use of shorter half-life drugs, improved pharmacological response, inter and intra patient variation and most importantly, patient compliance. Lipid based systems called liposomes have been developed for transdermal drug delivery due to its similarity with the phospholipid bilayers form in the biological membranes. These are suitable for both hydrophilic and lipophilic drug delivery because of the unique amphiphilic character of the lipids [3]. But one drawback of conventional liposomes in transdermal delivery is that they are unable to penetrate through the stratum corneum and are confined to only upper surface of the skin. For this reason, specially designed vesicles called Transfersomes were developed [4].

A Transfersome is an ultra-deformable vesicle which is a highly adaptable and stress responsive complex aggregate [1]. These Transfersomes tend to increase the hydrophilic pore size of the skin wide enough to be able to transport larger aggregates through the stratum corneum. The delivery of macro-molecules into and through the intact skin is due to the trans-barrier particle motion driven by the moisture gradient across the permeation barriers like the stratum corneum, thus allowing delivery of such macro-molecules of size greater than a 100kDa[5] .

Transfersomes are mainly composed of surfactants also called as the edge activators (EA) and phospholipids which are responsible for increasing the flexibility of the vesicle walls thus enabling transdermal delivery. Owing to their flexible membrane, these vesicles deliver the drug substances reproducibly into and through the various layers of the skin based on the way of administration. The Transfersomes are said to permeate through the stratum corneum by sqeezing their ultra-deformable and flexible membranes through the intracellular lipids of the skin [6]. In this process the Transfersomes undergo stress dependent changes in the local carrier composition in order to reduce the back pressure of the confining narrow channels. Thus the Transfersomes transfer drug substances entrapped in them across the skin faster than the conventional topical formulations [2]. The deformability of these Transfersomes is said to be to such an extent that they can pass through the skin pores which are at least 5 to 10 times smaller than the vesicle diameter and yet transfer the entrapped drug without any loss[7] [8].

The factors responsible to give ultra-deformable character to the liposomes are edge activators that are the special surfactants like sodium cholate, sodium deoxycholate tween 80, span 80 etc. Since surfactants are used in the formation of Transfersomes, they have better rheology and hydration properties in order to give superior skin permeation property. Traditional conventional liposomes stay on the skin surface only thus dehydrate and fuse together hence has reduced skin permeation [9].

SKIN:

The skin covers the entire external surface of the human body and is the principal site of interaction with the surrounding world. It serves as a protective barrier that prevents internal tissues from exposure to trauma, ultraviolet (UV) radiation, temperature extremes, toxins, and bacteria. Other important functions include sensory perception, immunologic surveillance, thermoregulation, and control of insensible fluid loss.

The integument consists of 2 mutually dependent layers, the epidermis and dermis, which rest on a fatty subcutaneous layer, the panniculus adiposus. The **epidermis** is derived primarily from surface ectoderm but is colonized by pigment-containing melanocytes of neural crest origin, antigen-processing Langerhans cells of bone marrow origin, and pressure-sensing Merkel cells of neural crest origin. The **dermis** is derived primarily from mesoderm and contains collagen, elastic fibers, blood vessels, sensory structures, and fibroblasts [10] .

The **stratum corneum** is the outermost of the 5 layers of the epidermis and is largely responsible for the vital barrier function of the skin. Before the mid-1970's the stratum corneum was thought to be biologically inert, like a thin plastic sheet protecting the more active lower layers of the skin. In the past 30 years, and especially the past 5 years, scientists have discovered that the biological and chemical activity of the stratum corneum is very intricate and complex.

Understanding the structure and function of the stratum corneum is vital because it is the key to healthy skin and its associated attractive appearance.

The transdermal delivery system is recognized as generations in the following manner:

The first generation of transdermal delivery is limited primarily by this barrier posed by skin’s outermost layer that is the stratum corneum, which is 10 to 20 µm thick. Underneath this layer is the viable epidermis, which measures 50 to 100 µm and is avascular.

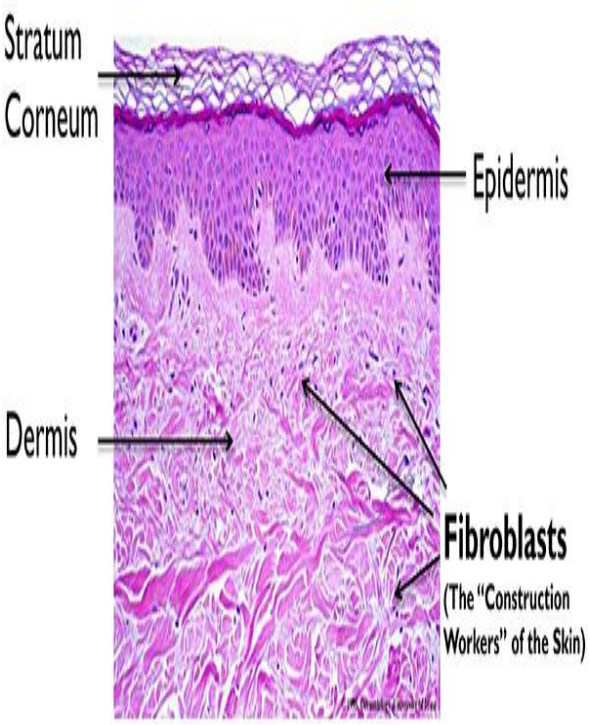


Fig 1: The Skin (H uman Anatomy)

Deeper still is the dermis, which is 1–2 mm thick and contains a rich capillary bed for systemic drug absorption just below the dermal–epidermal junction. Closer examination of the stratum corneum barrier reveals a brick and mortar structure, where the bricks represent non-living corneocyte cells composed primarily of cross-linked keratin and the intercellular mortar is a mixture of lipids organized largely in bilayers. The stratum corneum contains about 12-16 layers of corneocytes and each corneocyte has a mean thickness of 1 micrometer, depending on the following factors:

- Age
- Anatomical location
- Exposure to UV radiation

Drug transport across the stratum corneum typically involves diffusion through the intercellular lipids via a path that winds tortuously around corneocytes, where hydrophilic molecules travel through the lipid head group regions and lipophilic molecules travel through the lipid tails. This transport pathway is highly constrained by the structural and solubility requirements for solution and diffusion within stratum corneum lipid bilayers.

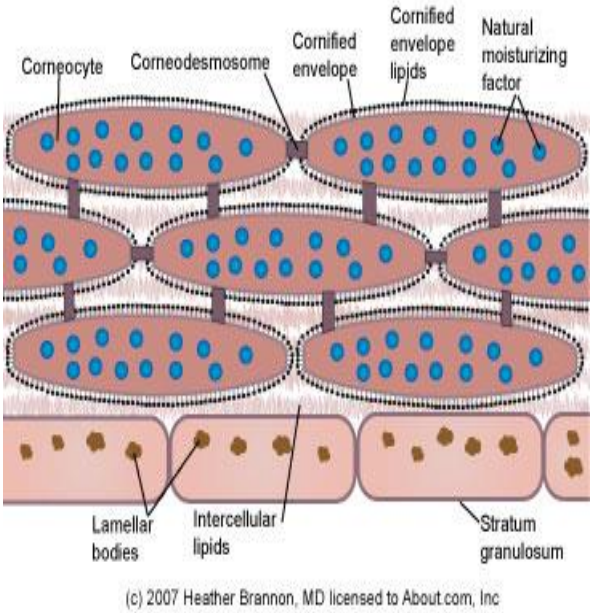


Fig 2: Layered structure of the skin

The second generation of transdermal delivery systems recognizes that skin permeability enhancement is needed to expand the scope of transdermal drugs. The ideal enhancer should (i) increase skin permeability by reversibly disrupting stratum corneum structure, (ii) provide an added driving force for transport into the skin and (iii) avoid injury to deeper, living tissues. However, enhancement methods developed in this generation, such as conventional chemical enhancers, iontophoresis and non-cavitational ultrasound, have struggled with the balance between achieving increased delivery across stratum corneum, while protecting deeper tissues from damage. As a result, this second generation of delivery systems has advanced clinical practice primarily by improving small molecule delivery for localized, dermatological, cosmetic and some systemic applications, but has made little impact on delivery of macromolecules.

Hence, in a gist we can say that cutaneous drug delivery offers many advantages over alternative routes of administration with regards to target specific impact, decreased systemic toxicity, avoidance of first pass metabolism, variable dosing schedules, and broadened utility to diverse patient

populations but a complicating factor is that the skin has evolved mechanisms to impede exogenous molecules, especially hydrophilic ones, from safe passage. The horny layer of the stratum corneum (the top most layer of the skin) is tightly bonded to an intercellular lipid matrix making the passage of therapeutics a serious challenge [12]. This strong barrier to molecular activity is quite effective at blocking large drugs (molecular mass > 500 Da), which of course make up the majority of active therapeutics [11].

TRANSFERSOMES: A TOOL FOR CROSSING THE STRATUM CORNEUM

The stratum corneum as mentioned above is the barrier which prevents passage of any foreign material through the skin into the dermis and inner layers. Thus many topically administered drugs also tend to stay on the surface and thus fail to show the desired activity. For this purpose, Transfersomes- the ultra-deformable liposomes were developed.

ADVANTAGES OF TRANSFERSOMES OVER CONVENTIONAL LIPOSOMES:

- Liposomes and Niosomes have poor skin permeability hence are not suitable for transdermal delivery. Transfersomes have an ability to deform and reform thus penetrates through the skin easily.
- Unlike conventional vesicles, Transfersomes can transdermally carry low as well as high molecular weight drugs.
- Transfersomes can respond to external stress by transforming in shape and size with low energy requirement.
- These vesicles are capable of carrying peptides, proteins and vaccines through the pores of stratum corneum transdermally.
- They have flexible vessel walls unlike liposomes and niosomes owing to the special surfactants used in their preparation, known as edge activators.
- Transfersomes are constructed using both hydrophobic and hydrophilic moieties together and thus can easily incorporate drugs having a wide range of solubility in them.

COMPOSITION AND MECHANISM OF ACTION:

Transfersomes contain atleast one amphiphatic agent such as phosphotidylcholine which will form a bilayer due to rearrangement of lipids in the aqueous solvent [TABLE.1]. Also, it consists of a bilayer softening agent such as surfactants namely Tween 80, Span 85, Span 80, Sodium cholate, Sodium deoxycholate etc which help in giving the vesicles their characteristic deformable and flexible property.

As a result of the strong bilayer deformability of the vesicle walls, Transfersomes have a better water retention and binding capacity. Hence these vesicles will always tend to transfer themselves towards more moisture rich areas i.e from the surface of the skin which has limited moisture content towards the deep strata which had a better moisture content which helps them stay hydrated always.

These ultradeformable vesicles undergo a 'reversible' lipid bilayer deformation upto an extent where there is no undesirable or unacceptable changes in the vesicle integrity and the entrappement efficiency [16].

Materials: [TABLE.1]

Edge activators	Increase flexibility	**Eg: Tween 80, Span 80, Sodium cholate, Sodium deoxycholate etc**
Phospholipids	Vesicle forming agents	**Eg: Soya Phosphatidyl choline, Egg lecithins, cholesterol etc**
Alcohols	Solvents	**Eg: Ethanol, Methanol**
Buffering agents	Hydration	**Eg: Water, Saline phosphate buffer pH 6.4**
Dyes	CSLM(confocal scanning laser microscopy)	**Eg: Rhodamine 123, Nile-red**

HOW TRANSFERSOMES PENETRATE THE STRATUM CORNEUM?

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 reason for this high flux rate is naturally occurring "transdermal osmotic gradients" i.e. another much more prominent gradient is available across the skin [2, 6]. 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. 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).

Two mechanisms of action have been documented:

1.Elastomechanics.

2. Trans-epidermal water activity gradient.

Cevc and coworkers proposed the first mechanism, suggesting that deformable liposomes penetrate the stratum corneum because of the transdermal

hydration gradient normally existing in the skin, and then cross the epidermis, and enter the systemic circulation. The recent studies propose that the penetration and permeation of the vesicles across the skin are due to the combination of the two mechanisms. Depending on the nature of the active substance (lipophilic or hydrophilic) and the composition of the Transfersomes, one of the two mechanisms prevails. (Fig 3 & 4)

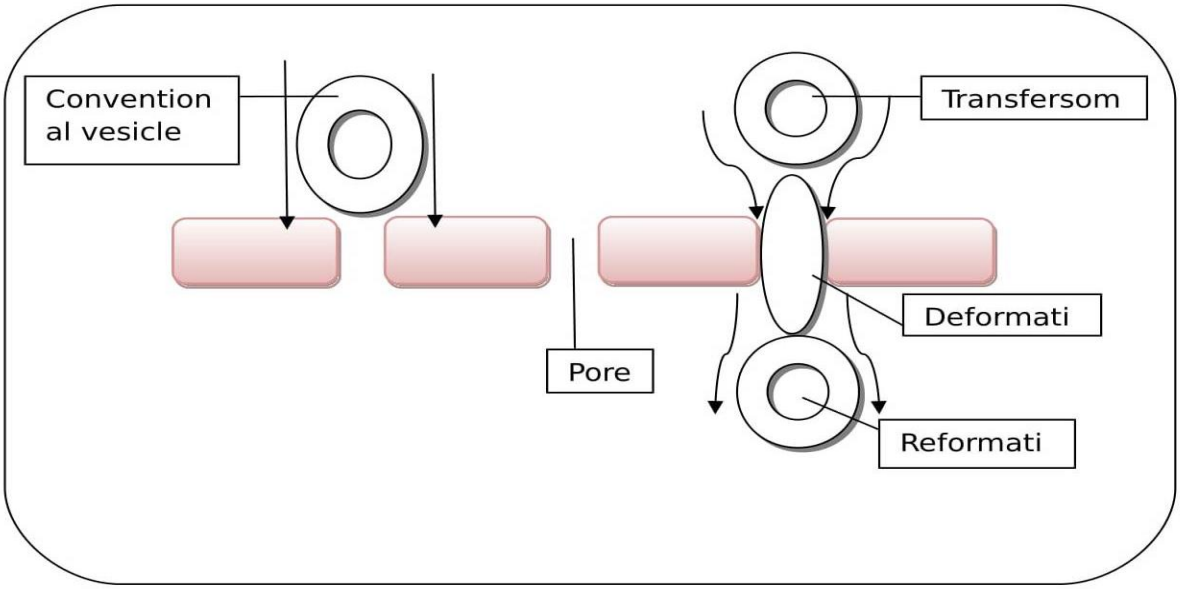


Fig: 3 Elastomechanics

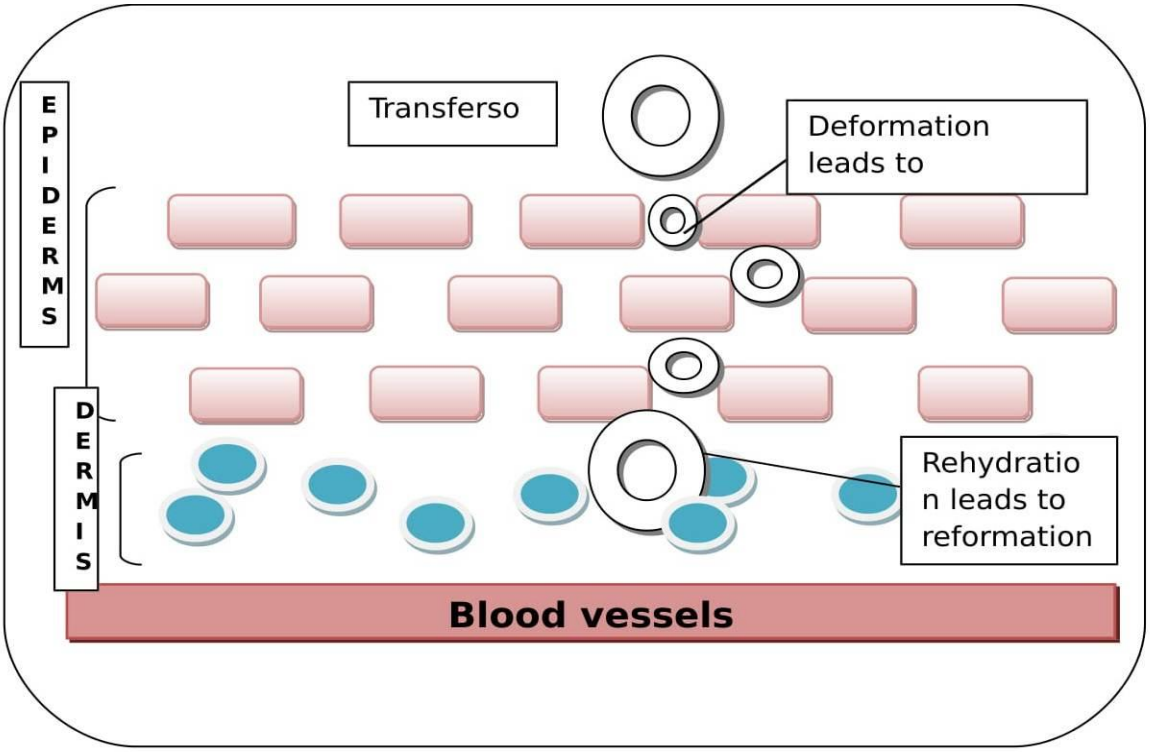


Fig: 4 Trans epidermal water activity gradient

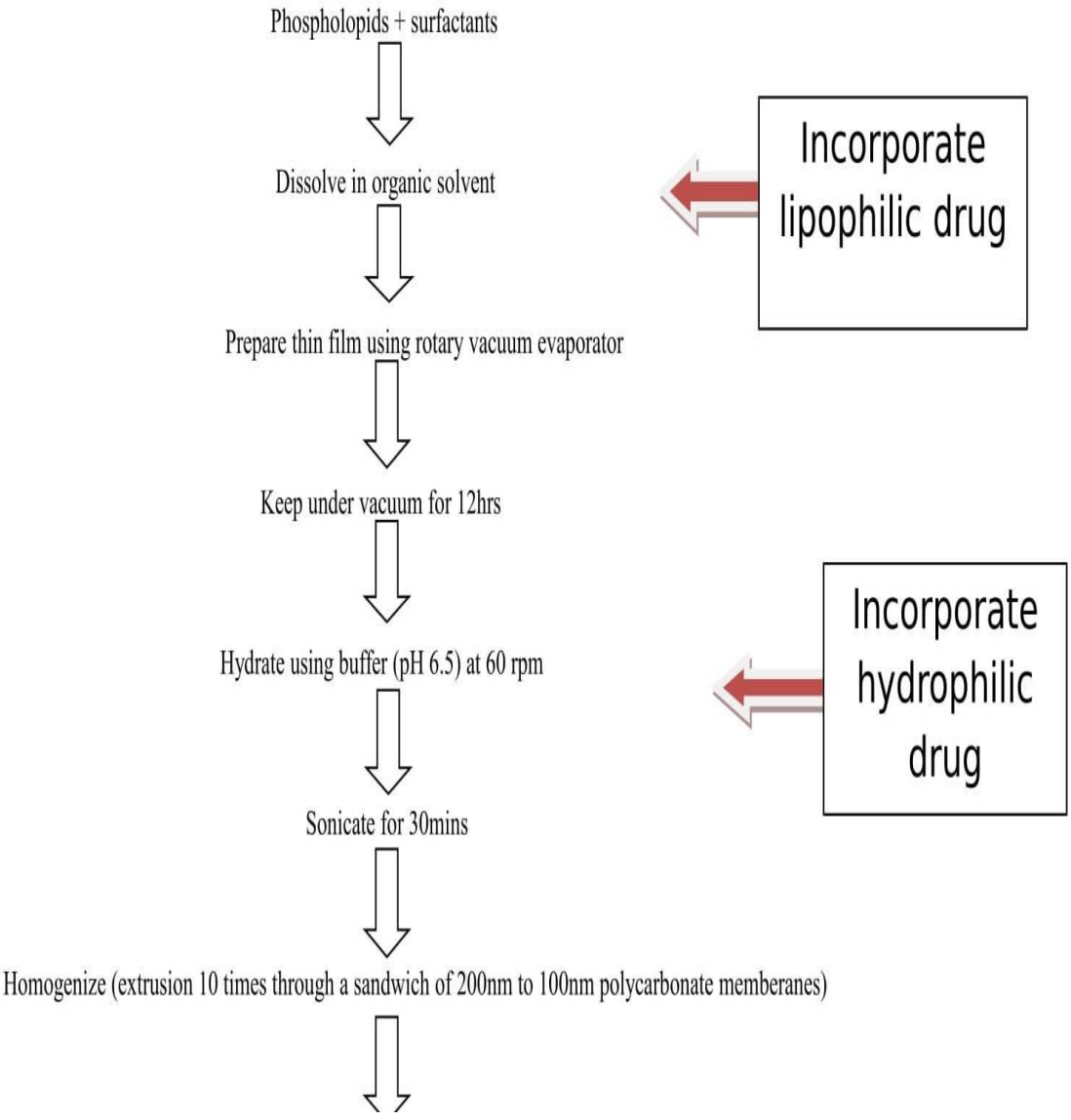
Transfersomes could also work as permeation enhancers across the skin [26]. One such example is of the 5-fluorouracil transfersome, the percentage drug penetrated (13.5%) was considerably higher than the percentage of drug entrapped (8.8%). This shows that the transferosomal components may have altered the skin structure to act as penetration enhancers [27].

METHODS OF PREPARATION:

a) Thin film hydration
b) Modified hand shaking
c) Reverse Phase Evaporation method

PREPERATION OF TRANSFERSOMES:

A] Thin film hydration technique-



Transfersomes

B] **MODIFIED HAND SHAKING METHOD:**
Drug, lecithin (PC) and edge activator were dissolved in ethanol: chloroform (1:1) mixture. Organic solvent was removed by evaporation while hand shaking above lipid transition temperature (43°C). A thin lipid film was formed inside the flask wall with rotation. The thin film was kept overnight for complete evaporation of solvent
2. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minute at corresponding temperature. The Transfersomal suspension further hydrated up to 1 hour at 2-8°C [15].
C]**REVERSE PHASE EVAPORATION METHOD**: The ingredients like cholesterol, phospholipids are taken in a clear beaker. Then, surfactant is poured in the same beaker and dissolved in a different solvent mixture. The beaker is kept at the room temperature for 24 h until the thin film is formed. Drug solution is poured onto the thin film and sonicated using probe sonicator at a frequency of 20 KHz for 2 min. After that, the film was hydrated using edge activator in phosphate buffer saline (pH 7.4) and then further sonicated for 2 min to obtain transfersomal suspension. Then various formulated transferosomal suspensions should be passed through Whitman filter paper (No. 40).

FACTORS AFFECTING FORMATION OF TRANSFERSOMES:
1.Effect of different Edge Activators- The amount and type of edge activators used in the preparation of Transfersomes affect its vesicle size, entrapment efficiency, stability, and deformability and permeation ability through the skin. Various edge activators have been used in the formulation of Transfersomes like Tweens, Spans, Sodium cholate, Sodium deoxycholate etc.
Gehanne A.S Awad et.al in his article suggested that entrapment efficiency of Transfersomes depends on the HLB value of the surfactants like Span 85 {1.8}, Span 80 {4.3}, Tween 80 {15}, Sodium deoxycholate and Sodium cholate {16.7}. The affinity of these surfactants towards lipids was seen to be of the order Span 85>Span 80>Tween 80>Sodium cholate/ Sodium deoxycholate. This suggests higher entrapment efficiency with Span 85 and Span 80. [18]
Also the author suggested another correlation of edge activators and vesicle deformability. The deformability of vesicles depends on the chemical structure of these surfactants. Tween 80 showed highest deformability due to its highly flexible and non-bulky hydrocarbon chains. Sodium cholate and sodium deoxycholate had lower deformability owing to their steroidal structure which is bulkier than the hydrocarbon chains of Tween 80. Span 85 and Span 80 show least deformability because of the highly hydrophobic structure which reduces the formation of hydrophilic orifices thus lowering the bilayer amphiphilicity in turn lowering the vesicle flexibility. [18]

EFFECT OF METHOD OF PREPARATION- Out of the methods mentioned earlier two are widely used namely vortexing and thin film hydration. Among these two, thin film hydration using rotary vacuum evaporator gave finer particles and better entrapment efficiency as compared t the other methods. This is due to the larger surface area obtained by the formation of a thin film which leads to complete hydration of vesicles and thus better vesicle characteristics. On the other hand, vortexing gives rise to aggregation of the lipids and thus sticking on the walls of the vial making hydration difficult. This gives a lumpy mass which sediments quickly upon storage.

EFFECT OF ORGANIC SOLVENTS USED- The choice of solvent used depends on the solubility of all the ingredients added and also their compatibility with the solvents. Ideally, all the excipients should fully dissolve in the solvent and a clear transparent solution should be formed. One such example is mentioned in the article by author *Wen-sheng Zheng* in preparation and quality assessment of itraconazole Transfersomes. Here the author explained the effect of organic solvent on solubility, film formation, hydration and stability of the so formed Transfersomes. In his study he can across results suggesting that the raw excipient dissolved in anhydrous ethanol and chloroform gave poor solubility and also non-uniform film formation. There was flocculation and precipitation seen after hydration. On the other hand, use of a mixture of these two solvents in 1:1 ratio gave a clear transparent solution and better film forming ability and good stability after hydration[19].

CHARACTERIZATION OF THE PREPARED TRANSFERSOMES: [13-14]
1.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. The entrapment efficiency is expressed as**: Entrapment efficiency= (amount entrapped/ total amount added) ×100**

2.Vesicle Diameter: Vesicle diameter can be determined using photon correlation spectroscopy or dynamic light scattering (DLS) method. 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 (DLS) measurements.

3.Vesicle Shape & Type: Transfersomes vesicles can be visualized by TEM, phase contrast microscopy, etc. The stability of vesicle can be determined by assessing the size and structure of vesicles over time. Mean size is measured by DLS and structural changes are observed by TEM.

4.Number of Vesicle 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. 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.Confocal Scanning Laser Microscopy (CSLM) 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 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 for comparison and differentiation of the mechanism of penetration of transfersomes with liposomes, niosomes and micelles.

6.Degree of Deformability or Permeability Measurement: In the case of transfersomes, the permeability study is one of the important and unique parameter for characterization. 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.

7.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.

8.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.

9.*In Vitro* Drug Released: In vitro drug release study is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from in-vitro studies are used to optimize the formulation before more expensive in vivo studies are performed. For determining drug release, transfersomes suspension is incubated at 32°C and samples are taken at different times and the free drug is separated by mini column centrifugation. The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released).

10.Turbidity measurement: Turbidity of drug in aqueous solution can be measured using nephelometer.

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

12.Stability Studies: Transfersomes stability was determined at 4°C and 37°C by TEM visualization and DLS size measurement at different time intervals (30, 45, and 60 days), following vesicles preparation.

APPLICATIONS:

A.] Transfer of large lipid molecules Trans dermally: Transfersomes have been widely 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. These are the reasons why these peptides and proteins still have to be introduced into the body through injections. The bioavaibility obtained from Transfersomes is somewhat similar to that resulting from subcutaneous injection of the same protein suspension. The transfersomal preparations of this protein also induced strong immune response after the repeted epicutaneous appilication, for example the adjuvant immunogenic bovine serum albumin in Transfersomes, after several dermal challenges is as

active immunologically as is the corresponding injected proteo-transfersomes preparations.
Delivery of insulin by Transfersomes is the successful means of non invasive therapeutic use of such large molecular weight drugs on the skin (Cevc et al, 1990). Insulin is generally administered by subcutaneous route that is inconvenient. Encapsulation of insulin into Transfersomes (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. [24]

B.] Pulmonary delivery through nebulizer: *Abdelbary M.A. Elhissi et.al* suggested in their article the use of ultra-deformable liposomes for pulmonary delivery using salbutamol sulphate. Aerosols of ultra-deformable liposomes were generated using air-jet, ultrasonic or vibrating-mesh nebulizers and their stability during aerosol generation was evaluated. They showed fine particle formation but the vesicles were unstable on nebulization and there was leakage of drug during the process. [17]

C.] Tumor treatment: *Lin Hou, Ming Kong* designed Transfersomes for tumor treatment. Tumor metastasis accounts for 90% of cancer-associated deaths and is almost inaccessible by chemotherapy, surgical operation or radiotherapy. Transdermal drug delivery could avoid the first-pass hepatic effect and fluctuation of blood concentration, and greatly facilitate drug accumulation in the lymphatics [20]. In this study, an amphiphilic hyaluronic acid (HA) derivative was assembled on the surface of a transfer some to form HA-T, which has a multilayered, spherical and highly flexible structure that facilitates transdermal penetration. The in vitro accumulative drug transdermal penetration of doxorubicin (DOX) loaded HA-T was 3 times higher than that of a solution of DOX. [21]

D.] Treating hypertension: *Abdul Ahad et.al* developed nanotransfersomes for enhanced transdermal of valsartan. Nanotransfersomes proved significantly superior in terms of amount of drug permeated in the skin, with an enhancement ratio of 33.97 ± 1.25 when compared to rigid liposomes. [25]

E.] Prevention and treatment of osteoporosis and invasive breast cancer in postmenopausal women: Raloxifene hydrochloride is a selective estrogen receptor modulator which helps in increasing the bone mineral density and reduces the levels of LDL cholesterol which is useful in treatment of osteoporosis. It also shows an antiestrogen effect on breasts thus lowering the risk of invasive breast cancer in post-menopausal women. This was proved in the research article by *Mahmood et al*. [22] [23]

F.] Non-invasive percutaneous induction of topical analgesics: Application of anesthetics in the suspension of highly deformable vesicles, transferosomes, induces a topical anesthesia, under appropriate conditions, with less than 10 min. Maximum resulting pain insensitivity is nearly as strong (80%) as that of a comparable subcutaneous bolus injection, but the effect of transferosomal anesthetics last longer.

G.]Transfersomes in 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. This approach offers at least two advantages, first: application without injection and second, they give rise 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 (Cevc et al, 1997). Transfersomes based cortiosteroids are biologically active at dose several times lower than the currently used formulation for the treatment of skin diseases (Cevc et al, 1997).

Table 2: List of drugs used in Transfersomal preparations:

Drug	Author and year	Composition	Advantages
Triamcinolone-acetonide[2] (Corticosteroid)	Gregor Cevc(2003)	Soybean phosphatidylcholine (SPC), chloroform:methanol(1:1), ethanol, buffer pH 6.5	High degree of drug localisation, increased drug potency and prolonged duration of drug action.
Diclofenac sodium[28] (NSAID)	Gregor Cevc(2001)		improve the regio-speci¢city and the e¤cacy of agent.
Emodin[29] (Anti-obesity)	Kun Lu, Shuanshuan Xie	Lecithin, Deoxycholic acid sodium salt, cholesterol, ether, phosphate buffer.	Uniform particle size, high entrapment efficiency and good stability.
Piroxicam[4] (COX-2 imhibitor)	Jessy Shaji(2014)	Phospholipon 90G, Chloroform, Methanol, Sodium deoxycholate,	Excellent release and improved permeation of drug through the skin.
Meloxicam[3] (NSAID)	Sureewan Duangjit(2013)	Egg phosphotidylcholine, Cholesterol, Chloroform, methanol, Tris buffer 7.4, Dodecyltrimethylammonium bromide (DTAB), stearylamine (SA) and cetylpyridinium chloride monohydrate (CPC)	Incorporation of cationic surfactants resulted in small size, positive charge and high entrapment efficiency. **Cationic surfactants helped increase dermal penetration of the vesicles.**
Griseofulvin[30] (Anti-fungal)	Nidhi Aggarwal(2012)	Phospholipon 90G, chloroform:methanol (1:1), span 85.	Showed good deformability making them flexible, able to penetrate partition and permeate the skin barrier very effectively. Can be used dermally without hampering drug efficacy.
Minoxidil[31] (stops hairloss & stimulates regrowth)	Simona Mura(2009)	Soya lecithin, chloroform, Dicetylphosphate, transcutol, labrasol, cineole.	Use of penetration enhancers improved ability to increase accumulation of drug in upper skin layers thus enhancing cutaneous BA.
Valsartan[32] (Anti-hypertensive)	Abdul Ahad(2012)	Phospholipon 90G, Sodiumdeoxycholate, cholesterol	Better activity and overcame low penetration ability as compared to liposomes.
Resveretrol+ 5-fluorouracil[33] **(**Anti-cancer**)**	Donato Cosco(2015)	Phospholipon 90G, cholesterol, ethanol, sodium cholate.	Improved the performance of the two drugs by enabling them to penetrate deeper into the skin tissues thus enhancing their synergistic action.
Sertraline[34] (Anti-depressant)	Ankit Gupta(2012)	Soya lecithin, span 80, ethanol.	Excellent release and permeation of drug. Simple production and simplistic scale-up.

CONCLUSION:

Non-invasive transdermal delivery has been a topic of public intrest recently. Transfersomal drug delivery seems to be a promising delivery system for transdermal route because of the many advantages it shows over liposomes and other carrier systems. These vesicles are said to improve efficacy of entrapped drug with ideally no side effects. They

penetrate into the skin pores which are smaller in diameter than the vesicles and thus supply drug to the active site. These are also said to act as penetration enhancers themselves. The ability of these vesicles to deform and reform in order to cross the stratum corneum is of great importance in developing delivery systems for drugs with higher molecular weight and molecular size thereby improving the efficacy, activity, Bioavailability and also patient compliance. More study and research is needed to be carried out in this area to bring these transfersomal preparations in market. Transfersomes may also have the ability to pass through many other barriers other than the stratum corneum thus extending its scope of use farther that transdermal delivery.

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