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TRANSFEROSOMES: A WIDE PERSPECTIVE OF NOVEL VESICULAR DRUG DELIVERY

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Abstract : Novel drug delivery is a recent development system for the effective drug delivery. Vesicular drug delivery is the most important among them. Among the emerging technologies, transferosomal-based formulations, has achieved a high popularity. They are also a prominent route for targeted delivery. Based on their biocompatible and biodegradable nature, better penetration they are selected and used for transdermal route. Phospholipids and surfactant mixture components helps to maintain deformability and flexibility of the vesicle. The infrastructure of transferosomes gives a promising concept to the delivery of poorly soluble drugs too. The major composition of transferosomes are edge activators and phospholipids. The preparation variables are depending upon the procedure involved for manufacturing of formulation and the preparation procedure for transferosomes. The permeablility nature of transferosome helps in the ease of transport of drugs to target site.

KEYWORDS: Transferosome, edge activator, phospholipid, deformability

I. INTRODUCTION

In current scenario, the novel drug delivery systems are achieving vital roles because of their efficiency of action. They can provide high therapeutic activity along with better patient compliance. Novel drug delivery can be considered as most suitable for developing therapeutic efficacy of pre-existing as well as new drugs.[1,2,3] Due to gastric irritations and hepatic first pass metabolism, the drug absorption is not occurring in a beneficiary manner. Those drugs which are unstable in gastric pH can also be given via vesicular transport. Due to the presence of a hostile environment in GIT where most drugs are degraded in variable pH conditions, or face solubility issues and most importantly first-pass metabolism. By encapsulating drug in vesicular systems, it leads to prolong the presence of drug in systemic circulation thus the toxicity can be reduced.[4] By the use of vesicular system, they helps to improve the bioavailability especially in the case of poorly soluble drugs. Drugs which are of bitter in taste, and pain associated due to needle in parenteral delivery make them less patient compliance.[5] Vesicular systems reduces the cost of therapy by improving the bioavailability of poorly soluble drugs. They can incorporate both hydrophilic lipophilic drugs. Among several novel drug delivery systems, a great concentration has been given on developing the transdermal drug delivery because it overcome several problems associated with oral drug delivery system and offer number of benefits. The vital role performed by vesicular system is to control the degradation of drug and its loss and sufficient availability of drug to the diseased site of action.[6]

Transfersome

Transferosomes are vesicular carrier systems and they are specially designed to have one inner aqueous compartment that is enclosed by a lipid bilayer, together with an edge activator. The active substance is enclosed with in the core or between the bilayer. The name ‘transfersome’ means “carrying body” which is derived from the Latin word 'transferre', means 'to carry across' and the Greek word 'soma', means 'a body'.

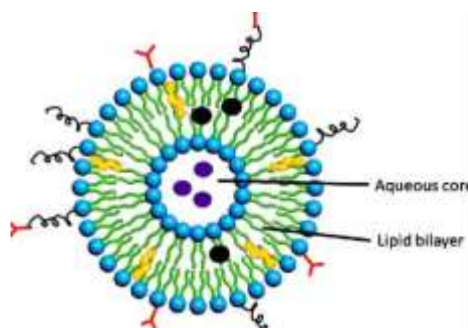


Fig. 1 Structure of Transfersome[7]

Transfersomes can be used in the form of phospholipid vesicles as transdermal drug carrier. Transferosomes is an artificial vesicle which is designed to exhibit the characteristics of cell vesicle and thus it is suitable for controlled and potentially, targeted drug delivery. They act as drug carriers to deliver entrapped drug molecule across the skin, as well as penetration enhancers because of their composition. They mainly composed of phospholipid, surfactant, and water which helps in enhanced drug delivery. It is said that, transfersome differs by its softer, more deformable and better adjustable artificial membrane they possess. The shape of bilayer

makes the vesicle both self-regulating and self-optimizing. They are first introduced in early 1990s. Transfersomes can efficiently cross the microporous barriers also. Even if the pore size is smaller than that of the vesicle size, they can reach to the target site.[8, 9] So the drug delivery using transferosomes can be considered as a convenient and safe method. The flexibility of the vesicle is controlled by the ratio of individual surfactants and total amount of surfactants. The vesicular transferosomes are more elastic than the standard liposomes thus they are well suited for the skin penetration. These vesicles can overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum which is shown in fig. 2.[10]

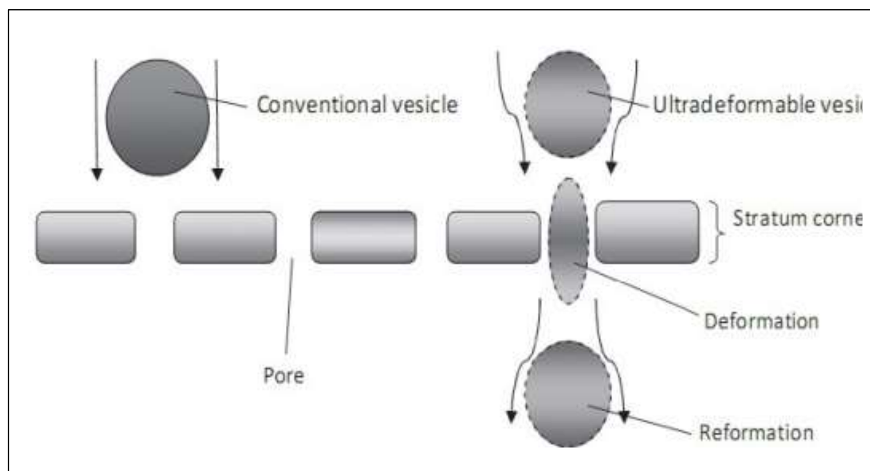


Fig 2: Schematic Diagram of micro routes of penetration by transferosome

Drugs which are suitable for transferosomes

Class	Drugs
NSAIDS	Ibuprofen, naproxen, curcumin
Antifungal:	Fluconazole, Itraconazole, Nystatin, Voriconazole
Steroids	Oestradiol, Norgestrone, Hydrocortisone
Proteins:	Human serum albumin, integral membrane proteins
Others	Interferons-α, interleukins-2, insulin

Advantages[11,12]

- Successively delivers drug either into or through the skin, with high efficiency, due to self-optimized and ultra-flexible membrane properties.
- Self-administration can be done.
- Permits the entry of drug due to the mechanical stress of surrounding, in a self-assembling manner.
- Effectively used for drugs with narrow therapeutic window.
- Can reduce dosing frequency due to longer duration of action.
- Convenient administration of drugs which would otherwise require frequent dosing and improved bioavailability.
- Helps to protect the entrapped drug from atmospheric degradation.
- Release the contents slowly and gradually, so act as depot.
- Less side effects and improved therapy because of plasma level maintenance.
- Transferosomes can be well used for topical delivery of drug.
- Scaling up is simple for transferosome due to the tiny and simple production method.

Disadvantages[13,14]

- Because of the predisposition to oxidative degradation, transferosomes are chemically unstable.
- Major drawback is high cost of the product.
- Not suitable for high drug doses.
- Drugs with hydrophilic nature permeates the skin slowly to produce therapeutic benefit.
- Skin irritation and hypersensitivity reactions may occur.
- Drug molecules which are using for transferosomal delivery must be potent in nature.
- Drugs that require high blood levels cannot be administered via transferosome.
- High susceptibility to oxidative degradation makes transferosomes unstable.

Composition of Transferosome

The major components in transferosome are:
Mainly 2 components

1. Phospholipids
2. Edge activators.

Phospholipids:

Phospholipids are the amphipathic agents which self-assemble into a lipid bilayer in aqueous environment and closes to form vesicle. They form the membrane and provide stability to vesicles.[15,16] The lipid bilayer flexibility and permeation are greatly increased, by addition of at least one bilayer softening component. The basic organization of the transferosome vesicles is broadly similar to liposomes.[17] Most commonly used phospholipids are soya phospholipids like soya phosphatidylcholine and hydrogenated soya phosphatidylcholine.

Edge activators:

The surfactant molecules are also called as "edge activators". Single chain surfactant of non-ionic nature increase its fluidity and elasticity is a major component. Tween 80, Span 85, Span 80, Sodium cholate, Sodium deoxycholate etc are used as bilayer softening agent such as surfactants. They help in giving the vesicles their characteristic flexible property by softening the lipid bilayer.[18,19] The total amount of surfactants and the proper amount of individual surfactants of phospholipids are responsible for the control of vesicles and their membrane flexibility and it leads to minimizing the risk towards vesicle ruptures in the skin.[20] The nature and ratio of different edge activators affect the physicochemical properties of vesicles.

Commonly used materials/additives for the preparation of transferosomes, shown in table 1;

INGREDIENT	EXAMPLES	FUNCTION
Alcohol	Ethanol, Methanol, Isopropyl alcohol	As a solvent
Phospholipids	Soya phosphatidyl choline, egg phosphatidyl choline, dipalmitoyl phosphatidyl choline	Vesicles forming component
Surfactants	Sodium Cholate, Sodium deoxy Cholate, Tween 80, Span 80	For Providing Flexibility
Buffering Agent	Saline phosphate buffer (PH 6.5) 7% v/v ethanol Tris buffer (PH 6.5)	As a hydrating medium
Dye	Fluorescein-DHPE, Nile red,Rhodamine-DHPE,rhodamine-123	For Confocal Scanning Laser Microscopy (CSLM) Study

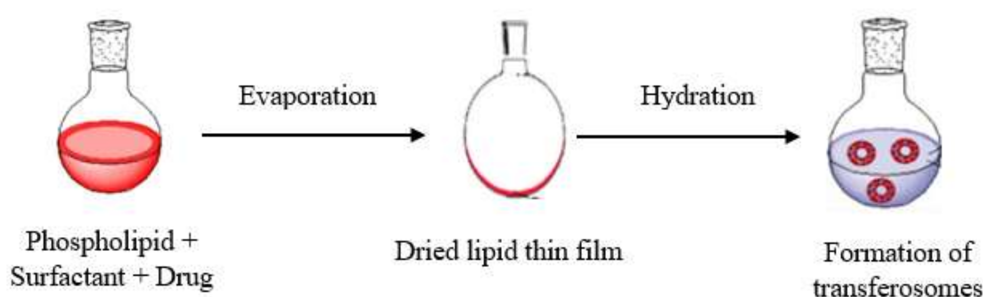
Table 1: Different additive ingredients used in the formulation of transferosomes

PREPARATION METHODS OF TRANSFERSOME

There is no general preparation formula for this process. Thin film hydration technique, also known as the rotary evaporation-sonication method, which is the conventional method of transfersome preparation. Some modified preparation methods used are vortexing-sonication, reverse-phase evaporation method, the modified handshaking process, centrifugation process, suspension homogenization, high-pressure homogenization technique and ethanol injection method.

1.ROTARY FILM EVAPORATION METHOD or THIN FILM HYDRATION TECHNIQUE

In this method, mixture of vesicle forming agents are added for the formation of a thin layer. It is done by dissolving phospholipids and surfactant (edge activator) in volatile organic solvent (chloroform, methanol). Inorder to remove the organic solvent from the mixture, a temperature above the transition temperature is applied. The mixing is done by hand shaking method. Then the thin film which is formed is hydrated with buffer by rotating at 60rpm for 1 hour. At room temperature, the leftover vesicles swell for 2 hours. By sonication of these leftover vesicles at room temperature, small vesicle can be prepared.



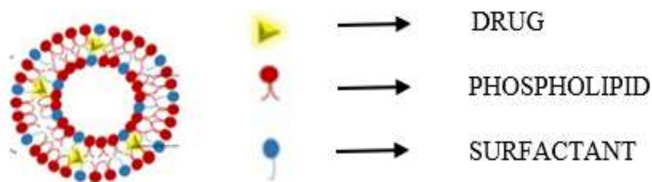


Fig 3: Rotary Film Evaporation Method

2.MODIFIED HAND SHAKING METHOD

In this method, drug, phosphatidyl choline or lecithin, edge activators were dissolved in ethanol: chloroform (1:1) mixture. While hand shaking the solution above lipid transition temperature (43°C), organic solvent was then removed followed by evaporation. After the formation of a thin film inside the flask, it is kept overnight for the complete evaporation of solvent.

The hydration of film was then done by adding phosphate buffer (pH 7.4) with gentle shaking for 15 minute at corresponding temperature. The transferosomes suspension further hydrated to 1 hr at 2-8° c.[21,22,23]

3.VORTEX OR SONICATION METHOD[24]

In this method, phospholipids and edge activators are mixed by vigorous shaking and blended in order to suspend them in phosphate buffer and made into a milky suspension. In a bath sonicator, it is then sonicated before being extruded through polycarbonate membranes.

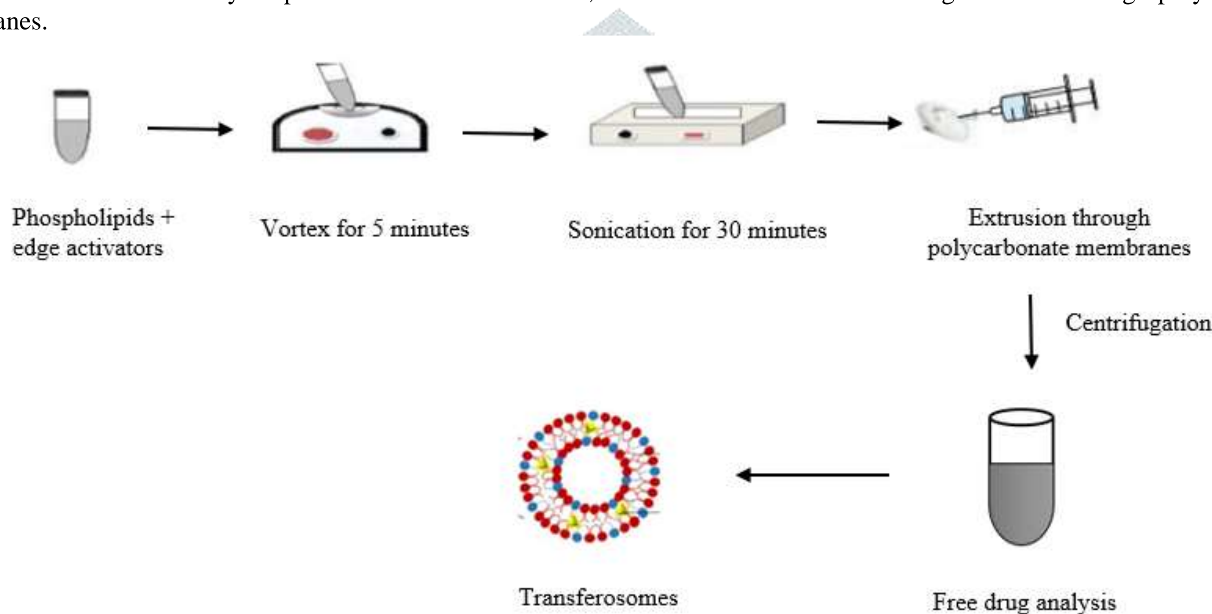


Fig 4: Sonication Method

4.ETHANOL INJECTION METHOD

In this method, phospholipids, and the lipophilic drug and edge activators are combined with an ethanolic solution in aqueous media reacted.[25, 26] Stir the contents using a magnetic stirrer for the given time, until a clear solution is formed. The aqueous phase can be produced by dissolving the water-soluble substances in the phosphate buffer.[27, 28] Heat the solutions up to 45–50ºC. Then the ethanolic phospholipid solution is injected into the aqueous solution dropwise with continuous stirring. Transfer the dispersion to a vacuum evaporator for ethanol removal and sonication is carried out for size reduction.[29,30]

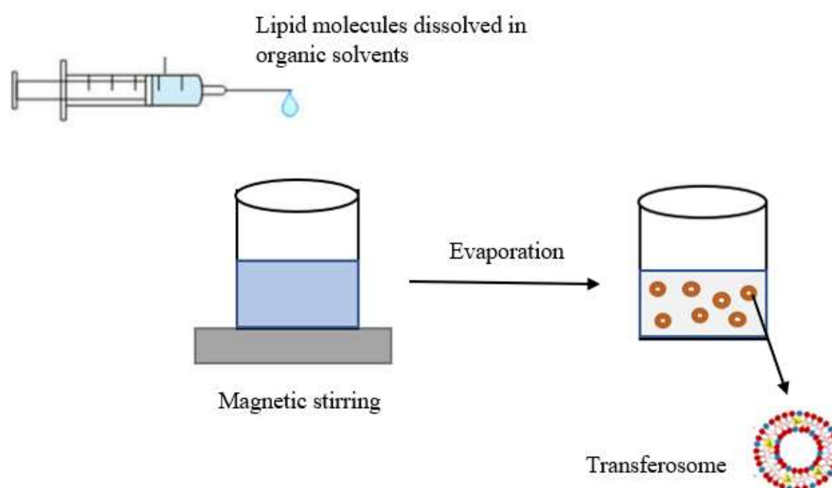


Fig 5: Ethanol Injection Method

5.FREEZE THAW METHOD[31]

In this method, the created multi lamellar vesicles suspension is freezed and then transferring it to a tube and dipping it in a nitrogen bath at -30ºC for 30 seconds. It is exposed to high temperature in a water bath after freezing. This process is repeated for 8-9 times.

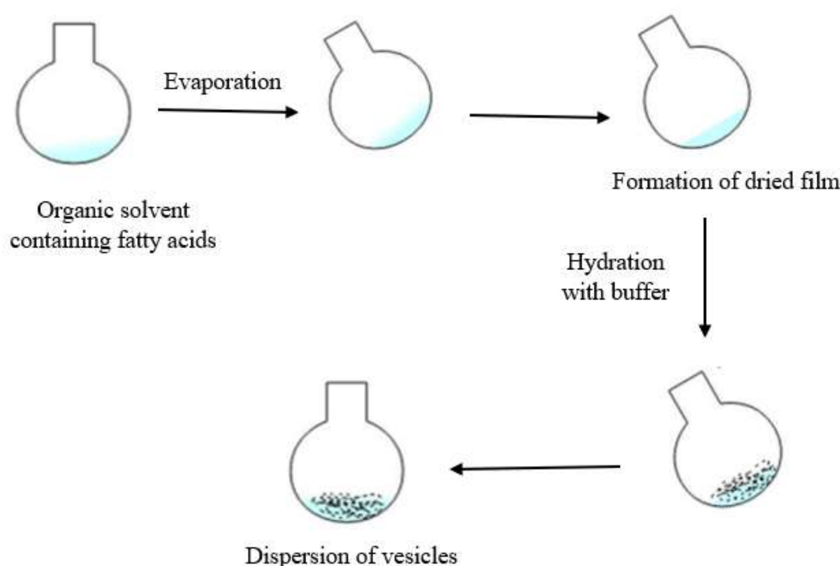


Fig 6: Freeze thaw method

6.REVERSE PHASE EVAPORATION METHOD

In this method, lipids and organic solvents were combined together in a round bottomed flask by using nitrogen purging aqueous media containing edge activators. It is then mixed with either a lipophilic or a lipophobic media depending on the drug's solubility. After that sonication is done and the prepared material is left for 30 minutes until it appears to be a homogeneous combination. When pressure is kept to a minimum, organic phase is eliminated. This leads to the formation of viscous gel that creates vesicles.

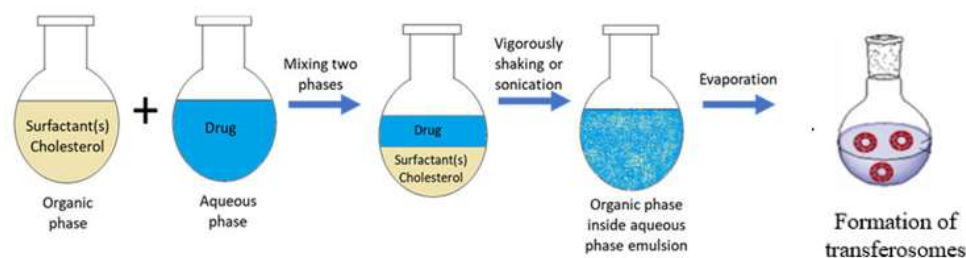


Fig 7: Reverse Phase Evaporation Method

CHARACTERIZATION OF TRANSFEROSOMES

Vesicle Size, Size Distribution and Vesicle Diameter[32]

Vesicle size of transferosomes before sonication determined by using a micrometer scale. And the poly dispersibility index measurement was carried out by dynamic light scattering with zeta sizer HAS 3000. Vesicle size, size distribution and zeta potential were determined by Dynamic Light Scattering system by Malvern Zeta sizer.

Vesicle morphology[33]

Photon correlation spectroscopy or dynamic light scattering (DLS) method are used to determine the diameter of vesicle. Samples are prepared and filtered through a membrane filter with a diameter of 0.2 mm and diluted with filtered saline. Photon correlation spectroscopy or dynamic light scattering measurements are used for size measurements. Transfersomes vesicles can be observe through Transmission electron microscope (TEM), phase contrast microscopy, etc. The size and structure of vesicles indicate the stability of vesicle.

No. of vesicles per cubic mm

This is an important parameter which used for optimizing the composition and other process variables. Sodium chloride solution (0.9%) is used to dilute non-sonicated transfersome formulations. A haemocytometer and optical microscope can then be used for further study of the vesicle.

Entrapment Efficiency[34]

It is expressed as the amount of the drug entrapped in percent of drug added. This can be determined by first separating the unentrapped drug using mini-column centrifugation method. After centrifugation process, the vesicles are disrupted using 0.1% Triton X-100 or 50% n-propanol.

The entrapment efficiency is expressed as:

Entrapment Efficiency = (Amount of drug entrapped/ Total amount of drug added) × 100

Drug content

The drug content can be determined by one of the instrumental analytical methods like modified high performance liquid chromatography method (HPLC) method using a UV detector, auto sample, pump, column oven and computerized analysis program depending upon the analytical method of the pharmacopoeial drug.

Turbidity measurement

Turbidity of drug can be measured using nephelometer.

Penetration ability[35]

Transferosomes have a better penetration capability. And it can be assessed and performed by using Fluorescence microscopy.

Occlusion effect

Occlusion of skin is helpful for the permeation of drug in case of traditional topical preparations. Hydrotaxis of water is the major driving force for permeation of vesicles through the skin. Occlusion affects hydration and it prevents evaporation of water from skin.

In-vitro drug release

In vitro drug release study is performed for determining the permeation rate of the vesicle. to optimize the formulation the information from in vitro studies are used before more expensive in vivo studies are performed. For determining drug release, transferosomes suspension is incubated at 32ºC and samples are taken at different times and the free drug is separated by mini column centrifugation.

In-vitro Skin permeation Studies[36]

For this study,. Fresh abdominal skin of goat were collected and used with phosphate buffer with a pH of 7.4. Using a cotton swab, the adipose tissue layer of the skin was removed by rubbing after the removal of hair. A modified franz diffusion cell was used with a 50 ml column and a receiver compartment with effective area of 2.5 cm^2. Skin can be kept at a low temperature with a 100rpm stirring speed and the stratum corneum towards the donor compartment of the diffusion cell. 1ml aliquot is withdrawn and replenished with fresh phosphate buffer on a regular basis.

Stability studies[37-39]

Vesicles which are prepared should be measured for vesicle magnitude and submitted to accelerated stability tests under accelerated storage conditions. The parameters evaluated are diffusion behaviours at predetermined time points, zeta potential.

APPLICATION OF TRANSFERSOMES

Delivery of Proteins

Usually the transport of big and large biogenic molecules such as body proteins and peptides into body are very difficult. And those drugs are unstable and become degrade when they administered via oral route. Such drugs can be effectively use with the vesicle.[40] Transfersomes are the best suitable approach for the delivery of all kinds of proteins into body. It is observed that bioavailability of the molecules delivered by transferosomes are similar to the drug administered by subcutaneous injections.

Delivery of Insulin

Transfersomes deliver insulin to the systemic circulation equivalent to subcutaneous injection. Transfersomes can transport their associated drugs, including the percutaneously applied insulin, into the body spontaneously.

Delivery of Anti-cancer drugs

Transfersomes are used as carrier for the delivery of anticancer drugs; they are suitable specially for treating skin cancers.[41]
Eg: Transfersomes loaded with Methotrexate was tried for treatment of skin cancer. Tamoxifen (TAM) an anti-breast cancer agent.

FUTURE PERSPECTIVES

The nanocarriers offer advanced local and systemic new therapies with agents that are unable to efficiently penetrate the stratum corneum via passive diffusion. And the high tolerability and efficiency of these vesicular systems open vast potential therapeutic uses. Transferosomes can also positioned nearly exclusively and essentially quantitatively into the viable skin region, when it is used under different application conditions.

CONCLUSION

Transferosomes are specially designed vesicles and they are capable of squeezing themselves through skin pores that are many times narrower than them. Transferosomes have several advantages over other vesicular systems, it including greater penetration power across skin, greater deformability, the ability to deliver systemic drugs, and higher stability. Due to its several advantages over other routes drug delivery transdermal drug delivery system is frequently used. The penetration of drug via the stratum corneum is a rate limiting step, its major limitations is, it cannot be able to transport the larger size molecule. So for the ease of drug delivery the transferosome vesicular system can be effectively used. Drug release can also be controlled according to the requirement. Thus, this approach can overcome the problems which occur in conventional techniques.

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