

Ultra Deformable Nanotransethosomes: A Novel Tool To Intensify Transdermal Drug Delivery A Review

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Abstract

Transdermal route has become a most favorable routes for the delivery of drugs from last few years. It conquered many disadvantages occurred with the oral route of drug delivery system such as major drawbacks is first pass metabolism. To overcome this limitation transdermic delivery system has been developed but the drug which can be delivered through transdermal route are facing barriers because few drugs' particles are unable to penetrate through stratum corneum efficiently. To overcome this challenge our scientist and researchers have developed a new system known as ultra deformable vesicle system (UDV). In this system the drug molecule either synthetic or herbal is incorporated into vesicles which can easily penetrate deeper into skin for targeted drug delivery. Among Transfersomes and Ethosomes Transethosomes is a novel prospect for enhanced transdermal drug delivery through skin. The effective penetrability of nanotransethosomes is due to ethanol, edge activator and phospholipids. There are different methods are there for the preparation of nanotransethosomes like hot method, cold method, transmembrane pH gradient method, ethanol injection method and thin film hydration method. The UDV can be utilized for the delivery of numerous classes of drugs such as anti-arthritic, antibiotic, anticancer, antiviral and analgesic through transdermal route.

Keywords: Nanotransethosomes, Transethosomes, Vesicular system, ultra deformable vesicle, Edge activator, Transdermal delivery.

INTRODUCTION:

The oral route of drug delivery is one of the most common routes of delivery of drugs. But the oral route has many disadvantages like first pass metabolism. To overcome this problem the topical drug delivery has been developed by the scientist and the researchers to avoid first pass metabolism effect, among this it can also improve the patient compliance and the localized effect. This topical route has increased the therapeutic effectiveness of the drug by delivering it through the central percutaneous layer of the skin.¹

The drugs which both have high and low partition coefficient find it difficult to get into systemic circulation. To overthrow this drawbacks ultradeformable vesicles (UDV) have been developed which include transfersomes, ethosome and transethosomes. Currently the vesicular system has recently been developed for the targeted drug delivery through skin. Ultradeformable vesicular structure has the ability to entrapped hydrophilic, hydrophobic and amphiphilic drugs. Other than synthetic drugs herbal drugs, proteins and peptides also has been incorporated in the vesicular form and can easily delivered transdermally.

The nano transethosomal system boost the chemical and physical standard of therapeutic drug that is incorporated in dermal and also in transdermal delivery. The ethanol which is used for the preparation of nanotransethosomes plays a very vital role by releasing the drug particles to targeted area with the help of inducing hydration mechanism, the pores of the outer layer get easily widened.²

The major Disadvantages of transfersomes is that in this it is difficult to load hydrophobic drugs. Due to this the ethosomal drug delivery system has been prepared which abolish the disadvantages of transfersomes. The major drawback of ethosomal drug delivery system is that it causes drying out of skin whenever it is applied on the skin. The ethanol which is present in the formulation causes complete dehydration. Therefore, to overcome these drawbacks nanotransethosomal drug delivery system has been developed which is a mixture of transfersomes and ethosomes. It effortlessly incorporates the drugs which have both high and low molecular weight.³

Comparison study Between Transferosomes, Liposomes, Ethosomes and Transethosomes:

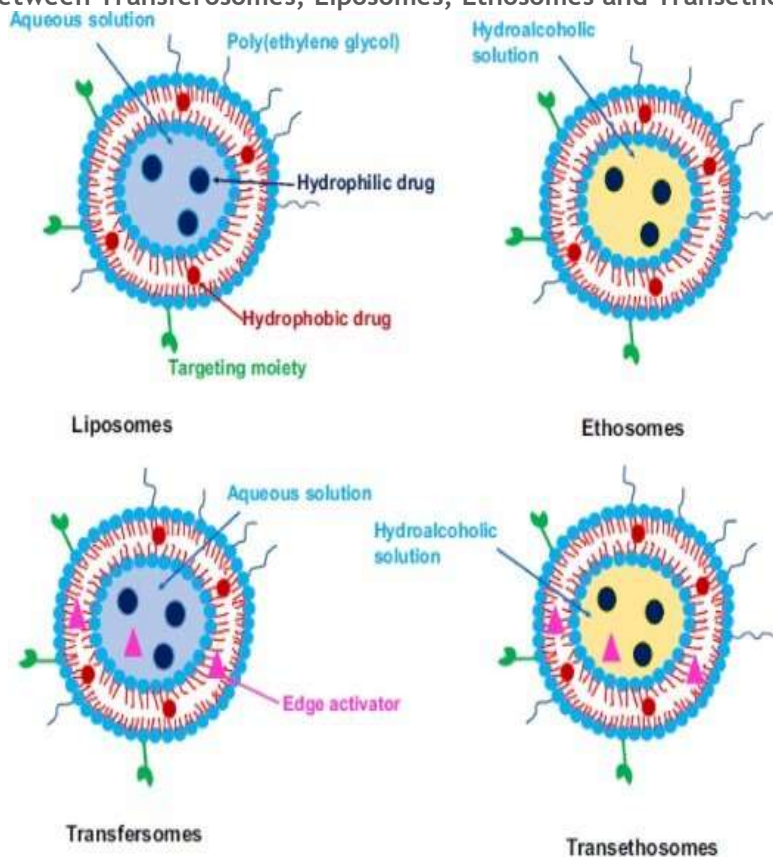


Figure 1- Comparison between Transferosomes, Ethosomes and Transethosomes

Table 1- Comparison between Transferosomes, Ethosomes and Transethosomes

Parameters						
Sr.no	UDV system	Composition	Entrapment efficiency	Flux Rate	Skin Permeation	Reference
1	Transferosomes	Water, phospholipid, edge activator	Higher than ethosomes	More or equal to ethosomes	Deformation of vesicles	3, 7, 12
2	Ethosomes	Water, phospholipid, ethanol	Higher than liposomes	More than liposomes	Lipid perturbation	14,15,4
3	Transethosomes	Water, phospholipid, ethanol, edge activator	Higher than ethosomes and transferosomes	Higher flux rate	Ultra deformation of vesicles	1,5,6,8

Transethosomes: 9,10,11,13

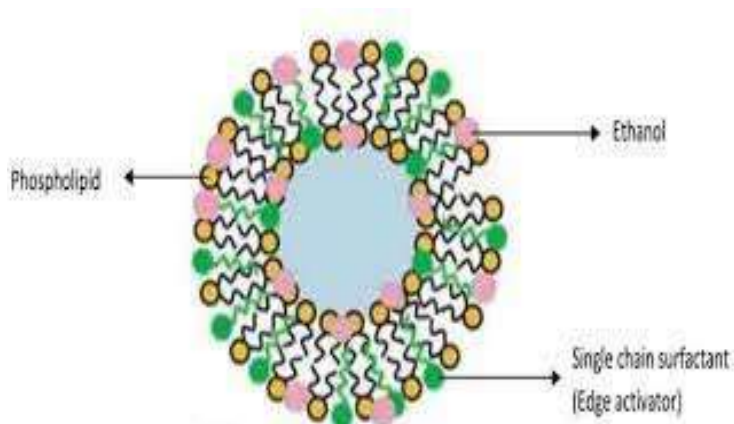


Figure-2 Transethosomes¹³

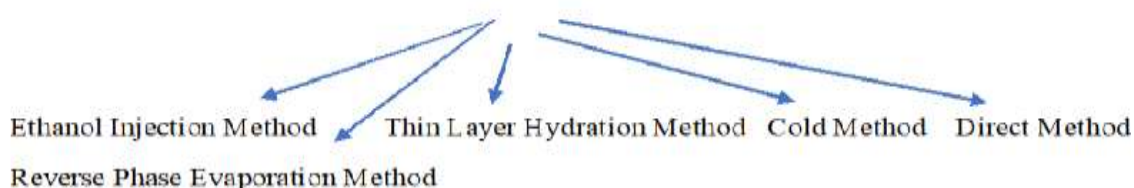
Transethosomes is a lipid based Vesicular drug carrier which containing phospholipid + Ethanol + Edge activator + water as observed in figure 2. The main objective of phospholipids contributes as a carrier to provide drug particles directly into the skin.¹⁴ when the drug particles enter into the stratum corneum which leads to improve in tissue hydration. The lipid

vesicular system contains both hydrophobic tail and hydrophilic head.⁴ Edge activator used in the preparation of transethosomes act as a bilayer softening agent. It can also be used to improve the permeation characteristics of vesicles¹⁶ Adaptability and flexibility are the most important propertie of ethanol for the formulation of nano-vesicular systems, which can easily permit them to perforate inside the stratum corneum through very small openings due to the process of fluidization. When edge activator and ethanol combined with each other then it cause the transposition of lipid bilayer which can also cause more deformation structure, which can easily penetrate into the deeper skin layer.

Methods of Preparation of Transethosomes:

The vesicular nano-transethosomal systems can be easily prepared and also it is very easy to formulate without any involvement of any high-tech machines. There are different methods are there by which we can easily prepare our nanotransethosomal vesicular system which can easily incorporate into gel form, creams or in patch form to increase penetrability into the skin. The following are commonly used methods for the preparation of vesicular system.³

Methods of Preparation of Transethosomes



1. Ethanol Injection Method

Figure-3 Methods of Preparation of Transethosomes

1. Ethanol Injection Method

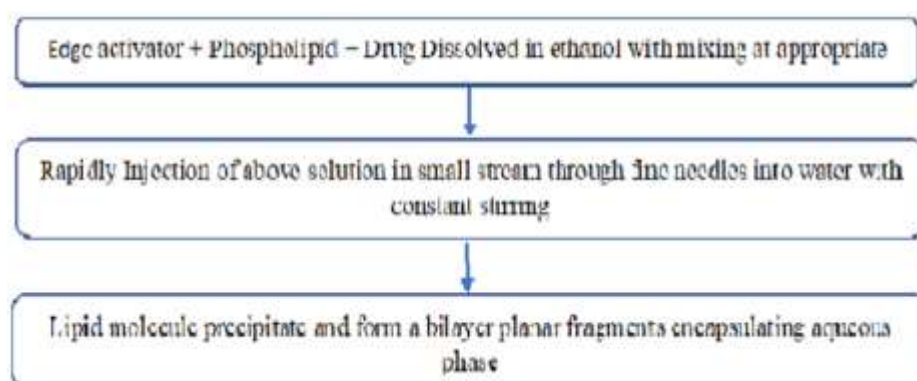


Figure- 4 Ethanol Injection System

2 Thin Layer Hydration Method:

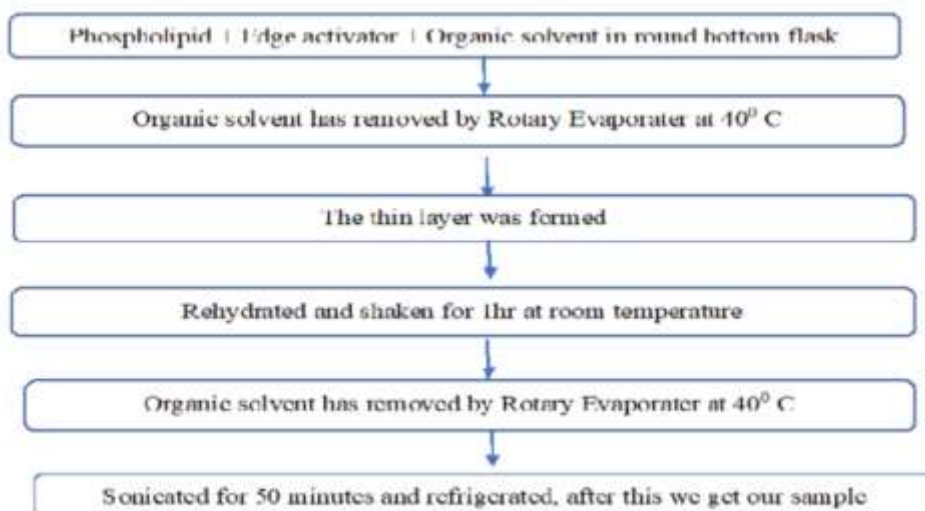


Figure-5 Thin layer hydration system

3. Cold Method:

In this method of preparation of transethosomes phospholipids added in ethanol and properly mixed with each other and heated to 30°C (Organic Phase). In a second step in a separate container the edge activator, drug and water all combined together and heated up to 30°C (Aqueous phase). Then an aqueous phase is added to alcoholic phase with constant stirring for 5 to 10 mins and temperature is maintained to 30°C throughout the procedure. Now the above mixture is sonicated in a sonicator.¹⁷

4. Direct method:

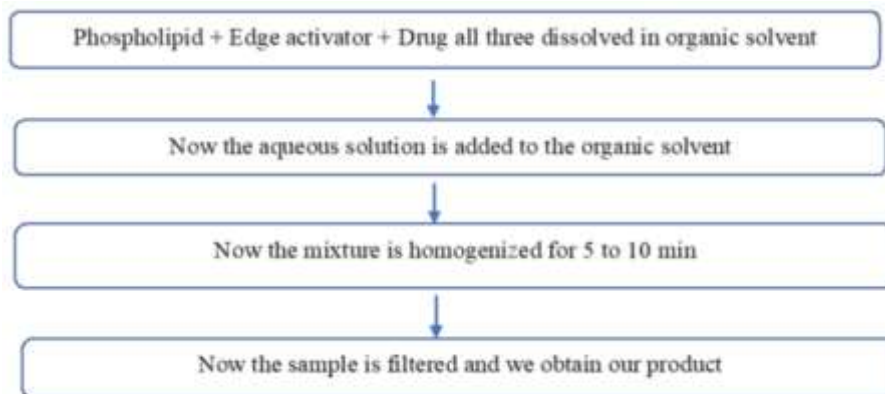


Figure-6 Direct method of formulation of Transethosomes

5. Reverse phase evaporation method:¹⁸

For the preparation of nanotransethosomes this method can also be preferred. In this particular method firstly the phospholipids can be dissolved in the organic solvent and drug and edge activator dissolved in aqueous solvent. Now aqueous phase is added into organic phase now the mixture is placed in ultrasonic bath at 0°C till the two-phase separates. Now the organic phase is removed, under low pressure gel formation occurs. After continuous agitation the lipid layer incorporated in aqueous layer now the sample is filtered.

Table-3 Excipients and Methods used in formulation of Nanotransethosomes

Sr.no	List of Phospholipid	List of Edge activator	Methods used	Author	Reference
1	Lipoid S100	Sodium cholate	Box Behnken	Thasleem Moolakhadath	9
2	PL90G	Cholestrol	Edge activators with different HLB values and SDC were employed to prepare vesicles using thin film hydration technique	Sajeev Kumar	11
3	Soy Lecithin S100	Sodium deoxycholate, tween 80	In this the Transethosomes were prepared by ultrasound guided injection method	Hui Song	13
4	Lipoid S 100	Tween 80	Transethosomes are prepared by the mechanical dispersion technique and the hot and cold method	Mudassir Farooq	20
5	L-αphosphatidylcholine from egg yolk	Span 20, Span 60, Sodium deoxycholate	Vesicles were prepared by adopting thin-film hydration method	Rofida Albash	21
6	Lipoid S100	Oleic acid	Transethosomes vesicles were prepared by Homogenization method	Lalit Kumar	22
7	Phospholipon 90 G	Sodium cholate	Transethosomes vesicles were prepared by cold method. This method is easy to scale up and can be used for both thermolabile and thermostable drugs.	Jessy Shaji	23
8	Soya Lecithin	Cholesterol, Tween 80	For the preparation of Transethosomes cold method were used.	Akshaykumar Verma	24
9	Soya phosphatidylcholine 70	Span 80	In this the thin film hydration method is used for the preparation of transethosomal vesicles.	Varun Garg	18
10	Soyaphosphatidyl choline	Tween 80	The thin film hydration method was used for the preparation of the vesicles.	Gadad AP	25

ADVANTAGES OF NANOTRANSETHOSOMES:^{3,4,5,21,22}

- 1) The flexibility of nanotransethosomes is very high and it also has very high skin permeation rate and high flux rate as compared to other vesicular systems.³
- 2) The main advantage of nanotransethosoms is that it can easily deform and easily move through the narrow obstructions.²¹
- 3) Biocompatible and biodegradable nanotransethosomes can be easily formulate with the help of natural phospholipids.
- 4) It is much more stable than other vesicular system.

- 5) It has very high entrapment efficiency, the drug can be easily incorporated and also protected from metabolic degradation.
- 6) The preparation method of nanotransethosomes is easy and it has high penetration power.
- 7) After preparing nanotransethosomes it can be easily administered into transdermal dosage form such as cream, gel and in patch.
- 8) Transethosomes prepared with nanosize known as nanotransethosomes can easily hit the target site.

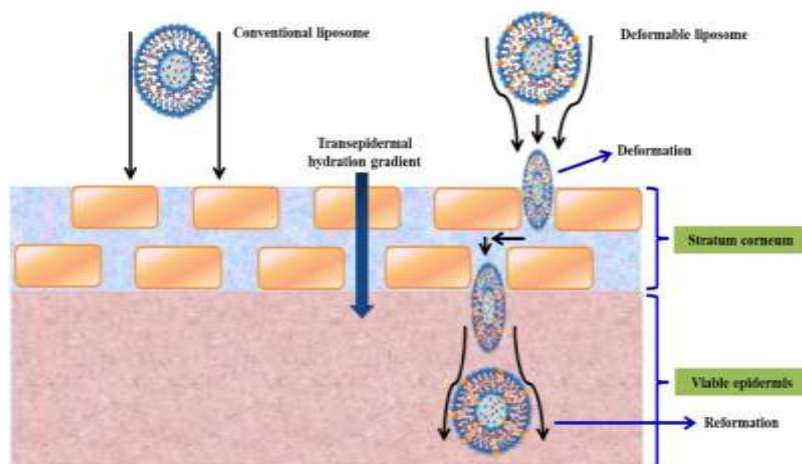


Figure-7 Mechanism of Ultra Deformable characteristics of Transethosomes

DISADVANTAGES OF NANOTRANSETHOSOMES^{22,23}:

- 1) In the preparation of nanotransethosomes ethanol is used which can cause irritation to skin. So, to overcome this problem nanotransethosomal patch can be prepared.
- 2) Agglomeration of nanotransethosomes takes place if it is not prepared in proper method.

CHARACTERIZATION OF NANOTRANSETHOSOMES:

- Morphological characteristics of nanotransethosomes
- Zeta potential of nanotransethosomes and its particle size
- Loading capacity and entrapment efficiency of nanotransethosomes
- Phase transition temperature
- In vitro drug release study
- Vesicular stability study
- In vitro skin permeation
- Ex vivo skin permeation
- Determination of pH

1) Morphology of Nanotransethosomes:

TEM and SEM study can be easily used to determine the morphological characteristics of nanotransethosomes.

2) Particle Size:

To determine the exact particle size of nanotransethosomes two methods are used

- I. Dynamic light scattering (DLS)
- II. Photon correlation spectroscopy (PCS).

3) Entrapment Efficiency:

By doing entrapment efficiency we can easily determine the actual amount of drug entrapped in the nanotransethosomes. It can be done by ultracentrifugation technique also known as column centrifugation technique. In this analysis the drug is first loaded in nanotransethosomes and then placed into a column and then the column is centrifuged. Speed and temperature can be easily controlled in ultracentrifugation method. After the completion of centrifugation process the upper layer is developed and is separated from the vesicles. Then these vesicles are treated with solvents like triton-X-2 propanol, methanol in order to set lysed. Then the drug content can be analyzed by UV visible spectrophotometry. The amount of drug entrapped in the vesicular system can be calculated by using formula- % Drug Entrapment = Amount of entrapped drug/Total amount of drug*100

$$EE\% = \frac{A_0 - A_U}{A_0} \times 100$$

$$LC\% = \frac{A_0 - A_U}{W} \times 100$$

$$Yield\% = \frac{A_V}{A_0 + W} \times 100$$

A_0 = Initial quantity of drug used

A_U = Non encapsulated drug

A_V = Amount of vesicular carrier product

Figure-7 Formula for Entrapment Efficiency

4) Phase Transition Temperature:

The phase transition temperature of Transethosomes can be easily determined by DSC. In DSC the sample can be easily analyzed at a range of temperature under a constant nitrogen stream.

5) In-vitro drug release study:

The quantity of drug release from the nanotransethosomes can be easily determined by in-vitro study by using Dialysis bag method.

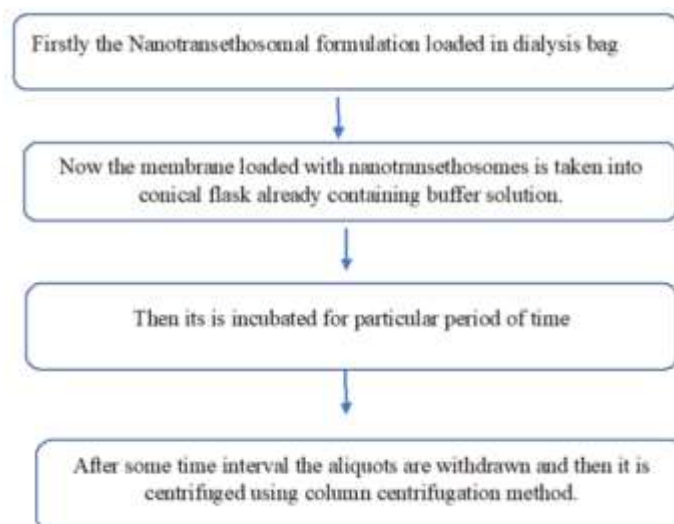


Figure-8 In-vitro drug release study

6) Vesicular stability study:

The vesicular stability study of nanotransethosomal vesicles can be done by deposit them at different temperature $25 \pm 2^\circ\text{C}$, $37 \pm 2^\circ\text{C}$, $45 \pm 2^\circ\text{C}$. DLS and TEM can be used to determine the size and morphology of nanotransethosomes.

7) In vitro skin permeation study:

Franz diffusion cell can be used to determine the in-vitro skin permeability study of nanotransethosomes. In this method the capability of nanotransethosomes to penetrate deeper into the skin for targeted drug delivery can be done by using CLSM. The instrument temperature should be maintained at $32^\circ\text{C} \pm 1^\circ\text{C}$. There is a receptor compartment cell which contain 10 ml of PBS. The skin on which the permeation study can be determined is placed in between the donor compartment and receptor compartment. Now the nanotransethosomal vesicles is applied to the outermost surface of the skin. After a particular time, interval, the samples can be withdrawn such as 1,2,3,4,8,12,16,20,24 hours. The samples which are withdrawn at a particular time interval can be analyzed by using HPLC.

8) Determination of Ph:

The Ph of Nanotransethosomal formulation can be determined by using digital ph meter.

APPLICATIONS OF NANOTRANSETHOSOMAL VESICULAR SYSTEM:

1 Delivery of Anticancer Drugs:⁹

thasleem et al conducted an experiment in which fiestin loaded nanotransethosomes vesicles were optimized by using a software known as Box Behnken design. Fiestin which is a natural flavonoid mostly found in ample amount in various fruits and vegetables. In this experiment the nanotransethosomal vesicles shows good EE with reasonable flux has been observed.

2 Delivery of Antiarthritic Drug:^{11,13,18,25}

Sajeev et al performed an experiment in which Naproxen-Sulphapyridine transethosomal vesicle was developed and evaluated for transdermal delivery of drugs in the management of Rheumatoid Arthritis. In this the ethosomal hydrogel has been combined and loaded with NAP-SULF (NSAID, DMARD) which could reduce the pain and inflammation. In the present study NAP-SULF EH was developed by modifying thin film hydration technique.

Song et al conducted research on Rheumatoid Arthritis. In which Sinomenine hydrochloride loaded ascorbic acid (Antioxidant) transthesosomes was decorated using ascorbyl palmitate as an antioxidant and transthesosomes as a basic transdermal carrier. AS-TE can be trans dermally delivered to inflamed joints of CFA rats with similar therapeutic efficacy to that of gastric administration of Sinomenine hydrochloride.

Garg et al conducted an experiment of piroxicam loaded transthesosomal hydrogel for the treatment of Rheumatoid Arthritis. In the present study the nanotransthesosomal hydrogel has been prepared by using lipid, ethanol and edge activator and their characterization also has been done. It can be easily concluded that the formulated piroxicam nanotransthesosomal hydrogel has an ability to penetrate deeper into the skin with targeted drug delivery.

Gadad et al demonstrated a research work in which flurbiprofen loaded transthesosomes has been formulated for the treatment of arthritis

In the present research it was demonstrated that TE containing of the highest percentage of ethanol. Thus, from the result it can be concluded that FLU-TELS gel could be a potential carrier for the dermal delivery of the hydrophobic drug Flurbiprofen.

3 Delivery of Antihypertensive drugs:^{21,22,24}

Albash et al performed an experiment in which transthesosomes were formulated as transdermal delivery system for Olmesartan medoxomil. The result has been concluded that transthesosomes could be considered as promising transdermal delivery system for OLM as they can avoid extensive first pass metabolism of OLM.

Lalit et al conducted an experiment in which nanotransthesosomes loaded with propranolol hydrochloride showed better skin in-vitro permeation with high controlled release of the drugs. Based on the recent research work it can be concluded that the nanotransthesosomal vesicles can be easily prepared for antihypertensive drugs.

Verma et al performed an experiment in which Irbesartan loaded with transthesosomes has been formulated. Irbesartan loaded with transthesosome formulations were successively prepared using cold method. Characterization of transthesosome as vesicle shape, vesicle size, PDI, zeta potential, entrapment efficiency, calibration curve of UV, % drug release, FTIR, SEM as responses.

4 Delivery of Antifungal Drug:²⁰

Farooq et al demonstrated an experiment in which formulation of Voriconazole loaded transthesosomes and incorporation into a hydrogel for antifungal and antileishmanial application has been observed. The result demonstrated that the developed Voriconazole transthesosomal hydrogel can be highly beneficial in treating topical fungal infections.

FUTURE PROSPECTS:

In the current scenario the nanotransthesosomal vesicular system have attracted attention of scientists and researchers. Due to its ultra deformable characteristics, it is on high demand for deeper skin penetration and for the targeted drug delivery through the transdermal route due to its nano size particles and deformable system. Edge activator has been shown better permeation and penetration property than Ethosomes and Transfersomes, Liposomes and Phytosomes. It is also suitable for both hydrophilic and hydrophobic drug and high and low molecular weight drugs. It is a recent vesicular system which is on high demand on present and on future. Scientist and Researchers are doing research on Nanoparticles (Nanotransthesosomes) so currently there is no marketed formulation is available. Nanotransthesosomes can also be loaded into novel drug delivery system such as cream, gel, emulgel and in patch form. Thus, the Nanotransthesosomal vesicular system has lot of potential to use as the carrier for transdermal drug delivery.

CONCLUSION:

Transdermal route has become a most favorable routes for the delivery of drugs from last few years. It conquered many disadvantages occurred with the oral route of drug delivery system such as major drawbacks is first pass metabolism. To overcome this limitation transdermic delivery system has been developed but the drug which is delivered through transdermal route is still a challenge as few drug molecules does not easily pass through the stratum corneum and enable to penetrate efficiently. To overcome this challenge our scientist and researchers have developed a new system known as ultra deformable vesicle system (UDV). In this system the drug molecule either synthetic or herbal is incorporated into vesicles which can easily penetrate deeper into skin for targeted drug delivery. Among Transfersomes and Ethosomes Transthesosomes is a novel prospect for enhanced transdermal drug delivery through skin. The effective penetrability of Nanotransthesosomes is due to ethanol, edge activator and phospholipids. There are different methods are there for the development of nanotransthesosomes such as by hot method, cold method, transmembrane pH gradient method, ethanol injection method and thin film hydration method. The UDV systems can be used for the transdermic delivery of various class of drugs like anti-arthritis, analgesic, anticancer, antibiotic and antiviral. The drugs which have both high and low partition coefficient has difficulty in get to the systemic circulation. To over through this drawback ultra deformable vesicles (UDV) have been developed which include Transfersomes, Ethosome and Transthesosomes. Currently the vesicular system has recently been developed for the targeted drug delivery through skin. Ultra deformable vesicular

structure has the ability to entrapped hydrophilic, hydrophobic and amphiphilic drugs. Other than synthetic drugs herbal drugs, proteins and peptides also has been incorporated in the vesicular form and can easily delivered transdermally. Nanotransethosomes can also be loaded into novel drug delivery system such as cream, gel, emulgel and in patch form. Thus, the Nanotransethosomal vesicular system has lot of potential to use as the carrier for transdermal drug delivery.

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