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TRANSETHOSOMES: A NOVEL CARRIER FOR TRANSCUTANEOUS DRUG DELIVERY AN OVERVIEW

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ABSTRACT: In recent years, the transdermal route has emerged as the most advantageous method for medication administration. It overcame several problems associated with the oral mode of drug administration, including significant issues with previous metabolism. To get around this restriction, transdermic administration systems have been created; however, the medications that can be administered via this route still encounter challenges since some of the drugs' particles are ineffective at efficiently penetrating the stratum corneum. Our scientists and researchers have created a novel technology called as the extremely deformable vesicle system to meet this difficulty. The medicinal molecule, whether synthetic or natural, is combined with vesicles in this method so that it may be delivered to specific areas of the skin. Transethosomes are a unique promise for improved transdermal medication administration via the skin among transferosomes and ethosomes. Nanotransethosomes' efficient penetration is facilitated by ethanol, edge activator, and phospholipids. The UDV can be used to administer a variety of medication classes via the transdermal route, including anti-arthritic, antibacterial, anticancer, antiviral and analgesic.

INTRODUCTION: One of the most popular methods of medication administration is through the oral route. However, the oral route has a number of drawbacks, including first-pass metabolism. To solve this issue, scientists and researchers created topical medication administration, which can enhance patient compliance and localized effects while avoiding the effects of first-pass metabolism. By delivering the medication through the central percutaneous layer of the skin, this topical method has improved the therapeutic efficiency of the medicine [1].

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It is challenging for medications with both high and low partition coefficients to enter the systemic circulation. Ultra-deformable vesicles (UDV), which include transferosomes, ethosomes, and transethosomes, have been designed to address these disadvantages. The development of the vesicular system recently made it possible to administer targeted medications *via* the skin. Hydrophilic, hydrophobic, or amphiphilic drugs can all be trapped inside an ultra-deformable vesicular structure.

Herbal medicines, proteins, and peptides have also been combined into vesicular form and are easily given transdermally in addition to synthetic pharmaceuticals. A therapeutic medication integrated into dermal and transdermal administration is improved chemically and physically by the nano transethosomal system. With the aid of the induced hydration process, the

ethanol utilized to make nanotransethosomes plays a very important function in releasing the drug particles to the targeted location, allowing the pores of the outer layer to readily enlarge [2]. The main drawback of transferosomes is that hydrophobic medicines are challenging to load. As a result, the ethosomal drug delivery method was developed, eliminating the drawbacks of transferosomes. The primary disadvantage of the ethosomal drug delivery method is that every time it is applied to the skin, it causes it to dry out. The formulation's ethanol ingredient promotes total dehydration. Therefore, a nanotransethosomal drug delivery method that combines ethosomes and transferosomes has been designed to address these disadvantages. It seamlessly combines medications with both high and low molecular weights [3].

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]: As shown in **Fig. 1**, Transethosomes are lipid-based vesicular drug carriers that include phospholipid, ethanol, edge activator, and water. Phospholipids' principal function is to act as a carrier to deliver medication particles straight into the skin. A hydrophilic head and a hydrophobic tail are present in the lipid vesicular system [4]. An edge activator that is used to make transethosomes softens the bilayer. Additionally, it can be used to enhance the vesicle's permeability properties. Adaptability and flexibility are the most important properties 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 the edge activator and ethanol are combined, it causes the transposition of the lipid bilayer, which can also cause a more deformation structure, which can easily penetrate into the deeper skin layer.

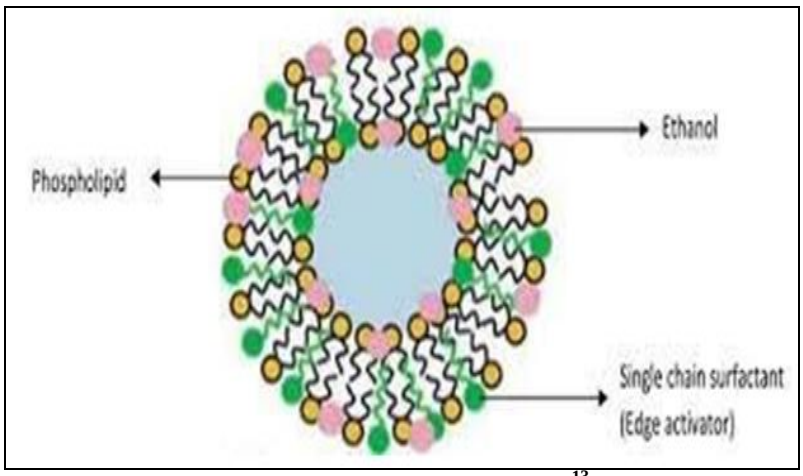

FIG. 1: TRANSETHOSOMES [13]

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 by which we can easily prepare our nano-transethosomal vesicular system which can easily incorporate into a gel form, creams, or patch form to increase penetrability into the skin. The following are commonly used methods for preparing the vesicular system [3].

Methods of Preparation of Transethosomes:

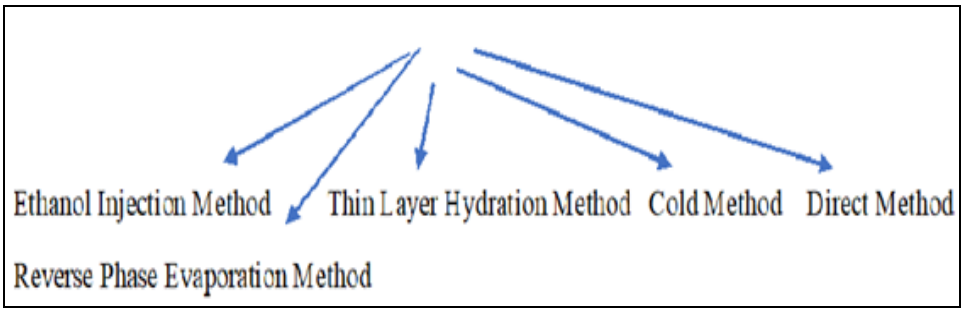

FIG. 2: METHODS OF PREPARATION OF TRANSETHOSOMES

Ethanol Injection Method:

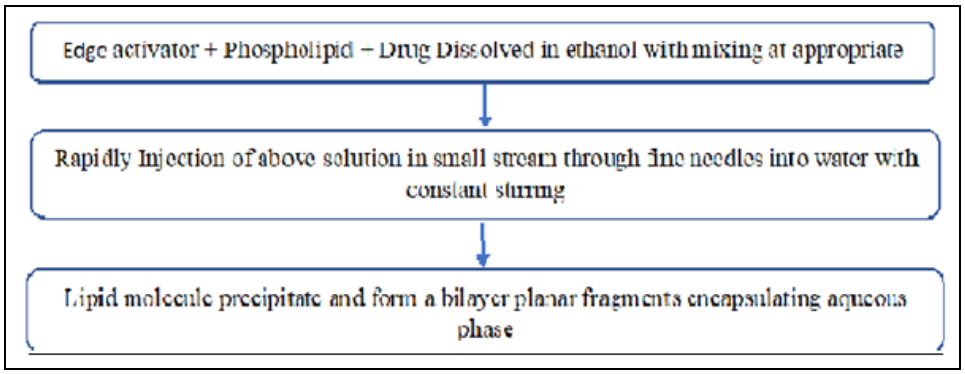

FIG. 3: ETHANOL INJECTION SYSTEM

Thin Layer Hydration Method:

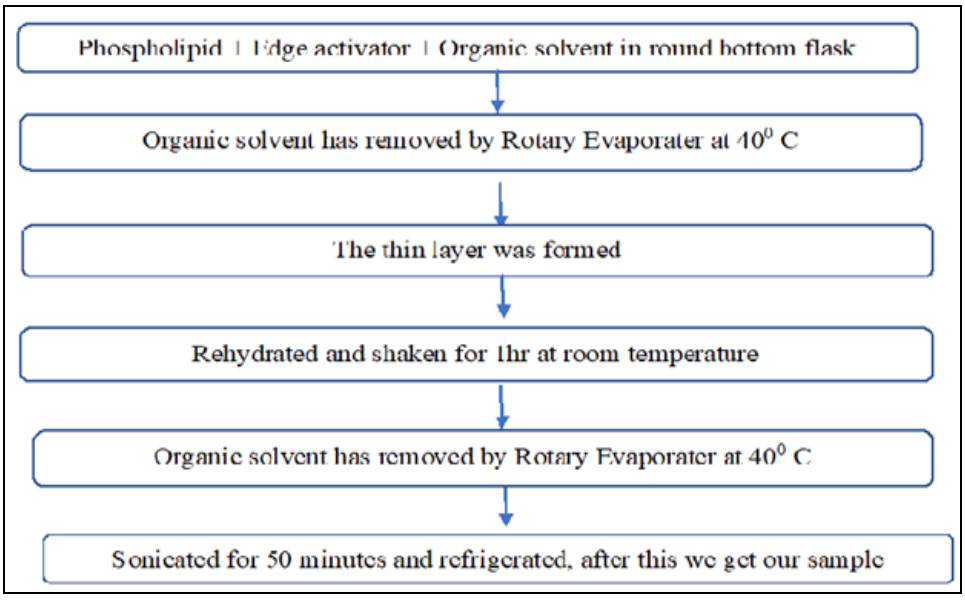

FIG. 4: THIN LAYER HYDRATION SYSTEM

Cold Method: This method of preparation of transethosomes phospholipids was added in ethanol, 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 the alcoholic phase with constant stirring for 5 to 10 mins and the temperature is maintained to 30°C throughout the procedure. Now the above mixture is sonicated in a sonicator [17].

Direct Method:

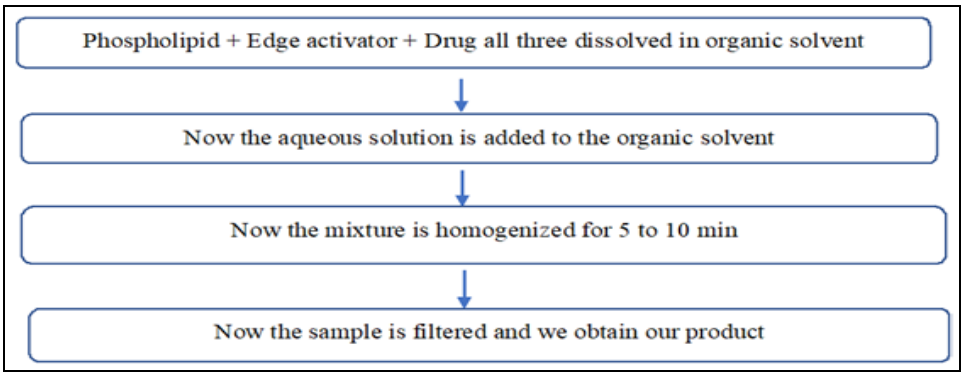

FIG. 5: DIRECT METHOD OF FORMULATION OF TRANSETHOSOMES

Reverse Phase Evaporation Method [18]: For the preparation of nanotransethosomes, this method can also be preferred. In this particular method, the phospholipids can be dissolved in the organic solvent and the drug and edge activator dissolved in an aqueous solvent. Aqueous phase is added to the organic phase; the mixture is placed in an ultrasonic bath at 0°C until the two-phase separation. Now the organic phase is removed, and under low pressure, gel formation occurs. After continuous agitation, the lipid layer is incorporated in the aqueous layer now the sample is filtered. Different excipients and methods used to formulate transethosomes are mentioned in **Table 2.**

TABLE 2: 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 Moolakhhadath	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 has a very high skin permeation rate and high flux rate compared to other vesicular systems.[3]
2. The main advantage of nanotransethosoms is that they can easily deform and easily move through the narrow obstructions.[21]
3. Biocompatible and biodegradable nanotransethosomes can be easily formulated with the help of natural phospholipids.
4. It is much more stable than another vesicular system.
5. It has very high entrapment efficiency, and 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 they can be easily administered in transdermal dosage forms such as cream, gel, and in a patch.
8. Transethosomes prepared with nanosize known as nanotransethosomes can easily hit the target site.

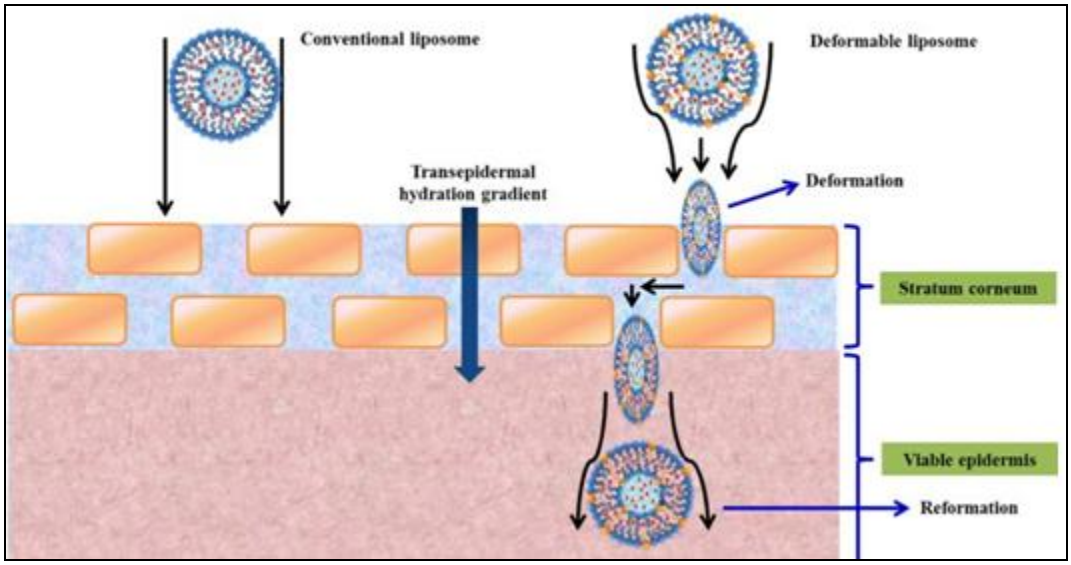

FIG. 6: MECHANISM OF ULTRA-DEFORMABLE CHARACTERISTICS OF TRANSETHOSOMES

Disadvantages of Nanotransethosomes [22, 23]:

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

Characterization of Nanotransethosomes:

- Morphological characteristics of nanotransethosomes
- Zeta potential of nanotransethosomes and their 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

Morphology of Nanotransethosomes: TEM and SEM studies can be easily used to determine the morphological characteristics of nano-transethosomes.

Particle Size: Two methods are used to determine the exact particle size of nanotransethosomes.

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

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 the column centrifugation. 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 the ultracentrifugation method.

After the centrifugation process, the upper layer is developed and separated from the vesicles. Then these vesicles are treated with solvents like triton-X-2 propanol, and 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 the formula shown in **Fig. 7.**

% Drug Entrapment = Amount of entrapped drug / Total amount of drug × 100

$$EE\% = A_0 - A_U / A_0 * 100$$

$$LC\% = A_0 - A_U / W * 100$$

$$Yield\% = A_v / A_0 + W * 100$$

A_0 = Initial quantity of drug used

A_u = Non encapsulated drug

A_V = Amount of vesicular carrier product

FIG. 7: FORMULA FOR ENTRAPMENT EFFICIENCY

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 temperatures under a constant nitrogen stream.

***In-vitro* Drug Release Study:** The quantity of drug release from the nanotransethosomes can be easily determined by an *in-vitro* study using the Dialysis bag method. The *in-vitro* drug release study can be easily depicted in **Fig. 8.**

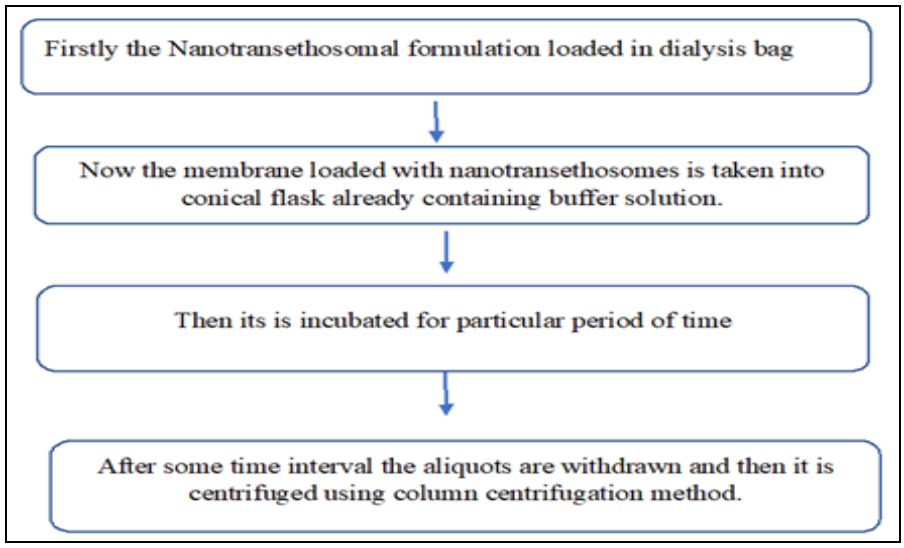

FIG. 8: *IN-VITRO* DRUG RELEASE STUDY

Vesicular Stability Study: The vesicular stability study of nanotransethosomal vesicles can be done by depositingthem at different temperatures 25±2°C, 37±2°C, and 45±2°C. DLS and TEM can be used to determine the size and morphology of nanotransethosomes.

***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 nano-transethosomes to penetrate deeper into the skin for targeted drug delivery can be done by using CLSM. The instrument temperature should be maintained at 32°C±1°C. There is a receptor compartment cell that contains 10 ml of PBS. The skin on which the permeation study can be determined is placed between the donor and receptor compartments. Now the nanotransethosomal vesicles are 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 withdrawn at a particular time interval can be analyzed using HPLC.

Determination of pH: The pH of Nanotransethosomal formulation can be determined by using a digital ph meter.

Applications of Nanotransethosomal Vesicular System:

Delivery of Anticancer Drugs [9]: Thasleem *et al* conducted an experiment in which fisetin-loaded nanotransethosomes vesicles were optimized using Box Behnken design software. Fiestin is a natural flavonoid mostly found in ample amounts in various fruits and vegetables. In this experiment, the Nanotransethosomal vesicles show good EE with reasonable flux has been observed.

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. The present study developed NAP-SULF EH by modifying the thin film hydration technique.

Song *et al.* researched Rheumatoid Arthritis. In Sinomenine hydrochloride loaded ascorbic acid (Antioxidant), transethosomes were decorated using ascorbyl palmitate as an antioxidant and transethosomes as a basic transdermal carrier. AS-TE can be transdermally 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 transethosomal hydrogel to treat Rheumatoid Arthritis. In the present study, the nanotransethosomal hydrogel has been prepared using lipid, ethanol, and edge activator, and their characterization has also been done. It can be easily concluded that the formulated piroxicam nanotransethosomal hydrogel has the ability to penetrate deeper into the skin with targeted drug delivery. Gadad *et al.* demonstrated a research work in which flurbiprofen-loaded transethosomes have been formulated for the treatment of arthritis

In the present research, it was demonstrated that TE contains 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.

Delivery of Antihypertensive Drugs [21, 22, 24]: Albash *et al.* performed an experiment in which transethosomes were formulated as a transdermal delivery system for Olmesartan medoxomil. The result has concluded that transethosomes could be considered promising transdermal delivery systems for OLM as they can avoid extensive first-pass metabolism of OLM.

Lalit *et al.* conducted an experiment in which nanotransethosomes loaded with propranolol hydrochloride showed better skin in-vitro permeation with highly controlled release of the drugs. Based on the recent research work it can be concluded that the nanotransethosomal vesicles can be easily prepared for antihypertensive drugs. Verma *et al.* performed an experiment in which Irbesartan loaded with transethosomes has been formulated. Irbesartan loaded with transethosomes formulations was successively prepared using the cold method. Characterization of transethosome as vesicle shape, vesicle size, PDI, zeta potential, entrapment efficiency, a calibration curve of UV, % drug release, FTIR, and SEM as responses.

Delivery of Antifungal Drug [20]: Farooq *et al.* demonstrated an experiment in which formulation of Voriconazole-loaded transethosomes and incorporation into a hydrogel for antifungal and antileishmanial application has been observed. The result demonstrated that the developed Voriconazole transethosomal hydrogel can be highly beneficial in treating topical fungal infections.

Future Prospects: Scientists and researchers have recently been interested in the nanotransethosomal vesicular system. It is highly sought after for targeted drug administration through the transdermal route and deeper skin penetration because of its ultra-deformable properties, nano-size particles, and deformable system. In comparison to Ethosomes and Transferosomes, Liposomes and Phytosomes, edge activator has been demonstrated to have greater permeability and

penetration characteristics. It is also appropriate for medications with high and low molecular weights and hydrophilic and hydrophobic compounds. It is a relatively new vesicular system that will continue to be in demand. There isn't yet a commercial formulation for nanoparticles (nanotransethosomes) because scientists and researchers are still researching them. Additionally, nano-transethosomes can be added to cutting-edge drug delivery systems likecream, gel, emulgel, and in patch form. Thus, the Nanotransethosomal vesicular system has a lot of potentials to use as a carrier for transdermal drug delivery.

CONCLUSION: Transdermal medication administration has emerged as the most advantageous method in the past few years. It overcame several drawbacks associated with the oral method of drug administration, including first-pass metabolism, which was a significant one. The transdermal method of drug administration has been devised to get over this restriction; however there are still some drug molecules that are difficult to pass through the stratum corneum and are unable to enter effectively. Our scientists and researchers have created a novel technology called as the extremely deformable vesicle system to meet this difficulty (UDV). The medicinal molecule, whether synthetic or natural, is combined with vesicles in this method so that it may be delivered to specific areas of the skin.

Transethosomes are a unique promise for improved transdermal medication administration *via* the skin among transferosomes and ethosomes. Nanotransethosomes' efficient penetration is facilitated by ethanol, edge activator, and phospholipids. The creation of nanotransethosomes may be accomplished using various techniques, including ethanol injection, hot method, cold method, transmembrane pH gradient method, and thin film hydration method. The transdermic distribution of several drug classes, including anti-arthritic, analgesic, anticancer, antibiotic, and antiviral medications, is possible with UDV systems. Drugs that have a high partition coefficient or a low partition coefficient have trouble entering systemic circulation. Ultra-deformable vesicles (UDV), such as Transferosomes, Ethosomes, and Transethosomes, have been designed to overcome this issue. The development of the vesicular system recently made it possible to administer targeted medications via the skin. Hydrophilic, hydrophobic, and amphiphilic medicines may all be captured by the ultra-deformable vesicular structure. In addition to manufactured medications, natural substances like proteins and peptides can also be delivered transdermally in vesicles. Additionally, nanotransethosomes can be included into cutting-edge drug delivery methods including cream, gel, emulgel, and patches. Therefore, there are several opportunities for using the Nanotransethosomal Vesicular System as a carrier for transdermal medication administration.

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