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A BRIEF REVIEW ON TRANSETHOSOMES - A NOVEL APPROACH TOWARDS TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT:

Transdermal medication delivery is a highly efficacious approach to drug administration. Additionally, a lot of medications are unable to cross the stratum corneum, which serves as the primary transdermal drug barrier delivery. The synthesis of ultra-deformable vesicles (UDVs) is a revolutionary approach for medication delivery transdermally. The UDs includes ethosomes, transferosomes, and transethosomes (TEs). Many physical as well as chemical methods were developed to overcome stratum corneum barrier and deliver the drug to target site by this route of administration in medical fields. Transethosomes offer better medication penetration through the stratum corneum due to their higher ethanol, phospholipid, and edge activator concentrations. Drug penetration into the deeper layer of skin also rises as a result of TEs' flexibility. There are several methods for preparing TEs, such as the cold method, Hot method, Mechanical dispersion method, Ethanol injection method. In this review article various methods and approaches were discussed in detail about transethosomes. In future aspects various formulations can be made with this advanced technology in the field of drug delivery via. Transdermal as well as topical drug administration. In this article various mode of enhancement of drugs to cross the stratum corneum were discussed and also the advanced technologies through transdermal route like development of vesicular drug delivery system in the field of nanotechnology.

Keywords: Transethosomes, Keratinocytes, SC, UDVs.

INTRODUCTION:

Currently, the most popular way to administer the medication is orally. Despite the obvious advantage of being the easiest way to take the medication,via other routes too. Additionally, there are a number of drawbacks, including as low bioavailability due to hepatic first-pass metabolism and the potential to alter plasma drug concentration, necessitating frequent dosage and perhaps leading to patient noncompliance [1]. Continuous intravenous infusion is thought to be the most effective way to deliver medication because it prevents the "first pass" metabolism and maintains a steady and sustained drug level in the body.

But that necessitates the patients being admitted to the hospital and appropriate medical supervision of the treatment. There are other advantages to the transdermal method as well.

TRANSDERMAL DRUG DELIVERY SYSTEM:

The transdermal drug delivery system (TDDS), which tries to distribute the medicine via the skin at a predetermined and regulated pace, is one way to accomplish controlled drug delivery (Rastogi and Yadav 2012). Roughly 74% most drugs used today are taken orally, although due to their limited solubility or reduced bioavailability, they are sometimes not as effective as expected. Transdermal delivery was developed to enhance these characteristics. With this delivery method, the medication can enter the bloodstream through the skin at a predetermined rate without causing any discomfort [2]. The transdermal method can be used to administer medications instead of orally and intravenously (Marwah et al., 2016).

The medication has been applied to the skin using the TDDS (Phatale et al. 2022). The blood arteries in the body absorb the medication that is delivered. existing in the skin before moving throughout the body (Hasan et al. 2020). As a result, using this method of delivery eventually improves patient compliance and lowers the frequency of therapeutic doses (Ramadon et al. 2021). Constant plasma levels and consistent medication absorption through the skin are two advantages of TDDS (Mishra and Jain 2022). According to Singh et al. (2015), TDDS is also effective in treating neuropathic pain, migraines, headaches, genital herpes, acne, and sexual dysfunction. However, the possibility of localized skin irritation is one of the primary disadvantages of application to the skin.

SKIN

Because it is the most accessible organ in the human body, the skin could be an option for medication administration. The skin's main function is to stop the body from losing too much water (Subedi et al. 2010).

The three layers of human skin seen in Figure 1 are called the hypodermis, and each one has a unique structure and set of purposes. Keratinocytes comprise the epidermis, the outermost layer of the skin. Additionally, it is made up of viable and non-viable epidermal layers.[3,4] The non-viable epidermal layer, also known as the stratum corneum or horny layer, is the outermost layer of the skin. It is composed of lipid bilayers that are closely packed and located between corneocytes

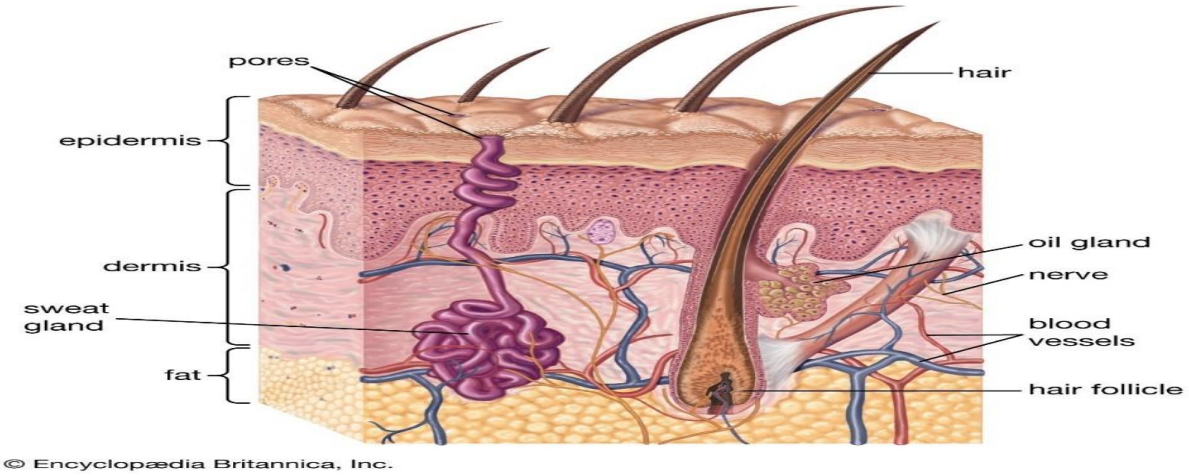

Fig-1. Structure of skin.

The stratum corneum is the lowest layer of the epidermis. It consists of 10–25 layers of longitudinal, dead corneocytes encased in a lipid matrix and highly keratinized. bilayers (Al Gawhari and Mohammed, 2021). Generally, medicines can reach the intact skin or subcutaneous layer through three fundamental pathways. The appendageal route (transport via sweat and sebaceous gland), transfollicular route (transport via hair follicle), transcellular route (transport via

corneocytes), and intercellular route are the first four routes, as shown in Figure 2 (Freinkel and Woodley 2001). Antisense oligonucleotides (ASOs), tiny peptides, and other medications can all be administered intracellularly (Agrawal 1996, Whitehead et al. 2009).

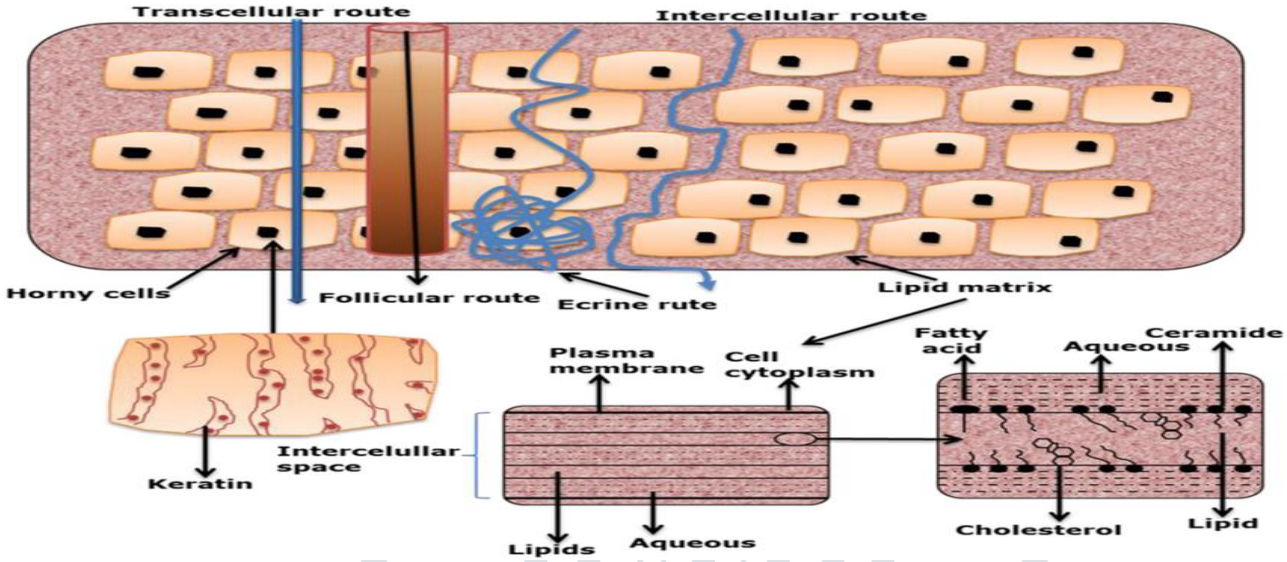

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Fig-2. Route of administration of drugs via. skin.

Transcellular route:

Through the epithelial cell, transmembrane proteins in the basal and apical plasma membranes, as well as the intervening cytoplasm, are successively passed through during transcellular transport. For the majority of transepithelial transport, this is the main route. The solute must penetrate the apical cell membrane in order for the drug to be transported by the passive transcellular pathway.

The composition of the phospholipids and proteins of the cell membranes varies from cell type to cell type, and may, theoretically, give rise to different permeability properties depending on the cell type. The transcellular diffusion basically encompasses the transport of solutes by driving force, namely, diffusion gradient moving across zone with higher content to zone having lower content; yet, the cell membrane is a hydrophobic milieu and will not permit the passive diffusion of charged, hydrophilic, or zwitterion substances. Active transport comprises the usage of energy to carry particular molecules transversely, even countering the concentration gradient. Macromolecules may occasionally be moved via transcytosis. In the transcellular route, drugs diffuse through SC cells during the absorption process. Therefore, drugs have to pass the membranes, which are composed of lipid bilayers. This route is mostly taken by hydrophobic drugs because of the hydrophobic properties of lipid complex in the cell membranes of the SC. Drugs pass through the corneocytes of the *stratum corneum* rather than the lipid 'mortar' that surrounds them. However, the drug has to exit the cell to enter the next corneocyte and therefore through the skin. It means that it has to encounter the external hydrophobic environment between the cells multiple times as it moves through the alternating cell and lipid layers of the epidermis. Drugs therefore have to have balanced hydrophilic and hydrophobic properties to enable this to happen.

Intercellular route:

The second pathway is intercellular, wherein the medications must permeate the lipid matrix of the keratinocytes' intercellular space where they are resident in the SC.

Hydrophilic compounds or small molecules are transported via this route to reach vascular capillaries in the dermis. The majority of molecules cross the *SC* via three main pathways [6,11,12]. The main pathway is the intercellular route through the lipid matrix located between the corneocytes.

This pathway allows small hydrophobic molecules (typically with a molecular weight below 500 Da) to permeate through tight lipid junctions between the cells in a tortuous route. The drug predominantly diffuses through the lipid rich "mortar" around the corneocytes of the epidermis. This lipid matrix can form a continuous route through the epidermis (avoiding entering the cells), but this route has been suggested to be less efficient because it increases the distance 50-fold3 compared to the direct route through the *stratum corneum* due to the interdigitating brick and mortar arrangement. Again, the chemical formulation used to carry the drug is important and drugs that more readily dissolve in lipids benefit from this route.

Physical techniques to overcome subcutaneous barrier.

Names	Technique	Descriptipn
Iontophoresis	It is a method for administering the drug through the skin by using a little electric charge. It is primarily an injection but without a syringe.	Azone (a permeation enhancer) and iontophoresis had a synergistic effect on the in vitro penetration of metoprolol into human epidermis, according to Ganga et al.
Sonophoresis	It is method that improves the topical delivery of drugs by using ultrasonic waves.	Through the use of ultrasound waves, absorption of topically given analgesics and anti-inflammatory drugs is shown to be increased according to Ogura et al. (2008)
Electroporation	This method involves applying a brief electric pulse to the skin (microseconds or milliseconds) in order to temporarily alter the structure of the lipid bilayer membranes. The lipid region of the stratum corneum may change as a result of electroporation	Transport of hydrophilic (e.g. metoprolol), lipophilic (e.g. timolol), charged (e.g. heparin), and neutral molecules (e.g. mannitol) is improved by this technique according to Denet et al. (2004)
Magnatophoresis	It is a process which enhances the drug penetration across biological barriers by using a magnetic field.	Magnetophoresis improves transdermal drug delivery, according to in vitro and in vivo investigationsaccording to Sammeta et al. (2011)
Skin abrasion	It includes the direct removal or disturbance of the topmost layers of skin to allow topically applied drugs to penetrate easily.	used to treat scars, hyperpigmentation, and other skin problems according to Benson (2005)
Thermophoresis	In this technique, heat is provided to the skin to increase drug delivery	The raised temperature at the site of administration increased in vivo delivery of medicines such as, tetracaine, nitroglycerine, testosterone, lidocaine, and fentanyl from transdermal patches with attached heating devices according to Patil et al. (2012)

Chemical techniques to overcome SC barrier:

Techniques	Description	Application
Prodrug	A promoiety is generally introduced to improve drug transport over the stratum corneum. After that, hydrolysis of the parent drug occurs in the viable layer of epidermis.	Prodrug administration could increase transdermal distribution of drugs with undesirable partition coefficients or low solubility according to Sloan and Wasdo (2003)
Chemical enhancers	Chemical enhancers are chemical compounds that weaken the stratum corneum's ability to act as a barrier	The enhancer could either engage with keratin in corneocytes to open the tight protein structure or disrupt lipid arrangement to increase drug diffusion coefficient according to Kumar and Philip (2007)

Table no -1

VARIOUS TRANSETHOSOMAL FORMULATIONS:

/YE	TITLE	CONCLUSION
	A DoE-based development and characterization of Nadifloxacin-loaded transethosomal gel for the treatment of Acne vulgaris	Researched to enhance the topical delivery of Nadifloxacin (NDFX) by incorpor formulation.The optimized transethosomal formulation displayed enhanced in vitro effects against Propionibacterium acnes in Wistar albino rats when compared to the
Munir	*A comprehensive review on transethosomes as a novel vesicular approach fordrug delivery through transdermal route.*	Explined about the major barriers involved in the TDDS, techniques that had bee these barriers, different vesicular approaches that had been used for the Transderma brief composition, methods of preparation, mechanism of penetration of transethoso as well as illustrates various drug formulations that had been made very recently v the ability to deliver drugs with high molecular weight, such as proteins and peptide Through various evaluation tests, TEs could be made very efficiently. Many drugs vesicular approach. Many findings still are required to improve its further complian
et al	*Preparation of paeoniflorin-glycyrrhizic acid complex transethosome gel and its preventive and therapeutic effects on melasma*	Aimed to enhance the transdermal delivery of paeoniflorin (PF) and glycyrrhizic ac beautifying effects (anti-inflammation, anti-oxidation, melanin inhibition, and red PF-GL-TE gel exhibited sustained release behavior and high transdermal pe transdermal tests.PF-GL-TE gel down-regulated melanin-related protein expressio contributing to melasma prevention and treatment.The study primarily focused on s long-term impact of PF-GL-TE gel use, including potential adverse effects, would e

l	*TPGS-mediated Transethosomes Enhance Transdermal Administration of Curcumin via Effects on Deformability and Stability*	Investigates the use of D-α-tocopherol acid polyethylene glycol succinate (TPGS) a delivery of curcumin.TPGS-mediated curcumin-loaded transethosomes (Cu optimized.Cur@TES demonstrated better stability and deformability compared (Cur@ES).In vitro transdermal experiments showed that Cur@TES significant retained in the skin.Cur@TES exhibited a significant inhibitory effect on inflam swelling model.Although the study demonstrates enhanced skin distribution, a deep mechanisms is essential
	Formulation and Characterization of Hesperidin-Loaded Transethosomal Gel for Dermal Delivery to Enhance Antibacterial Activity: Comprehension of In Vitro, Ex Vivo, and Dermatokinetic Analysis	Used hesperidin and examined the potential antibacterial properties of HSD again +ve and -ve bacteria. Transethosomes were successfully used to encapsulate he potential drug delivery method. Further investigation is necessary to ascertain th effects in a suitable clinical model. Although hesperidin is generally consid transethosomes containing HSD for topical administration has not been thoroughly not conducted in the current study.
ashvi	*Nanotransethosomes for enhanced transdermaldelievry of mangeferin against rheumatoid arthritis formulation,characterization,invivo pharmacokinetic and pharmacodynamic evaluation*	Used Mangeferin as source and their research The research study aims at transethosomes to improve MNF solubility,bioavailability and permeation ability MNF-TE gel has good anti-arthritic potential when compared to the standard diclo Wistar albino rats confirmed that the formulation was safe for skin application. Th the long term application and usage of drug formulation. the study could also symptoms of arthritis in the in-vivo models.
t al	*Numerical optimization of prednisolone-tacrolimus loaded ultraflexible transethosomes for transdermal delivery enhancement;Box-behnken Design,evaluation,optimization and pharmacokinetic study*	Used Prednisolone tacrolimus and successfully formulated a transethosomal tacrolimus. The optimized gel demonstrated high rat hind paw edema re pharmacokinetics parameters. These findings suggest promise for topical and systen formulation remains effective over time is crucial,so stability studies should be con The safety and toxicity studies should be performed.
t al	*Lipid Nano-System Based Topical Drug Delivery for Management of Rheumatoid Arthritis: An Overview"*	Review discusses about lipid-based nanocarrier systems for topical anti-rheumatic models and relevant patents were discussed. Discussing potential challenges that co system for RA could have been helpful. Also discussing about the adversities like s strengthened the article
l	*Development and optimization of transethosomal gel of apigenin for topical delivery: In-vitro, ex-vivo and cell line assessment*	0ptimized the transethosomes of apigenin formulated by the thin film hydration m cytotoxic study confirmed that TEL gel significantly reduces cell viability co optimized batch showed a reduction in cell viability against HaCat cells without suggested that topical application of apigenin transethosomal gel may be a better because of the prolonged sustained release of the drug and the better permeability of
if et	*Transethosomal Gel for the Topical Delivery of Celecoxib: Formulation and Estimation of Skin Cancer Progression*	Explores the potential of nano lipid vesciles (transethosomes) loaded w delivery,specifically targeting skin cancer management.Enhanced flux and permea compared to the control (free drug-loaded hydrogel).Importantly, the CXB-T cytotoxicity on normal skin cells than TES suspension and CXB powder.While results in vitro, further clinical validation is essential. Conducting well-designe subjects would provide more robust evidence of the efficacy and safety of the transe
ota et	*Designing and optimization of naproxen sodium deformable vesicular systems through factorial design:Box Behenken*	Aimed to design and optimize deformable vesicular systems containing napro inflammatory drug) using a Box Behnken factorial design approach. This form release (71.98%) within 12 hours.The optimized formulation demonstrated stabi

g et a	*model* *Transdermal delivery of inflammatory factors regulated drugs for rheumatoid arthritis*	insights for the development of deformable vesicular systems for transdermal drug in vivo performance or long-term stability.Further research could investigate permeation of the optimized formulation. Concluded, transdermal drug delivery systems offer promising efforts for trea overcoming the skin's stratum corneum barrier,these systems enhance drug delive effects. Various dosage forms have been explored. Hence, transethosomes hold gr RA patients. If there's more information about any practical patient outcomes, s dosage forms,the article would've enhanced my understanding
kumar al	*Transethosomal hybrid composites of naproxen-sulfapyridine in hydrogel carrier:anti-inflammatory response in complete Freund's adjuvant induced arthritis rats*	Naproxen sulfapyridine was their drug. The combination of naproxen and sulfapyric synergistic effect enhancing their therepeutic potential. The results show a reducti function. The study primarily focuses on short-term effects, so investigaating pote necessary. It would have been helpful if the pathway of the drug was figured out.
et al	*Formulation, development and evaluation of ketoprofen loaded transethosomes gel*	Used Ketoprofen and formulation and development of ketoprofen-loaded transetho approach for transdermal drug delivery. By combining the advantages of lipid-base offers a promising solution for topical administration of ketoprofen, providing pot and convenience. Conducting in vivo studies to evaluate the gel's efficacy and safe provide valuable insights. Assessing factors like skin permeation, drug release ki guide further optimization.
agdish	*Nano-transethosomes: A Novel Tool for Drug Delivery through Skin*	Perfectly captured everything we need to know about transethosomes like the p possible delivery of different drugs like anti-cancer drugs, anti-fungal drugs transethosomes passes the stratum corneum by intercellular as well as intracellular edge activator in its composition. Further studies should be done on rheological administration of combination of drugs, its toxicity and permeation efficacy.
S. et al	*Transethosomes a Novel Transdermal Drug Delivery System for Antifungal Drugs*	Aimed to show the utility of transethosomes as a novel vesicular delivery system fungal skin infections. The stability profile, solubility profile, and targeting power o can be improved using transethosomes and then increasing their efficacy. Increas since the drug is given as a semisolid dosage form.
t al	*Development and Characterization of Apremilast Transethosomal Gel for Transdermal Delivery*	Prepared a transethosome vesicle containing apremilast by using Rotary vacuu sonication and were found to be spherical and uniform in size based on TE transethosomal gel has a sustauined drug release characterisric with high % permeation which can be better option for the treatment of psoriasisand a viable alte
haxari	*Development and evaluation of flurbiprofen loaded transethosomes to improve transdermal delivery*	Encapsulated Flurbiprofen in transethosomes to increase permeability, to reduce do deposition. On comparison with the marketed gel, they revealed that the optimized concentration of Tween 80 had better ex-vivo profile and skin deposition. T understanding the long-term stability of the product skin permeation mechanism, b product by conducting human clinical trials.
al	*Mitigation of Rheumatic Arthritis in a Rat Model via Transdermal Delivery of Dapoxetine HCl Amalgamated as a Nanoplatform: In vitro and in vivo Assessment*	Used Dapoxetine HCl (DH) & investigated the therapeutic efficacy of transderma nanovesicles (TENVs). The pharmacokinetics analysis showed that the optim bioavailability of the DH by 2.42- and 4.16-fold compared to the oral DH s respectively. The future research required includes equipping the optimized DH-T allow drug targeting and improved RA management
t al	*Formulation and characterization of transethosomes for enhanced*	Aimed to develop transethosomes loaded with propranolol hydroc delivery.The researchers evaluated these transethosomes for prolonged release, in-

	transdermal delivery of propranolol hydrochloride	plasma concentration.Transethosomal gel prolonged in-vivo release of propranolol plasma concentration (Cmax) of propranolol hydrochloride was significantly high tablet. However,further investigation into stability studies,in-vivo pharmacokinetics performed.Transethosomal gel could be a promising alternative to oral propranolo like high dosing frequency, first-pass effect, and organ toxicity.
	Enhanced transdermal permeability and drug deposition of rheumatoid arthritis via sinomenine hydrochloride-loaded antioxidant surface transethosome	Used sinomenine hydrochloride & proven by showing the micro-dialysis of the syn drug concentration than the standard drug. AS-TE, which can enhance transderma for the oxidant stress of RA. Further research clinical trials have to be perform explore their practical applications in patient treatment. It was expected that AS-T other inflammatory diseases such as gout, synovitis, etc
et al	***Formulation and Characterization of Transethosomes for Enhanced Transdermal Delivery of Propranolol Hydrochloride***	Developed transethosomes loaded with propranolol hydrochloride using Lipoid S permeation enhancer and evaluate them for prolonged release effect, in-vitro ski concentration. The results suggested that transethosomal gel of propranolol hydroch oral propranolol hydrochloride as it can avoid various disadvantages of oral pr dosing frequency, first pass effect, and organ toxicity. Further clinical trials should b the article.
	Transethosomes of Econazole Nitrate for Transdermal Delivery: Development, In-vitro Characterization, and Ex-vivo Assessment	Developed and characterized (in-vitro and ex-vivo) econazole nitrate loaded tran with marketed cream of econazole nitrate. It was concluded that econazole nitrate l to deliver econazole nitrate transdermally in a controlled fashion for effective elimin
	Systematic Development of Transethosomal Gel System of Piroxicam:Formulation Optimization, In Vitro Evaluation, and Ex Vivo Assessment	Used Piroxicam and described the preparation, optimization, characterization, and transethosomal gel using the central composite design. The results of the stability s formulation was stable at refrigerated conditions (5 ± 3°C) for 28 days. The dev superior over other vesicular delivery systems and has been successfully applied as form of gel. Further studies should include clinical trials to access the safety transethosomeal gel in human subjects.
l	*Evaluation of paeonol-loaded transethosomes as transdermal delivery carriers*	Research was to develop a biocompatible paeonol formulation with impro pharmacokinetic efficiency. Paeonol-loaded vesicles were prepared using an e transethosomes had a narrow size distribution, high encapsulation efficiency, and demontrated. Results of in-vitro transdermal absorption and skin retention stud penetration (Qn) and deposition (Qs) of paeonol from the ethosomes were sig hydroethanolic solution, hence indicating not only enhanced transdermal absorption storage in the skin.
M al	*Transethosomal gels as carriers for the transdermal delivery of colchicine: statistical optimization, characterization, and ex vivo evaluation*	Explores an alternative drug delivery system for colchicine,a potent anti-inflamma rheumatoid arthritis and other inflammatory diseases. They tried to design a transet delivery, avoiding the adverse effects associated with oral administration.Tra vesicular formulations in terms of stability and elasticity.The ex vivo skin per transethosomal gels had superior skin permeation properties in comparison to the N focuses on colchicine, it would be valuable to discuss the clinical implications of t as well.Stability assessment and safety profile of the formulation should also be dis
	Systematic Development of Transethosomal Gel System of Piroxicam: Formulation Optimization, In Vitro Evaluation, and Ex Vivo Assessment	Explores an alternative delivery system for piroxicam, a drug used in the t osteoarthritis, and other inflammatory diseases.The optimized transethosomal gel qualities including high drug retention in the skin,efficient drug permeation and st formulation optimization and in vitro evaluation, further research should include efficacy, and tolerability of the transethosomal gel in human subjects.

t al	*Transethosomes and Ethosomes for enhanced Transdermal delivery of ketorolactromethamine:A comparative assessment*	Aimed to formulate, evaluate and compare the transdermal potential transethosomes and ethosomes. Both were prepared by cold method and wer entrapment efficiency, transmission electron microscopy (TEM), zeta poten vitro drug release, ex-vivo permeation studies and in-vivo study. Transet entrapment than ethosomes. So they concluded that transethosomes to be a compared to ethosomes for transdermal delivery of ketorolac tromethamine.

Table no-2

METHOD **OF PREPARATION OF TRANSETHOSOMES:**

COMPOSITION OF TRANSETHOSOMES:i

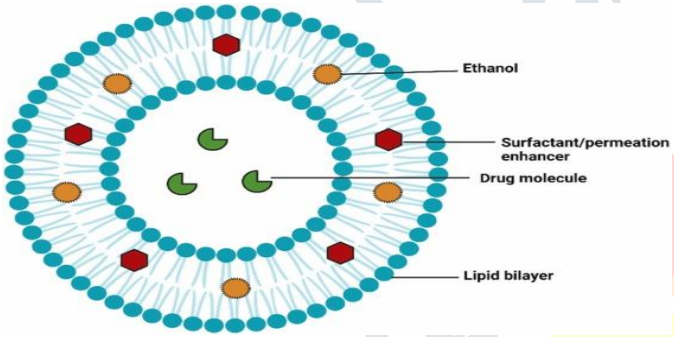

Fig no-3

COLD METHOD

The most popular way for creating TEs is the cold approach. Drugs that are heat-sensitive or heat-labile can benefit from this technique (Nimmy et al. 2017). This process involves swirling continuously while the lipids and ethanol are combined at ambient temperature. After adding the edge activator, the mixture is heated to 30 C while being vigorously stirred. After that, the mixture is whisked for five minutes in a covered container. Before adding the water to the alcohol mixture, it is heated in a different container to 30 degrees Celsius. Next, as illustrated in Figure 7, sonication is used to reduce the size of TEs (Shaji and Garude 2014). Lastly, a refrigerator is used to keep the created formulation (Nimmy et al.).

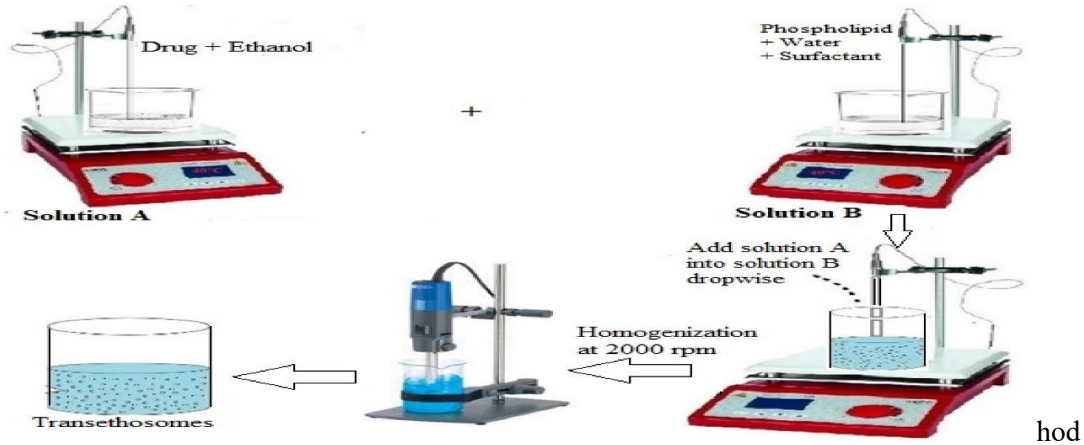

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Fig no-4

HOT METHOD

The skin penetration mechanism of various vesicles is achieved by dispersing the phospholipid in water to create a colloidal solution using this approach. The mixture of ethanol and glycol is maintained at a steady 40 degrees Celsius. After that, the ethanol and glycol phase is introduced to the water phase while being continuously stirred for a duration of seven to ten minutes. Depending on whether the medication is hydrophobic or hydrophilic, it can then be dissolved in either water or ethanol. The previously made solution is then combined with the medication solution. As seen in Figure 8 (Mbah et al. 2014), this process was completed at a constant temperature of 40 C. Sonication was then used to reduce the size of TEs.

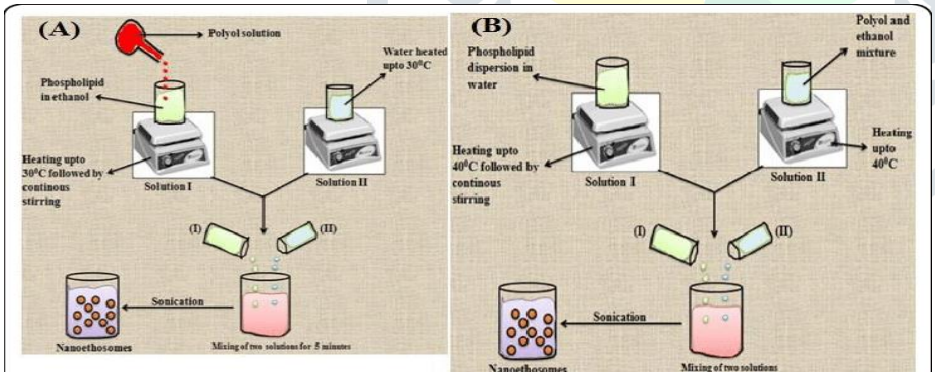

Fig no-5

MECHANICAL DISPERSION METHOD:

Using this approach, lipids and surfactant are combined with ethanol. This method is enhanced by combining ultrasonic homogenization with thin film hydration. A rotary evaporator forms a thin lipid coating above the lipid transition temperature. It is vacuum-sealed for a full night to remove any leftover excess organic solvent. Centrifugation at 60 rpm with 10% v/v ethanol and phosphate buffer pH 6.5 is used to hydrate the membrane. The medication is then added to the concoction. After that, the prepared TEs were homogenized for five minutes using ultrasonication. Lastly, a 0.22 mm filter is used for filtering (Pilch and Musiał 2018).

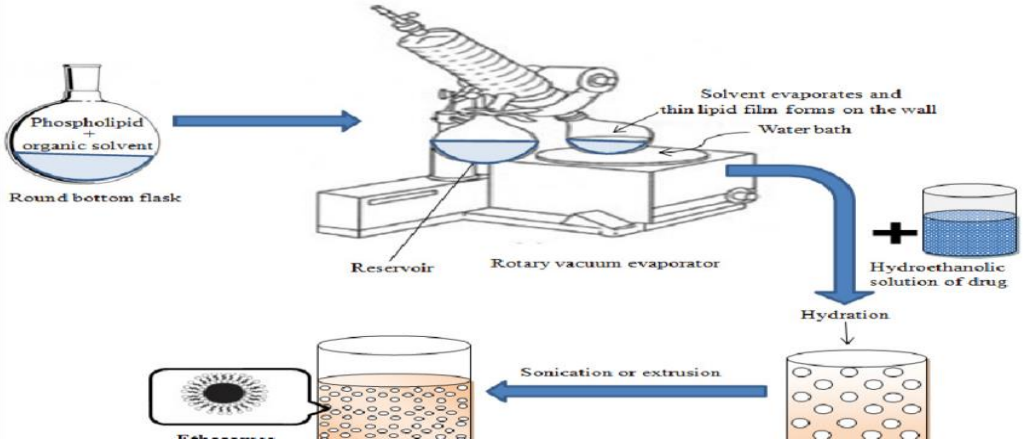

Fig no-6

Ethanol injection method

Using this procedure, phospholipid, surfactant, and medication are combined in ethanol and stirred continuously at 35 degrees Celsius to prepare the organic phase. To create a homogeneous mixture, the previously prepared organic phase was combined with the aqueous phase, which was made up of water and edge activator, while being constantly stirred. To stop ethanol from evaporating, the resultant solution is sealed with a glass bottle (Duangjit et al. 2014).

Fig no-7

Characterization of Transethosomes

1. Stability studies

The stability studies of the final optimized drug-loaded transethosomal gel formulation were carried out by placing freshly prepared samples of the gel in two different storage conditions; namely refrigerated at 4°C±2°C and room temperature at 25°C±2°C/60%±5% relative humidity (RH) for 3 months. The prepared formulations were evaluated in terms of vesicular size, *Đ*, ZP, pH, drug content, viscosity, yield, and rheological behaviour.

2. Determination of pH

It is crucial to use a digital pH meter to monitor the pH of TEs added to gel (Verma and Utreja 2019). The transdermal delivery system's pH can influence how well medications penetrate the skin. Skin irritation may result from a pH that is either too high or too low, which could lower patient compliance and the efficacy of the drug delivery method (Roy and Flynn 1990).

3.Vesicle shape

Vesicular morphology can be ascertained via Transmission Electron Microscopy (TEM). By putting the sample inside a copper grid covered in carbon, a thin film is created. It is stained negatively by the application of phosphotungstic acid (Samad et al. 2007). After producing a TE gel of curcumin, Kaur et al. saw, under TEM, that TEs were present in an unusual spherical shape (Kaur et al. 2018).

4. Zeta potential and vesicle size

The zeta potential is used to quantify electrostatic attraction and repulsion in colloidal dispersion. According to Radomska-Soukharev (2007), zeta potential can also provide information on the surface attraction. Figure 8: Dynamic light scattering (DLS). Hot process for transethosome production. 10 millimeters. Particle size and zeta potential can be assessed using the MUNIR ET AL computerized inspection system and photon correlation spectroscopy (PCS) techniques. Since various-sized particles are scattered by light at different wavelengths, DLS can also be used to determine the vesicular diameter (Pandey 2011). Past research indicates that Paeonol-loaded TEs with particle sizes between 200 and 300 nm were created. The stratum corneum layer can be penetrated by TEs formulation with particles smaller than 300 nm (Bajaj et al. 2021).

5.Entrapment efficiency

The % EE of transethosomal suspension was determined by ultracentrifugation technique. Optimized transethosomal formulation was centrifuged at 11,000 rpm for 2 hours at 4°C in a cold centrifuge. Further, the supernatant layer was separated and diluted with PBS (pH 7.4) and analyzed on UV–Vis spectrophotometer. The % EE was estimated indirectly by calculating the quantity of the unentrapped drug in the supernatant liquid from the total drug in the formulation. The drug entrapment percentage was calculated using the given equation.

EE (%) = T−C/T× 100

Where T is the total amount of drug,

C is the amount of drug obtained in the supernatant.

Spreadability

The Spreadability of the gel formulation was determined, by measuring the diameter of 1 g gel between horizontal plates (20×20 cm²) after 5 minutes. The standardized weight tied on the upper plate was 500g.

$$S = M \times L/T$$

Where, S = Spreadability,

M = Weight tied on the upper plate

L = Length (cm) of glass plate

T = Time taken (second)

In vitro drug release study

In-vitro drug release studies of optimized transethosomal gel were carried out with the use of dialysis membrane method, having pore size 0.4 µg. The dialysis membrane was soaked in 7.4 phosphate buffer for 24 hours. The dialysis membrane was cut in 2cm diameter and 1ml of transethosomal suspension was put on dialysis membrane and with the help of thread solution was packed in membrane. The beaker was filled with the PBS 7.4 medium. The beaker was placed on a magnetic stirrer agitated with the help of a magnetic bead with the stirring speed of 350 rpm and the temperature was kept at 37±1°C. The study was conducted for 24 hrs. and at a specific time interval (0.5,1,2,3,4,6,8,10,12,24 hours), 2 ml sample was collected and the same volume was replaced with a fresh solution of phosphate buffer (pH 7.4) and was analyzed by validated UV method.

Ex-vivo skin permeation studies

Ex-vivo drug release and permeation of the drug were investigated by using a modified. Franz diffusion cell with rat abdomen skin as a barrier medium. The temperature of the receptor medium was maintained at 37±1º C. The receptor compartment contained 13.3 ml phosphate buffer solution (PBS) of pH 7.4 and was constantly stirred by a magnetic stirrer at 350 rpm. Skin samples were fixed over the diffusion cells in such a way that the dermis faced the receptor compartment while the stratum corneum side faced the donor compartment. An amount of 1gm prepared gel formulation was administered in the donor compartment. 2 ml samples were withdrawn through the sample port of the diffusion cells at 30, 60, 90, 120, 180, 240, and 360 minutes and analyzed by validated UV method. To maintain a sink condition throughout the study period, the receptor phase, from which the sample was taken, was immediately replenished with an equal volume of dissolution medium. Once the permeation study is completed, the skin attached to the diffusion cell was removed to determine the amount of drug deposited in the skin layer. Skin samples were thoroughly washed with distilled water, and cleaned with cotton wetted in normal saline solution. The skin was homogenized with 5ml DMSO and 5ml acetonitrile to extract the drug which was retained in the skin sample. The suspension thus obtained was filtered with a 0.22-mm membrane filter. Then the processed sample, upon suitable dilution, was analyzed by the developed UV method.

CONCLUSION:

Ultra-deformable vesicular (UDVs) systems can assist achieve greater skin penetration. The constituents of the novel vesicular system are ethosomes, transferosomes, and TEs. In comparison to previous UDV systems, the transethosomal vesicular system can offer increased penetration, flexibility, and solubility because of its improved compatibility with both hydrophilic and hydrophobic medicinal compounds. The primary elements of the transethosomal system, which enhances topical medication distribution at the intended spot, are alcohol and edge activators. Because transethosomal systems have a high carrier capacity, they can transport medications with a high molecular weight, like peptides and proteins. TEs could be

created quickly using a variety of assessment exams. This kind of vesicular delivery has been used for many medications. As a future prospects this route of drug administration is a great challenge towards transdermal and topical drug delivery in medical fields. By this route of administration various adverse effects and contraindication of drugs can be minimized with better patient compliance and also enhances the rate of bioavailability of drugs.

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