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A Brief Review on: Vesicular Drug Delivery System - For Its Anti-Inflammatory Activity as Ethosomes and Transethosomes Gel Formulations

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ABSTRACT

This study includes development, characterization, and optimization of herbal ethosomal and transethosomal formulations. The aim of the present study is to develop drug loaded ethosomes capped with different herbal crude drugs which, was further incorporated in Carbopol 934 K thereby, resulting in the formation of ethosomal gel. The formulation is aimed at expressing effective treatment against inflammatory infection. Further the prepared drug loaded ethosomes were subjected to various evaluation parameters like particle size, zeta potential, polydispersity index (PDI) and % entrapment efficiency. For the evaluation of its surface morphology, transmission electron microscopy (TEM) was executed whereas, atomic force microscopy was carried out which contributes in detail and depth information of surface morphology. Viscosity, pH, spreadability and extrudability of the ethosomal gel were calculated to determine the suitability of the formulation for topical application. In vitro, drug permeation study and anti-inflammatory activity were executed out with different methodology. The aim of the review paper to focus on different herbal crude drugs and its importance in topical as well as in transdermal delivery were studied. In the near future various research will be carried out with herbal medicaments to reduce adverse effects and contraindications caused by drugs.

Keywords: Ethosomes, Transethosomes, TEM, Zeta potential

INTRODUCTION:

Inflammation is the defense mechanism of the body against injurious stimuli, trying to destroy injury and initiate healing. Although protective inflammation is acute in nature, unresolved it turns chronic and develops diseases such as allergies, heart diseases, cancer, and autoimmune disease.

Because of side effects of standard drugs, interest in natural anti-inflammatory compounds targeting similar pathways such as COX and NF-kB is on the rise. Nevertheless, poor absorption hinders their efficacy.

In order to overcome this, novel drug delivery systems such as nanovesicles and transdermal patches are being prepared to enhance uptake, minimize side effects, and maximize the therapeutic effect of natural and herbal agents.

Novel transdermal systems such as ethosomes have been formulated to enhance drug delivery as they facilitate easier drug absorption into deep skin layers i.e it can not only affect the surface of the skin but also transport medications into the bloodstream via the skin due to their greater elasticity and flexibility compared to liposomes. They are non-irritating, can be tailored, and are effective in the delivery of different drugs, particularly proteins and peptides, usually formulated in gels or creams for convenience.

Ethosomes are nanosized lipid vesicles (third-generation elastic carriers) applied for drug delivery with different solubility through the skin. They consist of lipids (such as phosphatidylcholine), high concentrations of ethanol (20–50%), other alcohols, cholesterol, and water. Ethanol imparts the vesicles softness, deformability, and a negatively charged surface, enhancing drug entrapment, stability, and skin penetration over conventional liposomes.[1]
The "ethanol effect" in the ethosome system makes the vesicular membranes highly flexible, allowing the ethosome to transport though pores much smaller than their diameters increasing permeability of the skin by disturbing the lipid matrix of the skin, making it more fluid.

The "ethosome effect" ensues, in which the elastic vesicles interact with lipids of the skin and create openings for intradermal drug delivery. Both these mechanisms render ethosomes useful in treatments such as wound healing.

Ethosomes possess several attributes that render them suitable as carrier drug, such as smaller size compared to liposomes; having the same composition of lipid, high payload capacity for both hydrophilic and lipophilic therapeutics and possess excellent physical stability on storage, Ethosomes have been used extensively as scaffold for various drugs employed in the treatment of hair disorders and sebum-related sebaceous gland associated diseases, photodynamic therapy, and anesthetic delivery therefor the transdermal drug delivery system is regarded as a promising method for administering active ingredients. [2.3]

Ethosomes offer better skin absorption and drug retention compared to traditional liposomes. Yet, they do not have targeted delivery to targeted skin disease locations, and they essentially depend on passive drug accumulation.

With the addition of surfactants to ethosomes, a novel class of carriers called transethosomes has come into existence. These are either considered the second generation of ethosomes or a subcategory of transferosomes. Transethosomes are prepared by mixing ethanol with a surfactant, which acts as an edge activator to increase the deformability of the vesicles. They possess increased flexibility and a greater capability for transdermal delivery.

Transethosomes combine the benefits of ethosomes and deformable liposomes. Moreover, transethosomes demonstrate enhanced ability to penetrate and deposit.

Transethosomes integrate the advantages of ethosomes and flexible liposomes. Transethosomes combine the composition of ethosomes with a penetration enhancer or a surface activator (surfactant) such as Tween 80, creating an ultra-deformable vesicular delivery system. Their nano size, surface charge, and flexibility facilitate improved diffusion and absorption into the skin both in vitro and in vivo. Additionally, their chemical makeup allows them to enter the bloodstream through the skin while maintaining their physicochemical characteristics.[4], [5], [6]

REVIEW ON ETHOSOMAL GEL:

SNO	TITLE	YEAR	CONCLUSION
1	Transethosomes: A Selective Tool for Transdermal Drug Delivery	2025	Many drugs of BCS Class II Drugs were found to be useful for formulation of transethosomes for transdermal drug delivery.
2	Plant-Based Nanovesicular Gel Formulations Applied to Skin for Ameliorating the Anti-Inflammatory Efficiency	2024	Nanotechnology has been used to deliver the drug. Due to this there have been less toxic effects of the drug and enhanced solubility, stability, absorption and bioavailability. Nanovesicular system promotes the capacity of drugs to penetrate the skin and increase the bioavailability of the drug.
3	Ethosomes and Transethosomes as Cutaneous Delivery Systems for Quercetin: A Preliminary Study on Melanoma Cells	2022	Transethosome loaded quercetin was found to be possibly used in the treatment of psoriasis. ET-QT was found to be used as an adjuvant in the treatment of melanoma cells.
4	Advances In Ameliorating Rheumatoid Arthritis By Andrographolide Ethosome-based Gel: Pharmacokinetic And Activity Study In Rats	2022	Andrographolide ethosomal gel showed relatively more bioavailability that ethosomal gel. It showed reduced oedema volume and decreased ankle joint diameter.
5	Central Composite Design (CCD) for the Optimisation of Ethosomal Gel Formulation of Punica granatum Extract: In Vitro and In Vivo Evaluations	2022	The ethosomal gel of P.granatum extract shows a promise to enhanced delivery for anti-inflammatory activity.
6	Vesicular nanocarriers for phytocompounds in wound care; Preparation and Characterization	2022	Information on preparation and characterization of lipid vesicle nanocarriers which contain herbal extracts and phytocompounds which will help in the wound dressings.
7	Ethosomes-based gel formulation of karanjin for treatment of acne vulgaris: in vitro investigations and preclinical assessment	2021	The treatment observed a significant decrease in the number and size of pilosebaceous units on the skin

8	Curcumin Loaded Ethosomal Gel for Improved Topical Delivery: Formulation, Characterization and Ex-vivo Studies	2021	Ethosomal gel of curcumin showed great potential of delivering the drug through transdermal delivery
9	Ethosomes and Transethosomes for Mangiferin Transdermal Delivery	2021	The expression of TNF-α is downregulated by MG under several conditions through the suppression of NF-κB activity, a key pathway in an inflammatory reaction, which can be significantly induced by TNF-α. MG's ability to antagonize inflammatory reactions makes it suitable for protection against cutaneous diseases such as contact dermatitis and psoriasis. E and TE5 effectively delivered MG to keratinocytes, which enhanced antioxidant defense mechanisms and provided protection against oxidative damage.
10	Ethosomal Gel Formulation of Alpha Phellandrene for the Transdermal Delivery in Gout	2020	The study exhibits the potential of an ethosomal formulation of Alpha Phellandrene in its anti-gout efficacy and it also shows anti-inflammatory activity when topically applied.
11	Performance of curcumin in nanosized carriers niosomes and ethosomes as potential anti-inflammatory delivery system for topical application	2020	Curcumin was successfully encapsulated in ethosomes with enhanced physicochemical stability and entrapment efficiency in an appropriate nanosize range suitable for skin permeation. HPMC15000-based gels promoted improved skin delivery and anti-inflammatory efficacy over free curcumin. Ethosomes are good carriers for transdermal curcumin delivery.
12	CD44 Assists the Topical Anti-Psoriatic Efficacy of Curcumin-Loaded Hyaluronan-Modified Ethosomes: A New Strategy for Clustering Drug in Inflammatory Skin	2018	For the delivery of curcumin, HA-Modified ethosomes were used using propylene glycol.Curcumin targeted CD44 protein in overexpressed psoriatic skin.
13	Preparation and Evaluation of Mangifera Indica Loaded Ethosomal Gel for Anti-Inflammatory Activity in Animal Model	2018	The studies show that M.indica posseses anti-inflammatory properties.
14	Enhanced transdermal delivery of sinomenine hydrochloride by ethosomes for anti-inflammatory treatment	2016	SH loaded ethosome was said to deliver sinomenine hydrochloride efficiently and was demonstrated to have an effect in the treatment of local inflammation as it is proved to have efficient skin permeation properties.
15	Ethosomes Loaded with Cryptotanshinone for Acne Treatment through Topical Gel Formulation	2016	CPT-loaded ethosomes showed smaller vesicle sizes, significant entrapment, and drug loading accompanied by impressive entrapment efficiency. Carbomer-based ethosomal gel exhibits superior permeation through the skin along with deposition relative to traditional hydroethanolic gel. Its in-vivo aspect delivered improves anti-acne performance with low irritation. For curing acne, CPT – loaded ethosomes are promising.

REVIEW ON TRANSETHOSOMAL GE:

SNO	TITLE	YEAR	CONCLUSION
16	Nanotransethosomal dual drug loaded gel of methotrexate and mangiferin as a potent synergistic intervention for rheumatoid arthritis via transdermal delivery.	2024	The current study aims to evaluate the impact and potential benefits associated with the combined use of methotrexate and mangiferin, incorporating these agents in their nanoparticulate for MTH-MFR-Transethosomes (TRS), which can improve the stability and solubility and the ability to permeate the testes arthritic tissues. TRS vesicles have been successfully used as a novel carrier for the transdermal delivery of MTH and MFR, demonstrating a new strategy for the treatment of rheumatoid arthritis.
17	A brief review on transethosomes - A novel approach towards transdermal drug delivery system	2024	Different techniques of formulation of transethosomes were studied and further can be used in the preparation of vesicular drug delivery system

18	Development and Characterization of Tinospora cordifolia extract Loaded Transethosomal Gel for Topical use	2024	Transethosomes show sustained drug release. Transethosomes containing Tinospora cordifolia has been proven to work for the treatment of arthritis.
19	Eugenol-Loaded Transethosomal Gel for Improved Skin Delivery and Treatment of Atopic Dermatitis	2024	Eugenol-loaded transethosomes were found to be effective in the treatment of Atopic Dermatitis. Carbopol 940 was used to make transethosomal gel. Eugenol-loaded transethosomal gel showed promising actions of drug delivery and anti-inflammatory action.
20	Ginger Extract–Loaded Transethosomes for Effective Transdermal Permeation and Anti-Inflammation in Rat Model	2023	TREs were successfully incorporated into an HPMC hydrogel, demonstrating suitable skin application properties and improved transdermal GE delivery with superior anti-inflammatory activity in a rat paw edema model
21	Preparation and characterization of transethosome formulation for the enhanced delivery of Sinapic acid	2023	Sinapic acid loaded transethosomes as a promising approach to enhance the transdermal delivery. It exhibits improved skin delivery and enhanced therapeutic activity.
22	Potential use of transethosomes as a transdermal delivery system for metabolites from Chenopodium murale	2022	The development of transethosomes has been reported successful for the delivery of a complex extract from the Chenopodium murale plant. The plant extract was effectively transported through the skin using transethosomes. Retained Bioactivity: The formulation preserved the chemical identity of the plant extract.
23	Preparation and In Vivo Evaluation of Rosmarinic Acid-Loaded Transethosomes After Percutaneous Application on a Psoriasis Animal Model	2021	The study explored the anti-inflammatory potential of rosmarinic acid delivered via transethosomes-in-Carbopol gel in a mouse model of psoriasis. In vivo, RA-TE-Gel significantly reduced edema and levels of TNF-α and IL-6, indicating anti-inflammatory activity.
24	Brucine-Loaded Ethosomal Gel: Design, Optimization, and Anti-inflammatory Activity	2021	The optimized ethosomal formulation had desirable vesicle size, high encapsulation efficiency, and increased skin permeation. Following incorporation into HPMC gel, the formulation was tested for physical characteristics, in vitro release, ex vivo skin permeation, and irritation. Results indicated that the ethosomal gel exhibited extended drug release for 6 hours and enhanced skin permeation with high transdermal flux and enhancement ratio.
25	Evaluation of paeonol-loaded transethosomes as transdermal delivery carriers	2017	Paeonol transethosomes showed better encapsulation efficiency, improved drug delivery both in laboratory tests and in living subjects, and increased drug deposition in the skin compared to transfersomes. This could mean a better treatment in that paeonol transethosomes would offer a chance to reduce dosing frequency, and therefore the chances of the patient adhering to the regimen could be increased.

METHOD OF PREPARATION:

COLD METHOD:

The cold technique is an effortless and uncomplicated approach for creating ethosomal and transethosomal gels.This method involves dissolving the drug and phospholipids in ethanol or a hydroalcoholic solution. Ethanol helps to liquefy the lipid bilayer, which improves the skin's ability to absorb substances.

The preparation of ethosomal and transethosomal gel forms starts by dissolving the needed ingredients—phospholipids, drug, an edge activator or surfactant like Tween 80 (for transethosomes), and a penetration enhancer like propylene glycol—in ethanol in a closed vessel. The mixture is then stirred by a magnetic stirrer at room temperature (~25°C) until all ingredients are completely dissolved. At the same time, distilled water is warmed separately to about 30°C. The aqueous phase is afterwards added to the ethanolic lipid phase gradually while continuously stirring at 700–1000 RPM for 30–60 minutes. The process helps create nanometric vesicles: ethosomes in the absence of a surfactant and transethosomes when a surfactant is added to improve deformability. The resultant dispersion is then sonicated or subjected to a high-pressure homogenizer to decrease the vesicle size and gain a more consistent particle distribution. The dispersion of the vesicles is added to a proper gelling agent, e.g., Carbopol 940,

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and mixed carefully to create a homogeneous gel. Lastly, the gel is neutralized with a proper neutralizing agent to achieve the required consistency and is kept at 4°C for stability. [8]

HOT METHOD:

The thermal method of preparing ethosomal and transethosomal gels is to heat phospholipids in a blend of glycol and ethanol to enable the development of vesicles. Phospholipids are suspended in aqueous ethanol that is heated to approximately 60°C for ethosomes, and transethosomes are prepared in the same way with the inclusion of edge activators such as sodium cholate or surfactants like Tween 80 to enhance permeability and deformability. In either instance, the lipid phase is dissolved in pre-heated distilled water at a temperature of 40–70°C, and ethanol, previously warmed to a temperature equal to that of the lipid phase, is employed for dissolving the drug. Ethanol phase is gradually added to the lipid dispersion under constant stirring at 700–1000 RPM for 30–60 minutes at the same temperature for effective vesicle formation. The resulting dispersion is then further treated with sonication or high-pressure homogenization to diminish vesicle size. For formulating transethosomal gel, a gelling agent such as Carbopol is added to develop the desired thickness.[9].[10]

ETHANOL INJECTION METHOD:

Ethanol injection method is a simple and effective method to prepare ethosomes and transethosomes. In this approach, the phospholipids in the lipid phase are dissolved in a limited quantity of an organic solvent such as ethanol. This solution is then slowly injected into the aqueous phase, i.e. water or an aqueous buffer with constant stirring. For transethosomes, surfactants like Tween 80 or Span 60 are used to enhance the deformability and penetration. To create a gel, gel-forming agents like Carbopol 934 or HPMC (hydroxypropyl methylcellulose) are added.

Phospholipid and surfactant (e.g. Tween 80) and drug in case of transethosomes and phospholipids and drug in case of ethosomes. These substances are mixed with ethanol and heated to a temperature ranging from 30 to 40°C. Keep stirring the solution until complete dissolution. Warm the distilled water to ~30 – 40°C. Now take the ethanolic phase in an injection and slowly inject it into the aqueous phase, slowly and dropwise, while doing continuous stirring with a magnetic stirrer or with a homogenizer. Ethosomes and transethosomes form from the ethanolic phase. They self-assembled to form vesicles. Now probe-sonication or extrusion are used to reduce the size of the vesicles and to also achieve uniform particle sizes. [11]

MECHANICAL DISPERSION/THIN FILM HYDRATION METHOD:

Thin film hydration method is used to prepare lipid vesicles by forming a thin lipid layer and then hydrating them to form vesicles. The creation of vesicular delivery systems usually starts with the dissolution of phospholipids in an organic solvent like chloroform, ethanol, or methanol in a round-bottom flask. The solvent is then completely evaporated under vacuum via a rotary evaporator, leaving a thin lipid film deposited on the flask's inner surface. The solvent is subsequently fully evaporated under reduced pressure using a rotary evaporator, resulting in a thin film of lipid remaining on the inner surface of the flask. This dried film is then hydrated with distilled water or isotonic phosphate-buffered saline (PBS) to create large multilamellar vesicles (MLVs), a process that can be enhanced using an ultrasound bath. These MLVs are subsequently subjected to sonication to generate small unilamellar vesicles (SUVs) (94,97). Phytoconstituents (PCs) that are meant for entrapment can be included at various stages of vesicle formation, depending on their solubility. Lipophilic PCs can be dissolved in organic solvents alongside phospholipids, as evidenced by extracts from Myrciaria jaboticaba (30), Narcissus tazetta (84), essential oils from Salvia triloba and Rosmarinus officinalis (102), Calendula officinalis (70) extract, cinnamon oil or (52), essential oil from Citrus limon var. Likewise, surfactants are utilized in niosome formation with certain agents. Alternatively, based on solubility properties, the PCs can be introduced into the hydration medium used for vesicle formation. The thin lipid film can be hydrated with PBS or other solutions containing herbal extracts or PCs. This can also include ethanolic (74) or aqueous (84) herbal solutions, or even the herbal extract itself. In some protocols, the extract is added after vesicle formation and blended into the vesicular dispersion.[12]. [13]

Drugs used to make ethosomal gels –

SOXHLET APPPARATUS	COLD METHOD	ETHANOL INJECTION METHOD	THIN FILM HYDRATION METHOD
Vitex negundo	Achillea millefolium	Curcumin longa	Andrographolide
Punica granatum	Curcumin longa	Sinomenium acutum	Karajin
			Cryptotanshinone

Drugs used to make transethosomal gels –

COLD METHOD	ETHANOL INJECTION METHOD	THIN FILM HYDRATION METHOD
Zingiber officinale	Eugenol	Mangiferin
	Zingiber officinale	Tinospora cordifolia
	Chenopodium murale	Sinapic acid
	Rosmarinic acid	Nux vomica (Brucine)
	Paeonia suffruticosa (Paeonol)	

EVALUATION:

ENTRAPMENT EFFICIENCY:

Entrapment efficiency, EE (%) is determined in order to quantify the amount of drug trapped inside the colloidal system. Little amount of formulation was initially taken in Eppendorf tube and then centrifuged at a rate of 14,000 rpm at 4 °C for 15 min. The process was repeated until unless cloudless form of supernatant was achieved by the help of ultracentrifuge (Remi) equipped with TLA-45 rotor. Cloudless supernatant was obtained, and concentration of drug was found with the assistance of UV/visible spectrophotometer at 299 nm wavelength for final result, additional amount of drug trapped in the colloidal system, was calculated although following formula. Each and every sample in estimated in triplicates.[6], [7], [15], [16]

$$\% \text{ Entrapment Efficiency} = \frac{Initial\ drug - final\ drug}{Initial\ drug} \times 100$$

IN-VITRO DIFFUSION STUDY:

In-vitro release of Vitex negundo extract from ethosomal systems was determined by using Franz diffusion cells. Cellulose membrane was used to separate the donor and receptor chambers, and PBS (pH 6.8) was used as the acceptor medium. The system was kept at 37°C and stirred at 50 rpm for 8 hours. Sink conditions were maintained by periodic sampling and replacement with fresh PBS. Samples were diluted and measured for drug release by using a UV spectrophotometer.

IN-VITRO SKIN PERMEATION TEST:

For the IVPT analysis, the total amount of drug permeated (QT) versus time was plotted. Fick's law was utilized, since it well explains steady-state drug permeation across the skin. This approach examines cases where, under sink conditions, the concentration of the drug in the receptor compartment is low compared to the concentration in the donor compartment. Steady-state drug flux per unit area, which is referred to as "Jss," is expressed as:

$$\text{Jss} = \frac{P \times Cd \times D}{e}$$

Here, P is the partition coefficient, Cd is the drug concentration in the donor compartment, D is the diffusion coefficient of QT, and e is the membrane thickness, either supplied by the supplier or experimentally determined. From the steady-state segment of the QT cumulative penetration profiles versus time, the permeability coefficient (Kp) and lag time (Tlag) were calculated. The gradient of the linear part of the graph was employed to compute the pseudo steady-state flux (Jss) in µg/cm²/h. The permeability coefficient (Kp) was subsequently calculated using Equation (3):

$$\text{Kp} = \frac{Jss}{Cd}$$

SCANNING ELECTRON MICROSCOPY (SEM):

The sample was covered with gold employing a sputter coater (JEOL, Tokyo, Japan) and examined under a scanning electron microscope (SEM) at an accelerating voltage of 20 kV. The surface characteristics of the nanovesicles were explored using SEM analysis.[17]

ZETA POTENTIAL:

Zeta potential, as determined by laser Doppler electrophoresis or dynamic light scattering, indicates the surface charge of particles in a formulation. Zeta potential is affected by the cumulative charge on lipid structures and serves to determine liposomal dispersion stability by providing an indication of how much electrostatic repulsion occurs between particles. Negative zeta potential, commonly from ethanol, improves vesicle stability through aggregation avoidance and facilitates higher percutaneous drug permeation. Values outside ±25 mV represent strong repulsive forces and stable dispersions, whereas those approaching zero indicate a tendency for vesicle flocculation and instability. Measurement of zeta potential of ethosomes and transethosomes is important to determine their stability and charge at the surface. Begin by diluting the formulation with double-distilled water or a buffer such as PBS to a concentration that avoids multiple scattering, ideally a 1:10 to 1:100 dilution. Avoid air bubbles; short sonication can be helpful but should not warm or burst the vesicular structure.

Following sample preparation, load the sample into a compatible cuvette or capillary cell of the zeta potential instrument, i.e., a Malvern Zetasizer or ELS instrument. Calibrate the instrument and set parameters like temperature (usually 25°C or 37°C), viscosity, refractive index, and dielectric constant. Aqueous systems are simulated with the Smoluchowski model to compute the zeta potential from electrophoretic mobility.[18], [19].

The measurement subjects the sample to an electric field, sensing particle motion to quantify zeta potential. Triplicate measurements are suggested for precision. Zeta potential measurements are a stability measure: >±30 mV is good stability, ±20–30 mV is moderate stability, and <±20 mV is poor stability and risk of vesicle aggregation. Ethanol in ethosomes can decrease surface charge, and edge activators in transethosomes can influence zeta potential values. They are utilized to measure short-term stability and follow changes in the course of time in a stability study.

PARTICLE SIZE:

The size of the particle and particle size distribution of ethosomes are essential for stability and efficient drug delivery. These are usually determined by methods such as dynamic light scattering. Particle size is determined by the lipid and ethanol content of the formulation and can be manipulated by methods such as sonication or extrusion. Smaller vesicles (ideally <300 nm) improve skin penetration and cellular uptake, with vesicles of about 70 nm having the optimal deposition in skin layers.

Particle size is also an important factor in lymphatic uptake and lymph node retention. A particle size of between 10 and 100 nanometers has been shown to be optimal for lymphatic uptake after subcutaneous injection. Particles below 10 nm are found to be taken up by systemic circulation, whereas particles above 100 nm are taken up by the lymphatic system but at a slower rate. Cholesterol, a steroid molecule, is usually incorporated in ethosomal systems to enhance their stability and entrapment efficacy of drugs. It reduces leakage by lowering vesicle permeability and fusion.

DIFFERENTIAL SCANNING CALORIMETRY (DSC) ANALYSIS:

DSC analysis is used to explore the physical condition of drug and excipients within ethosomal vesicles. Samples such as reference karanjin, a physical blend, and freeze-dried ethosomes (K-ETH) were scanned from 30–250 °C with a heating rate of 10 °C/min in a nitrogen environment using a Mettler DSC 60 system. Transition temperature (Tm) was noted to observe thermal behavior and potential interactions between the components.[20]

TRANSMISSION ELECTRON SPECTROSCOPY (TEM):

The shape and structure of APES were investigated using transmission electron microscopy (TEM) on a FEI Tecnai F20 G2. A sample was placed onto the specialized copper mesh of the electron microscope; any excess liquid was absorbed using filter paper; and a 2% phosphotungstic acid solution was applied for negative staining for 20 seconds. Following natural drying, the samples were examined using transmission electron microscopy (TEM). [21],[22]

DRUG CONTENT:

This is the weight of active ingredient trapped or entrapped in the formula. High drug content is indicative of good entrapment and uniform distribution of the vesicles in the gel base. To find out the content of the drug in ethosomal and transethosomal systems, a known volume (e.g., 1 mL) of the vesicular dispersion prepared is transferred to a centrifuge tube and centrifuged at 15,000 rpm for 1 hour at 4°C to isolate the unentrapped (free) drug from the drug encapsulated in the vesicles. The free drug supernatant is then carefully poured out after centrifugation, and the pellet containing the drug-loaded vesicles is kept. The pellet is subsequently resuspended in an appropriate solvent like methanol, which breaks the vesicles and releases the entrapped drug. The suspension is vortexed for 2–5 minutes to achieve complete disruption of the vesicles and release of the drug. The mixture obtained is filtered through Whatman No.1 filter paper or a 0.22 μm membrane filter to eliminate undissolved lipids or residues. Clear filtrate is analyzed on a UV-Visible spectrophotometer at the drug's λmax, or with HPLC for better precision, based upon the chemical nature of the drug. The amount of the drug is determined against a previously set standard calibration plot of pure drug in the same solvent.[23]

$$\% \text{ Entrapment Efficiency} = \frac{initial\ drug - final\ drug}{initial\ drug} \times 100$$

All operations are to be done in triplicate for statistical relevance and accuracy.

DRUG RELEASE:

The release profile indicates the manner in which the active ingredient is slowly released from the vesicles over time. This is typically quantitated using in vitro diffusion experiments with a dialysis membrane or Franz diffusion cell. Both ethosomes and transethosomes display sustained release, often because the lipid bilayer structure retards the diffusion of the active compound. To analyze the in vitro drug release from ethosomal and transethosomal formulations, the dialysis membrane technique is widely used. First, a dialysis membrane with a molecular weight cut-off of about 12,000–14,000 Da is left to soak overnight in distilled water to maintain flexibility and remove any remaining impurities and then rinsed with phosphate buffer (pH 6.8 or 7.4). A known quantity of the formulation is loaded into the pre-treated membrane, which is then sealed at both ends. The sealed membrane is submerged in a beaker or Franz diffusion cell filled with phosphate buffer as the release medium and kept at 37 ± 0.5°C to mimic physiological conditions. The medium is slowly agitated by a magnetic stirrer at 50–100 rpm or by a dissolution apparatus at 50–75 rpm. At predetermined time intervals, a predetermined volume of the buffer is removed for analysis, and an equivalent volume of fresh pre-warmed buffer is added to ensure sink conditions. The withdrawn samples are passed through a 0.22 µm membrane filter to eliminate any remaining vesicle components. Drug content in the samples is determined by a UV-Visible spectrophotometer at the drug's λmax or by HPLC for better specificity. [24], [25]

CONCLUSION:

Researching the diverse therapeutic qualities of naturally occurring drugs requires investigating novel drug delivery technologies. These methods are constrained by their reduced bioavailability and water solubility. Researchers have developed new methods for delivering drugs, such as encasing the drug in a carrier or altering the structure of the molecule by adding stabilizing groups. When developing any formulation, the most crucial consideration is that it needs to be produced in order to cross biological membranes. The drug's molecular size and lipid solubilities are the main considerations. According to recent research, ethosomal and transethosomal gel containing natural medications may be used to treat several illnesses, including skin inflammation.
the goal of the quickly emerging scientific field of pharmaceutical nanotechnology is to improve stability, solubility, absorption, and bioavailability of medications with low water solubility and restricted bioavailability. Furthermore, solutions based on nanotechnology enhance the long-term and accurate dispersion of the confined material, producing a potent therapeutic impact with fewer side effects. The need to create cutting-edge solutions that will increase therapeutic efficacy while avoiding the disadvantages of conventional approaches is highlighted by the prevalence of inflammatory illnesses and the urgent care they require in future aspects.

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