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REVIEW ON FORMULATION AND EVALUATION FOR ETHOSOMAL GEL

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ABSTRACT

Ethosomal gel is an advanced lipid-based vesicular system developed to improve the topical and transdermal delivery of drugs by enhancing their penetration through the stratum corneum. Ethosomes are composed mainly of phospholipids, ethanol, and water, with ethanol playing a key role in increasing vesicle flexibility and skin permeability. Incorporating ethosomes into a gel base enhances viscosity, spreadability, stability, and patient acceptability while prolonging drug retention at the application site. Ethosomal gels have shown promising results in delivering anti-inflammatory, antifungal, antiviral, analgesic, corticosteroid, and herbal drugs with improved bioavailability and reduced systemic side effects. This review highlights the composition, preparation methods, formulation strategies, evaluation parameters, advantages, limitations, and pharmaceutical applications of ethosomal gels as an efficient topical drug delivery system.

KEYWORDS: Ethosomes, Ethosomal Gel, Topical Drug Delivery, Transdermal Drug Delivery, Phospholipids, Ethanol, Vesicular Drug Delivery.

INTRODUCTION

Topical delivery can defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorder or general disease with the intent of possessing the therapeutic or other properties of the drug to the skin surface or within the skin. Topical preparations are frequently applied for the functioning at the site of their action with respect to penetration of drug into the underlying skin layers or mucous membranes. The wide range of topical products constitute semisolid preparations that comprise of ointment, cream, and gel.

Basic Principle of permeation

In the initial step, drugs molecules along the hair follicles or sweat ducts enter the skin and then absorption is done by the follicular epithelium and sebaceous glands. When a constant state has been achieved, diffusion by stratum corneum becomes the dominant pathway.

Drug Permeation incorporates the underlying steps

A) Sorption by stratum corneum.
B) Penetration of the drug through viable epidermis.
C) Drug uptake in the dermal papillary layer by capillary network.

Gels are system of semisolid preparation in which a liquid phase is contrived within a natural or synthetic gums polymeric matrix of three dimensional in which a vast degree of cross linking has been produced. The USP defines gels as a semisolid system consisting of dispersion produced by either inorganic particles of small size or organic molecules that are of larger size incorporated and penetrated by liquid.

ETHOSOMES

“Ethosomes are ethanolic liposomes”Ethosomes are drug delivery carriers that are noninvasive and causes the drugs to transfer to the deep layers of skin and/or the systemic circulation. These are vesicles that are soft, malleable and are designed for increasing the delivery of pharmaceutical agents. The vesicles are greatly known for their application in cellular communication and transportation of particle for no of years. Vesicle permit the controlling of rate of drug release for an extended time, by protecting the drug from immune response or other systems and thus has the potential to deliver just the right quantity of drug and maintain that concentration constant for larger periods of time. The major advancement in research of vesicle include finding of

a substitute of vesicle, which is also named as ethosomes. These are composed mainly of phospholipids such as phosphatidylcholine (PC), phosphatidyl serine (PS) and phosphatidic acid, high concentration of ethanol and water. The use of lipid vesicles in delivery systems for curing the skin disorders has influenced enhanced attention. Further, it is mostly concluded that classic liposomes are of no value as transdermal drug delivery carriers because they do not deeply penetrate the skin, but rather remain limited to the superficial layer of the stratum corneum. Only uniqually designed vesicles were proven to allow drug through transdermal delivery. Ethanol is known as an efficient permeation enhancer.

ADVANTAGES

1. Enhances drug penetration through the stratum corneum due to the high ethanol content. Improves topical and transdermal drug delivery.
2. Increases drug bioavailability at the site of application.
3. Suitable for the delivery of both hydrophilic and lipophilic drugs.
4. Provides high drug entrapment efficiency and loading capacity.Improves patient compliance because it is non-invasive, painless, and easy to apply. Offers controlled and sustained drug release, reducing dosing frequency.
5. Biocompatible, biodegradable, and generally safe for topical use.
6. Improves viscosity, spreadability, and residence time when incorporated into a gel base.
7. Reduces systemic side effects by delivering drugs directly to the target.
8. Improves viscosity, spreadability, and residence time when incorporated into a gel base.
9. Reduces systemic side effects by delivering drugs directly to the target.

DISADVANTAGES

1. High ethanol concentration may cause skin irritation, dryness, or erythema in sensitive individuals.
2. Ethanol evaporation during storage may reduce formulation stability.
3. Drug leakage may occur during prolonged storage.
4. Preparation requires careful optimization of formulation variables.
5. Phospholipids and other raw materials increase production cost.
6. Large-scale manufacturing is technically challenging.
7. Stability is affected by temperature and storage conditions.
8. Some drugs may be incompatible with phospholipids or other formulation components.
9. Requires airtight packaging to minimize ethanol loss.
10. Limited long-term clinical data are available for many ethosomal formulations.

Reasons for Better Performance

1. Enhanced skin permeation: The high ethanol content (20–45%) disrupts the lipid structure of the stratum corneum, allowing drugs to penetrate deeper into the skin.
2. Flexible vesicles: Ethosomal vesicles are highly deformable and can pass through narrow intercellular spaces without rupturing.
3. Synergistic effect: Ethanol increases skin permeability, while phospholipids facilitate drug transport into deeper skin layers, producing a synergistic enhancement.
4. Higher drug entrapment: Ethosomes can efficiently encapsulate both hydrophilic and lipophilic drugs, improving drug loading and stability.
5. Improved bioavailability: Greater drug penetration leads to higher local drug concentrations and enhanced therapeutic outcomes.
6. Sustained drug release: Incorporation into a gel base prolongs drug residence time, reducing dosing frequency.
7. Reduced systemic side effects: Localized drug delivery minimizes systemic exposure and associated adverse effects.
8. Better patient compliance: Ethosomal gels are non-invasive, easy to apply, and generally well tolerated

The properties of an ideal ethosomal gel

1. Appearance

The gel should be smooth, homogeneous, translucent or transparent, and free from lumps or phase separation.

2. Ph

Should be close to the physiological skin pH (about 5.0–6.5) to minimize skin irritation.

3. Viscosity

The gel should possess suitable viscosity to ensure easy application, good retention on the skin, and controlled drug release.

4. Spreadability

Good spreadability allows uniform application over the skin with minimal effort.

5. Extrudability

The gel should be easily extruded from the container without excessive force.

6. Homogeneity

The formulation should be uniform without any visible aggregates or coarse particles.

7. Drug Content Uniformity

Drug should be uniformly distributed throughout the gel to ensure accurate dosing.

8. Stability

The gel should remain physically and chemically stable during storage without phase separation or significant drug degradation.

9. Compatibility
It should be non-irritating, non-toxic, and safe for topical application.

10. Enhanced Skin
Permeation Ethosomal gels exhibit superior penetration through the stratum corneum because of the synergistic action of phospholipids and ethanol.

Applications of Ethosomal Gel
Ethosomal gel is widely used in topical and transdermal drug delivery because it enhances drug penetration through the skin and improves therapeutic efficacy.

1. Tropical Drug Delivery
*Delivers drugs directly to the skin for local treatment.
*Used in the management of acne, psoriasis, eczema, fungal infections, and wound healing.

2. Transdermal Drug Delivery
*Enhances drug permeation through the stratum corneum into systemic circulation.
*Helps avoid first-pass metabolism and improves bioavailability.

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4. Anti-inflammatory Therapy
*Used for delivering NSAIDs such as diclofenac, meloxicam, piroxicam, and celecoxib for the treatment of arthritis, muscle pain, and inflammation.

5. Antifungal Therapy
*Improves skin penetration of antifungal drugs such as ketoconazole and clotrimazole, leading to better treatment of fungal skin infections.

6. Antibacterial Therapy
*Used to deliver antibiotics for localized bacterial skin infections while minimizing systemic side effects.

7. Antiviral Therapy
*Ethosomal gels containing antiviral agents (e.g., acyclovir) enhance drug penetration and improve the treatment of herpes simplex infections.

8. Cosmeceutical Applications
*Used in formulations containing antioxidants, vitamins, retinoids, and skin-lightening agents to improve skin hydration, anti-aging effects, and pigmentation control.

9. Hormone Delivery
*Suitable for transdermal delivery of hormones such as testosterone and estradiol, providing sustained drug release and improved patient compliance.
*Improves skin penetration of antifungal drugs such as ketoconazole and clotrimazole, leading to better treatment of fungal skin infections.

10. Pain Management
*Delivers analgesics through the skin for localized and sustained pain relief in musculoskeletal disorders.

11. Delivery of Peptides and Proteins
*Ethosomal vesicles facilitate the transdermal delivery of certain peptides and protein-based drugs that normally exhibit poor skin permeability.

Brand name	Active ingredient	Indication
Voltaren Emulgel	Diclofenac 1%	Osteoarthritis, muscle and joint pain
Voveran Emulgel	Diclofenac diethylamine	Sprains, strains, arthritis

Omnigel	Diclofenac + Linseed oil + Menthol + Methyl salicylate	Pain and inflammation
Nise Gel	Nimesulide	Local pain and swelling
Moov Pain Relief Gel	Diclofenac + Menthol + Methyl salicylate + Linseed oil	Muscle and back pain
Iodex UltraGel	Diclofenac diethylami	Joint and muscle pain
Dynapar Gel	Diclofenac diethylamine	Musculoskeletal pain

There is no FDA approved marketed Ethosomal gel product with the my drug celecoxib.

CLASSIFICATION OF ETHOSOMES

1. Classical (Conventional) Ethosomes
*Composed of phospholipids, ethanol (20–45% w/w), water, and the drug.
*Ethanol imparts flexibility to the vesicles, enhancing penetration through the stratum corneum.
*Suitable for delivering both hydrophilic and lipophilic drugs.
*Advantages: High entrapment efficiency, improved skin permeation, and good stability.

2. Binary Ethosomes
*Contain phospholipids, ethanol, water, and an additional alcohol such as propylene glycol or isopropyl alcohol.
*The second alcohol further enhances vesicle flexibility and skin permeation.
*Provide better drug retention and permeability than classical ethosomes.

3. Transethosomes
*Consist of phospholipids, ethanol, water, and an edge activator or penetration enhancer (e.g., Tween 80, Span 60, sodium cholate).

*Combine the advantages of ethosomes and transferosomes.

*Exhibit superior deformability, deeper skin penetration, and enhanced transdermal drug delivery. ◆

Classification of Ethosomal Systems

S.NO.	Types	COMPOSITION	MAIN CHARACTERS
1.	Classical Ethosomes	Phosphilids +Ethanol+Water	High Skin Permeation,Good Stability
2.	Binary Ethosomes	Phosphilids +Ethanol+Water+Second Alcohol	Enhance Permeability and DruG Retention
3.	Transethosomes	Phosphilids +Ethanol+Surfactant+Water	Highest Deformability and Deepest Skin Peneteration.

Synthesis (Preparation) of Ethosomal Gel

Ethosomal gel is prepared in two stages

1) Preparation of the ethosomal suspension

2) Incorporation of the suspension into a gel base.

Step 1: Preparation of Ethosomes (Cold Method)

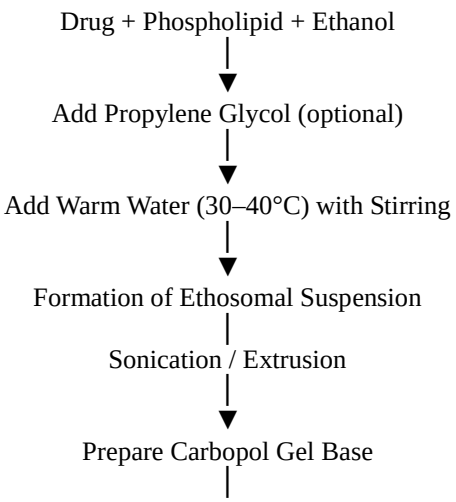
Dissolve the phospholipid (e.g., soya phosphatidylcholine) and the drug in ethanol under continuous stirring. Add propylene glycol (if used) and continue stirring until a clear solution is obtained. Heat distilled water separately to about 30–40°C. Add the warm water slowly to the ethanolic phase under continuous stirring to form ethosomal vesicles. Continue stirring for 5–10 minutes. Reduce the vesicle size by sonication or extrusion to obtain a uniform ethosomal suspension.

Step 2: Preparation of Gel Base

Disperse Carbopol 934 or Carbopol 940 in distilled water. Allow the polymer to hydrate for 2–4 hours. Add preservatives (e.g., methyl paraben and propyl paraben) if required. Neutralize with triethanolamine until a clear gel forms (pH approximately 6.0-7.0).

Step 3: Preparation of Ethosomal Gel

Slowly add the prepared ethosomal suspension to the gel base. Mix gently with a mechanical stirrer to avoid vesicle rupture. Stir until a homogeneous ethosomal gel is obtained. Transfer the gel into airtight containers and store at 4–8°C until evaluation.



ETHOSOMAL GEL PREPARATION METHODS

1. Cold Method

The most commonly used method. Phospholipids and drug are dissolved in ethanol. Water is added slowly with continuous stirring. Vesicles are reduced in size by sonication or extrusion. The ethosomal suspension is mixed with a gel base (e.g., Carbopol gel).

2. Hot Method

Phospholipids are dispersed in warm water (40–45°C). Drug is dissolved in ethanol and heated to the same temperature. Both phases are mixed under stirring. Sonication is performed if required. The ethosomal suspension is incorporated into the gel base.

3. Thin-Film Hydration (Mechanical Dispersion) Method

Phospholipids are dissolved in an organic solvent. The solvent is evaporated to form a thin lipid film. The film is hydrated with a hydroethanolic solution containing the drug. Vesicle size is reduced by sonication or extrusion. The resulting ethosomal suspension is converted into a gel.

4. Reverse-Phase Evaporation Method

Phospholipids are dissolved in an organic solvent. An aqueous phase is emulsified into the organic phase. The solvent is removed under reduced pressure to form vesicles. The suspension is incorporated into a gel base.

5. Injection Method

Lipids are dissolved in ethanol. The ethanolic solution is injected slowly into an aqueous phase under stirring. Ethosomes are formed spontaneously. The suspension is mixed with the gel base.

6. Sonication/Extrusion Method (Size Reduction Technique)

A supplementary technique used after ethosome preparation. Probe sonication, bath sonication, or membrane extrusion is employed to obtain smaller, uniformly sized vesicles before gel incorporation.

Drug Release Mechanism of Ethosomal Gel

The drug release from an ethosomal gel occurs through a combination of vesicle interaction with the skin, drug diffusion, and enhanced permeation produced by ethanol. The mechanism can be explained as follows:

i) Application to the Skin

- After topical application, the gel spreads uniformly over the skin surface.
- The gel base hydrates the stratum corneum and allows close contact of the ethosomal vesicles with the skin.

ii) Interaction of Ethosomes with the Stratum Corneum

- Ethanol present in the ethosomes fluidizes the lipids of the stratum corneum, reducing the barrier function of the skin.
- The phospholipid vesicles become highly flexible and penetrate into the deeper skin layers.

Drug Release from Ethosomes

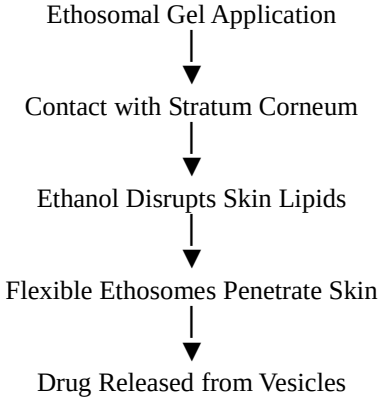
- The drug is released from the ethosomal vesicles by diffusion through the phospholipid bilayer.
- Vesicles may partially fuse with skin lipids, facilitating direct drug transfer into the skin.

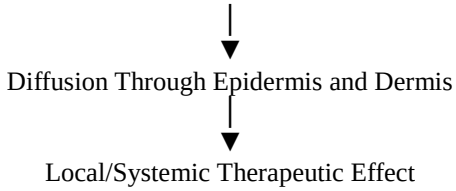
Drug Diffusion Through the Skin

- The released drug diffuses through the epidermis and dermis.
- Depending on the formulation, the drug can produce a local therapeutic effect or enter the systemic circulation.

Sustained Drug Release

- The gel matrix acts as a reservoir, slowing drug diffusion and providing prolonged drug release.
- Ethosomal vesicles also contribute to sustained release by gradually releasing the encapsulated drug.





Evaluation of Ethosomal dispersions

A] Optical Microscopy[34]

The cubosomal dispersions prepared were observedunder binocular compound microscope at 10X and40X magnification for studying the shape and surface morphology.

B] Particle Size and Polydispersity Index[44]

Particle size (z-average diameter) and polydispersity index (as a measure of particle size distribution) of celecoxib loaded cubosomal dispersion is performed by dynamic light scattering also known as photon correlation spectroscopy (PCS) using a Malvern Zetasizer 3000 Nano S (Malvern instruments, UK) at 25°C. Prior to measurements all samples were diluted using ultra–purified water to yield a suitable scattering intensity. The diluted cubosomal dispersion was poured into disposable sizing cuvette which is then placed in thecuvette holder of the instrument and analyzed. Airbubbles were removed from the capillary before measurement. Monodisperse samples have a lower PDI value, whereas higher PDI value indicates a wider particle size distribution and the polydisperse nature of the sample can be calculated by following equation:

$$PDI = d/d\ avg$$

Where,

d is the width of distribution denoted by SD, d avg is the average particle size denoted by MV(nm) in particle size data sheet.

C] Determination of percentage drug content[44]

5 ml of dispersion was taken and was further diluted with pH 7.4 phosphate buffer saline and the samples were analyzed spectrophotometrically at 252nm.

D] Determination of percentage entrapment efficiency[44]

The %EE of the vesicles was determined using centrifugation technique. The vesicular dispersion was centrifuged for 20 min. Supernatant containingunentrapped drug was withdrawn and measured UV spectrophotometrically at 252nm against phosphatebuffer saline pH 7.4. The amount of drug entrapped in cubosomes was determined.

E] SEM

The prepared samples of cubosomes are coated with a gold film under vaccum for 2min. The specimens are transferred to an ISI ABT SX-40A scanning electron microscope and digital images captured.

Evaluation of cubosomal gel

A] Appearance

About 1 week after preparation, the gel were visuall assessed for optical appearance (e.g., colour, turbidity, homogeneity, presence of macroscopic particles).

B] PH

PH of all formulations is determined by using digital pH meter by immersing the electrode in gel formulation and pH was measured.

C] Spreadability

Principle

Spreadability measures the ease with which the gel spreads on the skin. Good spreadability ensures uniform application and patient compliance.

Procedure

Place approximately 1 g of ethosomal gel between two clean glass slides.

Place a weight (typically 500 g) on the upper slide for 5 minutes to obtain a uniform film.

Tie the upper slide to a pulley and attach a 20 g weight.

Record the time (T, in seconds) required for the upper slide to move a fixed distance (e.g., 7.5 cm).

D] Viscosity

Principle

Viscosity indicates the flow behavior of the gel and influences drug release, spreadability, and stability.

Procedure

Transfer the ethosomal gel into the sample container of a Brookfield Viscometer.

Select a suitable spindle (e.g., Spindle No. 64).

Maintain the sample temperature at 25 ± 1°C.

Operate the viscometer at 10, 20, 50, and 100 rpm.

Record the viscosity in centipoise (cP) or mPa·s after the reading becomes constant.

Perform measurements in triplicate and report the mean ± standard deviation.

E] Stability Studies

Stability studies evaluate the physical, chemical, and formulation stability of the ethosomal gel during storage.

CONCLUSION

Celecoxib- and curcumin-loaded ethosomal gel is a promising topical delivery system that enhances skin penetration, provides sustained drug release, improves anti-inflammatory and analgesic effects, and minimizes systemic side effects. This formulation has significant potential for the effective management of inflammatory disorders and warrants further clinical investigation.

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