Formulation, Optimization and Characterization of Azelaic Acid Transethosomal Gel to Treat Hyperpigmentation

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Abstract*—Hyperpigmentation encompasses a group of common dermatological disorders characterized by excessive melanin deposition, resulting in conditions such as melasma, post-inflammatory hyperpigmentation, and solar lentigines. Despite the availability of numerous topical depigmenting therapies, their clinical efficacy is frequently compromised by the limited permeability of the stratum corneum, poor drug retention, low bioavailability, and undesirable adverse effects associated with prolonged use. Recent advances in nanotechnology have led to the development of transethosomal gel systems, which have emerged as promising carriers for enhancing topical drug delivery. Transethosomes are highly deformable lipid vesicles composed of phospholipids, ethanol, and edge activators that facilitate improved penetration through the skin barrier while maintaining drug stability and controlled release. Incorporation of these vesicles into gel formulations further enhances viscosity, spreadability, skin adherence, and patient acceptability, making them particularly suitable for long-term dermatological therapy. This review summarizes recent developments in transethosomal gel technology with a focus on its application in the topical management of hyperpigmentation. It discusses formulation strategies, mechanisms of enhanced skin permeation, physicochemical characterization, and critical evaluation parameters influencing formulation performance. The advantages of transethosomal gels over conventional topical formulations, including improved dermal penetration, sustained drug release, enhanced therapeutic efficacy, reduced systemic exposure, and better patient compliance, are critically examined. Furthermore, current challenges related to large-scale manufacturing, formulation stability, regulatory considerations, and clinical translation are discussed. Overall, transethosomal gel technology represents a versatile and innovative platform with significant potential to improve topical treatment outcomes for hyperpigmentation and to support the future development of advanced dermatological therapies.

***Index Terms*—Transethosomes; Transethosomal gel, Hyperpigmentation. Topical drug delivery, and Nanotechnology.**

I. INTRODUCTION

TRANSETHOSOMES

Transethosomes are an advanced vesicular drug delivery system developed to enhance the penetration of drugs through the skin. They are considered a third-generation lipid vesicular carrier that combines the advantages of ethosomes and transferosomes. Transethosomes are composed of phospholipids, a high concentration of ethanol, an edge activator (surfactant), and water. The presence of ethanol increases the fluidity of skin lipids, while the edge activator imparts flexibility and deformability to the vesicles, allowing them to pass through the narrow pores of the stratum corneum. This unique composition enables transethosomes to deliver drugs more efficiently into deeper layers of the skin or through the skin into systemic circulation. Conventional topical formulations such as creams,

ointments, and gels often exhibit poor skin penetration because the stratum corneum acts as a major barrier to drug absorption. Transethosomes overcome this limitation by enhancing drug permeation, increasing drug entrapment efficiency, improving stability, and providing sustained drug release. These advantages have made transethosomes a promising carrier system for the topical delivery of both hydrophilic and lipophilic drugs, particularly in the treatment of dermatological disorders such as acne, psoriasis, fungal infections, melasma, and hyperpigmentation.

Composition of Transethosomes:

The basic components of Transethosomes include:

- Phospholipids: Form the bilayer structure of the vesicles. Commonly used phospholipids include egg lecithin and soya lecithin.
- Ethanol: Usually present in concentrations of 20–40%. It increases the fluidity of both the vesicle membrane and the lipids of the stratum corneum, thereby enhancing skin permeation.
- Edge Activators (Surfactants): Surfactants such as Tween 80, Span 80, or sodium cholate provide elasticity and deformability to the vesicles, enabling them to penetrate through the skin more effectively.
- Water: Serves as the aqueous phase in which the vesicles are dispersed.

Mechanism of Skin Penetration:

The enhanced permeation ability of transethosomes is attributed to the combined action of ethanol and edge activators. Ethanol disrupts the highly ordered lipid structure of the stratum corneum and increases membrane fluidity, thereby reducing the skin barrier function. Simultaneously, the edge activator imparts flexibility to the vesicles, allowing them to deform and squeeze through the intercellular spaces of the skin without rupturing. Once the vesicles reach the deeper layers of the epidermis or dermis, the drug is gradually released, producing prolonged therapeutic action and improved bioavailability.

Advantages of Transethosomes:

- It improves patient compliance by providing semi-solid dosage forms for administration.
- Transethosomes ensures an enhanced permeation of drug through skin.
- It bypasses pre systemic metabolism.
- Raw material in the formulation is non-toxic in nature.
- Biocompatible and Biodegradable.
- Transethosomes are more stable.
- Reduced side effects like gastric irritation, vomiting.
- Controlled plasma level can be maintained.
- It is suitable for the drugs with short half-life and narrow therapeutic range.

Disadvantages of Transethosomes:

- Product loss during transfer from alcoholic and water media.
- Skin irritation or allergic reaction on contact dermatitis.
- Unsuccessful vesicle formation can Coalesce transethosomes.
- Since ethanol is used in the formulation, it can skin irritations.
- The molecular size of the drug should be Reasonable that it should be absorbed percutaneously. Information about the toxicological profile of Transethosomes is not known.

II. MATERIALS

Azelaic Acid was procured from Vijaya enterprises. Egg Lecithin, Span 60, Ethanol, Triethanolamine, Propylene Glycol, Methyl Paraben and Carbopol 940 were obtained from Merck Life Science Pvt. Ltd. Other chemicals and the reagents used were of analytical grade.

III. METHODOLOGY

Preparation of Transethosomal Azelaic Acid Gel by Mechanical Dispersion Method

Accurately weigh the required quantities of azelaic acid, egg lecithin, Span 60, and ethanol. Dissolve egg lecithin and Span 60 in ethanol under continuous magnetic stirring. Dissolve azelaic acid in the same ethanolic phase and stir until a clear solution is obtained. Add the required amount of distilled water dropwise to the ethanolic solution under continuous mechanical stirring (1000–1500 rpm) to facilitate the formation of transethosomal vesicles. Continue stirring for 30–60 minutes to obtain a homogeneous transethosomal dispersion. Separately, prepare the gel base by dispersing Carbopol 940 in distilled water and allow it to hydrate completely. Add propylene glycol

& methyl paraben followed by triethanolamine to adjust the pH and obtain a clear gel. Finally, incorporate the prepared transethosomal dispersion into the gel base with gentle stirring until a smooth, homogeneous transethosomal azelaic acid gel is obtained. The prepared gel was then transferred into suitable containers and stored for further evaluation.

Composition of Transethosomal Gel

Table no.1 Formulation table

Formulation	API(g)	Egg lecithin(polymer) (g)	Ethanol (%)	Cholesterol (g)	Span 60(g)	Propylene glycol (ml)	Carbopol (g)	Triethanolamine (ml)	Methyl paraben (g)	Dist. water
F1	2	2	30	0.1	0.5	3	2	2	0.1	q.s
F2	2	3	30	0.1	0.4	2	1	2	0.1	q.s
F3	2	2	40	0.1	0.5	4	2	2	0.1	q.s
F4	2	3	40	0.1	0.4	4	1	2	0.1	q.s
F5	2	2	35	0.1	0.5	3	2	2	0.1	q.s
F6	2	3	35	0.1	0.4	5	1	2	0.1	q.s

IV. EVALUATION STUDIES OF TRANSETHOSOMES:

IN-VITRO DIFFUSION STUDIES:

FRANZ DIFFUSION CELL METHOD:

Release investigations were conducted using the glass diffusion cell (Keshary-Chien type). The egg membrane was positioned on the receptor compartment, sandwiched between the donor and receptor compartments. The donor and receptor compartments were clamped together, and the transdermal gel was secured to them before being set in a water bath that was kept at 37.5°C. The receptor cell's volume was 20 ml. pH 7.2 phosphate buffer filled in the receptor compartment. The fluid was stirred at 600 rpm with a star head magnet to preserve the hydrodynamics of the receptor fluid. 2 ml samples were taken at predetermined intervals of time. The samples were analysed at 200 - 400 nm with the same volume of phosphate buffer pH 7.2 supplied to the receptor compartment to maintain sink conditions.

pH AND VISCOSITY:

The pH and viscosity are crucial parameters that influence the stability, drug release, and skin compatibility of the formulation. Typical ph range is 5.0-7.4 and the typical viscosity range is between 25000-40,000 (cP).

MELTING POINT:

The melting point of the transethosomal azelaic acid gel was determined using a digital melting point apparatus. A small quantity of the gel sample was placed in a clean, dry capillary tube and inserted into the apparatus. The temperature was increased gradually, and the temperature at which the sample softened or melted was recorded. The determination was performed in triplicate, and the average value was reported.

PARTICLE SIZE:

A drop of the freshly prepared transethosomal dispersion was placed on a clean, dry glass slide. A coverslip was gently placed over the sample to avoid trapping air bubbles. The slide was then observed under an optical microscope at suitable magnification (e.g., 40× or 100×) to examine the presence, shape, and distribution of the vesicles. Images were captured, and the vesicles were visually assessed for uniformity and spherical morphology.

SPREADABILITY:

The spreadability of the transethosomal gel was evaluated using the glass slide method. Approximately 1 g of the gel was placed between two clean glass slides. A standard weight was placed on the upper slide for 5 minutes to obtain a uniform gel layer and remove any trapped air. After removing the weight, an additional weight (e.g., 50 g) was attached to the upper slide through a pulley, allowing it to move freely. The time taken by the upper slide to travel a fixed distance (usually 7.5 cm) was recorded. The test was performed in triplicate, and the average value was calculated. Spreadability was determined using the formula:

S = (M × L) / T
Where:

- S = Spreadability (g·cm/s)
- M = Weight tied to the upper slide (g)
- L = Length moved by the slide (cm)
- T = Time taken to move the specified distance (s)

V. RESULTS AND DISCUSSIONS

POST FORMULATION STUDIES:
Melting point:
The melting point of Azelaic acid Transethosomal gel was found to be 108°C.

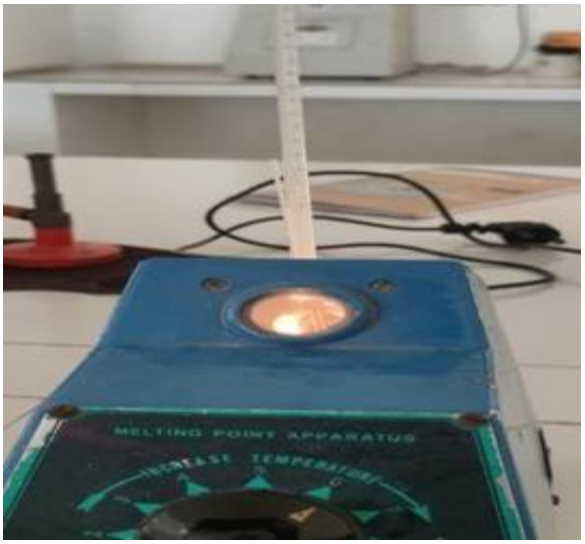

Fig.no.1. Melting Point

Viscosity: The Viscosity of Azelaic acid Transethosomal gel was found to be 8,000 cp.

Fig.no.2. Brookfield Viscometer

Spreadability:
Where:
Spreadibility(S) =

$$S = \frac{M \times L}{T}$$

- S = Spreadability (g·cm/s)
- M = Weight tied to the upper slide (g)
- L = Length moved by the glass slide (cm)
- T = Time taken to separate the slides (s)

Result:

- Weight (M) = 100 g
- Distance (L) = 6 cm
- Time (T) = 12 s

$$S = \frac{100 \times 6}{12} = 50\ \text{g} \cdot \text{cm/s}$$

Franz Diffusion:

Fig.no.3. Franz diffusion cell

VI. CHARACTERIZATION OF TRANSETHOSOMES

Particle Size:
Where:

$$\text{Mean Particle Size (nm)} = \frac{P_1 + P_2 + P_3}{3}$$

- P_1 = Particle size of Trial 1 (nm)
- P_2 = Particle size of Trial 2 (nm)
- P_3 = Particle size of Trial 3 (nm)

Table 2: Particle size

Trial	Particle Size (nm)
1	168.4
2	171.2
3	169.8

$$\text{Mean Particle Size (nm)} = \frac{168.4 + 171.2 + 169.8}{3}$$

= 169.8nm

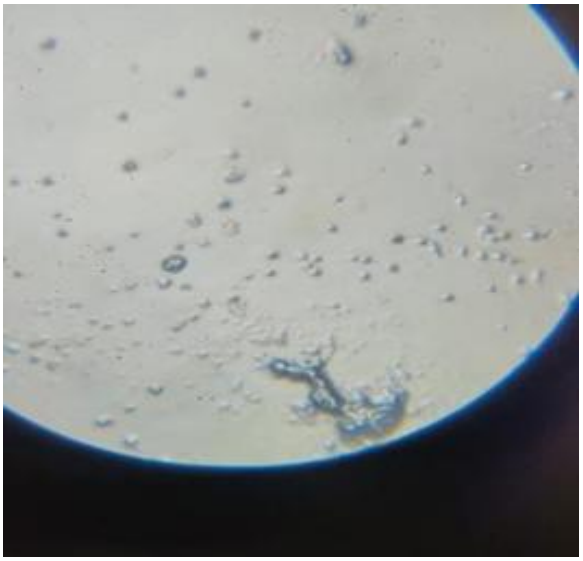

Fig.no.4. Particle size.

VII. CONCLUSION

The present study was successfully carried out to formulate and evaluate an Azelaic Acid-loaded transethosomal gel for the topical treatment of hyperpigmentation. The transethosomal formulation was prepared by the mechanical dispersion method using egg lecithin, ethanol, Span 60, and other suitable excipients, followed by incorporation into a Carbopol 940 gel base. Preformulation studies confirmed that Azelaic Acid possessed suitable physicochemical properties for formulation. The drug exhibited a melting point of 106.5°C, and maximum solubility was observed in phosphate buffer (pH 7.2), which was selected as the dissolution medium for further studies. The standard calibration curve demonstrated good linearity, indicating the suitability of the analytical method for drug estimation.

The prepared transethosomal gel exhibited satisfactory post-formulation characteristics. The gel showed good consistency, acceptable viscosity (8000 cP), and excellent spreadability (50 g·cm/s), indicating ease of application on the skin. Themelting point of the formulated gel (108°C) suggested compatibility of the drug with the selected excipients. The transethosomal vesicles exhibited an average particle size of 169.8 nm, confirming the successful preparation of nanosized vesicles suitable for enhanced skin permeation.

Overall, the developed Azelaic Acid-loaded transethosomal gel demonstrated desirable physicochemical properties and is expected to improve topical drug delivery by enhancing skin penetration and prolonging drug release. Therefore, the formulated transethosomal gel represents a promising topical drug delivery system for the effective management of hyperpigmentation. Further in vitro permeation, stability, and in vivo studies are recommended to establish its long-term therapeutic efficacy and safety before clinical application.

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