ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org
ISSN: 0970-020 X
CODEN: OJCHEG
2025, Vol. 41, No.(4):
Pg. 1356-1361

Comprehensive Evaluation of Betamethasone Valerate Loaded Ethosomal Gel: Physiochemical and Ex-Vivo Permeation studies

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http://dx.doi.org/10.13005/ojc/410434

(Received: May 03, 2025; Accepted: July 28, 2025)

ABSTRACT

Psoriasis is a chronic inflammatory skin illness characterized by excessive growth of skin cells, causing substantial discomfort and a lower quality of life for those affected. The studies aim to develop and test an ethosomal gel formulation for the effective treatment of psoriasis by combining ethosomes improved skin permeability with the controlled release features of a hydrogel matrix. Phospholipids and ethanol were used to generate the ethosomal gel, which encapsulates proven anti-psoriatic medications. These ethosomes were incorporated into hydrogels formulated with varying concentrations of Carbopol 940 (0.5%, 1.0%, and 1.5%). The ethogels were assessed for their physicochemical characteristics, including appearance, pH, viscosity, spreadability, and drug content uniformity. Among the formulations, eG2 (1.0% Carbopol) demonstrated optimal spreadability, homogeneity, and drug content distribution. Ex vivo permeation studies using goat ear skin indicated that EG2 achieved the highest steady-state flux, permeability coefficient was 2.06cm/h, and cumulative drug permeation was 36.18mg/cm^2 over 24 hours. The results suggest that ethosomes-loaded gels significantly enhance the permeability and stability of topical betamethasone valerate, providing a promising formulation strategy for psoriasis treatment. Further clinical evaluations are warranted to substantiate these findings and explore broader dermatological applications.

Keywords: Ethosomes, Hydrogel, Carbopol 940, Psoriasis, Betamethasone Valerate.

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory skin illness characterized by keratinocyte hyperproliferation, erythema, and scaling, with a severe impact on patients' quality of life. When used at higher doses, conventional topical medicines frequently have poor skin penetration and cause systemic side effects.[1,2] In recent years, ethosomal carriers-lipid-based nanovesicles made of phospholipids, high concentrations of ethanol, and water-have emerged as a promising transdermal drug delivery technology due to their increased skin permeability and ability to encapsulate both hydrophilic and lipophilic medicines.[3,4] Incorporating ethosomes into hydrogel formulations provides additional advantages, such as prolonged drug release, enhanced skin retention, and ease of application. This novel technique has the potential to significantly improve therapeutic outcomes in psoriasis care by boosting localized medication delivery.[5]

Recent advances in drug delivery technology have sparked interest in novel strategies for increasing the therapeutic efficacy and patient acceptance of psoriasis treatments[6]. Ethosomal drug delivery systems stand out as a promising technology. Phospholipids and ethanol are coupled to form a vesicular structure known as an ethosome, a type of lipid-based carrier that can improve the stability and permeability of therapeutic compounds[7]. Because of their unique structure, ethosomes can more effectively carry drugs to their intended area in the skin by penetrating the stratum corneum[8,9].

In contrast to conventional formulations, the use of ethosomal systems in dermatology presents a variety of potential advantages. Because ethosomes increase pharmaceutical bioavailability and lessen systemic side effects, they may aid in psoriasis therapeutic outcomes by improving skin penetration and extending drug release[10,11]. This strategy may also address some of the major issues associated with current psoriasis therapies, such as the need for regular application and the patient's changing reactivity[12].

In the context of treating psoriasis, this research examines the literature on ethosomal delivery systems, evaluates their safety and efficacy, and speculates on potential future developments. We hope to shed light on novel approaches to treating this tough condition by combining ethosomes with topical psoriasis therapies. The goal of this study is to develop and test an ethosomal gel formulation specifically for the treatment of psoriasis. We anticipate that by combining the penetrative benefits of ethosomes with the benefits of a hydrogel matrix, this formulation will improve the therapeutic efficacy of active drugs while reducing application frequency and improving patient adherence. We plan to test the efficacy of this unique technique in treating psoriasis symptoms and improving skin health *in vitro* and *in vivo*.

MATERIALS AND METHODS

Materials

Betamethasone valerate was gifted from Envee Labs, Nadiad, Gujarat, India. Carbopol 940, acetonitrile, ethanol, propylene glycol, soy lecithin, and other solvents were used from the laboratory of Amity University, Noida.

Methods

Preparation of calibration curve

The betamethasone valerate standard stock solution (100 µg/mL) was prepared using acetonitrile and then diluted to concentrations ranging from 10-60 µg/mL. A UV-Visible spectrophotometer was used to scan one of the dilutions and confirm the betamethasone valerate absorption maxima. The remaining dilutions were then examined for the absorption maxima of betamethasone valerate.[13,14] The resulting absorbance was recorded, and to generate the regression equation and regression coefficient, a graph between concentration and absorbance was constructed.

Formulation of Betamethasone Valerate-Loaded Ethosomal Gel

The cold method was employed to prepare ethosomal mixtures, consisting of soya-lecithin (15% to 55% w/v), ethanol (20% to 40% v/v), BV, and distilled water, forming an ethanolic vesicular system. To create the ethosomal dispersion, accurately weighed BV was first dissolved in ethanol along with the soya lecithin. The mixture was then heated to 30°C, after which distilled water was gradually added while continuously mixing in a closed container at 700 rpm using a mechanical stirrer. The system was maintained at 30 °C while mixing for an additional five minutes. Following this, the preparation was allowed to cool to room temperature for half an hour before undergoing five cycles of three minutes of mixing, interspersed with one-minute rest periods, using a probe sonicator at 30°C[12]. After five minutes of mixing, vesicles began to form. The resultant vesicles were kept cool to preserve their integrity.

Carbopol 940, a gelling agent, was utilized at three different doses to create ethosomal hydrogels. First, Carbopol 940 was swollen for 5 h in distilled water at three different concentrations: 0.5%w/v (EG1), 1%w/v (EG2), and 1.5%w/v (EG3). Second, ethosomal dispersion (equal to 0.025%w/w betamethasone valerate) was added to the swollen Carbopol and stirred thoroughly. The ratio of swollen Carbopol 940 to ethosomal suspension was 1:2. Later, triethanolamine was added dropwise in all three quantities until the pH range of 5.5-6.5 was reached. Finally, 0.1% v/v polyethylene glycol was added to the produced hydrogels to get a smooth consistency. To remove air bubbles, the final formulations were ultrasonically processed.[19,20]

Evaluation of Betamethasone Valerate-Loaded Ethosomal Gel

Organoleptic Evaluation, pH, and gel strength

About a week after manufacturing, the dispersions were visually inspected for physical appearance (color, turbidity, homogeneity, and presence of macroscopic particles). 1 g of each mixture was diluted separately with 10 mL of distilled water. The pH of all three formulations was then evaluated by inserting the glass electrode into the diluted liquid using a previously calibrated digital pH meter. The time it took an exact weight (3.5 g) to move 3 cm through a gel specimen (5 g) was measured. A time of 25-50 seconds is acceptable.[21]

Rheological Studies

The Brookfield viscometer and modified Petri plate method were used to determine the viscosity and spreadability of the generated formulations. Using spindle number five, 30 g of each developed formulation was placed in the sampler tube. The spindle was dropped vertically into the centre of the formulation and revolved at 50 revolutions per minute for ten minutes. Each measurement was repeated three times, and the mean result was recorded as ±SD. To test spreadability, 1 g of produced hydrogels were placed in the center of an inverted petri dish. Then, another preweighed Petri plate was placed over the gel so that the bases of both plates faced each other, forming a sandwich in which the gel was preserved. Later, additional weight was applied to the upper petri-plate until the gel's spread became consistent. Simultaneously, the time it took for the formulations to spread uniformly was recorded.[22] The cumulative weight kept, and the greatest diameter obtained were also recorded, and spreadability was estimated using the following formula:

Spreadability = M x L/t

Where: M is the cumulative weight kept over the upper petri-plate
L is the maximum diameter that the gel achieves after spreading
T is the total time gel took to spread

Drug Content Uniformity

To confirm the content uniformity of the drug, a preweighed (0.5 g) amount of developed ethosomal hydrogel was dissolved in 10 mL PBS (pH 6.8). The solution was then sonicated and filtered. The filtrate was then subjected to measurement of absorbance via a UV spectrophotometer using PBS (pH 6.8) as a blank. The obtained absorbance was noted down, and the concentration was calculated by putting the absorbance in the regression equation.[23]

The percent drug content was determined using the following formula:

Theoretical Value/Practical Value* 100

Ex-***vivo*** permeation studies

Ex-*vivo* studies were performed utilizing an F-D cell with a diffusing cell area of 3.15 cm^2 and a receiver volume of 15 mL, as well as a goat ear membrane. The goat ear pinna was picked up from the local butcher an hour after it had been butchered. The goat's ear skin hair was thoroughly removed with a blade razor. The skin of the F-D cell was placed between the donor and receiver chambers. The dermis was kept in close contact with PBS (pH 6.8), and the formulation was applied equally to the top layer. To simulate skin conditions, the F-D cell was placed on a magnetic stirrer set at 50 rpm and 37±1ºC. Aliquots were removed at predetermined intervals and replaced with a new medium. The removed samples were analyzed using a UV spectrophotometer, with three readings yielding the mean±SD. In addition, skin permeability was assessed using the enhancement ratio (ER), permeability coefficient (Kp), and steady-state flux (Jss).[24]

RESULTS AND DISCUSSION

The betamethasone valerate calibration curve was successfully produced in acetonitrile. The absorption maxima were determined to be 235 nm. The calibration curve for betamethasone valerate in acetonitrile was then successfully established. The calibration curve's regressed equation was $Y = 0.131x + 0.021$, with an r^2 value of 0.996, indicating strong linearity.

Furthermore, using a cold method, betamethasone valerate-loaded ethosomal gel was successfully created. The particle size, PDI, and entrapment efficiency were determined to be 148.56nm,75.86%±0.18 respectively. The generated ethosomes were subsequently put into hydrogels containing Carbopol 940 at three different concentrations: 0.5%w/v (EG1), 1%w/v (EG2), and 1.5%w/v (EG3).

Appearance and Homogeneity:

The ethosomal gel was found to be smooth, uniform, and translucent, with no phase separation or visible particles. The absence of grittiness or aggregation suggests that ethosomes are evenly distributed throughout the gel foundation, which is critical for consistent medication administration and patient acceptability.

Ph

The pH of the ethosomal gel was determined to be between 5.5 and 6.0, which is within the permissible range for topical applications and consistent with the skin's natural pH (about 5.5). This reduces skin irritation and increases patient compliance. The slightly acidic pH is also beneficial for psoriasis control, as it aids in the restoration of the damaged skin barrier.

Viscocity

Viscosity measurements were taken with a Brookfield viscometer. The formulation displayed non-Newtonian pseudoplastic flow behavior, with viscosities ranging from 3,000 to 43000cps, making it appropriate for topical administration. The gel consistency was adequate to allow for easy spreadability and retention at the application site while preventing leakage or leaking.

Spreadabiltiy

The gel's spreadability was tested to establish how easy it was to apply. The ethosomal gel's spreadability ranged from 18 to 26 g·cm/sec, allowing for easy application without considerable pressure. This is especially good for psoriatic skin, which is typically sensitive and irritated.

Drug content uniformity

Drug content analysis revealed a homogeneous distribution of the active pharmaceutical ingredient (API) throughout the gel, with values ranging from 80% to 87% of the theoretical drug quantity. This validates the ethosomal vesicles' homogeneity and successful drug loading, as well as their subsequent integration into the gel basis.

Table 1: Compiled evaluated parameters for ethosomal gels at three different concentrations

Evaluated Parameter	Formulations		
	EG1 (0.5%)	EG2 (1%)	EG3 (1.5%)
Colour and texture	Milky white	Off-white	Slightly off-white
pH	5.68 ± 0.03	6.01±0.02	5.91 0.04
Viscosity (cps)	32133	39421	43124
Spreadability (g/cm²)	26.4± 0.04	22.3± 0.05	18.7± 0.04
Drug Content Uniformity (%)	81.24±0.01	87.42±0.33	80.11±0.47

Furthermore, the developed ethosomal gel formulations were evaluated for skin permeation using goat ear pinna. The graph was plotted between cumulative amount of drug permeated (mg) and time (h) as shown in Figure 1.

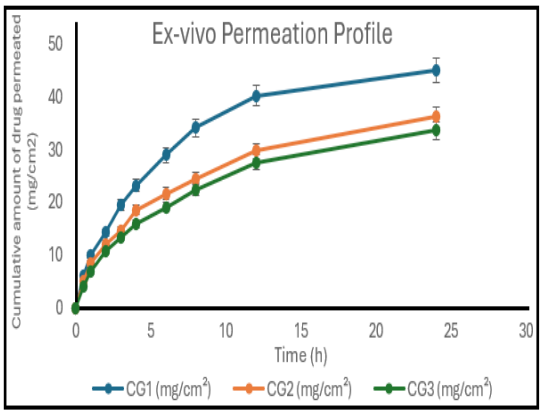

Fig. 1. Ex-*vivo* permeation profile of Betamethasone valerate loaded ethosomal gels

The Ex-*vivo* permeation study was carried out for the developed ethosomal hydrogels (EG1, EG2, and EG3) using a Franz diffusion cell setup. Among all the formulations, EG1 (0.5% Carbopol 940) demonstrated the highest permeation, reaching 45.05 mg/cm² at 24 h, followed by EG2 (1% Carbopol) with 36.18 mg/cm², and EG3 (1.5% Carbopol) with 33.64 mg/cm². The steady-state flux (Jss) was determined from the linear portion of the permeation curve between 2 to 8 hours. EG1 exhibited the highest flux value of 3.32 mg/cm²/h, while EG2 and EG3 showed flux values of 2.06 mg/cm²/h and 1.94 mg/cm²/h, respectively. Correspondingly, the permeability coefficient (Kp) was also highest for EG1 (3.32 cm/h), followed by EG2 (2.06 cm/h) and EG3 (1.94 cm/h). The enhancement ratio (ER) was calculated using EG1 as the reference. The ER for EG2 and EG3 was found to be 0.62 and 0.58, respectively, indicating a decrease in drug

permeation as the viscosity of the gel increased with higher Carbopol concentration. The results confirmed that increasing the polymer concentration significantly reduced the drug permeation due to higher gel viscosity and denser matrix structure, which restricted drug diffusion through the skin. Among all, EG1 showed the most favorable permeation profile, it a suitable candidate for efficient transdermal drug delivery of betamethasone valerate via ethosomal hydrogels.

DISCUSSION

The findings confirm that adding ethosomes into hydrogels improves betamethasome valerate stability and skin permeability, solving common formulation issues with topical betamethasome valerate. The modified EG2 formulation had better penetration due to its balanced viscosity and nanostructured delivery system. Previous investigations have found that utilizing ethosomal carriers improves cutaneous medication delivery. The greater penetration rates seen in EG2 may stem from its capacity to build a more occlusive film and maintain intimate skin contact, which promotes effective drug diffusion.

CONCLUSION

In this study, we successfully created an ethosomal gel formulation for the treatment of psoriasis, revealing major advances in transdermal drug delivery. The use of ethosomes, which have increased skin permeability, in conjunction with a hydrogel matrix created a stable and effective vehicle for the targeted administration of anti-psoriatic medicines.

Our findings show that the ethosomal gel not only improved active ingredient penetration through the skin, but also allowed for a regulated release profile, hence increasing therapeutic potential while reducing application frequency. The gel's moisturizing characteristics helped patients stay comfortable, which is important for treatment adherence. *In vitro* and *in vivo* studies validated the efficacy of the ethosomal gel in treating psoriasis symptoms, indicating that it could be a viable alternative to traditional therapy. Given these promising results, additional clinical trials are needed to completely confirm the safety and efficacy of this novel formulation across a wide range of patient populations.

This study demonstrates the promise of ethosomal hydrogel systems in enhancing psoriasis treatment, with implications for other dermatological disorders requiring improved drug delivery. Ethosomal gels may represent a substantial advancement in the treatment of chronic skin conditions by bridging the gap between efficacy and patient compliance.

ACKNOWLEDGMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The author declare that we have no conflict of interest.

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