DIFLUNISAL TRANSETHOSOMAL GEL FOR TOPICAL DRUG DELIVERY: FORMULATION AND CHARACTERIZATION

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ABSTRACT

Transethosomes are modern vesicular systems designed to enhance the transdermal delivery of various types of drugs, including lipophilic and hydrophilic drugs. This system features a flexible and easily deformable membrane resulting from the combination of phospholipids, ethanol, and surfactants as edge activators. Diflunisal, a lipophilic non-steroidal anti-inflammatory drug classified in the BCS class II, requires a delivery system that can overcome the limitations of permeation through the skin. The objective of the present research work is to develop a diflunisal-loaded transethosomal system, incorporate it into gel formulations, and characterize the developed transethosomal gel to optimize its applicability for topical delivery. Diflunisal transethosomes were produced by thin film hydration and sonication using Phospholipon 90G and Span 80 as edge activators in 30% ethanol. The vesicles were characterized based on their size, zeta potential, entrapment efficiency, and polydispersity index. The transethosome suspension was incorporated into Carbopol 934 gel at 0.5%, 1%, and 2%. The gels were tested for organoleptic properties, homogeneity, pH, viscosity, and spreadability. Transethosomes were nanosized (75.74 ± 1 nm), monodisperse (PDI of 0.244 ± 0.014), exhibited high entrapment efficiency (76.66 ± 0.99%), and demonstrated stability with a zeta potential of –32.67 ± 0.38 mV; gel incorporation maintained vesicle integrity. Increasing the gel-base concentration increases viscosity and reduces spreadability. However, 1% carbopol 934 concentration provided the optimal balance, offering the best physicochemical properties, including ideal pH (5.89 ± 0.06), spreadability (6.45 ± 0.06 cm), and viscosity (236770 ± 41.33 cPs), making it most suitable for topical delivery.

Keywords: Diflunisal, Characterization, Formulation, Topical Delivery, Transethosomal Gel

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to relieve inflammation (Dirga et al., 2024). Diflunisal is a commonly used for this purpose. Its mechanism of action involves the inhibition of cyclooxygenase (COX) enzyme, which catalyzes the conversion of arachidonic acid into prostaglandin precursors, thereby reducing prostaglandin synthesis (Blasco et al., 2024). Diflunisal is a lipophilic active ingredient with a log P value of 4.44 and molecular weight of 250.2 Da. This lipophilic compound is well-suited for formulation as a topical dosage form. By utilizing a transdermal delivery system, diflunisal can reach high concentrations at the site of inflammation. Additionally, transdermal delivery minimizes the risk of systemic side effects, providing a significant advantage in its application (Kuznetsova et al., 2021)

However, despite its favorable physicochemical characteristics for skin permeation, studies have indicated that only a small fraction of diflunisal from conventional cream formulations effectively penetrates the dermal layer (Kaur et al., 2017). Therefore, penetration-enhancing technologies are needed to increase the amount of diflunisal that successfully passes through the stratum corneum and reaches the dermis (Ramadon et al. 2022).

Hosam et al. (2019) formulated diflunisal into liposomal, transfersomal, and ethosomal vesicles for transdermal delivery. However, the resulting vesicles had relatively large particle sizes (>450 nm) and low entrapment efficiency (<66%), resulting in a reduced

cumulative amount of diflunisal permeating through the skin. Vesicular systems are biocompatible and biodegradable drug carriers designed for transdermal delivery. These systems enhance drug stability and efficacy while protecting the active compounds and reducing toxicity and side effects. Their lipid composition, which resembles that of the stratum corneum, enables deeper penetration into the epidermal layer (Rajan and Jose, 2011). One widely developed vesicular system is the transethosome.

Transethosomes are vesicles that combine the advantages of ethosomes and transfersomes. Transethosomes contain surfactants and ethanol at high concentrations to increase vesicle flexibility and reduce their size (Eloy et al., 2018). The use of surfactants affects the size, entrapment efficiency, and flexibility, thus increasing permeability and increasing the amount of drug penetration (Mishra et al., 2011). The use of non-ionic surfactants in transethosomes for lipophilic compounds has been shown to produce good characteristics and penetration capabilities (Albash et al., 2019). Incorporating transethosomal systems into gel formulations offers a promising solution for further optimizing the topical delivery of diflunisal. Gels are highly versatile platforms that facilitate controlled drug release, improving the efficacy of the active ingredient and patient compliance owing to their ease of application and stability. The gel base concentration is particularly critical as it influences the viscosity and spreadability of the formulation, both of which are key factors in determining the rate and efficiency of drug release at the target site. By adjusting the gel base concentration, it is possible to achieve a balance between the desired drug release and formulation properties. This study aimed to develop a diflunisal-loaded transethosomal system, incorporate it into gel formulations, and evaluate the physicochemical properties of the resulting gel.

RESEARCH METHODS

Tools and Materials

The equipment used in this study included a rotary evaporator (Hahn Shin HS-2005s-N), glass beads, UV-Vis spectrophotometer (Shimadzu UV-1800, Japan), pH meter (Jenway 550 pH meter, USA), ultrasonicator (Qsonica), analytical balance (type 210-LC, Adam, USA), magnetic stirrer (IKA, Germany), particle size analyzer (Malvern Zetasizer, UK), centrifuge (Kubota 5100, Japan), refrigerator (Toshiba, Japan), vortex mixer (Digisystem Laboratory, Taiwan), water bath, and general laboratory glassware such as stirring rods, cuvettes, and centrifuge tubes.

The materials used in this study included diflunisal (Sigma Aldrich, Singapore), phosphatidylcholine (Phospholipon 90G) (Lipoid, Germany), Span 80 (Croda, Singapore), ethanol (Merck, Germany), methanol (Merck, Germany), dichloromethane (Merck, Germany), triethanolamine (Croda, Singapore), Carbopol 934 (Shree, India), potassium dihydrogen phosphate (Merck, Germany), sodium hydroxide (Merck, Germany), triethanolamine (Merck, Germany), propylene glycol, methyl paraben, and distilled water (Brataco, Indonesia).

Research Procedure

Preparation of Diflunisal Transethosome

The transethosome formulation was prepared according to the methodology described byAprianti (2023). Transethosomes were prepared using the thin-film hydration method with slight modifications to optimize vesicle formation and stability. The detailed formulations are presented in **Table I**. Diflunisal, Phospholipon 90G, and the selected edge activators were accurately weighed and dissolved in a mixture of dichloromethane and methanol at a ratio of 7:3 (v/v) to ensure complete solubilization of all lipid components. The organic solvents were then removed under reduced pressure using a rotary evaporator at 52℃ for 1 hour, producing a thin, uniform lipid film on the inner wall of the round-bottom flask. The rotation speed was gradually increased to 50, 100, and 150 rpm during the process. The resulting thin film was flushed with nitrogen gas for 2 minutes and stored at 4 ℃ for 24 hours to optimize vesicle formation. The resulting thin film was hydrated using a hydroalcoholic solution consisting of ethanol and phosphate buffer (pH 7.4) in a ratio of 3:7 (v/v). The hydration process was carried

out for one hour using glass beads with gentle stirring. The subsequent step was vesicle size reduction, which was performed by sonication at 30% amplitude for 5 minutes. The resulting transethosome suspension was stored at 4 ℃ until further characterization.

Table I. Diflunisal Transethosome Formulation

Material	Concentration (%)
Diflunisal	1
Phospholipon 90G	2,5
Span 80	0,75
Ethanol:buffer phosphate (pH 7,4)	ad 100

Transethosomes Characterizations

Vesicle Size, Zeta Potential, and Polydispersity Index (PDI)

The vesicle size and size distribution were measured using a particle size analyzer (Zetasizer, Malvern) at a controlled temperature of 25 ℃. Prior to measurement, each transethosome suspension was diluted with water at a ratio of 1:10 to prevent double light scattering and ensure accurate measurement results. The particle size analyzer measured the average vesicle diameter, polydispersity index (PDI), and size distribution profile based on the Dynamic Light Scattering (DLS) principle. The zeta potential was determined using the same instrument through electrophoretic light scattering (ELS), in which diluted samples were placed into folded capillary cells to measure particle mobility under an applied electric field. This value reflects the surface charge and colloidal stability of the vesicles. All formulations were analyzed three times, and the results were expressed as the mean ± standard deviation to ensure data reliability and reproducibility (Sen et al., 2025)

Entrapment Efficiency (EE)

Ultracentrifugation was used to assess the entrapment efficiency. The vesicular system was centrifuged at 10,000 rpm at 4℃ for one hour to separate the unentrapped diflunisal. The supernatant was diluted with methanol, and the amount of unentrapped drug was quantified using UV-Vis spectrophotometry at 255 nm (Kaur et al., 2017). The entrapment efficiency was calculated using the following equation:

$$\%EE = \frac{Total\ drug - amount\ of\ the\ unentrapped\ drug}{Total\ drug} \times 100\%$$

Preparation of Transethosomal Gel

The gel formulation was prepared using a slightly modified method described by (Mahmoud et al., 2022). The transethosomal vesicle suspension was incorporated into a gel base containing carbopol 934. Carbopol 934 was dispersed in distilled water and homogenized at 1000 rpm until a uniform dispersion was achieved. Three different concentrations of Carbopol (0.5%, 1%, and 2%) were selected to evaluate the influence of variations in the gelling agent levels on the physical properties of the transethosomal gel. These concentrations were chosen because they represent low, medium, and high polymer contents, which are expected to produce differences in viscosity, spreadability, and stability. This comparison allowed the identification of an optimal concentration that provided suitable gel consistency and desirable application performance. The pH of the gel was adjusted to 5 using triethanolamine (TEA) to facilitate its formation. Methyl paraben, which was previously dissolved in propylene glycol, was added to the gel base as a preservative. After the gel base was formed, the transethosomal vesicles were gradually incorporated into the Carbopol gel with continuous stirring at 1000 rpm for 15 minutes to obtain a homogeneous transethosomal gel.

Table II. Formulation of Transethosomal Gel

Material	Concentration (%)		
	F1	F2	F3
Diflunisal transethosome suspension	0.3	0.3	0.3
Carbopol 934	0.5	1	2
Triethanolamine (TEA)	Qs	Qs	Qs
Propylene glycol	7.5	7.5	7.5
Methyl paraben	0.1	0.1	0.1
Distilled water	Ad 100	Ad 100	Ad 100

Transethosomal Gel Characterizations

Organoleptic Properties

The transethosomal gel formulation was visually evaluated for its appearance, color, and odor (Rahangdale & Pandey, 2021).

Homogeneity Test

The homogeneity of the transethosomal gel was assessed by spreading a small amount of gel onto a glass slide and observing its uniformity. A good gel exhibits a homogeneous texture without any visible coarse particles (Wahidah et al., 2024).

pH Measurement

The pH of topical formulations should be compatible with the physiological pH of the skin. The pH of the gel was determined using a digital pH meter calibrated with standard buffer solutions of pH 4 and 7. The measurement was performed by immersing the electrode in a 1% (w/v) dispersion of the gel in distilled water at room temperature (Rahangdale and Pandey, 2021).

Spreadability Test

A spreadability test was conducted to ensure uniform distribution of the gel when applied to the skin. The test was performed immediately after preparing the gel. Approximately 1 g of the gel sample was carefully placed on a 20 × 20 cm glass plate, covered with another glass plate, and a 100 g weight was placed on top of it. After 1 minute, the diameter of the spread gel was measured to determine its spreadability (Wahidah et al., 2024).

Viscosity

The viscosity of the transethosomal gel was measured using a Cole-Parmer viscometer equipped with spindle number L4. The sample was placed in a beaker, and the spindle was immersed in the gel up to the marked level before switching on the instrument. The viscosity was measured at a rotational speed of 2 rpm. The viscosity readings displayed on the viscometer were recorded and multiplied by a correction factor of 1.2336.

Data Analysis

The organoleptic properties and homogeneity were analyzed descriptively using IBM SPSS version 24. The parameters of pH, viscosity, and spreadability were assessed using one-way ANOVA, followed by a Post Hoc Tukey test. The Post Hoc Tukey test was performed to identify differences between groups.

RESULTS AND DISCUSSION

Diflunisal is a lipophilic non-steroidal anti-inflammatory drug classified as BCS class II, making it theoretically suitable for topical formulations (Kuznetsova et al., 2021). However, its permeation is still limited by the stratum corneum barrier, requiring a delivery system capable of enhancing drug penetration into deeper skin layers. Transethosomes, which combine ethosomal and transfersomal technologies, offer vesicles with more flexible and permeable membranes due to the presence of ethanol and surfactants as edge activators.

Therefore, they are expected to increase the amount of drug reaching the target tissue (Garg and Jain, 2022).

Transethosomes possess several advantages, including nanometer-sized particles, deformable vesicle membranes, and lipid compositions resembling those of the stratum corneum, which enable them to penetrate both intra- and intercellular skin pathways more efficiently. The incorporation of nonionic surfactants, such as Span 80, helps reduce vesicle surface tension, enhance membrane fluidity, and improve drug entrapment efficiency (Danaei et al., 2018). Additionally, the presence of ethanol in the formulation affects vesicle size and surface charge and increases skin permeability by disrupting the lipid arrangement of the stratum corneum (Eloy et al., 2018).

The transethosome characterization results of diflunisal showed that the vesicle size was 75.74 ± 1,00 nm, indicating that the vesicle system formed was included in the nanoparticle category. The small particle size indicates good physical stability and optimal skin penetration potential of the formulation. Vesicles below 200 nm can generally increase the ability of drug diffusion through the stratum corneum due to their large particle surface area and high deformability. According to Albash et al. (2019), the small particle size in the transethosome system is caused by the presence of edge activators such as Span 80, which reduce lipid surface tension and increase membrane flexibility, resulting in smaller vesicles that easily adapt to the skin layer. The PDI value of 0.244 ± 0.014 indicates a homogeneous particle distribution (PDI < 0.3), indicating that the system has good physical stability and is not prone to clumping (Danaei et al., 2018). This is important because the homogeneity of vesicle size directly affects the consistency of drug release and penetration efficiency.

The zeta potential of -32.67 ± 0.38 mV suggests adequate electrostatic stability, as particles with a charge greater than ±30 mV generate a repulsive force that helps to prevent aggregation (Honary and Zahir, 2021). The entrapment efficiency of 76.66 ± 0.99% indicates that most of the diflunisal was successfully entrapped within the vesicle lipid layer. These results are consistent with those of Esposito et al. (2024), who reported that the double lipid structure of transethosomes can increase the entrapment capacity of lipophilic drugs through hydrophobic interactions between drug molecules and phospholipids. The high entrapment efficiency also indicates that the vesicle formation process is optimal and does not experience significant degradation during lipid hydration. Vesicle size, polydispersity index (PDI), and entrapment efficiency collectively influence the transdermal penetration performance of the transethosomal system. Smaller vesicle sizes increase the surface area and deformability of the particles, enabling easier passage through the stratum corneum and deeper skin layers. A low PDI value reflects a uniform size distribution, which promotes consistent vesicle movement across the skin barrier and improves penetration uniformity. High entrapment efficiency ensures that a greater amount of drug is encapsulated within the vesicles, allowing more active compounds to be delivered into the skin rather than remaining on the surface or being lost during application. These parameters work synergistically to enhance dermal drug deposition and improve the overall efficiency of topical delivery. Overall, these characterization results demonstrate that diflunisal transethosomes have a small particle size, uniform distribution, good stability, and high entrapment capacity, potentially increasing the topical bioavailability of diflunisal.

Table III. Diflunisal Transethosome Characteristic

Characterization	Value (Mean ± SD)
Vesicle Size (nm)	75.74 ± 1,00
Zeta Potential (mV)	-32.67 ± 0.38
Polydispersity Index (PDI)	0.244 ± 0.014
Entrapment Efficiency(%)	76.663 ± 0.998

Incorporating transethosomal systems into gel formulations is a viable strategy for optimizing the transdermal delivery of diflunisal. Gels offer a convenient medium for the

controlled release of drugs, improving both the stability of the formulation and patient adherence by making application easier and more reliable. The transethosome gel was prepared using 1% carbopol as the base because of its ability to form gels at low concentrations, provide good viscosity, remain stable at high temperatures, and maintain compatibility with transethosomes (Amalia et al., 2024). Gel formation is highly pH-dependent; therefore, triethanolamine (TEA) was added to neutralize the carbomer, forming a stable polymer network and achieving the desired gel consistency. As the gel contains a high proportion of water, an antimicrobial agent is necessary to prevent microbial growth. Methylparaben was used as a preservative, which is most effective at pH 4–8, and its solubility and effectiveness were enhanced by propylene glycol, which also served as a humectant (Rowe et al., 2009).

The organoleptic properties of the transethosome gel were assessed in terms of odor, appearance, and color (Rahangdale and Pandey, 2021). The results showed that all the transethosomal gels had a white appearance, which was attributed to the transethosome suspension used as the dispersing phase. Additionally, all formulations displayed consistent odors across the samples. Images of the gel formulations are shown in **Figure 1**.

(a) (b) (c)

Figure 1. Physical Appearance Of The Gel

(a) F1 (b) F2 (c) F3

The pH was measured using a pH meter at room temperature. Topical gel preparations should have a pH within the physiological range of the skin (4.5–6.5) to prevent irritation (Amalia *et al.*, 2024). The results showed that The pH values of the formulations were 6.05 ± 0.04 (F1), 5.89 ± 0.06 (F2), and 5.71 ± 0.03 (F3). ANOVA revealed significant differences among the formulations ($p < 0.05$), and post hoc analysis indicated that F3 differed significantly from F1. The highest pH was observed in F1; however, all formulations fell within the physiological pH range of the skin, indicating their safety for use. These findings suggest that variations in the characteristics of the transethosomes, such as vesicle size and surface charge, may influence the final pH of the gel (Abdellatif et al., 2023). The concentration of Carbopol affects the pH of the gel owing to its inherent acidic properties. Higher concentrations of Carbopol release a greater number of hydrogen ions (H^+), which lowers the pH, whereas lower concentrations result in fewer ions being released, leading to a higher pH value. Moreover, higher Carbopol concentrations necessitate the addition of more pH adjusters to neutralize the gel, which further affects the final pH value.

Table IV. Characterization Results of Diflunisal Transethosomal Gel Formulations

Parameter	F1 (Mean ± SD)	F2 (Mean ± SD)	F3 (Mean ± SD)
pH	6.05 ± 0.04	5.89 ± 0.06	5.71 ± 0.03*
Spreadability (cm)	9.31 ± 0.03	6.45 ± 0.06*	3.96 ± 0.02*
Viscosity (cPs)	192793 ± 44.46	236770 ± 41.33*	320901 ± 19.01*

Where *: Significant difference ($p<0.05$) from F1

A spreadability test was conducted to evaluate the ability of the transethosomal gel to spread on the skin. An ideal gel has a spreadability value of 5–7 cm (Rakhim and Ermawati, 2024). Formula 1 showed the highest spreadability (9.31 ± 0.03 cm), followed by Formula 2 (6.45 ± 0.06 cm) and Formula 3 (3.96 ± 0.02 cm). The data were normally distributed and

homogeneous, allowing ANOVA, which showed significant differences among the formulas ($p < 0.05$). Post-hoc analysis indicated that F2 and F3 differed significantly from F1. Although F1 had the highest value, it exceeded the ideal range; therefore, F2 was considered the optimal formulation. In comparison, several studies have reported that increasing the Carbopol concentration leads to a decrease in spreadability. For instance, Nurman et al. (2019) demonstrated that gel formulations with higher Carbopol concentrations exhibited reduced spreadability owing to increased viscosity, making it difficult for the gel to spread easily on the skin. Similarly, the findings highlighted that gels with higher Carbopol concentrations showed a significant decline in spreadability as the gel structure became more rigid. These results align with our study, where the spreadability decreased as the Carbopol concentration increased (Peneva et al., 2018)

The viscosity of the transethosomal gels was measured using a Cole-Parmer viscometer with an L4 spindle at 2 rpm. Viscosity for F1, F2, and F3 was 192793 ± 44.46 cPs, 236770 ± 41.33 cPs, and 320901 ± 19.01 cPs, respectively. ANOVA showed significant differences ($p < 0.05$), with post hoc analysis indicating F2 and F3 differed from F1. Increasing the concentration of Carbopol in gel formulations typically leads to an increase in viscosity, a relationship that is well documented in the pharmaceutical formulation literature. For instance, one study found that increasing the concentration of Carbopol in the gel base increased the viscosity of emulgel formulations. In another study, doubling the polymer concentration (from 0.5 % to 1 % w/w) significantly increased the consistency index of the hydrogel formulation, indicating a more rigid internal structure (Vlaia et al., 2022).

The pH, spreadability, and viscosity of the diflunisal transethosomal gel formulations were influenced by Carbopol concentration. While all formulations remained within the ideal pH range for skin compatibility, significant differences were observed, particularly with F1, which showed the highest pH value. The spreadability test revealed a decrease in spreadability with increasing Carbopol concentration, which aligns with previous studies demonstrating the effect of Carbopol on gel spreadability by increasing viscosity. Viscosity measurements further confirmed that higher concentrations of Carbopol resulted in more rigid gel structures. F2, despite having a lower spreadability than F1, remained within the optimal range, suggesting that it may offer the best balance of performance and skin compatibility. These findings underscore the importance of carefully balancing the Carbopol concentration to optimize the gel performance for topical delivery.

CONCLUSION

The diflunisal transethosome system successfully produced nanosized vesicles with a negative surface charge and high entrapment efficiency, indicating good stability and strong potential for improving the topical delivery of lipophilic drugs. Incorporating these vesicles into Carbopol 934 gel resulted in noticeable changes in the gel's physical properties, including pH, viscosity, and spreadability. Among the three tested formulations, Formula 2 (Carbopol 1%) demonstrated the most balanced characteristics, with acceptable viscosity, suitable pH for skin application, and spreadability within the ideal range of values.

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