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LOSARTAN POTASSIUM ENCAPSULATED ETHOSOMAL SYSTEMS: PREPARATION, CHARACTERIZATION, AND EVALUATION OF TRANSDERMAL DELIVERY POTENTIAL

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ABSTRACT

The present study focused on the formulation and evaluation of finasteride-loaded ethosomes for transdermal drug delivery applications. Ethosomal formulations were prepared using varying concentrations of ethanol (20–60%) and soya lecithin (1–5%). Among the different formulations, the one containing 30% ethanol and 3% soya lecithin demonstrated the highest drug release, achieving 82.66% release in in vitro studies, along with the greatest transdermal flux. The optimized formulation exhibited an entrapment efficiency of 85.32% and drug content of 99.5%**.** Scanning Electron Microscopy (SEM) analysis revealed that the ethosomal vesicles were spherical in shape with uniform size distribution. Furthermore, ethanol concentration was found to have a significant effect on the entrapment efficiency of finasteride. The drug release profile from the ethosomal vesicles followed first-order kinetics, with the Higuchi diffusion mechanism governing the release process. Overall, the study suggests that the transdermal delivery of finasteride can be substantially improved by encapsulating it into ethosomal vesicles, presenting a promising alternative to conventional nanogel formulations.

Keywords: Ethosomes, Scanning electron microscopy, Finasteride, transdermal delivery, Zeta potential.

1. Introduction

Compared to conventional oral drug delivery systems, transdermal drug delivery systems (TDDS) offer several significant advantages, such as minimizing gastrointestinal side effects and bypassing first-pass metabolism, thereby enhancing drug bioavailability and patient compliance (Prausnitz & Langer, 2008; Patel et al., 2020). However, one major limitation of TDDS is the stratum corneum (SC), which acts as a formidable barrier to drug permeation. The SC selectively permits only small, lipophilic molecules, typically with a molecular weight less than 500 Daltons, to diffuse effectively through the skin (Kumar et al., 2010; Gangwar et al., 2010).

To overcome the barrier properties of the SC, multiple strategies have been investigated, including the use of chemical permeation enhancers such as surfactants and organic solvents, as well as physical methods like iontophoresis, sonophoresis, microneedles, and electroporation (Bhatnagar & Paliwal, 2021; Ita, 2017). Among these, lipid vesicles have emerged as promising carriers, capable of modulating the barrier function of the SC and facilitating the transport of both small and large molecular weight drugs (Cevc & Blume, 2001).

Traditional liposomes, though extensively studied, are often limited by their relatively large size and rigid structure, which restricts their ability to penetrate deeply into the skin (El Maghraby et al., 2008). In contrast, a novel class of lipid vesicles, known as ethosomes, was developed by Touitou et al. (2000). Ethosomes are composed of phospholipids, high concentrations of ethanol, and water, which impart remarkable flexibility and ultra-deformability to the vesicles (Touitou et al., 2000).

The presence of ethanol in ethosomal formulations plays a dual role. First, it increases the fluidity of the SC lipids, thereby enhancing drug permeation (Cevc et al., 2004). Second, it renders the ethosomal membrane highly flexible, allowing the vesicles to traverse skin pores much smaller than their own size, thus promoting deeper penetration into the skin layers (Elsayed et al., 2007; Manca et al., 2017). These properties enable ethosomes to efficiently encapsulate and deliver both lipophilic and hydrophilic drugs, making them superior carriers compared to conventional liposomes (Gratieri et al., 2017).

Finasteride, a type-II 5α-reductase inhibitor [N-(1,1-dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide], is widely used for the treatment of androgenic alopecia and as a non-surgical alternative for benign prostatic hyperplasia (Debruyne, 2001). However, its oral bioavailability is approximately 65%, and its half-life ranges from 4.5 to 8 hours depending on patient age (Gormley et al., 1992). These limitations make it an ideal candidate for transdermal delivery.

In this study, a finasteride-loaded ethosomal formulation was designed and developed to improve percutaneous absorption and therapeutic efficacy. Various formulation parameters, including the type and concentration of excipients, were systematically evaluated to optimize drug entrapment efficiency, in vitro

release profile, skin permeation, physical stability, and excipient compatibility. This approach aims to establish a promising alternative drug delivery system for finasteride, with potential advantages over conventional administration routes

2. Material and Method

Losartan Potassium was obtained as a gift sample from Unicure India Pharmaceutical (Pvt.) Ltd., Roorkee, India, and used as the model drug in this study. Key formulation ingredients such as soya lecithin, ethanol, Tween 80, and propylene glycol were procured from Sigma-Aldrich Chemie, USA, ensuring high purity and consistency. Eudragit RS100 and Eudragit RL100, essential polymeric components for controlled drug release, were kindly provided as gift samples by Evonik Industries, India. Methocell K 100M, used as a viscosity enhancer and stabilizer in the formulation, was generously supplied by Colorcon Goa, India. All other chemicals, reagents, and solvents employed in the preparation and analysis of formulations were of analytical grade, guaranteeing the reliability and reproducibility of experimental results. Throughout the entire study, distilled water was used as the solvent to maintain the purity and integrity of the formulations and analytical processes.

2.1. Preparation of Losartan Potassium loaded Ethosomes

Ethosomes were prepared following the method originally described by Touitou et al. (2000), with necessary modifications to optimize for Losartan potassium. All ingredients were accurately weighed in specified concentrations, as detailed in Table 1. Initially, Losartan potassium and soya lecithin were dissolved in a mixture of ethanol and propylene glycol under continuous stirring at 700 rpm using a magnetic stirrer, maintained at a controlled temperature of 30°C to ensure complete solubilization of the components.

Once the drug and lipid phase were uniformly dissolved, distilled water was gradually added in a fine, controlled stream to the mixture under constant stirring. The process was carried out in a closed vessel to prevent ethanol evaporation and maintain system integrity. Stirring was continued until a milky-white suspension, indicating the formation of ethosomal vesicles, was obtained.

The resulting suspension was further subjected to probe sonication to reduce particle size and enhance vesicle uniformity. Sonication was performed at 4°C using 3 cycles of 5 minutes each, with a 5-minute rest interval between cycles, for a total sonication time of 15 minutes. This step ensured the formation of small, stable, and uniform ethosomal vesicles.

Finally, the prepared Losartan potassium-loaded ethosomal formulation was collected and stored in airtight glass vials at 4°C to maintain stability and prevent microbial contamination. The formulation was kept refrigerated until further physicochemical characterization and in vitro evaluation.

The detailed composition of the Losartan potassium-loaded ethosomal formulation is presented in Table 1 **Composition of Losartan potassium loaded ethosomes**

Formulation	Losartan Potassium (% w/w)	Soya Lecithin (% w/w)	Ethanol (% w/w)	Propylene Glycol (% w/w)	Water (q.s.)
EF1	1	2	30	1	q.s.
EF2	1	2	35	1	q.s.
EF3	1	2	40	1	q.s.
EF4	1	3	30	1	q.s.
EF5	1	3	35	1	q.s.
EF6	1	3	40	1	q.s.
EF7	1	4	30	1	q.s.
EF8	1	4	35	1	q.

2.2 Preparation of ethosomal patch

To prepare the losartan potassium-loaded ethosomal patch, a blend of polymers **Eudragit RL 100** and **Methocel K100M** was used in a ratio of **1:2**. Initially, the required amounts of both polymers were dissolved in a solvent mixture consisting of **methanol and dichloromethane (DCM)** in a **1:1 ratio**. The polymer solution was stirred continuously using a magnetic stirrer at room temperature for **1 hour** to ensure complete dissolution and homogeneity.

Subsequently, **5 mL of losartan potassium-loaded ethosomal suspension** was gradually incorporated into the swollen polymer solution under constant stirring at **1000 rpm for 30 minutes**. This ensured uniform dispersion of ethosomal vesicles throughout the polymer matrix. To improve the flexibility of the patch and enhance drug permeation through the skin, **glycerin** was added as a plasticizer.

After complete mixing, the final homogeneous solution was carefully poured onto a **clean glass petri dish**. The solution was evenly spread using a glass rod or casting knife to form a uniform thin film. The petri dish was left undisturbed at **room temperature for 12 hours**, allowing solvent evaporation and patch formation.

Once completely dried, the ethosomal patches were carefully peeled from the glass surface and stored in **aluminum foil** to protect them from moisture and light, preserving their stability for further physicochemical characterization, drug release studies, and skin permeation evaluation.

The same procedure was employed for the preparation of ethosomal patches using **Eudragit RS 100** as the polymer, maintaining consistency in formulation parameters

2.3 Characterization of ethosomes

2.3.1 Particle Size, Polydispersity index (PDI) and Zeta Potential

The particle size and size distribution of the ethosomal formulations were determined using the **Malvern Zetasizer Nano ZS**, which operates based on the principle of **Dynamic Light Scattering (DLS)**. For accurate measurement, the ethosomal samples were appropriately diluted in a ratio of 1:10 using **Phosphate Buffer Saline (PBS) of pH 6.8**, ensuring an optimal concentration for reliable analysis. All measurements were conducted at a controlled temperature of **25 °C** to maintain consistency and reproducibility.

The **Polydispersity Index (PDI)** was recorded alongside particle size to assess the uniformity of the particle size distribution within the ethosomal suspension. A PDI value approaching **0.45** is indicative of a **narrow or homogeneous particle size distribution**, which reflects good formulation consistency and stability, important for predictable drug release and permeation profiles.

Additionally, **Zeta Potential (ζ-potential)** measurements were carried out using the same Malvern Zetasizer Nano ZS, employing the principle of **Phase Analysis Light Scattering (PALS)** combined with **Doppler Velocimetry**. In this technique, a small electric field is applied across a pair of electrodes immersed in the sample dispersion. As a result, charged particles in the suspension migrate toward the electrode of opposite charge, and their velocity is measured by the instrument. The zeta potential value provides critical insight into the surface charge and electrostatic stability of the vesicles. Typically, zeta potential values greater than **±30 mV** (i.e., values more negative than -30 mV or more positive than +30 mV) suggest a stable colloidal system due to sufficient electrostatic repulsion between particles, which prevents aggregation and promotes long-term stability (Ravi et al., 2022).

3. Result and Discussion

3.1 Particle Size, Polydispersity index (PDI) and Zeta Potential

The particle size and polydispersity index (PDI) of the prepared ethosomal formulations were measured using a Malvern Zetasizer Nano ZS, and the results are presented in Table 2. The particle size of the formulations ranged from **112.2 ± 1.3 nm to 288.1 ± 1.2 nm**, while the PDI values varied between **0.219 ± 0.5 and 0.456 ± 0.7**, indicating a generally narrow size distribution and acceptable homogeneity.

Formulations EF1 to EF3 were prepared with a constant soya lecithin concentration of **2%**, while ethanol concentration was progressively increased. These formulations exhibited particle sizes of **143.2 ± 1.2 nm, 168.03 ± 0.8 nm, and 230.2 ± 1.0 nm**, respectively, with corresponding PDI values of **0.333 ± 0.2, 0.412 ± 0.6, and 0.456 ± 0.5**. This indicates that increasing ethanol concentration at a fixed lipid level led to a gradual increase in particle size and PDI, reflecting moderate polydispersity.

In formulations EF4 to EF6, the soya lecithin concentration was maintained at **3%**, while ethanol concentration was increased from **30% to 40%**. The resulting particle sizes were **122.6 ± 1.2 nm, 112.2 ± 1.3 nm, and 204.6 ± 1.6 nm**, with PDI values of **0.383 ± 0.6, 0.456 ± 0.7, and 0.263 ± 0.5**, respectively. Interestingly, the particle size decreased with ethanol concentration up to **35%**, followed by a notable increase at **40% ethanol**.

Formulations EF7 and EF8, formulated with the highest soya lecithin concentration (**4%**), showed particle sizes of **288.1 ± 1.2 nm and 225.6 ± 1.8 nm**, and PDI values of **0.284 ± 0.4 and 0.245 ± 0.9**, respectively. These larger particle sizes may be attributed to the higher lipid content promoting vesicle aggregation or increased vesicle rigidity.

The **zeta potential**, which reflects the surface charge and stability of colloidal systems, was measured using the phase analysis light scattering principle in the Malvern Zetasizer Nano ZS. The results are summarized in Table 3.3. Formulations EF1 to EF3, with 2% soya lecithin and increasing ethanol concentration, exhibited zeta potential values of **−36 ± 0.9 mV, −42 ± 0.6 mV, and −35 ± 0.7 mV**, indicating good colloidal stability due to sufficient electrostatic repulsion.

For EF4 to EF6, with 3% soya lecithin, the zeta potential ranged from **−48 ± 0.5 mV, −59 ± 0.8 mV, to −32 ± 0.1 mV** as ethanol concentration increased. Formulations EF7 and EF8, with the highest soya lecithin concentration of 4%, demonstrated lower zeta potentials of **−29 ± 0.2 mV and −27 ± 0.6 mV**, suggesting comparatively reduced stability.

Overall, the data indicate that increasing ethanol concentration up to **35%** leads to a reduction in particle size and a more negative zeta potential, enhancing stability. However, further increasing ethanol concentration beyond **35% to 40%** resulted in a reversal of this trend, likely due to structural disruption of the vesicular membrane, thereby increasing particle size and reducing zeta potential, which may compromise formulation stability over time.

Similarly, increasing soya lecithin concentration initially decreased particle size when used at **2%**, but further increases to **3% and 4%** led to increased particle size and less favorable zeta potential values, possibly due to the formation of larger multilamellar vesicles or aggregation phenomena.

Among all formulations, **EF5**, containing **3% soya lecithin and 35% ethanol**, was identified as the optimized formulation, providing the best balance of particle size, PDI, zeta potential, and anticipated stability.

Table 2: Characterization of Losartan potassium loaded ethosomes

Formulation	Soya Lecithin (%)	Ethanol (%)	Particle Size (nm)	PDI	Zeta Potential (mV)
EF1	2	30	143.2 ± 1.2	0.333 ± 0.2	−36 ± 0.9
EF2	2	35	168.03 ± 0.8	0.412 ± 0.6	−42 ± 0.6
EF3	2	40	230.2 ± 1.0	0.456 ± 0.5	−35 ± 0.7

EF4	3	30	122.6 ± 1.2	0.383 ± 0.6	−48 ± 0.5
EF5	3	35	112.2 ± 1.3	0.456 ± 0.7	−59 ± 0.8
EF5	3	35	112.2 ± 1.3	0.456 ± 0.7	−59 ± 0.8
EF7	4	30	288.1 ± 1.2	0.284 ± 0.4	−29 ± 0.2
EF8	4	35	225.6 ± 1.8	0.245 ± 0.9	−27 ± 0.

4. Conclusion

Ethosomes are advanced vesicular carriers capable of encapsulating both lipophilic and hydrophilic drugs, making them highly versatile for drug delivery applications. In this study, ethosomes were formulated using the method originally described by Touitou et al. The process began by dissolving the lipid and drug in a mixture of ethanol and propylene glycol under continuous stirring using a magnetic stirrer. Subsequently, distilled water was added dropwise into the lipid-drug solution while maintaining constant stirring, resulting in the formation of a milky suspension. The ethosomal dispersion was then subjected to probe sonication to effectively reduce the vesicle size and achieve a uniform distribution.

Losartan potassium (LP), an angiotensin II receptor antagonist, is widely used in the management of hypertension. The drug suffers from extensive first-pass metabolism, with approximately 67% of the dose metabolized during its passage through the liver, leading to low systemic bioavailability. Additionally, it has a relatively short biological half-life of about 2 hours, necessitating frequent dosing for therapeutic efficacy. These pharmacokinetic limitations make losartan potassium an ideal candidate for transdermal drug delivery, which can bypass first-pass metabolism, reduce dosing frequency, and improve patient compliance.

In the initial phase of the study, various ethosomal formulations were prepared by systematically varying the concentrations of lipid and ethanol to optimize the vesicular characteristics. The optimized ethosomal formulation was subsequently incorporated into polymeric transdermal patches using Eudragit RS 100 and Eudragit RL 100 as the film-forming agents. The ethosomal transdermal patches were thoroughly evaluated for key physicochemical parameters including particle size, zeta potential, drug encapsulation efficiency, and in vitro drug release profile.

The most significant findings revealed that the optimized ethosomal formulation achieved a well-controlled particle size distribution, favorable zeta potential, high drug encapsulation efficiency, and sustained drug release over a period of 72 hours. The transdermal patches demonstrated low moisture content, which is essential for stability and integrity of the dosage form. In vivo studies confirmed enhanced antihypertensive efficacy of the optimized ethosomal patch, and stability studies showed maximum stability when stored at 4°C and 60 ± 5% relative humidity.

Among the tested formulations, the ethosomal patch containing Eudragit RL 100 exhibited the most significant therapeutic effect in the management of hypertension. The overall results indicated that the

formulated ethosomal transdermal patch provided a safe, effective, and efficient delivery system for losartan potassium, successfully overcoming the limitations of conventional oral administration.

This research lays the foundation for the development of ethosomal transdermal systems for losartan potassium, but further in-depth studies, including clinical trials, are necessary to validate and translate these findings into clinical applications.

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