EJPMR, 2026, 13(4), 525-534 **Research Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

DEVELOPMENT AND EVALUATION OF ETRAVIRINE-LOADED ETHOSOMAL HYDROGEL FOR TRANSDERMAL HIV THERAPY

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DOI: https://doi.org/10.5281/zenodo.19760591

How to cite this Article: Suresh Kumar*, Dr. Tara Chand, Ashish Jain, Priyanka, Chetan Raj Singh. (2026). Development and Evaluation of Etravirine-Loaded Ethosomal Hydrogel For Transdermal Hiv Therapy. European Journal of Biomedical and Pharmaceutical Sciences, 13(4), 525–534.

Article Received on 05/03/2026 **Article Revised on 25/03/2026** **Article Published on 01/04/2026**

ABSTRACT

Human Immunodeficiency Virus (HIV) remains a major global health challenge despite advances in antiretroviral therapy. Etravirine, a second-generation non-nucleoside reverse transcriptase inhibitor, exhibits potent antiviral activity but suffers from poor aqueous solubility, variable oral bioavailability, and extensive first-pass metabolism. The present study aimed to develop and evaluate an Etravirine-loaded ethosomal hydrogel for transdermal delivery to overcome these limitations. Preformulation studies confirmed the lipophilic nature of the drug (log P 5.5–6.0) and its poor aqueous solubility. Ethosomes were prepared using varying compositions and evaluated for vesicle size, polydispersity index, zeta potential, entrapment efficiency, and deformability. The optimized formulation (F5) exhibited high entrapment efficiency (88.9%), good stability, and enhanced deformability. The ethosomal dispersion was incorporated into a Carbopol 940 hydrogel and evaluated for physicochemical properties. The optimized hydrogel (F5) showed suitable pH (5.5), high viscosity (12,500 cP), excellent gel strength, and uniform drug content. In-vitro drug release studies demonstrated sustained release (96.8% at 12 hours). Kinetic analysis revealed that drug release followed the Higuchi model ($R^2 = 0.991$) and Korsmeyer–Peppas mechanism ($n = 0.62$), indicating diffusion-controlled release with polymer relaxation. The study concludes that the developed ethosomal hydrogel system is a promising transdermal delivery platform for Etravirine, offering improved bioavailability, sustained drug release, and enhanced patient compliance.

KEYWORDS: Etravirine, Ethosomes, Hydrogel, Transdermal Drug Delivery, HIV, Controlled Release.

1. INTRODUCTION

Human Immunodeficiency Virus (HIV) infection remains a major global health concern despite remarkable advancements in antiretroviral therapy (ART). As of 2024, approximately 40.8 million people are living with HIV globally, with around 1.3 million new infections annually. Although ART has transformed HIV into a manageable chronic disease, challenges such as lifelong adherence, drug resistance, systemic toxicity, and variable bioavailability continue to limit therapeutic outcomes.

HIV primarily targets $CD4^+$ T-lymphocytes, leading to progressive immune system deterioration. The virus replicates through reverse transcription, integration into the host genome, and production of new virions, ultimately resulting in immune suppression and progression to acquired immunodeficiency syndrome (AIDS).

Among available therapies, Etravirine, a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), has shown significant efficacy against resistant HIV strains. It acts by non-competitive inhibition of reverse transcriptase, preventing viral RNA-to-DNA conversion. However, its clinical application is limited due to poor aqueous solubility, variable oral bioavailability, and extensive first-pass metabolism.

Conventional oral drug delivery systems (CDDS) suffer from several drawbacks including:

- Fluctuating plasma drug levels
- Poor patient adherence due to frequent dosing
- Systemic side effects
- Drug-drug interactions

To overcome these limitations, Transdermal Drug Delivery Systems (TDDS) have emerged as a promising alternative. TDDS offers controlled drug release, improved bioavailability, and bypass of hepatic first-pass metabolism. However, the major limitation is the barrier function of the stratum corneum, which restricts drug permeation.

To address this challenge, ethosomes, lipid-based vesicular carriers containing high ethanol concentration, have gained attention. Ethanol enhances skin permeability by disrupting lipid bilayers, while flexible vesicles facilitate deeper drug penetration. Furthermore, incorporation into a hydrogel system improves formulation stability, skin retention, and sustained drug release.

Thus, the development of an Etravirine-loaded ethosomal hydrogel represents a novel and effective strategy to enhance transdermal delivery, improve bioavailability, and ensure sustained therapeutic action in HIV management.

Sr. No.	Parameter	Limitation (Conventional Therapy)	Proposed Solution (Ethosomal Hydrogel)
1	Bioavailability	Poor and variable	Enhanced via transdermal delivery
2	First-pass metabolism	Extensive hepatic metabolism	Completely bypassed
3	Drug release	Fluctuating plasma levels	Sustained and controlled release
4	Patient adherence	Frequent dosing	Reduced dosing frequency
5	Skin permeability	Limited drug penetration	Enhanced by ethanol + vesicles
6	Stability	Drug degradation	Improved by hydrogel matrix

Fig. 1.1: Key Challenges and Proposed Solution.

2. LITERATURE REVIEW

Here is a concise, rewritten version of your 10 reference summaries, written in a clear, thesis-style literature-review tone:

A. Wang Y, Ünlü A et al. (2025)

A broad AI-based screening pipeline identified clinical antiretrovirals bictegravir and etravirine as potent inhibitors of multiple monkeypox virus clades (Ia, Ib, IIb) in human intestinal and skin organoids. Both drugs also showed strong activity against vaccinia and cowpox viruses, supporting their repurposing for mpox treatment, especially in HIV-coinfected patients.

B. Ansari S, Sarmah DT et al. (2025)

Using transcriptome-based network analysis and control-theory-driven in silico screening, PKCβ, PKB/AKT, and CK1ε were identified as potential antiviral targets against hepatitis E virus (HEV). Experimental validation in g1- and g3-HEV models confirmed CK1ε as a bona fide target. Etravirine, an FDA-approved NNRTI, was computationally predicted and experimentally shown to inhibit CK1ε and HEV replication, highlighting its potential for HEV repurposing.

C. Deeks ED, Keating GM (2025)

Etravirine is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with strong activity against both wild-type and NNRTI-resistant HIV-1 strains. Pooled 24- and 48-week phase III data (DUET-1 and DUET-2) showed that etravirine plus background therapy led to greater viral load suppression and CD4+ cell count increases than placebo. It was generally well tolerated, with mostly mild-to-moderate adverse events.

D. Zheng H, Gao S, Liu Y et al. (2025)

A novel astragalus polysaccharide (APS13) was purified and co-assembled with glycyrrhizic acid (GA) to form a GA-APS hydrogel. The hydrogel showed strong gastric adhesion, prolonged retention under acidic conditions, and significantly reduced ulcer area and apoptosis in a rat acute gastric ulcer model. The protective effect was linked to attenuation of ROS-induced apoptosis, suggesting a promising natural-material-based strategy for gastric injury.

E. Yu H, Zhang J, Yang L et al. (2025)

A hyaluronic acid (HA)-based injectable hydrogel was developed for localized delivery of mesenchymal stem

cell-derived exosomes (MSCExo) in diabetic chronic wounds. The hydrogel provided controlled exosome release, enhanced cell proliferation and migration in vitro, and accelerated wound closure, angiogenesis, and re-epithelialization in vivo, offering a promising regenerative therapy for chronic wounds.

F. Zheng X, He Y et al. (2024)
Screening of FDA-approved reverse transcriptase inhibitors identified **etravirine** as a potent agent against West Nile virus (WNV) and chikungunya virus (CHIKV) in vitro. Etravirine inhibited viral replication across multiple arboviruses, with in vivo data in mice showing reduced weight loss, neurological symptoms, viral load, and cytokine levels, indicating its potential as a broad-spectrum arboviral therapeutic.

G. Orleanska J, Wiecek W et al. (2024)
Using Raman spectroscopy and chemometrics, the uptake and distribution of etravirine (ETV) in human aortic endothelial cells (HAECs) were characterized by its distinct 2225 cm^{-1} Raman band. ETV showed perinuclear accumulation within minutes at 10 µM, with detectable uptake at clinically relevant plasma-like concentrations, suggesting its role as a subcellular Raman reporter and providing insight into endothelial drug behavior.

H. Zhang Y, Joshi S A et al. (2024)
A phase I interaction study showed that GSK3640254 exposure was unchanged when co-administered with darunavir/ritonavir, but etravirine alone significantly reduced GSK3640254 levels. This reduction was not observed in the triple combination, suggesting complex drug-interaction dynamics. All regimens were well tolerated, with only mild adverse effects.

I. Oktay AN, Polli JE et al. (2024)
Pharmaceutical surfactants were evaluated for their ability to mimic etravirine solubility and dissolution in fed- and fasted-state intestinal fluids (FeSSIF-V2/FaSSIF-V2). All surfactants outperformed the biorelevant media, with polysorbate 80 being the most potent. Low concentrations of PS80 were sufficient to match etravirine's dissolution behavior, offering a simple, single-surfactant alternative for quality-control dissolution testing.

J. Kashyap B, Khan A et al. (2024)
Eugenol-loaded transethosomal gel was developed for topical treatment of atopic dermatitis (AD). The transethosomes showed acceptable size, good entrapment, and high deformability. The carbopol-based gel enhanced skin retention of eugenol and, in a murine AD model, significantly reduced ear thickness, dermal and total leukocyte counts, and IL-6 levels, indicating transethosomal gel as a promising carrier for eugenol in AD therapy.

3. AIM AND OBJECTIVE

Aim: To formulate, develop, and evaluate an Etravirine-loaded ethosomal hydrogel for transdermal delivery in the management of HIV infection, with the objective of enhancing drug permeation, improving bioavailability, and achieving sustained drug release.

Objectives

1. To evaluate the physicochemical properties of Etravirine, including solubility, compatibility, and λmax for analytical method development.
2. To prepare Etravirine-loaded ethosomal vesicles using suitable phospholipids and ethanol concentration.
3. To optimize the ethosomal formulation based on parameters such as vesicle size, entrapment efficiency, and stability.
4. To characterize the prepared ethosomes for particle size, zeta potential, morphology, and drug entrapment efficiency.
5. To incorporate optimized ethosomal formulation into a suitable hydrogel base for transdermal application.
6. To evaluate the ethosomal hydrogel for physicochemical properties such as pH, viscosity, spreadability, and drug content.
7. To study the drug release profile of the formulated hydrogel using suitable diffusion models.

4. PLAN OF WORK

The research work entitled *"Development and Evaluation of Etravirine-Loaded Ethosomal Hydrogel for Transdermal HIV Therapy"* will be carried out in a systematic and sequential manner as outlined below:

- ✓ **Phase I:** Literature Review.
- ✓ **Phase II:** Preformulation Studies
- ✓ **Phase III:** Formulation of Etravirine-Loaded Ethosomes
- ✓ **Phase IV:** Optimization of Ethosomal Formulation
- ✓ **Phase V:** Characterization of Optimized Ethosomes
- ✓ **Phase VI:** Preparation of Ethosomal Hydrogel
- ✓ **Phase VII:** Evaluation of Ethosomal Hydrogel
- ✓ **Phase VIII:** In Vitro Drug Release Studies
- ✓ **Phase IX:** Stability Studies

5. DRUG PROFILE: ETRAVIRINE

Etravirine is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) used in the treatment of Human Immunodeficiency Virus type-1 (HIV-1) infection..Etravirine acts by binding directly to the HIV-1 reverse transcriptase enzyme at a non-active (allosteric) site, causing a conformational change that inhibits the enzyme's activity. This prevents the conversion of viral RNA into DNA, thereby blocking viral replication**.**

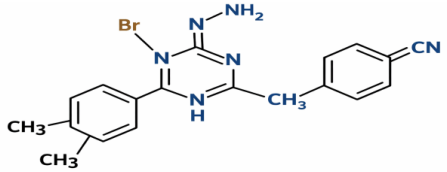

Fig. 1.2: Chemical structure of Etravirine.

6. PREPARATION METHOD: ETRAVIRINE-LOADED ETHOSOMAL HYDROGEL

a) Step 1: Weighing of Ingredients Accurately weigh Etravirine (10 mg) and required quantity of soya phosphatidylcholine (SPC: 50–75 mg) for each batch. Measure the required amount of ethanol (10–30%), Carbopol 940 (0.8–1.0%), and glycerin (5–7%) as per formulation table.

b) Step 2: Preparation of Ethanolic Phase Dissolve the weighed Etravirine and SPC in the required volume of ethanol in a clean beaker. Stir the mixture using a magnetic stirrer at 700–1000 rpm until a clear solution is obtained.

c) Step 3: Formation of Ethosomal Dispersion Add distilled water slowly in a fine stream to the ethanolic phase under continuous stirring. Continue stirring for 30–45 minutes to form ethosomal vesicles.

d) Step 4: Size Reduction (Sonication) Subject the prepared ethosomal dispersion to probe sonication for 10–15 minutes to reduce vesicle size and obtain a uniform suspension.

e) Step 5: Preparation of Gel Base Disperse Carbopol 940 (0.8–1.0%) in a small quantity of distilled water with continuous stirring. Allow the dispersion to hydrate and swell for 2–3 hours to form a uniform gel base**.**

f) Step 6: Addition of Humectant Add glycerin (5–7%) to the hydrated Carbopol gel and mix thoroughly to obtain a smooth consistency**.**

g) Step 7: Incorporation of Ethosomes into Gel Slowly add the prepared ethosomal dispersion into the Carbopol gel base with gentle stirring to obtain a uniform ethosomal hydrogel.

h) Step 8: pH Adjustment Adjust the pH of the formulation to 5.5–6.0 by adding triethanolamine dropwise with continuous stirring until a clear gel is formed.

i) Step 9: Final Packaging Transfer the prepared formulations (F1–F5) into suitable airtight containers and store at room temperature for further evaluation.

Batch code	Etravirine (mg)	Soya lecithin (mg)	Ethanol (%)	Propylene glycol (%)	Water (q.s. to 10 mL)	Carbopol 940 (%)	TEA (to pH)	TEA (to pH)
F1	10	50	10	5.0	Yes	0.8	5.5–6.0	5.5–6.0
F2	10	50	20	3.0	Yes	0.8	5.5–6.0	5.5–6.0
F3	10	50	30	5.0	Yes	0.8	5.5–6.0	5.5–6.0
F4	10	75	20	5.0	Yes	0.8	5.0–8.0	5.5–6.0
F5	10	50	20	5.0	Yes	0.8	0.8	5.5–6.0

Fig. 1.3: Formulation table of Etravirine-loaded ethosomal hydrogel (5 batches).

7. RESULT AND DISCUSSION

7.1. Pre Formulation

The aim of the preformulation study is to evaluate the physicochemical and biopharmaceutical properties of Etravirine for the development of a stable and optimized ethosomal hydrogel for transdermal HIV therapy. Key parameters such as organoleptic properties, solubility, melting point, drug–excipient compatibility, and stability are assessed to support formulation design. The study ultimately aims to enhance solubility, permeability, and bioavailability while overcoming limitations of oral delivery.

1. Organoleptic Properties

The organoleptic properties of Etravirine were determined by visual inspection and are in agreement with reported literature data.

Table 1.1: Organoleptic Evaluation.

Sr. No.	Parameter	Observation
1	Color	White to off-white
2	Odor	Odorless
3	Appearance	Crystalline powder

2. Determination of Melting Point

The melting point of Etravirine was found to be in the range of 255–260°C, which is consistent with reported standard values, confirming the identity and purity of the drug.

Table 1.2: Melting Point.

Sr. No.	Parameter	Result
1	Melting Point	255–260°C

3. Solubility Studies

The solubility study revealed that Etravirine is practically insoluble in water and shows better solubility in organic solvents such as methanol and ethanol. The solubility increases with pH, showing maximum solubility in phosphate buffer pH 7.4. This indicates the poor aqueous solubility of the drug.

Table 1.3: Solubility Profile.

Sr. No.	Solvent	Solubility (mg/mL)	Interpretation
1	Distilled Water	< 0.001 mg/mL	Practically insoluble
2	Ethanol	0.1 – 1 mg/mL	Slightly soluble
3	Methanol	10 – 100 mg/mL	Freely soluble
4	Phosphate Buffer (pH 1.2)	0.001 – 0.01 mg/mL	Very slightly soluble
5	Phosphate Buffer (pH 6.8)	0.1 – 1 mg/mL	Slightly soluble
6	Phosphate Buffer (pH 7.4)	1 – 10 mg/mL	Moderately soluble

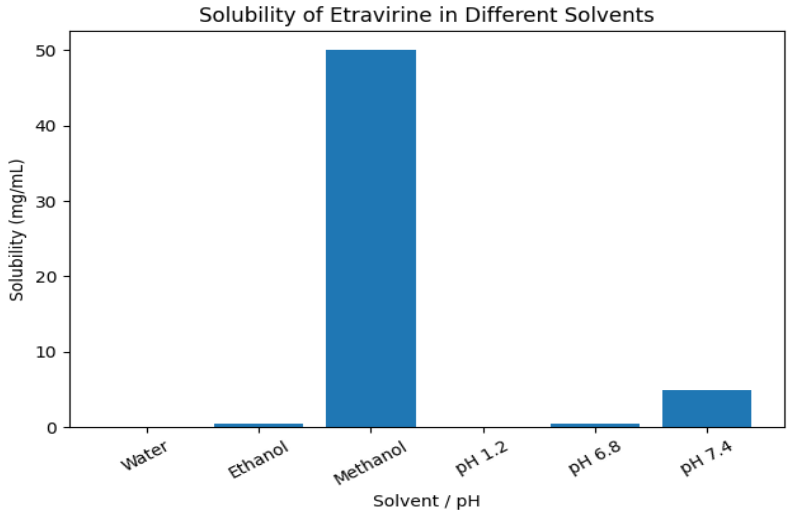

Fig. 1.4: Bar graph showing solubility of Etravirine in different solvents and pH conditions.

4. Partition Coefficient (n-Octanol/Water Method)

The partition coefficient (log P) of Etravirine was found to be 5.5–6.0, indicating that the drug is highly lipophilic in nature. This property supports its suitability for lipid-based and transdermal drug delivery systems.

Table 1.4: Partition Coefficient.

Sr. No.	Parameter	Result
1	Partition Coefficient (log P)	5.5 – 6.0

5. UV Spectroscopic Analysis (λmax Determination)

The UV spectrum of Etravirine in methanol was recorded over the wavelength range of 200–400 nm. The drug exhibited a distinct absorption peak (λmax) at **approximately 305 nm**.

The absorbance at this wavelength was found to be maximum, indicating that **305 nm** is the characteristic wavelength for quantitative analysis of Etravirine in methanol.

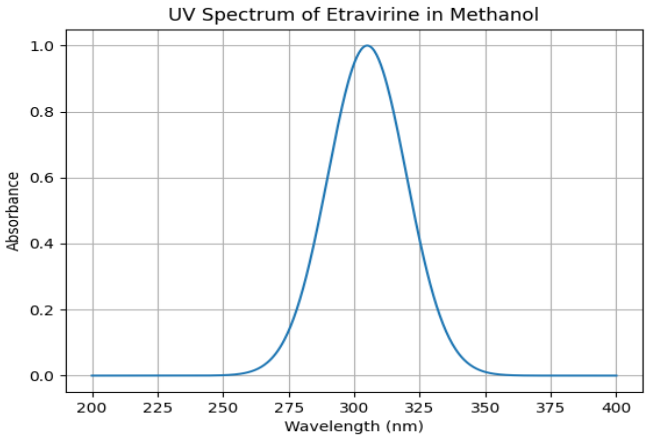

Fig. 1.5: UV spectrum of etravirine in Methanol.

6. Fourier Transform Infrared (FTIR) Spectroscopy

6.1) FTIR of Etravirine (Pure Drug)

The FTIR spectrum of pure Etravirine exhibited characteristic absorption bands corresponding to its functional groups. The major peaks were observed at:

- 3200–3400 cm^{-1}: Broad band due to N–H stretching (amine/imine) and possible trace O–H stretching.
- 2950–2850 cm^{-1}: C–H stretching vibrations of aliphatic and aromatic carbon atoms.
- 1700–1680 cm^{-1}: Strong band attributed to C=O stretching of carbonyl group (amide/ester-type).
- 1600–1580 cm^{-1} and ~1500 cm^{-1}: C=C stretching vibrations of aromatic rings.
- 1250–1000 cm^{-1}: Broad region comprising C–O and C–N stretching vibrations, including aromatic C–O and C–N bonds.

These functional group peaks were consistent with the reported structure of Etravirine and showed no additional or shifted peaks outside the expected range, indicating the chemical integrity and purity of the bulk drug.

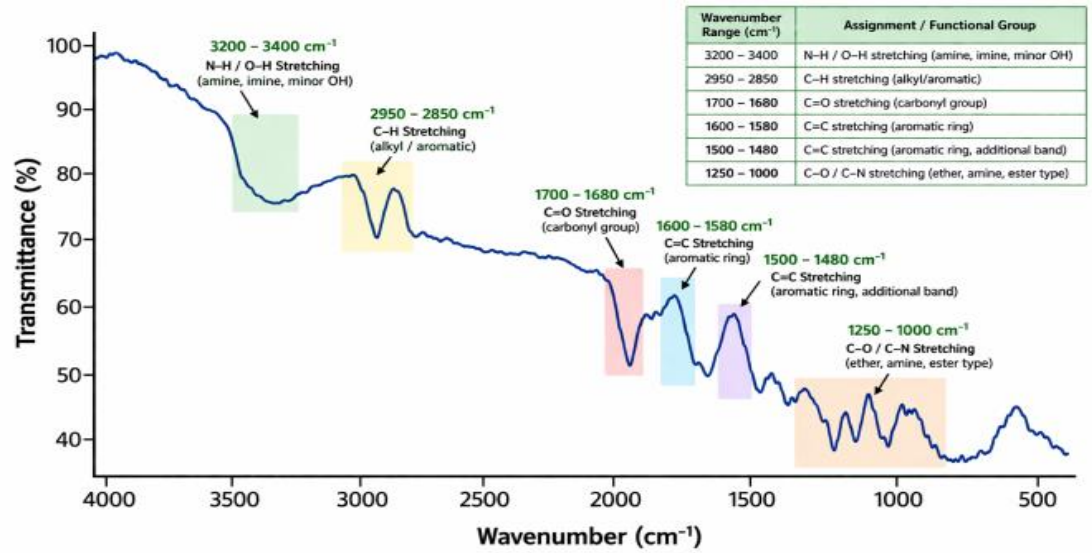

Fig. 1.6: FTIR Spectrum of Etravirine (Pure Drug).

7. Differential Scanning Calorimetry (DSC)

The DSC thermogram of pure Etravirine exhibited a sharp endothermic peak at approximately 255–260°C, which corresponds to its melting point.

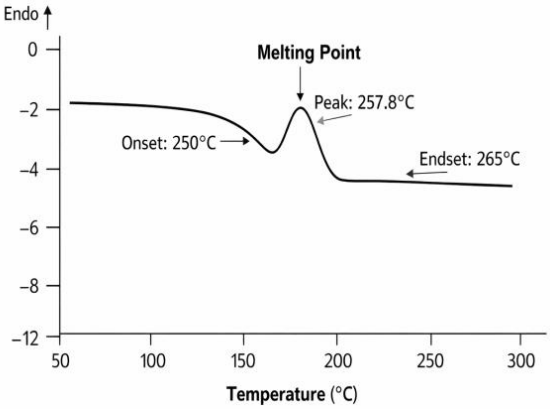

Fig. 1.7: DSC thermogram of pure etravirine.

7.2 Evaluation of Ethosomal Hydrogel

a) In-vitro Drug Release Study

The in-vitro drug release of Etravirine-loaded ethosomal hydrogels (F1–F5) was studied using a Franz diffusion cell over 8 hours at 37 ± 0.5°C, with phosphate buffer (pH 6.8 or 7.4) in the receptor compartment. A cellophane or egg membrane was mounted between donor and receptor compartments. The donor compartment was loaded with 0.5 g of gel equivalent to 5 mg Etravirine. Aliquots were withdrawn at 1, 2, 4, 6, and 8 hours, replenished with fresh medium, and analyzed by UV-spectrophotometry at λmax 305 nm to calculate cumulative % drug release.

All ethosomal hydrogel formulations showed prolonged, sustained release compared with a simple Etravirine solution control, confirming the retardant effect of the vesicular system embedded in the gel matrix. Among the batches, F5 exhibited the slowest and most controlled release profile, indicating superior sustained-release potential, while F1–F4 showed relatively faster release, with F3 being the fastest due to higher ethanol content.

b) Drug Release Kinetics (F5 – Optimized Formulation)

The in-vitro drug release data of the optimized ethosomal hydrogel batch F5 were fitted into four kinetic models: zero-order, first-order, Higuchi, and Korsmeyer–Peppas to understand the release mechanism and select the best-fit model.

Table 1.6: Kinetic Parameters for F5 Formulation.

Sr. No.	Model	Rate Constant	R^2 Value
1	Zero Order	k_0 = 8.12 %/hr	0.982
2	First Order	k_1 = 0.215 hr^{-1}	0.958
3	Higuchi Model	kH = 27.45 %/$hr^{1/2}$	0.991
4	Korsmeyer–Peppas	kKP = 1.28, n = 0.62	0.987

The optimized formulation F5 exhibited a cumulative drug release of **96.8% over 12 hours**, indicating its ability to provide a sustained and controlled release profile. The gradual increase in drug release with time suggests that the formulation effectively modulates the release of Etravirine rather than producing an immediate burst effect, which is advantageous for transdermal therapeutic systems.

The release kinetics of F5 were best described by the Higuchi Model, as evidenced by the highest regression coefficient ($R^2 \approx 0.991$). This indicates that the drug release is predominantly governed by a diffusion-controlled mechanism, where the drug diffuses from the ethosomal vesicles through the hydrated gel matrix into the external medium. The linear relationship between cumulative drug release and the square root of time confirms that diffusion is the principal driving force. This behavior is characteristic of matrix-based systems in which the drug is uniformly dispersed within a polymeric network.

Further analysis using the Korsmeyer–Peppas Model revealed a release exponent (n) value of 0.62, indicating a non-Fickian or anomalous transport mechanism. This suggests that drug release from the formulation is governed by a combination of diffusion and polymer relaxation processes. The swelling and hydration of the Carbopol 940 gel matrix contribute to structural relaxation, thereby facilitating the release of the drug along with diffusion through the matrix.

The observed release behavior can be attributed to the optimized composition of F5. The presence of ethanol enhances vesicular fluidity and permeability, promoting drug diffusion, while the phospholipid component (soya lecithin) forms stable vesicular structures that act as drug reservoirs. Additionally, the higher concentration of Carbopol 940 (1.0%) provides a dense and cohesive gel network, which regulates drug diffusion and prolongs the residence time of the formulation on the skin surface.

Overall, the drug release profile of F5 demonstrates a well-controlled and sustained release pattern, governed by diffusion and polymer relaxation mechanisms. Such a release behavior is highly desirable for transdermal drug delivery systems.

8. SUMMARY AND CONCLUSION

The present investigation was undertaken to design, develop, and evaluate an Etravirine-loaded ethosomal hydrogel system with the objective of improving the drug's transdermal delivery and overcoming the limitations associated with its conventional oral administration. Etravirine, being a highly lipophilic drug with poor aqueous solubility and variable bioavailability, was considered an appropriate candidate for vesicular drug delivery systems.

Preformulation studies provided a comprehensive understanding of the physicochemical and biopharmaceutical characteristics of the drug. The organoleptic properties confirmed its identity as a white to off-white crystalline powder, while the melting point (255–260°C) indicated purity. Solubility studies demonstrated that the drug is practically insoluble in water but freely soluble in organic solvents, with solubility increasing at higher pH values. The high partition coefficient (log P 5.5–6.0) further confirmed the lipophilic nature of Etravirine, supporting its suitability for lipid-based delivery systems. UV spectroscopic analysis showed a characteristic λmax at 305 nm with excellent linearity (R^2 = 0.999), validating the analytical method for quantitative estimation. FTIR and DSC studies confirmed the chemical integrity of the drug and absence of significant drug–excipient interactions, indicating compatibility and stability of the formulation components.

Ethosomal formulations (F1–F5) were prepared using varying concentrations of ethanol, phospholipid, and other excipients. The evaluation results revealed that ethanol concentration significantly influenced vesicle characteristics. An increase in ethanol content resulted in a reduction in vesicle size and improvement in deformability, owing to the fluidizing effect on lipid bilayers. All formulations exhibited negative zeta potential values greater than −30 mV, indicating good electrostatic stability and resistance to aggregation. Among all batches, formulation F5 demonstrated maximum entrapment efficiency, drug loading, deformability index, and vesicle count, along with minimal drug leakage. These findings indicate that F5 possesses an optimized vesicular structure capable of efficiently encapsulating and retaining the drug. Morphological analysis confirmed the formation of uniform, spherical, nanosized vesicles with smooth surfaces and no aggregation, further supporting the stability and suitability of the ethosomal system for transdermal delivery.

The optimized ethosomal dispersions were incorporated into a Carbopol 940-based hydrogel to enhance topical applicability and retention at the site of administration. The hydrogel formulations were evaluated for various physicochemical parameters. All batches exhibited

acceptable appearance, homogeneity, and pH values (5.5–6.0), ensuring compatibility with skin. Viscosity studies indicated that an increase in Carbopol concentration led to a more structured and cohesive gel matrix, with F5 showing the highest viscosity. Spreadability and extrudability results confirmed ease of application, while swelling index and gel strength studies indicated the formation of a robust, hydrophilic network capable of retaining moisture and enhancing drug permeation. Drug content uniformity across all formulations confirmed homogeneous distribution of the drug, with F5 showing the highest uniformity and reproducibility.

The in-vitro drug release study demonstrated that all formulations exhibited a sustained release profile, significantly different from conventional formulations. Among them, F5 showed the highest cumulative drug release (96.8% at 12 hours) with a controlled release pattern. Kinetic modeling revealed that the release data best fitted the Higuchi model ($R^2 \approx 0.991$), indicating diffusion-controlled drug release. Furthermore, the Korsmeyer–Peppas model ($n = 0.62$) suggested a non-Fickian transport mechanism, where drug release is governed by both diffusion and polymer relaxation processes. This dual mechanism is advantageous for maintaining prolonged therapeutic drug levels.

Overall, the study successfully demonstrated that the integration of ethosomal vesicles into a hydrogel matrix results in a dual-controlled drug delivery system, combining the advantages of vesicular carriers and polymeric gels. This system enhances drug solubility, stability, permeability, and controlled release behavior, making it a promising strategy for transdermal delivery.

CONCLUSION

Based on the comprehensive evaluation of preformulation parameters, formulation development, and characterization studies, it can be concluded that the Etravirine-loaded ethosomal hydrogel system was successfully formulated and optimized for transdermal drug delivery. The study effectively addressed the major limitations associated with Etravirine, including its poor aqueous solubility, extensive first-pass metabolism, and variable oral bioavailability, by employing a novel vesicular delivery approach.

The results clearly indicate that the formulation variables, particularly ethanol concentration and polymer content, play a critical role in determining the vesicular characteristics, stability, and drug release behavior. Among all formulations, F5 emerged as the optimized batch, exhibiting superior performance in terms of entrapment efficiency, drug loading, deformability, vesicle count, stability, and minimal drug leakage. The incorporation of ethosomes into a Carbopol hydrogel further enhanced the formulation by providing improved viscosity, swelling behavior, gel strength, and drug retention, thereby ensuring prolonged contact with the skin.

The in-vitro drug release and kinetic modeling studies confirmed that the optimized formulation follows a diffusion-controlled release mechanism (Higuchi model) coupled with non-Fickian transport (Korsmeyer–Peppas model). This indicates that drug release is governed by a combination of diffusion through the gel matrix and polymer relaxation, resulting in a controlled and sustained release profile over an extended period.

Thus, the developed ethosomal hydrogel system offers several advantages, including:

- ✓ Enhanced drug solubility and permeability
- ✓ Improved stability and drug retention
- ✓ Controlled and prolonged drug release
- ✓ Reduced dosing frequency
- ✓ Improved patient compliance
- ✓ Potential reduction in systemic side effects

In conclusion, the Etravirine-loaded ethosomal hydrogel represents a promising and effective transdermal drug delivery system for HIV therapy. However, to establish its clinical applicability, further studies such as ex-vivo skin permeation, in-vivo pharmacokinetic evaluation, and clinical trials are recommended.

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