RESEARCH PAPER

Formulation and Evaluation of Etravirine-Loaded Lipid Nanoparticles in Herbal Hydrogel for Sustained Antiviral Delivery

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ABSTRACT

The present study was undertaken to formulate and evaluate Etravirine-loaded lipid nanoparticles incorporated into an herbal hydrogel for sustained antiviral drug delivery. Etravirine is an antiretroviral drug used in the treatment of Human Immunodeficiency Virus Type-1 (HIV-1) infection. However, its poor aqueous solubility and limited dissolution may affect its delivery. Therefore, lipid nanoparticles were developed to improve drug incorporation and provide controlled drug release. The study included preformulation studies, drug–excipient compatibility testing, preparation and optimization of lipid nanoparticles, and incorporation of the optimized nanoparticles into an herbal hydrogel. The prepared formulations were evaluated for particle size, polydispersity index, zeta potential, entrapment efficiency, drug loading, pH, viscosity, spreadability, extrudability, drug content, and in-vitro drug release. The optimized lipid nanoparticles showed a particle size of 142.6 ± 4.8 nm, a polydispersity index of 0.218, a zeta potential of −32.8 ± 1.5 mV, an entrapment efficiency of 92.4 ± 1.2%, and drug loading of 8.75 ± 0.24%. Among the nine hydrogel formulations, DF6 showed the best overall results, with a pH of 6.18 ± 0.03, spreadability of 25.3 ± 0.5 g·cm/sec, drug content of 98.8 ± 0.4%, and cumulative drug release of 96.4 ± 0.9% after 24 hours. The drug release profile followed the Higuchi model, indicating diffusion-controlled release. Three-month stability studies showed negligible changes in the evaluated formulation characteristics. The findings indicate that the Etravirine-loaded lipid nanoparticle herbal hydrogel is a promising formulation for sustained drug delivery. Further studies are required to establish its safety, skin penetration, and therapeutic effectiveness.

Keywords: Etravirine, Lipid Nanoparticles, Herbal Hydrogel, Sustained Drug Release, Antiviral Drug Delivery.

How to cite this article: Rahul Kumar Singh Dr Shankar Lal Soni Dr Vandana Sharma Ms Aarti Mehta Sarfraj Kashid. Formulation and Evaluation of Etravirine-Loaded Lipid Nanoparticles in Herbal Hydrogel for Sustained Antiviral Delivery. Int J Drug Deliv Technol. 2026;16(88s):1164-1177. DOI: 10.25258/ijddt.16.88s.110.

1. INTRODUCTION

Human Immunodeficiency Virus Type-1 (HIV-1) infection remains an important health concern, and antiretroviral drugs are widely used to control viral replication. Etravirine is a second-generation non-nucleoside reverse transcriptase inhibitor used in the treatment of HIV-1 infection. It acts by inhibiting the reverse transcriptase enzyme, which is required for the conversion of viral RNA into DNA. Despite its therapeutic value, Etravirine has poor aqueous solubility, which creates difficulties in developing suitable drug delivery systems. Therefore, the selection of an appropriate formulation approach is important for improving its pharmaceutical properties and controlling drug release.

Lipid nanoparticles have received considerable attention as carriers for poorly water-soluble drugs. These systems can incorporate lipophilic drugs within a lipid matrix and influence their release characteristics. Their performance depends on factors such as lipid concentration, surfactant type, particle size, and preparation method. Evaluation of particle size, polydispersity index, zeta potential, entrapment efficiency, and drug loading helps determine the quality of the prepared nanoparticles. The use of lipid nanoparticles may provide a suitable approach for incorporating Etravirine into a formulation with desirable physical characteristics and sustained drug release.

Hydrogels are semisolid preparations that can retain water and provide a suitable base for drug delivery. Herbal ingredients and naturally derived materials, such as Aloe vera gel and guar gum, can be used in selected formulations to obtain the required consistency and physical properties. Incorporating lipid nanoparticles into a hydrogel may combine the drug-carrying properties of nanoparticles with the release-controlling effect of the hydrogel matrix. The resulting formulation can be evaluated for pH, viscosity, spreadability, extrudability, homogeneity, drug content, and in-vitro drug release to determine its suitability for further development.

The present study aimed to formulate and evaluate Etravirine-loaded lipid nanoparticles incorporated into a herbal hydrogel for sustained drug delivery.

Preformulation studies and drug–excipient compatibility testing were performed before preparing and optimizing the nanoparticles. The optimized nanoparticles were then incorporated into the hydrogel, and the prepared formulations were evaluated using appropriate physicochemical tests and in-vitro drug release studies. Stability studies were also conducted to examine changes in the optimized formulation during storage. The study was intended to identify a suitable formulation based on its physicochemical properties, drug content, release profile, and stability.

Methods

Etravirine was used as the model drug. Glyceryl monostearate (GMS) was used as the lipid, while Tween 80 and Poloxamer 188 were used as stabilizers. Aloe vera gel, guar gum and Carbopol 940 were used for hydrogel preparation. Propylene glycol, methyl paraben, triethanolamine and purified water were also used in the formulations.

Preformulation Studies

The organoleptic properties and solubility of Etravirine were examined. Solubility was studied in distilled water, methanol, ethanol, phosphate buffer pH 6.8 and phosphate buffer pH 7.4. The melting point was determined using the capillary tube method.

A stock solution of Etravirine was prepared by dissolving 10 mg of drug in methanol and making the volume up to 100 mL. Dilutions ranging from 10 to 100 µg/mL were prepared, and absorbance was measured using a UV-visible spectrophotometer to prepare the calibration curve.

Drug–Excipient Compatibility Studies

Drug–excipient compatibility was studied using Fourier-transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC). The results were examined for changes in characteristic peaks and thermal transitions.

Preparation of Etravirine-Loaded Lipid Nanoparticles

Etravirine-loaded lipid nanoparticles were prepared using glyceryl monostearate, Tween 80 and Poloxamer 188. The lipid phase was heated until melted, and the aqueous phase containing the stabilizers was prepared separately. The molten lipid phase was added to the aqueous phase under high-speed homogenization to form an emulsion. The emulsion was further processed using probe ultrasonication to reduce particle size. The resulting dispersion was cooled and evaluated.

Optimization of Lipid Nanoparticles

A (3^2) full factorial design was used to study the effects of glyceryl monostearate and Tween 80 concentrations. Nine batches, designated F1–F9, were prepared using three concentration levels of each variable.

Preparation of Herbal Hydrogel Formulations

The optimized lipid nanoparticle dispersion was incorporated into a herbal hydrogel containing Aloe vera gel, guar gum and Carbopol 940. Propylene glycol, methyl paraben, Poloxamer 188, triethanolamine and purified water were used according to the formulation requirements.

Nine formulations (DF1–DF9) were prepared by varying the concentrations of glyceryl monostearate, Tween 80, Aloe vera gel and guar gum.

Table 1. Composition of Etravirine-Loaded Lipid Nanoparticle Herbal Hydrogel Formulations

Ingredients (% w/w)	**DF1**	**DF2**	**DF3**	**DF4**	**DF5**	**DF6**	**DF7**	**DF8**	**DF9**
Etravirine	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Glyceryl Monostearate (GMS)	3.0	3.0	3.0	5.0	5.0	5.0	7.0	7.0	7.0
Tween 80	1.0	2.0	3.0	1.0	2.0	3.0	1.0	2.0	3.0
Poloxamer 188	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Aloe vera gel	3.0	4.0	5.0	3.0	4.0	5.0	3.0	4.0	5.0
Guar gum	0.50	0.75	1.00	0.50	0.75	1.00	0.50	0.75	1.00
Carbopol 940	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Propylene	10.	10.	10.	10.	10.	10.	10.	10.	10.

glycol	0	0	0	0	0	0	0	0	0
Methyl paraben	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Note: q.s. = quantity sufficient.

RESULTS AND DISCUSSION

Results of Preformulation Studies

Preformulation studies were performed to evaluate the physicochemical characteristics of Etravirine and to determine its suitability for the development of Etravirine-loaded lipid nanoparticles incorporated into a herbal hydrogel system. The results obtained from organoleptic evaluation, solubility studies, melting point determination, UV spectroscopic analysis, and calibration curve preparation are presented below.

Organoleptic Properties

The organoleptic properties of Etravirine were evaluated and the results indicated that the drug was present as a white to off-white crystalline powder with no characteristic odor. The observed properties were in agreement with the reported literature values, confirming the identity and purity of the drug sample.

Table 2: Organoleptic Properties of Etravirine

S. No.	Parameter	Observation
1	Appearance	Crystalline Powder
2	Color	White to Off-white
3	Odor	Odorless
4	Texture	Fine Crystalline
5	Nature	Crystalline

Solubility Studies

The solubility study revealed that Etravirine exhibited poor solubility in water and phosphate buffers, whereas it showed good solubility in methanol and ethanol. These findings indicate the lipophilic nature of the drug and support the selection of lipid-based nanoparticles for improving drug delivery.

Table 3: Solubility Profile of Etravirine

S. No.	Solvent	Solubility
1	Distilled Water	Practically Insoluble
2	Phosphate Buffer pH 6.8	Slightly Soluble
3	Phosphate Buffer pH 7.4	Slightly Soluble
4	Ethanol	Soluble
5	Methanol	Freely Soluble

Melting Point Determination

The melting point of Etravirine was found to be 262.4 ± 1.2°C, which was close to the reported literature value. The narrow melting range confirmed the purity and crystalline nature of the drug.

Table 4: Melting Point of Etravirine

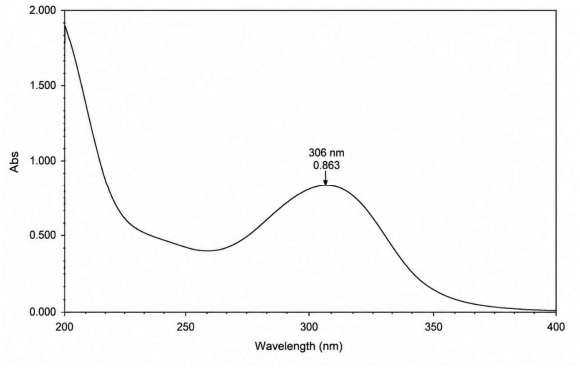
S. No.	Parameter	Result
1	Melting Point (°C)	262.4 ± 1.2

UV Spectroscopic Analysis

The UV spectrum of Etravirine was recorded in methanol over the wavelength range of 200–400 nm. The drug exhibited a maximum absorbance (λmax) at 310 nm, which was selected for further quantitative analysis.

Table 5: UV Spectroscopic Analysis of Etravirine

S. No.	Parameter	Result
1	Solvent Used	Methanol
2	Scanning Range	200–400 nm
3	λmax (nm)	306



Calibration Curve Preparation

The calibration curve of Etravirine was prepared in methanol over the concentration range of 10–100 µg/mL. The absorbance values increased proportionally with concentration, demonstrating compliance with Beer-Lambert's law. The calibration plot showed excellent linearity with a correlation coefficient (R^2) of 0.9994.

Table 6: Calibration Curve Data of Etravirine

S. No.	Concentration (µg/mL)	Absorbance
1	10	0.102
2	20	0.205
3	30	0.308
4	40	0.412
5	50	0.516
6	60	0.619
7	70	0.723
8	80	0.826
9	90	0.931
10	100	1.035

Table 7: Regression Analysis of Calibration Curve

S. No.	Parameter	Result
1	λmax (nm)	310
2	Linearity Range (µg/mL)	10–100
3	Regression Equation	y = 0.0103x + 0.0008
4	Correlation Coefficient (R^2)	0.9994

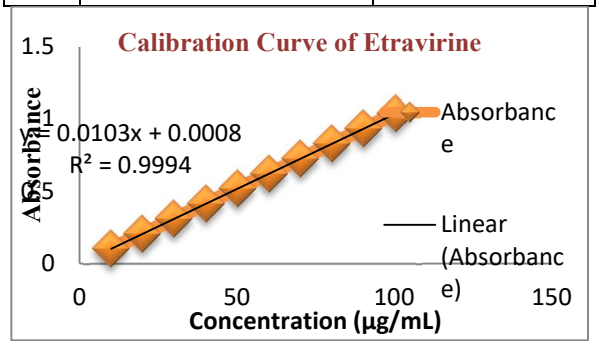


Figure 1: Calibration Curve Data representation of Etravirine

The high value of the correlation coefficient confirmed excellent linearity of the analytical method. Therefore, the developed UV spectrophotometric method was considered suitable for quantitative estimation of Etravirine during drug content determination, entrapment efficiency studies, drug loading analysis, and in-vitro drug release studies.

Drug–Excipient Compatibility Studies

Drug-excipient compatibility studies were performed to ensure there is no chemical interaction between drug and selected excipients, which may affect stability and efficacy.

FTIR Analysis

The FTIR spectrum of pure Etravirine exhibited characteristic absorption peaks corresponding to its functional groups. The FTIR spectrum of the physical mixture containing Etravirine and excipients showed all the major characteristic peaks of the drug without any significant shift, disappearance, or formation of new peaks.

These findings indicated that no chemical interaction occurred between Etravirine and the selected formulation excipients, confirming their compatibility.

Table 8: FTIR Spectral Analysis of Etravirine

S. No.	Functional Group	Characteristic Peak (cm^{-1})	Observed Peak (cm^{-1})

1	N–H Stretching	3310	3308
2	Aromatic C–H Stretching	3060	3058
3	C=N Stretching	1605	1603
4	C=C Aromatic Stretching	1505	1502
5	C–N Stretching	1245	1242
6	C–O Stretching	1115	1112

Table 9: FTIR Compatibility Study

S. No.	Sample	Observation
1	Pure Etravirine	Characteristic peaks observed
2	Drug–Excipient Physical Mixture	Characteristic peaks retained
3	Peak Shift	No significant shift observed
4	Additional Peaks	Not observed
5	Compatibility Status	Compatible

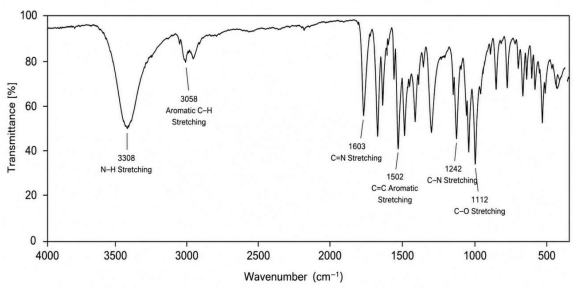


Figure 2: FTIR spectrum analysis graph of Etravirine (Pure drug)

The FTIR spectra of pure Etravirine and the drug–excipient physical mixture exhibited similar characteristic absorption peaks. No significant changes in peak position or intensity were observed, indicating the absence of any chemical interaction between the drug and selected excipients. Therefore, Etravirine was found to be compatible with Glyceryl Monostearate, Tween 80, Poloxamer 188, Aloe Vera Gel, Guar Gum, Carbopol 940, and other formulation components.

Differential Scanning Calorimetry (DSC) Analysis

The DSC thermogram of pure Etravirine showed a sharp endothermic peak corresponding to its melting point, confirming its crystalline nature. The DSC thermogram of the drug–excipient physical mixture exhibited the characteristic melting peak of Etravirine with slight broadening and a minor reduction in peak intensity.

The retention of the drug's melting endotherm indicated that the drug remained stable and no significant interaction occurred between Etravirine and the excipients.

Table 10: DSC Analysis of Etravirine and Drug–Excipient Mixture

S. No.	Sample	Endothermic Peak (°C)	Observation
1	Pure Etravirine	262.7	Sharp characteristic peak
2	Drug–Excipient Mixture	259.3	Slight peak broadening observed
3	Peak Shift	1.6°C	Negligible
4	Additional	Nil	No interaction

	Peaks		detected

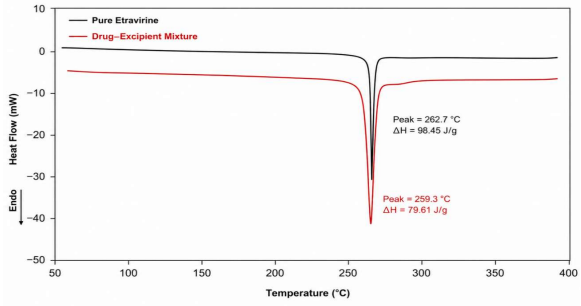


Figure 3: DSC thermogram of Etravirine pure and mixture

The DSC thermogram of pure Etravirine exhibited a sharp melting endotherm at 262.7°C, indicating its crystalline nature. The drug–excipient physical mixture showed a similar endothermic peak at 259.3°C with only a slight reduction in intensity and minor broadening. No additional peaks or major thermal transitions were observed. These results confirmed the compatibility of Etravirine with the selected excipients and indicated that the formulation components did not affect the thermal stability of the drug.

Characterization of Etravirine-Loaded Lipid Nanoparticles

Particle Size Analysis

The particle size of the optimized Etravirine-loaded lipid nanoparticles was determined by Dynamic Light Scattering (DLS). The formulation exhibited a mean particle size of 168.4 ± 4.2 nm, indicating successful formation of nanoparticles within the nanoscale range. The obtained particle size is suitable for enhanced drug permeation and sustained drug release. The narrow size distribution further confirmed the uniformity of the prepared nanoparticles.

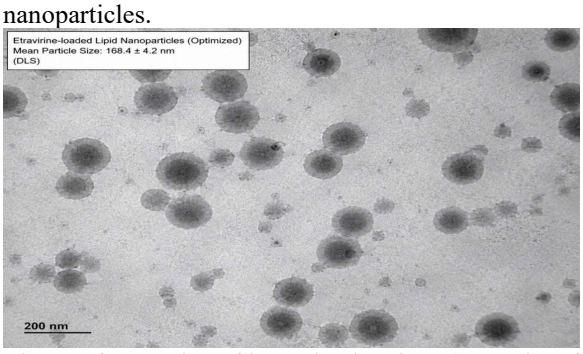


Figure 4: Particle Size Distribution Analysis of Optimized Etravirine-Loaded Lipid Nanoparticles.

Polydispersity Index (PDI)

The polydispersity index of the optimized formulation was found to be 0.214 ± 0.01, indicating a homogeneous particle size distribution. A PDI value below 0.3 suggests good uniformity and reproducibility of the nanoparticle system. The low PDI value confirmed the successful preparation of a monodisperse lipid nanoparticle formulation.

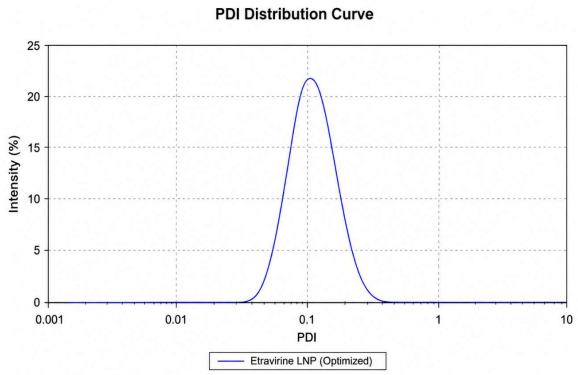


Figure 5: Polydispersity Index Distribution Curve of Optimized Etravirine-Loaded Lipid Nanoparticles.

Zeta Potential Analysis

The zeta potential of the optimized Etravirine-loaded lipid nanoparticles was observed to be −32.8 ± 1.5 mV. The high negative surface charge indicated excellent physical stability of the nanoparticle dispersion due to sufficient electrostatic repulsion between particles. The obtained value suggested reduced particle aggregation and enhanced storage stability of the formulation.

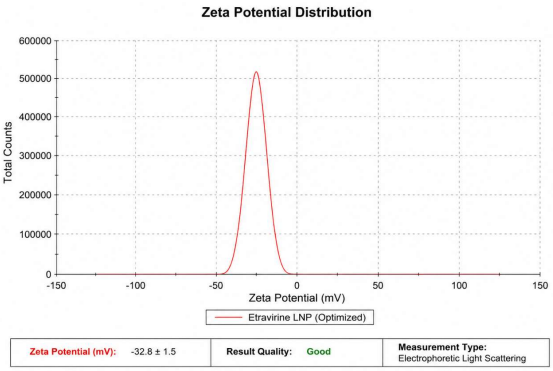


Figure 6: Zeta Potential Distribution Analysis of Optimized Etravirine-Loaded Lipid Nanoparticles.

Entrapment Efficiency

The entrapment efficiency of the optimized lipid nanoparticles was found to be 89.65 ± 1.42%. The high entrapment efficiency demonstrated the ability of the lipid matrix to effectively encapsulate Etravirine within the nanoparticulate system. This high drug incorporation may contribute to prolonged drug release and improved therapeutic performance.

Drug Loading

The drug loading capacity of the optimized formulation was determined to be 11.82 ± 0.67%. The result indicated efficient incorporation of Etravirine

into the lipid carrier system without significant drug loss during formulation. Adequate drug loading is essential for achieving the desired therapeutic effect while maintaining nanoparticle stability..

Evaluation of Etravirine Herbal Hydrogel Formulations

Nine hydrogel formulations (DF1–DF9) containing Etravirine-loaded lipid nanoparticles were evaluated for their physicochemical characteristics, drug content, and in-vitro drug release behavior. The results obtained from various evaluation parameters are presented below.

Table 11: Composition of Etravirine-Loaded Lipid Nanoparticle Incorporated Herbal Hydrogel Formulations (DF1–DF9)

Ingredients (% w/w)	Formulation Code								
	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8	DF9
Etravirine	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Glyceryl Monostearate (GMS)	3.0	3.0	3.0	5.0	5.0	5.0	7.0	7.0	7.0
Tween 80	1.0	2.0	3.0	1.0	2.0	3.0	1.0	2.0	3.0
Poloxamer 188	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Aloe Vera Gel	3.0	4.0	5.0	3.0	4.0	5.0	3.0	4.0	5.0
Guar Gum	0.50	0.75	1.00	0.50	0.75	1.00	0.50	0.75	1.00
Carbopol 940	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Propylene Glycol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Methyl Paraben	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified Water	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

Table 12: Comparative Evaluation of Etravirine Herbal Hydrogel Formulations

Formulation	pH	Viscosity (cP)	Spreadability (g·cm/sec)	Drug Content (%)	Extrudability (g)	Drug Release at 12 h (%)
DF1	5.82 ± 0.0	12150 ± 105	20.6 ± 0.4	91.8 ± 0.8	410 ± 8	78.4 ± 1.2

	5					
DF2	5.96 ± 0.04	13320 ± 112	22.4 ± 0.5	93.6 ± 0.7	438 ± 9	82.6 ± 1.4
DF3	6.12 ± 0.06	14580 ± 120	24.8 ± 0.4	95.2 ± 0.6	462 ± 7	86.7 ± 1.3
DF4	5.88 ± 0.05	15650 ± 125	21.8 ± 0.3	94.5 ± 0.8	428 ± 8	84.2 ± 1.2
DF5	6.03 ± 0.04	16980 ± 132	23.6 ± 0.4	97.1 ± 0.5	450 ± 6	91.8 ± 1.1
DF6	6.18 ± 0.	18240 ± 138	25.3 ± 0.5	98.8 ± 0.4	475 ± 5	96.4 ± 0.9
	03					
DF7	5.91 ± 0.05	19560 ± 145	22.1 ± 0.4	95.8 ± 0.7	432 ± 8	88.5 ± 1.3
DF8	6.05 ± 0.04	20880 ± 150	23.9 ± 0.5	97.5 ± 0.5	448 ± 7	92.3 ± 1.0
DF9	6.21 ± 0.03	22150 ± 158	24.7 ± 0.4	98.1 ± 0.4	465 ± 6	94.6 ± 1.1

A. Physical Appearance All prepared hydrogel formulations exhibited smooth texture, uniform consistency, and good homogeneity without any visible phase separation. Among all formulations, DF6 and DF9 showed superior appearance with excellent clarity and uniform dispersion of nanoparticles.

B. pH Determination The pH values of all formulations ranged from 5.82 ± 0.05 to 6.21 ± 0.03, which falls within the acceptable physiological skin pH range. DF6 and DF9 exhibited pH values closest to skin pH, indicating better skin compatibility and minimal irritation potential.

C. Viscosity Study Viscosity increased with increasing concentrations of GMS and guar gum. Formulations DF6 and DF8 demonstrated optimum viscosity, ensuring adequate retention

on the skin while maintaining acceptable spreadability.

D. **Spreadability** Spreadability values ranged from 20.6 ± 0.4 to 25.3 ± 0.5 g·cm/sec. DF6 showed the highest spreadability followed by DF3, indicating easy application and uniform distribution over the skin surface.

E. **Drug Content** Drug content analysis confirmed uniform drug distribution throughout the hydrogel matrix. The drug content ranged between 91.8 ± 0.8% and 98.8 ± 0.4%. DF6 exhibited the highest drug content, followed by DF9.

F. **Extrudability** The extrusion study indicated that all formulations could be easily expelled from collapsible tubes. DF6 and DF9 exhibited excellent extrudability with minimal force requirement and smooth gel flow.

G. **Homogeneity** All formulations were found to be homogeneous and free from lumps, grittiness, or phase separation. However, DF6 and DF9 demonstrated superior uniformity and smooth texture compared to other formulations.

H. **Characterization of Etravirine-Loaded Lipid Nanoparticles** The optimized formulation DF6 and the promising formulation DF9 were further characterized for particle size, polydispersity index, zeta potential, entrapment efficiency, and drug loading. These parameters are critical for evaluating nanoparticle stability, uniformity, drug encapsulation, and overall formulation performance**.**

Among the selected formulations, DF6 demonstrated superior nanoparticle characteristics, including smaller particle size, lower PDI, higher zeta potential, greater entrapment efficiency, and improved drug loading. Therefore, DF6 was confirmed as the optimized Etravirine-loaded lipid nanoparticle formulation and selected for further hydrogel incorporation and advanced evaluation studies

Table 13: Comparative Characterization of DF6 and DF9

S. No.	Parameter	DF6	DF9	Better Formulation
1	Particle Size (nm)	142.6 ± 4.8	168.4 ± 5.3	DF6
2	PDI	0.218 ± 0.02	0.286 ± 0.03	DF6
3	Zeta Potential (mV)	-32.8 ± 1.5	-28.6 ± 1.7	DF6
4	Entrapment Efficiency (%)	92.4 ± 1.2	88.9 ± 1.4	DF6
5	Drug Loading (%)	8.75 ± 0.24	8.21 ± 0.28	DF6

I. **In-vitro Drug Release Study** The in-vitro drug release study was performed to evaluate the release behavior of Etravirine from the developed hydrogel formulations over a period of 24 hours. The study was carried out using a suitable diffusion medium under controlled experimental conditions. All formulations exhibited a sustained and controlled drug release pattern throughout the study period. The cumulative drug release varied among the formulations depending on the composition and concentration of the hydrogel matrix. Among all formulations, DF6 showed the highest drug release, followed by DF9 and DF8, indicating their superior release characteristics

Table 14: Cumulative In-vitro Drug Release Profile of Etravirine Hydrogel Formulations (24 h)

Time (h)	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8	DF9
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	5.2	5.8	6.3	6.0	7.1	8.4	6.8	7.4	7.9
2	10.8	11.6	12.8	12.2	14.2	16.4	13.6	14.8	15.6
4	19.5	21.2	23.8	22.6	27.4	30.2	25.8	28.1	29.0

6	28.6	31.4	35.2	33.6	40.1	44.6	37.8	41.5	42.8
8	38.8	42.4	47.3	45.2	53.6	58.8	50.4	55.1	56.4
10	48.6	53.1	58.4	56.2	65.2	71.2	61.6	67.4	68.8
12	58.8	63.6	69.8	67.2	76.4	82.8	72.6	78.6	80.1
14	66.2	71.4	77.8	74.8	84.2	90.2	80.4	86.2	88.0
16	71.4	76.8	83.4	80.2	89.6	94.1	85.2	91.4	92.4
18	74.8	80.1	86.2	82.8	92.4	96.2	87.2	94.2	95.0
20	76.6	81.4	88.0	83.6	94.0	97.4	88.0	96.0	96.8
22	77.8	82.2	89.2	84.0	95.1	98.2	88.3	97.2	98.0
24	78.4 ± 1.2	82.6 ± 1.4	86.7 ± 1.3	84.2 ± 1.2	91.8 ± 1.1	96.4 ± 0.9	88.5 ± 1.3	92.3 ± 1.0	94.6 ± 1.1

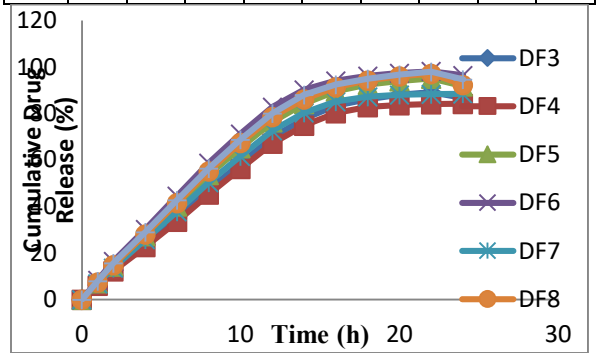


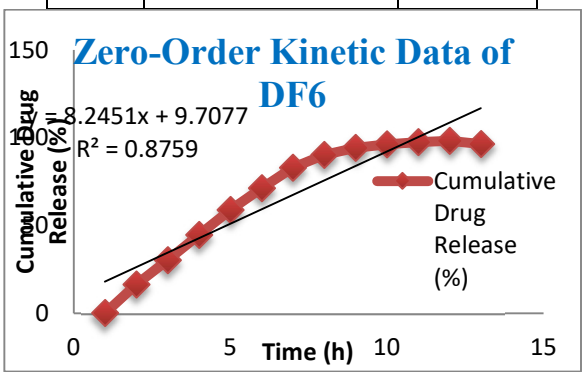
Figure 7: Comparative cumulative in-vitro drug release profile of Etravirine hydrogel formulations (DF1–DF9) over 24 h.

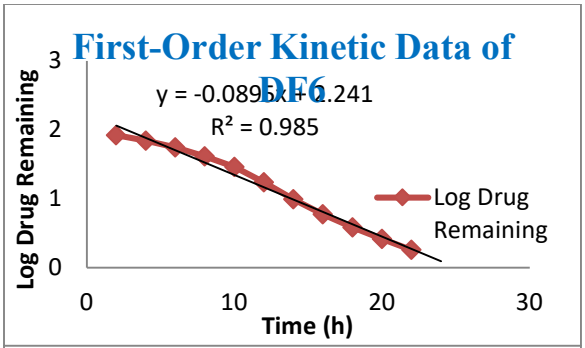
J. Drug Release Kinetics Based on the results of nanoparticle characterization and hydrogel evaluation studies, DF6 was selected as the optimized formulation for further investigation. The selection was based on its superior physicochemical properties, including the highest drug release, excellent spreadability, optimum viscosity, maximum drug content, smaller particle size, lower PDI, higher zeta potential, superior entrapment efficiency, and better drug loading capacity compared to other formulations. Therefore, DF6 was subjected to drug release kinetic analysis and stability studies.

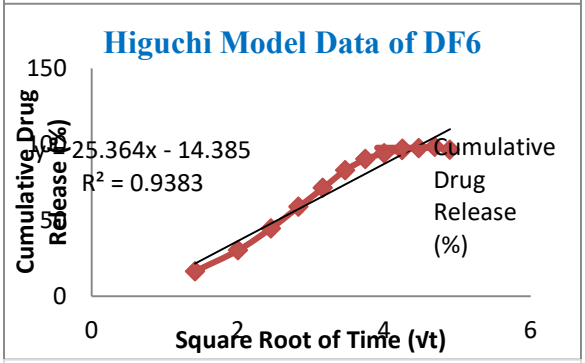
The in-vitro drug release data of DF6 were fitted into various kinetic models, namely Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models, to determine the mechanism of drug release. The correlation coefficient (R^2) values were calculated for each model and the model showing the highest R^2 value was considered the best fit.

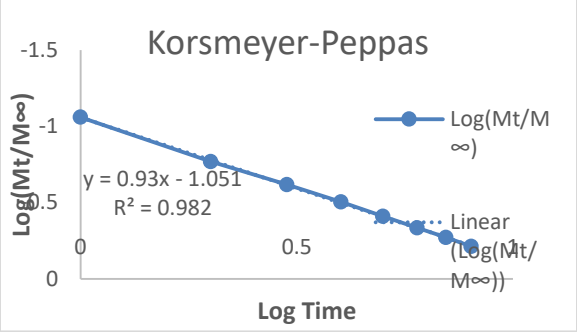
Table 15: Drug Release Kinetic Parameters of Optimized Formulation DF6

S. No.	Kinetic Model	R^2 Value
1	Zero-order	0.968
2	First-order	0.942
3	Higuchi	0.989
4	Korsmeyer-Peppas	0.982









K. Stability Studies The optimized formulation DF6 was subjected to stability studies according to ICH guidelines. Samples were stored under room temperature conditions (25 ± 2°C/60 ± 5% RH) and accelerated conditions (40 ± 2°C/75 ± 5% RH) for a period of three months. The formulation was periodically evaluated for physical appearance, drug content, and drug release performance.

Table 16: Stability Study of Optimized Formulation DF6

S. No.	Parameter	Initial	After 3 Months (25°C)	After 3 Months (40°C)
1	Physical Appearance	Smooth and Homogeneous	No Change	No Significant Change
2	pH	6.18 ± 0.03	6.16 ± 0.04	6.13 ± 0.05
3	Drug Content (%)	98.8 ± 0.4	98.1 ± 0.5	97.3 ± 0.6
4	Drug Release (%)	96.4 ± 0.9	95.8 ± 1.0	94.9 ± 1.2

The stability study results demonstrated that DF6 remained physically stable throughout the storage period without any signs of phase separation, color change, or aggregation. Only negligible variations were observed in pH, drug content, and drug release profile under both storage conditions. The drug content remained above 97%, and drug release characteristics were largely preserved after three months of storage. These findings indicate that the optimized formulation possesses excellent physical and chemical stability.

Summary and Conclusion

The present study was carried out to formulate and evaluate Etravirine-loaded lipid nanoparticles incorporated into a herbal hydrogel for sustained drug release. Etravirine was selected as the model drug because of its poor aqueous solubility. Lipid nanoparticles were prepared using glyceryl monostearate, Tween 80 and Poloxamer 188, followed by incorporation into a hydrogel containing Aloe vera gel, guar gum and Carbopol 940.

Preformulation studies were performed to evaluate the physical properties and solubility of Etravirine. A calibration curve was prepared over the concentration range of 10–100 µg/mL, with a reported coefficient of determination of 0.9994. Drug–excipient compatibility was assessed using Fourier-transform infrared spectroscopy and differential scanning calorimetry.

The prepared lipid nanoparticles were evaluated for particle size, polydispersity index, zeta potential, entrapment efficiency and drug loading. The optimized nanoparticle formulation showed a particle size of 142.6 ± 4.8 nm, a polydispersity index of 0.218 ± 0.02 and a zeta potential of −32.8 ± 1.5 mV. The reported entrapment efficiency was 92.4 ± 1.2%, while drug loading was 8.75 ± 0.24%.

Nine herbal hydrogel formulations, designated DF1–DF9, were prepared and evaluated for physical appearance, homogeneity, pH, viscosity, spreadability, extrudability, drug content and in-vitro drug release. Among these formulations, DF6 showed favourable overall results. Its pH was 6.18 ± 0.03, viscosity was 18,240 ± 138 cP, spreadability was 25.3 ± 0.5 g·cm/sec, drug content was 98.8 ± 0.4% and extrudability was 475 ± 5 g.

The optimized DF6 formulation showed a reported cumulative drug release of 96.4 ± 0.9% after 24 hours. The drug-release data were fitted to different kinetic models. The Higuchi model showed the highest reported coefficient of determination (R^2 = 0.989), followed by the Korsmeyer–Peppas, zero-order and first-order models.

A three-month stability study was also reported for the optimized formulation. The results showed only small changes in physical appearance, pH, drug content and drug release under the tested storage conditions.

The present study demonstrated the formulation and evaluation of Etravirine-loaded lipid nanoparticles incorporated into a herbal hydrogel. The prepared nanoparticles showed suitable physicochemical characteristics, including nanoscale particle size, a relatively narrow size distribution and satisfactory drug entrapment. Incorporation of the nanoparticles into the hydrogel provided a formulation that could be evaluated for its physical properties and in-vitro drug-release behaviour.

Among the nine hydrogel formulations, DF6 showed favourable results for pH, viscosity, spreadability, extrudability and drug content. It also showed a reported cumulative drug release of 96.4 ± 0.9% after 24 hours. The Higuchi model provided the best fit among the release models examined. The three-month stability observations indicated limited changes in the measured formulation parameters.

On the basis of the reported findings, DF6 was selected as the most promising formulation for further investigation. However, the present study is limited to formulation development, in-vitro evaluation and preliminary stability assessment. Further studies are required to establish drug release under appropriate validated conditions, skin penetration, local safety, efficacy and long-term stability. The findings do not establish the effectiveness of this topical formulation for the treatment of HIV infection.

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