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Formulation and evaluation of Famotidine-loaded ethosomal vesicles for ulcer therapy

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Abstract

Background: Famotidine, an H_2-receptor antagonist, suffers from variable bioavailability and frequent dosing requirements. Ethosomes, lipid-based nanocarriers, offer improved encapsulation, stability, and sustained release.
Objective: To formulate, optimize, and characterize Famotidine-loaded ethosomes, assessing physicochemical properties, entrapment efficiency, release behavior, kinetics, and stability.
Methods: Famotidine-loaded ethosomes were prepared using the ethanol injection method by varying the concentrations of soya lecithin and ethanol. Prior to formulation, the drug was characterized through organoleptic evaluation, solubility analysis, melting point determination, partition coefficient measurement, UV-visible spectrophotometric analysis, and Fourier-transform infrared (FTIR) spectroscopy. The prepared formulations (F1–F5) were evaluated for particle size, polydispersity index, zeta potential, scanning electron microscopy (SEM), entrapment efficiency, in vitro drug release using the dialysis bag diffusion method, release kinetics, and accelerated stability studies under ICH-recommended storage conditions.
Results: Preformulation studies confirmed the identity and purity of Famotidine, with a melting point of 154°C, maximum absorbance (λmax) at 294 nm, and a partition coefficient of 2.16. FTIR analysis demonstrated the preservation of the characteristic functional groups, indicating the absence of significant chemical interactions during formulation. Among the five formulations, F4 exhibited the most desirable characteristics, with the smallest particle size (149.1 nm), zeta potential of −12.1 mV, and the highest entrapment efficiency (89.63%). SEM analysis revealed uniformly distributed, spherical vesicles with smooth surface morphology. The optimized formulation achieved 96.83% cumulative drug release within 14 h, demonstrating sustained release behaviour. Drug release followed the Higuchi diffusion model (R^2 = 0.979),indicating diffusion-controlled release from the vesicular matrix. Accelerated stability studies conducted for 90 days showed negligible changes in particle size and entrapment efficiency, confirming the physicochemical stability of the optimized ethosomal formulation.
Conclusion: Optimized Famotidine ethosomes showed high entrapment, sustained release, and excellent stability. Ethosomal nanovesicles are promising carriers to enhance Famotidine's performance. Further in vivo studies are needed to confirm clinical potential.

Keywords: Famotidine; Ethosomes; Vesicular drug delivery; Nanocarrier; Entrapment efficiency; Sustained drug release; Higuchi kinetics; Stability study

1. Introduction

Gastrointestinal disorders, including peptic ulcer disease, gastroesophageal reflux disease (GERD), Zollinger–Ellison syndrome, and stress-induced gastric ulceration, continue to be major global health concerns affecting millions of individuals worldwide [1]. These disorders are primarily associated with excessive gastric acid secretion, impairment of mucosal defense mechanisms, *Helicobacter pylori* infection, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs), smoking, alcohol consumption, and psychological stress [2]. Despite considerable advances in pharmacotherapy, the effective management of acid-related gastrointestinal diseases remains challenging due to disease recurrence, patient non-compliance, and limitations associated with conventional oral drug delivery systems [3].

Histamine H_2-receptor antagonists represent one of the major therapeutic classes used for suppressing gastric acid secretion [4]. Among these agents, Famotidine is a potent, selective, and reversible H_2-receptor antagonist that

inhibits histamine-induced gastric acid secretion by competitively blocking H_2 receptors located on gastric parietal cells [5]. In comparison with earlier H_2 antagonists such as cimetidine and ranitidine, Famotidine possesses greater potency, a longer duration of action, and a more favourable safety profile [6]. Consequently, it has been extensively prescribed for the treatment of gastric and duodenal ulcers, gastroesophageal reflux disease, erosive esophagitis, hypersecretory conditions, and dyspeptic disorders [7].

Although Famotidine is clinically effective, conventional dosage forms are associated with several pharmaceutical limitations. Following oral administration, the drug exhibits variable gastrointestinal absorption and requires repeated administration to maintain therapeutic concentrations. Rapid gastric emptying, fluctuations in gastrointestinal pH, and relatively short systemic persistence may contribute to variability in drug availability at the site of action. Therefore, the development of advanced drug delivery systems capable of providing controlled drug release and improved pharmaceutical performance remains an important area of research [8].

Nanotechnology-based drug delivery systems have attracted considerable attention because of their ability to overcome several limitations of conventional formulations [9]. Lipid-based nanocarriers, including liposomes, niosomes, transferosomes, solid lipid nanoparticles, nanostructured lipid carriers, and ethosomes, have demonstrated significant potential for improving drug encapsulation, stability, controlled release, and therapeutic performance. Among these vesicular systems, ethosomes have emerged as one of the most promising phospholipid-based carriers due to their unique composition and physicochemical characteristics [10].

Ethosomes are soft, flexible lipid vesicles composed primarily of phospholipids, a relatively high concentration of ethanol, and water [11]. Unlike conventional liposomes, the presence of ethanol increases membrane fluidity, decreases phospholipid transition temperature, and imparts remarkable deformability to the vesicles. Ethanol also enhances the flexibility of the phospholipid bilayer, resulting in improved vesicle stability and more efficient drug incorporation. These structural characteristics enable ethosomes to accommodate both hydrophilic and lipophilic drug molecules while providing sustained drug release and enhanced pharmaceutical performance [12].

The physicochemical properties of ethosomes are greatly influenced by formulation variables such as phospholipid concentration, ethanol content, preparation technique, and vesicle size. Optimization of these variables is essential because they directly affect particle size distribution, surface charge, drug encapsulation efficiency, release kinetics, and storage stability [13]. Small, uniformly distributed vesicles with adequate surface charge generally exhibit improved colloidal stability and reproducible drug release behaviour. Consequently, systematic optimization and characterization of ethosomal formulations are crucial for the successful development of stable vesicular drug delivery systems [14].

Comprehensive physicochemical characterization is necessary to establish the quality and performance of newly developed nanosystems. Preformulation studies provide valuable information regarding drug identity, purity, solubility, partition behaviour, and compatibility with formulation components [15]. Fourier transform infrared (FTIR) spectroscopy is widely employed to evaluate drug–excipient compatibility, whereas dynamic light scattering and zeta potential measurements are essential for determining vesicle size distribution and colloidal stability. Scanning electron microscopy provides detailed information regarding vesicle morphology and surface characteristics [16]. In addition, determination of drug entrapment efficiency and in vitro drug release kinetics provides critical information regarding drug loading capacity and release behaviour. Stability studies conducted according to International Council for Harmonisation (ICH) recommendations further establish the suitability of the developed formulation for long-term pharmaceutical application [17].

Controlled-release vesicular systems are particularly advantageous because they can maintain therapeutic drug concentrations for prolonged periods while minimizing fluctuations associated with immediate-release dosage forms. Drug release kinetics also provide valuable insight into the mechanism governing drug diffusion from the vesicular matrix. Mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations are routinely applied to identify the predominant release mechanism and to optimize formulation performance.

In the present investigation, Famotidine-loaded ethosomal formulations were prepared using varying concentrations of soya lecithin and ethanol to optimize vesicle characteristics. The prepared formulations were systematically evaluated through preformulation studies, particle size analysis, zeta potential measurement, scanning electron microscopy, drug entrapment efficiency, in vitro drug release, release kinetic modelling, and accelerated stability studies. The objective of the study was to identify an optimized ethosomal formulation capable of producing nanosized vesicles with high encapsulation efficiency, sustained drug release, and acceptable physicochemical stability. The findings of this work provide valuable

information regarding the potential application of ethosomal nanocarriers as an alternative pharmaceutical delivery platform for Famotidine and contribute to the growing body of research on lipid-based vesicular drug delivery systems [18].

2. Materials and Methods

2.1 Materials

Famotidine was obtained as a gift sample from a pharmaceutical manufacturer. Soya lecithin was procured from Acros Organics (New Delhi, India), while cholesterol was purchased from HiMedia Laboratories Pvt. Ltd. (Mumbai, India). Ethanol, methanol, and propylene glycol of analytical reagent grade were obtained from Merck India Ltd. (Mumbai, India). Distilled water was used throughout the study. All chemicals and reagents were of analytical grade and were used without further purification.

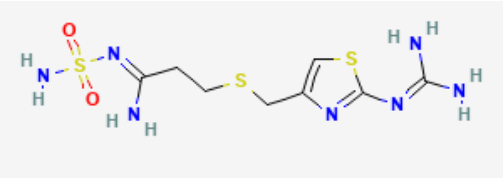

Figure 1: Structure of Famotidine

2.2 Preformulation Studies

2.2.1 Organoleptic Evaluation

The organoleptic properties of Famotidine, including colour, odour, appearance, and physical state, were evaluated by visual inspection. These parameters were compared with the pharmacopoeial specifications to verify the identity and quality of the drug.

2.2.2 Solubility Study

The qualitative solubility of Famotidine was determined in various solvents, including distilled water, methanol, ethanol, dimethyl sulfoxide (DMSO), and n-hexane. Approximately 1 mg of the drug was transferred into separate test tubes containing 1 mL of each solvent and gently shaken until equilibrium was achieved. The solubility behaviour was assessed visually and categorized as freely soluble, soluble, sparingly soluble, or insoluble.

2.2.3 Melting Point Determination

The melting point of Famotidine was determined using the open capillary method. A small quantity of the powdered drug was filled into a capillary tube sealed at one end. The capillary tube was gradually heated, and the temperature range at which the drug completely melted was recorded.

2.2.4 Determination of Partition Coefficient

The partition coefficient of Famotidine was determined using the n-octanol/water partitioning method. Five milligrams of the drug were added to a separating funnel containing 20 mL each of n-octanol and distilled water. The mixture was shaken continuously for 2 h to attain equilibrium. After complete phase separation, the aqueous phase was analyzed spectrophotometrically at 294 nm, and the partition coefficient was calculated using the ratio of drug concentration in the organic phase to that in the aqueous phase.

2.2.5 UV–Visible Spectrophotometric Analysis

A primary stock solution of Famotidine (1000 µg/mL) was prepared in distilled water and further diluted to obtain a working standard solution. The solution was scanned between 200 and 400 nm using a double-beam UV–Visible spectrophotometer to determine the wavelength of maximum absorbance (λmax). Calibration standards ranging from 5 to 35 µg/mL were prepared, and their absorbance was measured at λmax. A calibration curve was constructed by plotting absorbance against concentration, and linear regression analysis was performed.

2.2.6 Fourier Transform Infrared Spectroscopy (FTIR)

Drug-excipient compatibility and functional group identification were evaluated using Fourier Transform Infrared Spectroscopy. Samples were prepared by the potassium bromide (KBr) pellet method using approximately 1 mg of Famotidine and 100 mg of dried spectroscopic-grade KBr. The spectra were recorded over the scanning range of 4000–400 cm^{-1}.

2.2.7 Preparation of Famotidine-Loaded Ethosomes

Ethosomal formulations were prepared using the cold method. Predetermined quantities of soya lecithin were dissolved in ethanol under continuous magnetic stirring. Famotidine was incorporated into the ethanolic phase until complete dissolution was achieved. Distilled water was then added slowly under constant stirring to facilitate spontaneous vesicle formation. Five formulations (F1–F5) were prepared by varying the concentrations of soya lecithin (1.5–3.5%, w/v) and ethanol (10–50%, v/v), while maintaining a stirring time of 30 min at room temperature. The prepared ethosomal dispersions were stored under refrigerated conditions until further evaluation.

2.3 Characterization of Ethosomal Formulations

2.3.1 Particle Size and Polydispersity Index

The average vesicle size and polydispersity index (PDI) were determined by dynamic light scattering using a Malvern Zetasizer. Prior to analysis, each formulation was diluted appropriately with filtered distilled water to avoid multiple scattering effects. Measurements were carried out at 25 ± 1°C, and the mean values were recorded.

2.3.2 Zeta Potential

The surface charge of the prepared ethosomes was measured using the same zeta analyzer based on electrophoretic mobility. Samples were diluted with distilled water and sonicated before measurement. The zeta potential values were recorded to evaluate colloidal stability.

2.3.3 Entrapment Efficiency

Entrapment efficiency was determined by disrupting the ethosomal vesicles with ethanol. An accurately measured quantity of the formulation was mixed with ethanol, vortexed thoroughly, and diluted appropriately. The solution was filtered, and the drug concentration was determined spectrophotometrically at 294 nm. Entrapment efficiency was calculated.

2.3.4 Scanning Electron Microscopy

The surface morphology of the optimized ethosomal formulation was examined by scanning electron microscopy. Samples were dried under vacuum, mounted on aluminium stubs, sputter-coated with a thin gold layer, and examined under suitable magnification to evaluate vesicle shape and surface characteristics.

2.3.5 In Vitro Drug Release Study

The in vitro release of Famotidine from the prepared ethosomes was investigated using the dialysis bag diffusion technique. An accurately measured quantity of the formulation was placed inside a dialysis membrane, which was immersed in 100 mL phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C under continuous magnetic stirring at 100 rpm. At predetermined time intervals, aliquots of dissolution medium were withdrawn and replaced with an equal volume of fresh buffer to maintain sink conditions. The collected samples were analyzed spectrophotometrically at 294 nm, and the cumulative percentage drug release was calculated.

2.3.6 Drug Release Kinetics

The release profile of the optimized formulation was evaluated using various mathematical kinetic models, including Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The model showing the highest coefficient of determination (R^2) was considered to best describe the mechanism of drug release.

2.3.7 Stability Studies

The optimized ethosomal formulation was subjected to accelerated stability testing according to ICH guidelines. Samples were stored at 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/70 ± 5% RH for a period of 90 days. At predetermined intervals (0, 30, 45, 60, and 90 days), formulations were evaluated for physical appearance, particle size, and entrapment efficiency to assess their physicochemical stability.

3. Results

3.1 Preformulation Studies

3.1.1 Organoleptic Evaluation

Famotidine was obtained as a white, crystalline powder with a characteristic odour. The drug exhibited the expected physical appearance and complied with the pharmacopoeial specifications, confirming its suitability for formulation studies.

3.1.2 Solubility Analysis

The qualitative solubility profile demonstrated that Famotidine was freely soluble in distilled water and dimethyl sulfoxide (DMSO), soluble in methanol and ethanol, and insoluble in n-hexane. The observed solubility characteristics supported the selection of hydroalcoholic media for ethosomal formulation.

3.1.3 Melting Point Determination

The melting point of Famotidine was determined to be 154°C, which is within the reported pharmacopeial range of 145–155°C, indicating the purity and identity of the drug substance.

3.1.4 Partition Coefficient

The partition coefficient of Famotidine in the n-octanol/water system was found to be 2.16, suggesting moderate lipophilicity, which is advantageous for incorporation into phospholipid vesicular systems.

3.1.5 UV–Visible Spectrophotometric Analysis

The UV absorption spectrum of Famotidine exhibited a maximum absorbance (λ_{max}) at **294 nm**, which was selected for all subsequent quantitative analyses. The calibration curve prepared over the concentration range of **5–35 µg/mL** demonstrated good linearity with the regression equation:**y = 0.027x + 0.040**and a correlation coefficient of **R^2 = 0.977**, confirming the suitability of the analytical method for drug estimation.

3.1.6 Fourier Transform Infrared Spectroscopy

The FTIR spectrum of Famotidine showed all characteristic absorption bands corresponding to its functional groups. Major absorption peaks were observed at **3368.49** and **3294.09 cm^{-1}** (O–H stretching), **1707.61 cm^{-1}** (C=O stretching), **1542.16 cm^{-1}** (aromatic C=C stretching), **1340.38–1203.53 cm^{-1}** (C–O stretching), and **868.62–731.23 cm^{-1}** (aromatic C–H bending). The preservation of these characteristic peaks indicated the absence of significant chemical degradation during formulation.

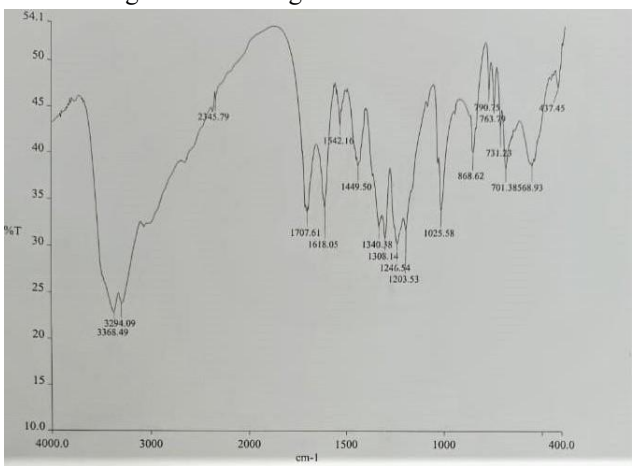

Figure 2: FTIR of Famotidine

3.2 Characterization of Famotidine-Loaded Ethosomes

3.2.1 Particle Size and Polydispersity Index

The particle size analysis demonstrated successful formation of nanosized ethosomal vesicles. The average vesicle diameter ranged from **149.1 to 552.2 nm**. Among all formulations, **F4** exhibited the smallest particle size (**149.1 nm**) with a polydispersity index of **0.374**, indicating a comparatively narrow particle size distribution. Formulations F2 and F5 showed larger vesicle sizes (>550 nm), whereas F1 and F3 produced intermediate particle sizes.

3.2.2 Zeta Potential

The zeta potential values of the prepared ethosomal formulations ranged from **−3.9 to −12.1 mV**. The optimized formulation (F4) exhibited the highest negative surface charge (**−12.1 mV**), suggesting improved colloidal stability compared with the remaining formulations.

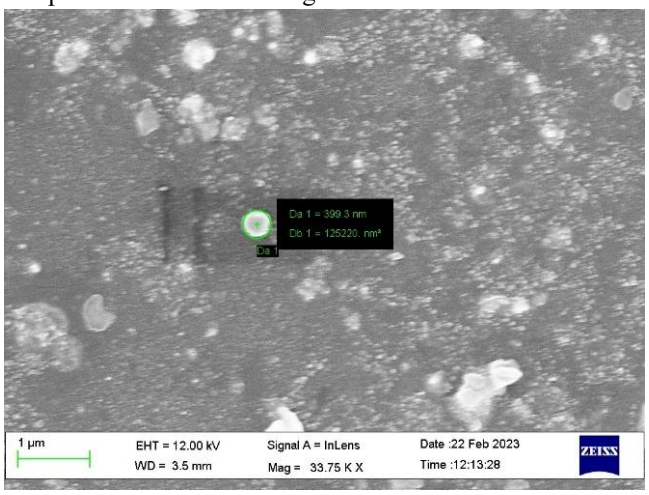

Figure 3: SEM for formulation F4

3.2.3 Surface Morphology

Scanning electron microscopy of the optimized formulation (F4) revealed well-formed spherical vesicles with smooth surface morphology. The vesicles appeared discrete without noticeable aggregation, indicating successful formation of the ethosomal carrier system.

3.2.4 Entrapment Efficiency

Entrapment efficiency varied among the formulations depending on the phospholipid composition. Drug entrapment ranged from **67.03% to 89.63%**. Formulation F4 exhibited the highest entrapment efficiency (**89.63%**), followed by F3 (**83.69%**), whereas F1 showed the lowest encapsulation efficiency (**67.03%**).

3.2.5 In Vitro Drug Release

The cumulative in vitro release profile demonstrated sustained drug release from all prepared ethosomal formulations over a period of **14 h**. Considerable variation in release behaviour was observed among the formulations.

The optimized formulation (F4) released **16.13%** of Famotidine during the first hour, followed by a gradual increase to **50.64%** at 6 h, **77.23%** at 10 h, and **96.83%** at the end of 14 h. The sustained release profile indicated efficient drug retention within the phospholipid vesicles while allowing continuous diffusion of the encapsulated drug into the dissolution medium.

Table 1: In- vitro drug release Study

S. No	Time (hr)	F1	F2	F3	F4	F5
1	0	0	0	0	0	0
2	1	23.27	16.00	19.32	16.13	21.01
3	2	33.97	28.48	35.12	28.18	42.71
4	4	41.04	39.90	47.67	39.05	58.83
5	6	53.78	43.51	58.24	50.64	64.25
6	8	69.11	59.80	63.11	66.87	70.88
7	10	77.20	68.18	79.17	77.23	81.11
8	12	86.09	77.11	85.10	83.62	88.69
9	14	93.25	89.63	90.57	96.83	92.06

3.2.6 Drug Release Kinetics

The release data of the optimized formulation (F4) were fitted to different mathematical kinetic models.

The correlation coefficients (R^2) obtained were:

- Zero-order model: **0.976**
- First-order model: **0.833**
- Higuchi model: **0.979**
- Korsmeyer–Peppas model: **0.694**

Among these models, the **Higuchi model** exhibited the highest correlation coefficient (**R^2 = 0.979**), indicating that drug release from the optimized ethosomal formulation was predominantly governed by diffusion through the vesicular matrix.

Table 2: Release kinetics study of optimized (F4) formulation

S. No	Time (hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	Log cumu % drug released
1.	0	0	100	0.000	2.000	0.000	0.000
2.	1	16.13	83.87	1.000	1.924	0.000	1.208
3.	2	28.18	71.82	1.414	1.856	0.301	1.450
4.	4	39.05	60.95	2.000	1.785	0.602	1.592
5.	6	50.64	49.36	2.449	1.693	0.778	1.704
6.	8	66.87	33.13	2.828	1.520	0.903	1.825
7.	10	77.23	22.77	3.162	1.357	1.000	1.888
8.	12	83.62	16.38	3.464	1.214	1.079	1.922
9.	14	96.83	3.17	3.742	0.501	1.146	1.986

3.2.7 Stability Studies

The optimized formulation (F4) was subjected to accelerated stability testing for **90 days** under **25 ± 2°C/60 ± 5% RH** and **40 ± 2°C/70 ± 5% RH**.

No visible changes in colour, appearance, or phase separation were observed throughout the storage period. Particle size remained essentially unchanged, varying from **149.1 to 149.9 nm** under long-term conditions and from **148.2 to 149.8 nm** under accelerated conditions. Similarly, entrapment efficiency showed only minimal variation, remaining between **89.16% and 89.63%** throughout the study period.

The negligible changes in physicochemical characteristics indicated excellent stability of the optimized ethosomal formulation under the tested storage conditions.

Table 31: Stability Study of (F4) formulation

S. No	Time (Days)	25⁰C±2 ⁰C and 60 ± 5% RH		40⁰C±2 ⁰C and 70 ±5% RH	
		Particle size (nm)	Entrapment efficiency (%)	Particle size (nm)	Entrapment efficiency (%)
1.	0	149.1 nm	89.63 %	149.1 nm	89.63 %
2.	30	149.9 nm	89.60 %	148.2 nm	89.50 %
3.	45	149.6 nm	89.59 %	148.5 nm	89.48 %
3.	60	148.0 nm	89.58 %	149.6 nm	88.97 %
4.	90	149.9 nm	89.61 %	149.8 nm	89.16 %

4. Discussion

The present study successfully developed and characterized Famotidine-loaded ethosomal vesicles to enhance drug encapsulation, achieve sustained drug release, and improve formulation stability. The prepared formulations exhibited desirable physicochemical properties, nanosized vesicles, high entrapment efficiency, controlled drug release, and good storage stability, demonstrating the suitability of ethosomes as an effective carrier for Famotidine.

Preformulation studies confirmed the identity and purity of Famotidine. The melting point (154°C) was within the reported range, while the partition coefficient (2.16) indicated moderate lipophilicity, favouring incorporation into phospholipid vesicles. The UV spectrophotometric method showed good linearity, confirming its suitability for quantitative drug estimation. FTIR analysis revealed no significant changes in the characteristic peaks of Famotidine, indicating compatibility between the drug and formulation components and confirming chemical stability during formulation.

Ethosomes, composed of phospholipids and a high concentration of ethanol, provide flexible vesicles that facilitate efficient drug incorporation. All formulations produced nanosized vesicles, although particle size varied with phospholipid and ethanol concentrations. Among the formulations, F4 exhibited the smallest particle size (149.1 nm) and a low polydispersity index, indicating a uniform vesicle distribution. This suggests that an optimum phospholipid-to-ethanol ratio is essential for efficient vesicle formation, whereas excessive phospholipid or ethanol may increase vesicle size through membrane thickening or destabilization.

Zeta potential values ranged from −3.9 to −12.1 mV, with formulation F4 exhibiting the highest negative surface charge. Although these values were below the conventional threshold for electrostatic stabilization, the absence of aggregation during storage suggests that steric stabilization provided adequate colloidal stability.

SEM analysis confirmed that the optimized formulation consisted of spherical vesicles with smooth surfaces and no evidence of aggregation or structural collapse, indicating successful vesicle formation and good morphological stability.

Entrapment efficiency ranged from 67.03% to 89.63%, with formulation F4 showing the highest drug loading. The improved entrapment efficiency is attributed to the optimized phospholipid-to-ethanol ratio, which enhanced vesicle integrity and drug incorporation while minimizing drug leakage.

The in vitro release study demonstrated sustained drug release over 14 h. The optimized formulation released 96.83% of the drug, indicating efficient controlled release without an initial burst effect. Such sustained release may improve therapeutic efficacy, reduce dosing frequency, and enhance patient compliance.

Drug release kinetics showed the highest correlation with the Higuchi model ($R^2 = 0.979$), indicating that diffusion through the phospholipid matrix was the primary mechanism controlling drug release. This release pattern is consistent with the diffusion-controlled behaviour commonly observed in vesicular drug delivery systems.

Accelerated stability studies performed for 90 days showed negligible changes in particle size and entrapment efficiency, with no evidence of phase separation or aggregation, confirming the physicochemical stability of the optimized formulation.

Overall, formulation F4 demonstrated superior performance in terms of particle size, zeta potential, entrapment efficiency, sustained drug release, release kinetics, and stability. The optimized balance of phospholipid and ethanol contributed to efficient vesicle formation and enhanced formulation performance. These

findings indicate that Famotidine-loaded ethosomes are a promising vesicular delivery system with potential advantages over conventional formulations. However, further pharmacokinetic, pharmacodynamic, and in vivo studies are required to confirm their therapeutic potential and clinical applicability.

5. Conclusion

The present study successfully developed and optimized Famotidine-loaded ethosomal vesicles using a phospholipid-based nanocarrier system. Preformulation studies confirmed the suitability of Famotidine for formulation, while FTIR analysis demonstrated drug–excipient compatibility without significant chemical interactions.

Among the five formulations, F4 showed the best performance, with the smallest particle size (149.1 nm), highest negative zeta potential (−12.1 mV), highest entrapment efficiency (89.63%), and smooth, spherical vesicles confirmed by SEM. The optimized formulation exhibited sustained drug release (96.83% over 14 h), following the Higuchi kinetic model ($R^2 = 0.979$), indicating diffusion-controlled release. Stability studies conducted for 90 days under ICH conditions showed negligible changes in particle size and entrapment efficiency, confirming excellent physicochemical stability.

Overall, the optimized ethosomal formulation effectively encapsulated Famotidine, produced stable nanosized vesicles, and provided sustained drug release, highlighting its potential as an alternative to conventional dosage forms. Further ex vivo permeation, pharmacokinetic, pharmacodynamic, and long-term stability studies are needed to establish its clinical applicability and therapeutic potential.

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