

Development of Lafutidine-Loaded Polymeric Nanoparticles: Design, Characterization and In Vitro Evaluation for Controlled Drug Delivery

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Abstract

The present study was undertaken to design, prepare, and evaluate Lafutidine-loaded polymeric nanoparticles for a controlled drug delivery system. Pre-formulation studies confirmed the identity, purity, and suitability of Lafutidine, with organoleptic properties, melting point (100 °C), pH (6.7), and UV absorption maximum (λ_{max} 280.5 nm) found within acceptable reference limits. The drug exhibited poor aqueous solubility but was freely soluble in methanol and DMSO, supporting the need for nanoparticulate formulation. A validated UV spectrophotometric method showed excellent linearity ($R^2 = 0.9974$). Polymeric nanoparticles (PNF1–PNF5) were successfully formulated and characterized. All formulations exhibited nanoscale particle size ranging from 190–204 nm with relatively narrow size distribution and good homogeneity. Zeta potential values (–25.0 to –33.8 mV) indicated acceptable colloidal stability, with PNF1 showing the highest stability. SEM analysis confirmed spherical nanoparticles with suitable morphology. Among all formulations, PNF1 demonstrated the highest entrapment efficiency (92.88%). *In-vitro* drug release studies revealed sustained drug release up to 16 hours with 98.96% cumulative release, following zero-order kinetics ($R^2 = 0.9883$). Stability studies conducted for 90 days under accelerated conditions showed no significant changes in particle size or entrapment efficiency. Overall, the optimized Lafutidine-loaded polymeric nanoparticle formulation exhibited excellent stability, high drug entrapment, and controlled drug release, indicating its potential as an effective controlled drug delivery system for enhancing the therapeutic performance of Lafutidine.

Keywords: Lafutidine; Polymeric nanoparticles; Controlled drug delivery; Entrapment efficiency; *In-vitro* drug release; Stability studies

I. INTRODUCTION

A novel drug delivery system (NDDS) refers to advanced and innovative approaches that are specifically designed to enhance the therapeutic efficacy and safety of drugs by improving their delivery to the target site (Begum *et al.*, 2024). Unlike conventional dosage forms such as tablets, capsules, or injections, which often face challenges like poor solubility, low bioavailability, short half-life, and nonspecific distribution, NDDS aims to overcome these limitations by offering more controlled, sustained, and targeted drug release. The primary goal of an NDDS is to deliver the right amount of drug at the right site and at the right time, thereby maximizing therapeutic effects while minimizing side effects. This is achieved through the development of new carriers, technologies, and formulations that can modify the pharmacokinetics and pharmacodynamics of therapeutic agents (Khadamet *et al.*, 2024).

Polymeric nanoparticles are colloidal carriers ranging from 10–1000 nm, made from biodegradable and biocompatible polymers. They can deliver small molecules, proteins, peptides, nucleic acids, and vaccines (Elmowafy *et al.*, 2023). Natural polymers (chitosan, alginate, gelatin) and synthetic ones (PLA, PGA, PLGA) are commonly used. The polymer matrix stabilizes drugs, prevents degradation, and enables controlled release, improving pharmacokinetics (Saini *et al.*, 2024). Based on structure, they are classified as nanospheres (drug dispersed in polymer) or nanocapsules (drug enclosed in a polymeric shell). Both enhance solubility, stability, and bioavailability, with nanocapsules being more suitable for lipophilic drugs. Advantages include sustained release, reduced dosing, prolonged circulation, ability to cross barriers like the blood–brain barrier, and preferential accumulation in diseased tissues via the EPR effect (Wu, 2021).

Surface modifications with antibodies, peptides, or aptamers allow targeted delivery with fewer side effects. Limitations include challenges in large-scale production, variable size and loading, possible toxicity, burst release, low encapsulation efficiency, and storage instability. Current research in polymer chemistry and nanotechnology aims to create safer, more efficient, and targeted nanoparticle systems (Paliwalet *et al.*, 2014).

Lafutidine is a yellowish white crystalline powder, with a melting point of (98.87-101.57 °C), It is freely soluble in glacial acetic acid, DMF, soluble in methanol, sparingly soluble in dehydrated ethanol, very slightly soluble in ether, practically insoluble in water with $\log p = 3.8$ (Dawoodet *et al.*, 2018). Lafutidine has $pka = 3.9$ and according to Biopharmaceutical Classification System (BCS), It belongs to class II of drug category. Lafutidine is a new H₂-receptor antagonist, after absorption in the small intestine; it reaches gastric cells by the systemic circulation, then directly and quickly binds to gastric cell histamine H₂ receptors, resulting in prompt inhibition of gastric acid secretion. It is selectively absorbed from the upper part of small intestine (absorption window) (Plamondonet *et al.*, 2024). The drug is predominantly metabolized in the liver mainly by microsomal enzyme CYP3A4, and CYP2D6 and its major metabolites are sulfonyl lafutidine and hydroxylated lafutidine (Liu *et al.*, 2022).

In-vitro evaluation of the prepared nanoparticles is an essential step to assess their performance and stability. Parameters such as particle size, polydispersity index, zeta potential, drug entrapment efficiency, and surface morphology are evaluated to ensure uniformity and stability of the formulation. Additionally, in-vitro drug release studies are conducted to understand the release kinetics and mechanism, which are further analyzed using mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models (Paarakhet *et al.*, 2018).

The present study focuses on the design, preparation, and in-vitro evaluation of Lafutidine-loaded polymeric nanoparticles as a controlled drug delivery system. The objective is to enhance the therapeutic efficacy, improve patient compliance, and provide sustained drug release over an extended period. This approach is expected to offer a promising alternative to conventional Lafutidine formulations and contribute to the advancement of novel drug delivery technologies.

II. MATERIAL AND METHODS

2.1 Chemicals

Ethanol, Acetonitrile, Chloroform, Polyvinyl alcohol (PVA), Propyleneglycol and Methylparaben were obtained from Merck. Salvavidas Pharmaceutical Pvt. Ltd provided the Lafutidine. Sigma-Aldrich provided the PLGA and Ethylcellulose. Vibgyor Chemical Industries provided the Alcohol while Vinipul Chemicals Pvt. Ltd supplied Magnesium. Ammonia was supplied by Performance Chemi serve Ltd (PCL) (DFPCL). Loba were obtained from Triethanolamine. Sulab supplied Carbopol 934.

2.2 Pre-formulation Evaluation

The pre-formulation study aimed to assess the essential physicochemical characteristics of Lafutidine to determine their compatibility and suitability for formulation into a stable and effective dosage form. The findings indicated that both compounds possess favorable properties with no major formulation challenges, confirming their potential for successful incorporation into a pharmaceutical product.

2.2.1 Organoleptic and Physical Characteristics

The sensory qualities of a substance that are perceived by the senses, especially through sight, smell and touch, are referred to as organoleptic traits. These characteristics include characteristics like color, form, texture, and clarity when evaluated visually (Patil *et al.*, 2018).

2.2.2 Solubility study

The solubility study of Lafutidine was carried out by visual inspection method in different solvents, namely water, ethanol, methanol, chloroform, and dimethyl sulfoxide (DMSO) (Jabir *et al.*, 2018).

2.2.3 Melting Point

To perform a melting point study of Lafutidine using melting point apparatus. This helps determine the purity and identity of the substances according to their melting points (Chu *et al.*, 2009).

2.2.4 pH Measurement

Determining the pH of active pharmaceutical ingredients is an essential step in pre-formulation studies, as it helps evaluate the compound's chemical stability and compatibility with other formulation components. In this analysis, the pH values of Lafutidine were measured using a calibrated digital pH meter (Balamuralidhara *et al.*, 2011).

2.2.5 UV-Visible Spectrophotometric Analysis (λ_{max})

- Preparation of Lafutidine stock solution in methanol

To prepare the standard stock solutions, exactly 5 mg of Lafutidine were individually weighed using

an analytical balance. Each sample was then transferred into separate 5 mL volumetric flasks. Methanol was added gradually to each flask until the volume reached the 5 mL mark, yielding primary stock solutions with a concentration of 100µg/mL. For further use, 1 mL aliquots of these stock solutions were pipetted into new volumetric flasks and diluted with methanol up to 10 mL, producing working standard solutions at a concentration of 100µg/mL for both compounds. These solutions were used for subsequent analytical procedures(Kumar *et al.*, 2017).

• **Lambda max determination**

A stock standard solution of Lafutidine was prepared at a concentration of 1 mg/mL using 80% methanol as the solvent. From this stock, a working standard solution with a concentration of 100µg/mL was obtained by diluting it appropriately with the same 80% methanol. The working solution was then analysed using a Shimadzu 1700 double beam UV spectrophotometer, scanning across the wavelength range of 200 to 400 nm to obtain the UV absorption spectrum of Lafutidine.

• **Preparation of Calibration Curve**

Calibration curves for Lafutidine were established to assess the linearity of their UV-Visible spectrophotometric response. Starting from a 100 µg/mL stock solution, serial dilutions were prepared to obtain a range of concentrations: 5 to 30µg/mL for Lafutidine. Each dilution was transferred to a 5 mL volumetric flask and brought up to volume with the appropriate solvent. The absorbance of these solutions was measured at their respective wavelengths 280.5nm for Lafutidine. The absorbance values were plotted against concentration to generate calibration curves(Tsvetkovaet *al.*, 2023).

• **Functional group identified by FTIR**

Fourier Transform Infrared (FTIR) spectroscopy is a valuable analytical technique commonly used to identify functional groups and investigate molecular interactions in pharmaceutical samples. It works by exposing the sample to infrared radiation, which is absorbed at specific wavelengths corresponding to the vibrations of chemical bonds within the molecules. Each functional group absorbs infrared light at characteristic frequencies, producing a distinct

absorption spectrum that acts as a molecular signature. In this study, FTIR analysis of the lafutidine was performed using the potassium bromide (KBr) pellet technique. Approximately 1 mg of Lafutidine was homogeneously blended with 100 mg of dried KBr powder. The mixture was then compressed into a clear, thin pellet under high pressure. These pellets were scanned over the spectral range of 400 to 4000 cm⁻¹ to record their infrared absorption profiles. This method allowed the identification of key functional groups and helped evaluate potential interactions between the drugs and other formulation components, ensuring compatibility and stability of the final product(Patty *et al.*, 2016).

2.3 Preparation of Loaded Polymeric Nanoparticles formulation

The solvent evaporation technique was utilized for the preparation of Lafutidine nanoparticles. Initially, Polymer PLGA and Lafutidine (10mg) were dissolved in a solvent system comprising Chloroform and methanol to ensure complete solubilization. This organic phase was then slowly introduced into an aqueous phase containing polyvinyl alcohol (PVA) as a stabilizing surfactant, under continuous magnetic stirring to promote emulsification. The resulting coarse emulsion underwent sonication for 3 minutes to reduce droplet size and achieve a uniform nanoscale dispersion. Following sonication, the organic solvents were removed by sustained magnetic stirring over 2 to 3 hours, leading to the formation of nanoparticles as the solvent evaporated. The nanoparticle suspension was subsequently centrifuged at 1000 rpm for 30 minutes to obtain the nanoparticles from the dispersion medium. To improve long-term stability and prevent aggregation, the nanoparticle formulation was lyophilized for 48 hours. Poly (lactic-co-glycolic acid) (PLGA) was employed as the polymeric matrix to encapsulate Lafutidine, offering a controlled release profile and enhancing the physicochemical stability of the nanoparticles. This approach ensures effective drug delivery with improved bioavailability and sustained therapeutic effect(Ayuhastutiet *al.*, 2024).

Table 1: Composition of Loaded Polymeric Nanoparticles formulation

Formulation Code	Drugs Lafutidine (%)	PLGA Polymer Concentration (mg)	PVA Surfactant Concentration (%)	Methanol Chloroform (5 ml)	Aqueous solution Water (ml)	Stirring Time (Hrs.)
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PNF1	1.0	300	0.3	1:1	10	3
PNF2	1.0	250	0.3	1:1	10	3
PNF3	1.0	200	0.3	1:1	10	3
PNF4	1.0	150	0.3	1:1	10	3
PNF5	1.0	100	0.3	1:1	10	3

2.4 Evaluation parameter of drug loaded Polymeric Nanoparticles formulation

2.4.1 Physical properties

The Polymeric Nanoparticles formulation was carefully evaluated for its physical attributes, including color, odor, texture, and homogeneity.

2.4.2 Particle Size and Polydispersity Index Measurement

The particle size of the drug-loaded Polymeric Nanoparticles was measured using a Malvern Zetasizer, which utilizes dynamic light scattering (DLS) technology (Shekunov *et al.*, 2007).

2.4.3 Zeta Potential Evaluation

Zeta potential measurement was performed to evaluate the surface charge and electrophoretic mobility of the Polymeric Nanoparticles particles, which are key indicators of formulation stability. The zeta potential was then measured using a Malvern Zeta sizer (Honary *et al.*, 2013).

2.4.4 SEM analysis

The surface morphology of the formulated Polymeric Nanoparticles was analyzed using scanning electron microscopy (SEM) (Mohammed *et al.*, 2004).

2.4.5 Drug Encapsulation and Loading Efficiency

The entrapment efficiency of the drug-loaded Polymeric Nanoparticles was evaluated by subjecting the formulation to centrifugation using a REMI Ultra Centrifuge for 30 minutes. Following centrifugation, the supernatant containing unencapsulated drug was carefully separated and filtered. The concentration of the free drug in the supernatant was quantified using UV spectrophotometry at 280.5nm. The percentage of drug entrapped within the Polymeric Nanoparticles (% EE) was calculated by comparing the initial drug amount to the untrapped drug present in the supernatant, using the standard entrapment efficiency formula:

$$\%EE = \frac{(\text{Initial amount of drug added} - \text{Drug amount in supernatant}) \times 100}{\text{Initial amount of drug added}}$$

2.5 In vitro drug release study (kinetics model)

The dialysis bag diffusion method was used to evaluate the in-vitro drug release of Lafutidine-loaded polymeric nanoparticles. The formulation was placed in a dialysis bag and immersed in 100 mL of pH 7.4 phosphate buffer, maintained at 37 ± 1°C with continuous stirring at 100 rpm. At predetermined intervals, 2 mL samples were withdrawn and replaced with fresh buffer, followed by analysis using a UV-Visible spectrophotometer at 280.5 nm. The release data were fitted to various kinetic models, including zero-order (cumulative % drug release vs time), first-order (log % drug remaining vs time), Higuchi model (cumulative % drug release vs square root of time based on Fickian diffusion), and Korsmeyer-Peppas model (log cumulative % drug release vs log time). The corresponding equations used were:

$$C = k_0 t \quad (1)$$

Where, C is the concentration of drug at time t, t is the time and k₀ is zero-order rate constant expressed in units of concentration/time.

$$\text{Log } C_0 - \text{Log } C = \frac{k_1 t}{2.303} \quad (2)$$

Where, C₀ is the initial concentration of drug and k₁ is the first order rate constant.

$$C = K_H \sqrt{t} \quad (3)$$

Where, K_H is the constant reflecting the design variables of the system

$$\frac{M_t}{M_\infty} = K_{KP} t^n$$

Where M_t / M_∞ is the fraction of drug released at time t, K_{KP} is the rate constant and n is the release exponent.

2.6 Stability testing

Stability is a critical parameter in pharmaceutical development, referring to the ability of a drug or formulation to maintain its physical, chemical, and therapeutic properties under specific storage conditions. In this study, the optimized batch of Lafutidine-loaded polymeric nanoparticles was subjected to stability testing as per ICH guidelines. The formulation was stored in airtight containers under two conditions: 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/70 ± 5% RH. Evaluations were performed at 30, 45, 60, and 90 days to assess parameters such as drug entrapment efficiency, particle size, and

physical appearance. The results were compared with the initial formulation to determine any significant changes. This study helped confirm the stability of the formulation under accelerated

conditions and provided essential data for predicting shelf life and ensuring product reliability (Bajaj *et al.*, 2016).

III. RESULT AND DISCUSSION

3.1 Pre-formulation study of drug

3.1.1 Organoleptic properties

Table 2: Organoleptic properties of Lafutidine

Drug	Organoleptic properties	Observation
Lafutidine	Color	White, off-white
	Odor	Odorless
	Appearance	Fine crystalline powder
	State	Solid

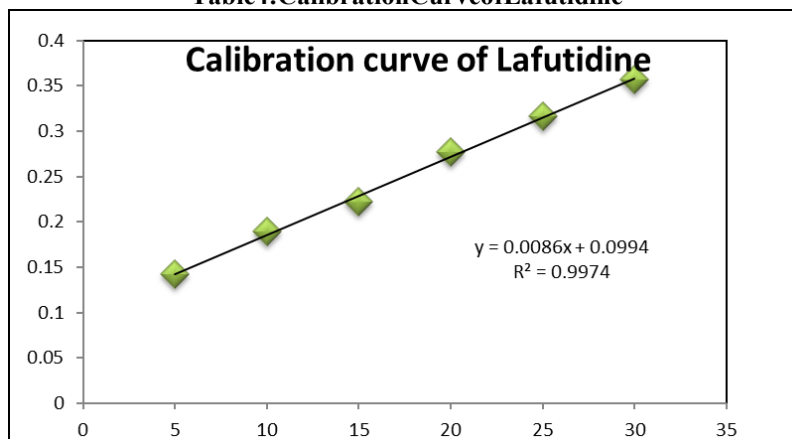
3.1.2 Determination of Melting Point and pH

Table 3: Determination of Melting Point and pH

Drugs	Observed (Melting point)	Reference (Melting point)	Observed (pH)	Reference (pH)
Lafutidine	100°C	96 to 101	6.7	6.2- 6.8pH

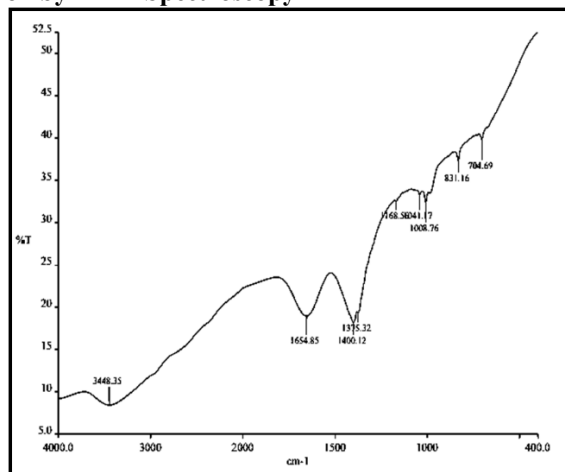
3.1.3 Standard calibration curve

Table 4: Calibration Curve of Lafutidine



Graph 1: Calibration curve of Lafutidine

3.1.4 Structural Confirmation by FTIR Spectroscopy



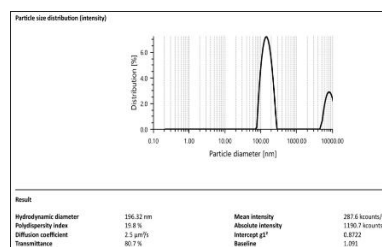
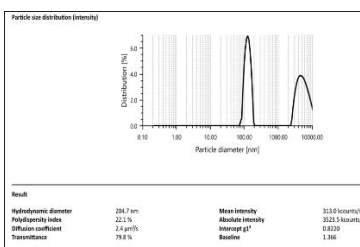
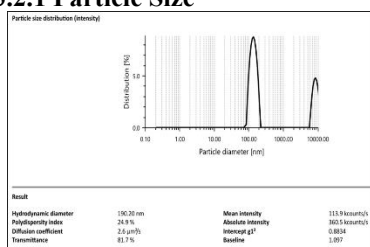
Graph 2: Structural Confirmation by FTIR Spectroscopy

Table 4: Interpretation of IR spectrum of Lafutidine

Peak obtained	Reference peak	Functional group	Name of functional group
3448.35	3500- 3400	N-H stretching	Primary amine
1654.85	1690-1640	C=N stretching	Imine / oxime
1400.12	1415-1380	S=O stretching	Sulfate
1375.32	1390-1310	O-H bending	Phenol
1168.51	1210-1163	C-O stretching	Ester
831.16	840-790	C=C bending	Alkene

3.2 Characterization of drug loaded Polymeric Nanoparticles formulation

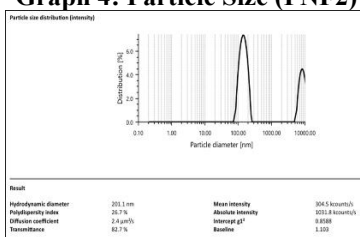
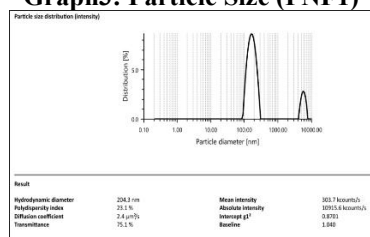
3.2.1 Particle Size



Graph 3: Particle Size (PNF1)

Graph 4: Particle Size (PNF2)

Graph 5: Particle Size (PNF3)



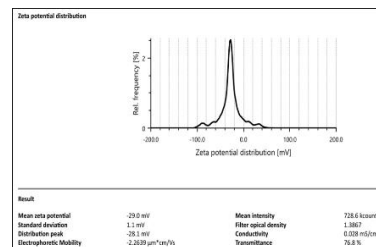
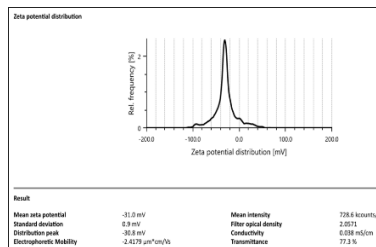
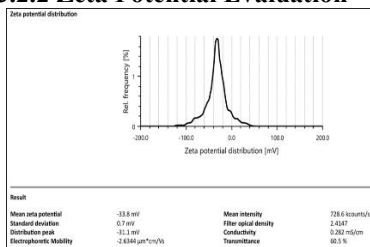
Graph 6: Particle Size (PNF4)

Graph 7: Particle Size (PNF5)

Table 5: Particle size of Polymeric Nanoparticle

Formulation code	Particle size (nm)	PI Value %
PNF1	190.20 nm	22.1
PNF2	204.7 nm	24.9
PNF3	196.32 nm	19.8
PNF4	204.3 nm	23.1
PNF5	201.1 nm	26.7

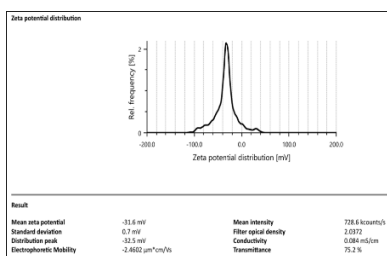
3.2.2 Zeta Potential Evaluation



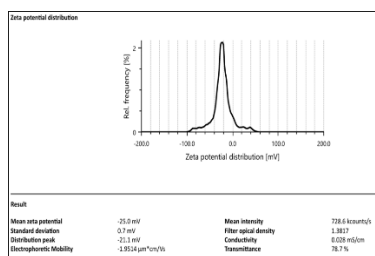
Graph 8: Zeta Potential PNF1

Graph 9: Zeta Potential PNF2

Graph 10: Zeta Potential PNF3



Graph 11: Zeta Potential PNF4



Graph 12: Zeta Potential PNF 5

Table 6: Zeta Potential

Formulation code	Zeta potential (mV)
PNF 1	-33.8 mV
PNF 2	-31.0 mV
PNF 3	-29.0 mV
PNF 4	-31.6 mV
PNF 5	-25.0 mV

3.2.3 Morphological Analysis by Scanning Electron Microscopy (SEM)

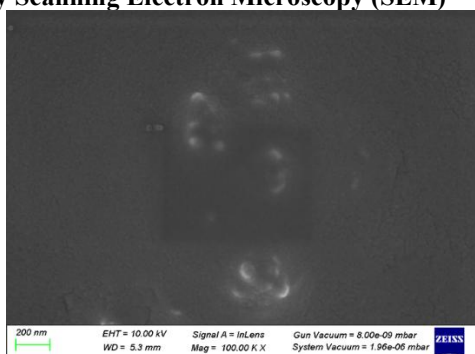
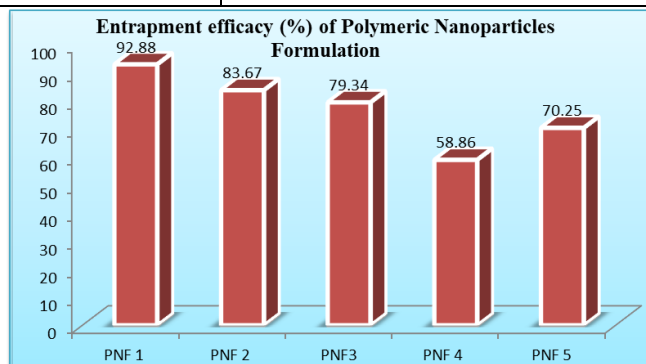


Figure 1: Scanning electron microscope (SEM)

3.2.4 Drug Encapsulation and Loading Efficiency

Table 7: Entrapment efficacy (EE) of Polymeric Nanoparticles Formulation

Formulations	Entrapment efficacy (%)
PNF 1	92.88
PNF 2	83.67
PNF3	79.34
PNF 4	58.86
PNF 5	70.25

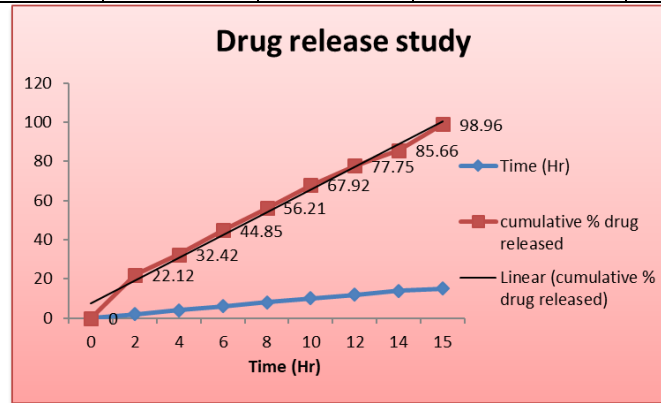


Graph 13: Graphical Data of EE of Polymeric Nanoparticles Formulation

3.3 In-vitro drug release

Table 8: In-vitro drug release studies

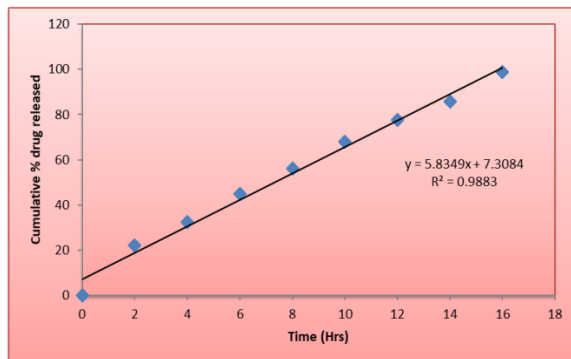
Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released
0	0	100	0.000	2.000	0.000	0.000
2	22.12	77.88	1.414	1.891	0.301	1.345
4	32.42	67.58	2.000	1.830	0.602	1.511
6	44.85	55.15	2.449	1.742	0.778	1.652
8	56.21	43.79	2.828	1.641	0.903	1.750
10	67.92	32.08	3.162	1.506	1.000	1.832
12	77.75	22.25	3.464	1.347	1.079	1.891
14	85.66	14.34	3.742	1.157	1.146	1.933
15	98.96	1.04	4.000	0.017	1.204	1.995



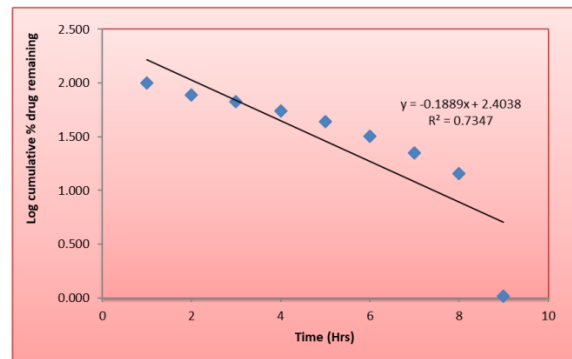
Graph 14: In-vitro drug release studies

Table 9: Correlation value (R² value)

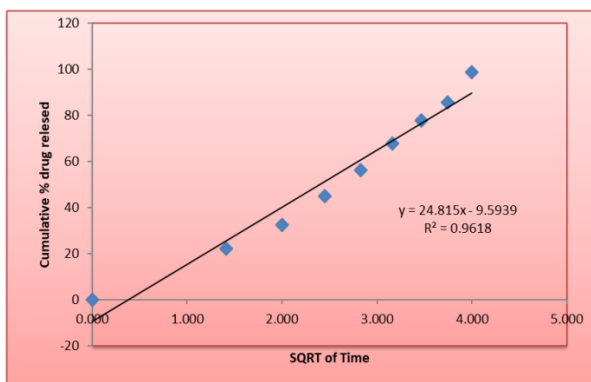
Formulation	Model	Kinetic parameter values
PNF Formulation	Zero Order	R ² = 0.9883
	First Order	R ² = 0.7347
	Higuchi	R ² = 0.9618
	Korsmeyerpeppas	R ² = 0.8267



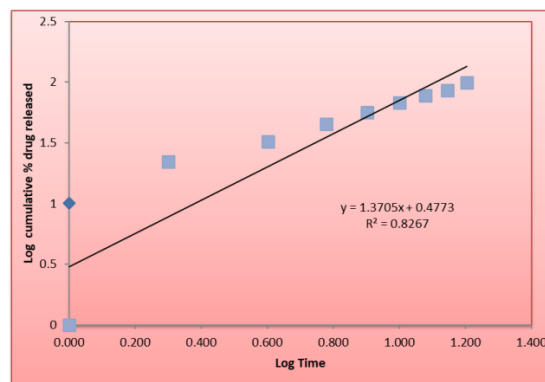
Graph 15: Zero order



Graph 16: First order



Graph 17: Higuchi



Graph 18: Korsmeyer peppas

3.4 Stability study

Table 10: Stability Study of optimized formulation (Polymeric Nanoparticles)

Time (Days)	25°C±2 °C and 60 ± 5% RH		40°C±2 °C and 70 ±5% RH	
	Particle size	Entrapment efficacy (%)	Particle size	Entrapment efficacy (%)
0	190.20 nm	92.88%	190.20nm	92.83%
30	191.22 nm	92.80%	192.21 nm	92.85%
45	190.19 nm	91.88%	192.20 nm	92.88%
60	190.22 nm	93.85%	190.21nm	92.81%
90	190.21 nm	92.84%	190.22 nm	92.88%

Discussion

The evaluation of Lafutidine confirmed its suitability for formulation development through various physicochemical and analytical studies. Organoleptic properties showed the drug to be a white to off-white, odorless, crystalline solid, indicating good purity. It exhibited poor aqueous solubility but better solubility in organic solvents such as methanol, ethanol, chloroform, and DMSO, which is important for formulation design. The observed melting point (100°C) and pH (6.7) were within reported ranges, confirming the drug's identity and stability. The calibration curve demonstrated excellent linearity ($R^2 = 0.9974$), indicating accurate and reliable quantitative analysis. FTIR studies confirmed the presence of characteristic functional groups, supporting drug authenticity. Polymeric nanoparticle formulations showed particle sizes in the nano-range (190–204 nm) with acceptable polydispersity, indicating uniform distribution. Zeta potential values (–25.0 to –33.8 mV) suggested good colloidal stability, with PNF1 showing the highest stability. SEM analysis revealed spherical morphology with distinct surface features. Stability studies conducted under accelerated conditions showed no significant changes in particle size or entrapment efficiency over 3 months, confirming that the formulation

remained physically and chemically stable. Overall, the results indicate that the developed polymeric nanoparticle formulation of Lafutidine is stable, reliable, and suitable for further pharmaceutical applications.

IV. CONCLUSION

The present study concludes that Lafutidine-loaded polymeric nanoparticles were successfully developed and evaluated with satisfactory results. Pre-formulation studies confirmed the identity, purity, and suitability of Lafutidine for formulation development, as all physicochemical parameters were found within the acceptable reference range. The prepared nanoparticle formulations exhibited nanoscale particle size, good homogeneity, adequate surface charge for stability, and high drug entrapment efficiency, particularly in the optimized formulation (PNF1). In-vitro drug release studies demonstrated a sustained and controlled release pattern following zero-order kinetics, indicating efficient drug delivery characteristics. Furthermore, stability studies confirmed that the optimized formulation remained physically and chemically stable under accelerated conditions. Overall, the findings suggest that polymeric nanoparticles are a promising and

effective drug delivery system for improving the performance and therapeutic efficacy of Lafutidine.

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