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FORMULATION AND DEVELOPMENT OF MUCOADHESIVE MICROSPHERES OF LANSOPRAZOLE USING NATURAL POLYMER

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Abstract

This study investigates the formulation and characterization of mucoadhesive microspheres for Lansoprazole using chitosan as the primary polymer. The objectives were to enhance the drug's solubility and prolong its gastric retention. Various formulations were prepared via the solvent evaporation method, and their properties, including percentage yield, entrapment efficiency, stability in acidic conditions, flow characteristics, and drug release profiles, were evaluated. The results demonstrated that formulation F3 exhibited the highest percentage yield (75.45%) and entrapment efficiency (74.45%). Stability studies showed a gradual decline in transmittance in 0.1 N HCl, indicating some degradation of microspheres over time. The cumulative drug release in simulated gastric fluid revealed significantly lower release from chitosan microspheres compared to plain Lansoprazole, indicating a sustained release effect. Kinetic analysis suggested a zero-order release profile for formulation F3, highlighting its potential for controlled drug delivery. Overall, chitosan-based mucoadhesive microspheres present a promising approach to improving the therapeutic efficacy of Lansoprazole.

Keywords: Lansoprazole, mucoadhesive microspheres, chitosan, entrapment efficiency, drug release, gastric retention, controlled release.

Introduction

Lansoprazole is a widely used proton pump inhibitor effective in the treatment of various gastric disorders, including peptic ulcers and gastroesophageal reflux disease (GERD). While it provides significant therapeutic benefits, the oral bioavailability of Lansoprazole is limited due to its poor solubility and rapid degradation in the acidic environment of the stomach [1]. To enhance the efficacy and bioavailability of Lansoprazole, innovative formulation strategies are essential. One such strategy involves the development of mucoadhesive microspheres, which can significantly improve drug retention and absorption in the gastrointestinal tract.

Mucoadhesive microspheres are small spherical particles designed to adhere to the mucosal surfaces of the gastrointestinal tract. This adherence increases the residence time of the drug, enhancing its local availability and absorption [2]. The use of natural polymers in the formulation of these microspheres provides several advantages, such as biocompatibility, biodegradability, and the ability to form hydrophilic gels that improve mucoadhesive properties [3]. Common natural polymers used for this purpose include chitosan, alginate, and guar gum, which can effectively encapsulate the drug and control its release [4].

The preparation of mucoadhesive microspheres typically involves techniques such as solvent evaporation, coacervation, and spray drying. Solvent evaporation is particularly favored for its

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simplicity and effectiveness in achieving microspheres with suitable characteristics [5]. The formulation parameters, including polymer type, concentration, and processing conditions, significantly influence the physical properties, size distribution, and drug release behavior of the microspheres.

Characterization of the formulated microspheres is crucial to assess their performance. Techniques such as scanning electron microscopy (SEM), Fourier-transform infrared spectroscopy (FTIR), and in vitro drug release studies are commonly employed to evaluate the morphology, chemical interactions, and release kinetics of the microspheres [6].

This study aims to formulate and characterize mucoadhesive microspheres of Lansoprazole using natural polymers. By optimizing the formulation parameters and evaluating the resulting microspheres, the objective is to enhance the solubility and therapeutic efficacy of Lansoprazole through improved gastric retention and controlled drug release.

Material and Methods

Material

The formulation development of mucoadhesive microspheres for Lansoprazole involved several key materials sourced from reputable suppliers. Lansoprazole, the active pharmaceutical ingredient, was obtained as a gift sample from Pharmaceutical Company. Methanol, ethanol, and chloroform from Qualigens Fine Chemicals, Mumbai, were used as solvents during the microsphere preparation process. To maintain the desired pH, potassium dihydrogen phosphate, sodium hydroxide, and hydrochloric acid were sourced from S. D. Fine Chem. Ltd., Mumbai. Chitosan, a natural polymer known for its biocompatibility and mucoadhesive properties, was procured from Himedia Pvt. Ltd., Mumbai. Lastly, sodium tripolyphosphate from Loba Chemie Pvt. Ltd. was utilized as a cross-linking agent to enhance the structural integrity of the microspheres. Together, these materials contribute to the effective formulation of Lansoprazole-loaded mucoadhesive microspheres.

Methods

Preparation of chitosan mucoadhesive microspheres of Lansoprazole

Chitosan microspheres were prepared by ionotropic gelation method [7].

Chitosan stock solution (1% w/v) was prepared by dissolving chitosan in acetic acid (5% v/v) at room temperature. The drug (30 mg) was dissolved in chitosan solution (5ml), 1% Sodium tripolyphosphate solution was prepared in water. Sodium tripolyphosphate solution was added drop wise with a 5ml syringe to chitosan solution while stirring. The solution was magnetically stirred for half an hour followed by filtration and rinsing with distilled water. Microspheres were obtained which were airs dried for twenty four hours followed by oven drying for six hours at 40˚C.

Table 1: Formulations of chitosan mucoadhesive microspheres

S. No.	Formulation Code	Lansoprazole (mg)	Chitosan (mg)	Sodium tripolyphosphate (mg)
1.	**F1**	30	100	500
2.	**F2**	30	150	500
3.	**F3**	30	200	500

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4.	**F4**	30	100	750
5.	**F5**	30	150	750
6.	**F6**	30	200	750

Evaluation of mucoadhesive microspheres

Percentage Yield

The prepared microspheres (F1-F6) were collected and weighed for each formulation code. The percentage yield (%) was calculated using formula given below:

$$\% \text{ Yield } = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} x\ 100$$

Entrapment Efficiency

Amount of Lansoprazole in each formulation was calculated according to procedure given below [8]: Equivalent to 10mg of chitosan microspheres from each batch were accurately weighed. The powder of chitosan microspheres were dissolved in 10 ml 0.1 N HCl and centrifuged at 1000 rpm. This supernatant solution is then filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The supernant was analyzed for drug content by measuring the absorbance at 296nm.

Stability of chitosan microspheres in 0.1 N HCl

The stability of chitosan microspheres in 0.1 N HCl was determined by incubating 0.5% wt/vol suspension of the microspheres in 0.1N HCl for 12 hrs. and measuring the transmission of the samples at 296nm (Labindia 3000+ spectrophotometer) as reported by Berthold *et al.,* (1996) [9]. Chitosan is soluble in acidic pH, therefore, the purpose of carrying out this study was to determine the effect of different cross-linking methods on the solubility of chitosan, which in turn reflects the stability at acidic pH.

Measurement of mean particle size

The mean particle size of the microspheres was determined by Photon Correlation Spectroscopy (PCS) on a submicron particle size analyzer (SAIF RGPV Bhopal, Malvern Zetamaster, ZEM 5002, Malvern, UK) at a scattering angle of 90°. A sample (0.5mg) of the microsphere suspended in 5 ml of distilled water was used for the measurement [10].

Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zetasizer (Malvern particle size analyser) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate [11].

Flow property determination of the microspheres

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\textbf{LBD (Loose bulk density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

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$$\textbf{TBD (Tapped bulk density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\textbf{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X100}$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

$$\textbf{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

Shape and surface characterization of microspheres by Scanning Electron Microscopy (SEM)

From the formulated batches of microsphere, formulations (F3) which showed an appropriate balance between the percentage drug release was examined for surface morphology and shape using scanning electron microscope (Jeol Japan 6000). Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

***In-vitro* drug release studies in gastrointestinal fluids**

The prepared microspheres were evaluated for *in vitro* drug release. The drug release studies were carried out using USP I Basket type dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 100 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows:

A weighed quantity of formulation (equivalent to 10mg) was filled in capsule and kept in basket of dissolution apparatus with dissolution media 0.1 N HCl (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 5ml by media. The samples withdrawn were assayed spectrophotometrically at 296nm for percent of release from mucoadhesive microspheres using UV visible spectrophotometer. The release of mucoadhesive microsphere was calculated with the help of Standard curve of Lansoprazole [11].

Results and Discussion

The formulation and evaluation of mucoadhesive microspheres for Lansoprazole demonstrate promising results across various metrics, including percentage yield, entrapment efficiency, stability, flow properties, drug release, and kinetic analysis.

Table 2 indicates that the percentage yield of the formulations ranged from 68.85% to 75.45%, with formulation F3 achieving the highest yield of 75.45±0.14%. This suggests that the microsphere preparation process was efficient, allowing for a substantial recovery of the product. Table 3 presents the entrapment efficiency, which varied from 65.45% to 74.45%. Formulation F3 again showed the highest efficiency at 74.45±0.32%, indicating effective encapsulation of Lansoprazole. High entrapment

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efficiency is crucial for maximizing the therapeutic potential of the microspheres, as it ensures that a significant amount of the drug is retained within the formulation.

The stability of chitosan microspheres in 0.1 N HCl is critical for their performance in the gastric environment. As shown in Table 4, the percentage transmittance values decreased over time for all formulations, indicating degradation of the microspheres in acidic conditions. Formulation F2 showed the best stability at 2 hours with a transmittance of 74.45%, while F3 exhibited a decline to 32.23% by 8 hours. These results highlight the importance of optimizing the polymer formulation to enhance the stability of the microspheres in acidic conditions.

Flow properties are vital for the processing and handling of microspheres. Table 5 presents the flow properties for the different formulations, with Carr's Index values ranging from 22.407% to 24.183%. These values indicate that the microspheres exhibit fair flowability, which is essential for uniformity during processing. The Hausner's Ratio values, ranging from 1.289 to 1.319, also suggest good flow characteristics, which are important for successful manufacturing.

The cumulative drug release data from Table 6 show that Lansoprazole released from plain drug form was significantly higher than that from chitosan microspheres over 12 hours in simulated gastric fluid (SGF). The plain drug reached nearly complete release (98.98%) compared to only 45.65% from the chitosan microspheres at 4 hours. This delayed release profile is desirable, as it indicates that the microspheres can provide sustained release of Lansoprazole, potentially improving its therapeutic efficacy by prolonging the drug's presence in the gastrointestinal tract.

The regression analysis presented in Table 7 indicates that the drug release from formulation F3 best fits the zero-order model ($R^2 = 0.987$), suggesting a constant release rate over time. The Higuchi model also showed a high correlation ($R^2 = 0.978$), indicating that drug diffusion through the microsphere matrix is a significant factor in the release mechanism. The Pappas plot further supports this by demonstrating a strong fit ($R^2 = 0.974$). Collectively, these analyses imply that the release of Lansoprazole from chitosan microspheres is governed by a combination of diffusion and erosion mechanisms.

Table 2: Percentage yield for different formulation

S. No.	Formulation	Percentage yield* (Mean ± S.D)
1	F1	68.85±0.25
2	F2	70.23±0.32
3	F3	75.45±0.14
4	F4	68.85±0.26
5	F5	69.98±0.32
6	F6	70.23±0.14

***Average of three determinations (n=3)**

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Table 3: Entrapment efficiency for different formulations

S. No.	Formulation	% Entrapment Efficiency* (Mean ± S.D)
1	F1	69.98±0.12
2	F2	70.25±0.25
3	F3	74.45±0.32
4	F4	65.45±0.17
5	F5	68.85±0.20
6	F6	68.12±0.15

***Average of three determinations (n=3)**

Table 4: Stability of Chitosan microspheres in 0.1 N HCl

S. No.	Formulation code	% Transmittance		
		2 hrs	8 hrs	12 hrs
1	F1	68.85	50.23	15.25
2	F2	74.45	45.52	17.85
3	F3	62.23	32.23	9.96
4	F4	72.23	50.23	14.45
5	F5	69.98	40.14	17.78
6	F6	68.78	46.65	15.65

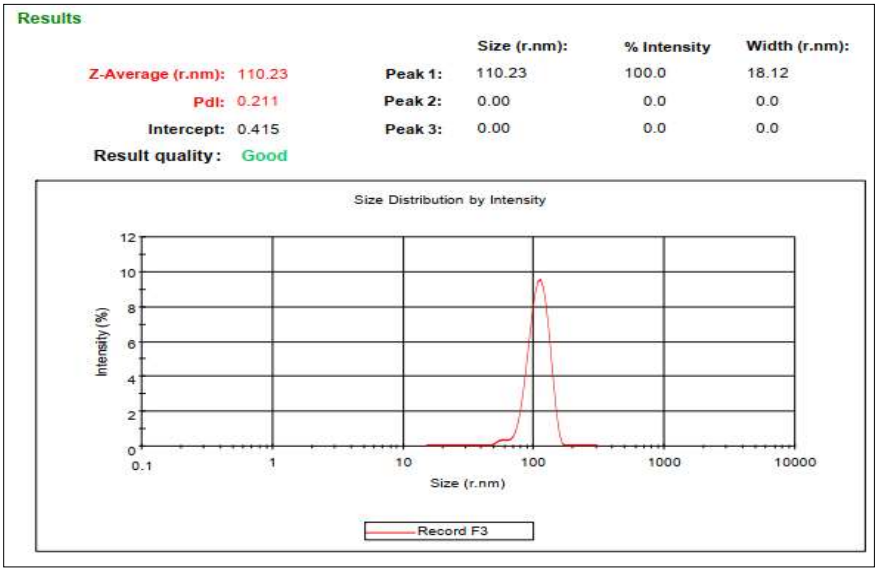

Figure 1: Particle size data of chitosan microspheres (F3)

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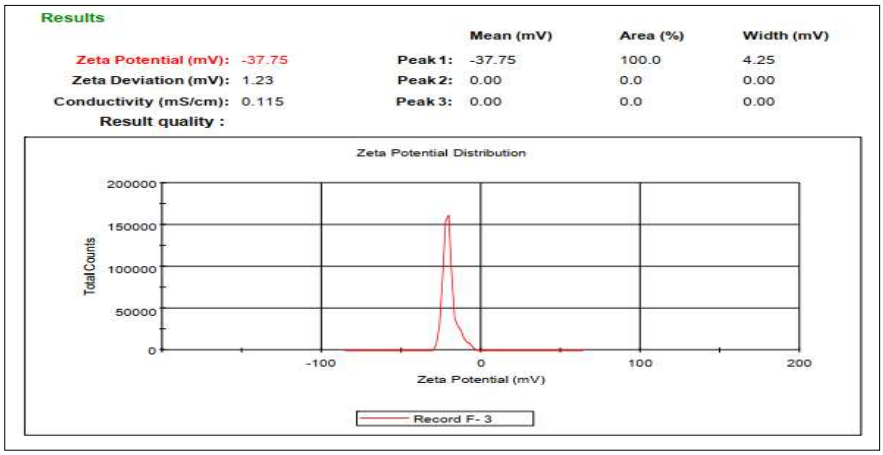

Figure 2: Zeta potential data of chitosan microspheres (F3

Table 5: Result of Flow Properties of different microspheres formulations

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.345	0.452	23.673	1.310
F2	0.365	0.472	22.669	1.293
F3	0.348	0.459	24.183	1.319
F4	0.365	0.473	22.833	1.296
F5	0.374	0.482	22.407	1.289
F6	0.363	0.476	23.739	1.311

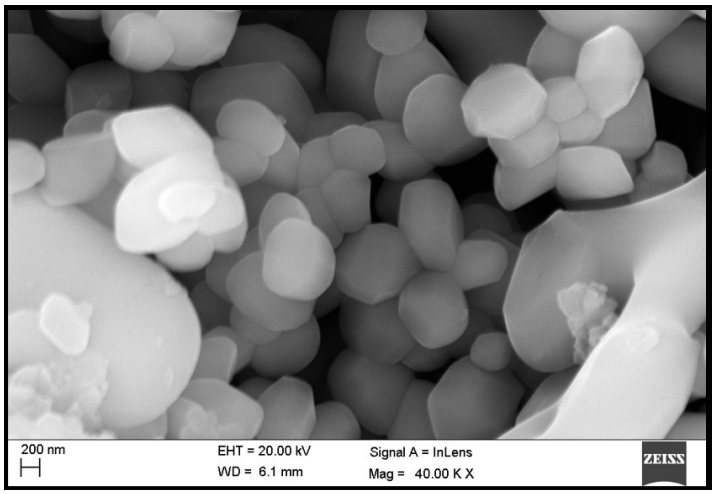

Figure 3: Scanning Electron Microscope of optimized formulation (F3)

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Table 6: Cumulative % drug release of Lansoprazole from plain drug and Chitosan microspheres

S. No.	Dissolution medium	Time (hrs)	% Cumulative Drug Release	
			Plain drug	Chitosan microspheres
1	SGF (pH 1.2)	1	36.65	10.23
2		2	55.45	16.65
3		3	85.56	22.23
4		4		45.65
5		5		52.23
6		6		59.98
7		7		67.74
8		8		78.85
9		9		86.65
10		10		92.23
11		12		98.98

***Simulated gastric fluid (SGF)**

Table 7: Regression analysis data of microsphere formulation

Formulation	Zero order	First order	Higuchi	Pappas plot
F3	$R^2 = 0.987$	$R^2 = 0.791$	$R^2 = 0.978$	$R^2 = 0.974$

Conclusion

The development of mucoadhesive microspheres for Lansoprazole using chitosan has shown favorable results in terms of yield, entrapment efficiency, stability in acidic conditions, and sustained drug release. These findings suggest that chitosan microspheres can be an effective delivery system for Lansoprazole, enhancing its therapeutic potential by improving solubility and prolonging gastric retention.

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