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FORMULATION AND EVALUATION OF GASTRO-RETENTIVE MUCOADHESIVE MICROSPHERES OF LAFUTIDINE HYDROCHLORIDE USING NATURAL POLYMERS

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ABSTRACT

Gastro-retentive drug delivery systems are pivotal in enhancing the therapeutic efficacy of drugs requiring prolonged gastric residence time. This study focuses on the formulation, characterization, and evaluation of chitosan microspheres loaded with Lafutidine HCl for targeted treatment of gastric disorders. Six formulations (F1 to F6) were prepared and assessed for yield, entrapment efficiency, stability in simulated gastric fluid (0.1 N HCl), particle size, zeta potential, mucoadhesive strength, and in vitro drug release kinetics. Formulation F3 emerged as optimal, demonstrating high yield (74.65%), significant drug entrapment efficiency (73.25%), and sustained release properties over 12 hours in acidic conditions. Particle size analysis revealed suitable dimensions for gastro-retentive applications, while strong mucoadhesive properties and controlled release kinetics were confirmed through mucoadhesion testing and kinetic modeling. These findings highlight chitosan microspheres as promising carriers for Lafutidine HCl, offering potential improvements in bioavailability, patient compliance, and therapeutic outcomes in gastric therapy.

Key Words: Gastro-retentive drug delivery, chitosan microspheres, Lafutidine HCl, mucoadhesion, sustained release

INTRODUCTION

Gastro-retentive drug delivery systems have emerged as innovative solutions to enhance the efficacy of therapeutics by prolonging their residence time in the stomach (Prajapati *et al.,* 2011; Das and Suresh, 2012; Kulkarni *et al.,* 2012). These systems are particularly advantageous for drugs like Lafutidine hydrochloride, a histamine H2 receptor antagonist used to treat gastric ulcers and gastroesophageal reflux disease (GERD). Lafutidine's therapeutic potential is hindered by its rapid gastrointestinal clearance and short plasma half-life, necessitating frequent dosing for sustained efficacy (Kothari *et al.,* 2011; Vora *et al.,* 2016).

Mucoadhesive microspheres represent a promising approach within gastro-retentive systems (Zeb *et al.,* 2016; Raval *et al.,* 2012). These microspheres adhere to the gastric mucosa, prolonging drug release and improving absorption. Natural polymers, such as chitosan, alginate, and pectin, are preferred for their biocompatibility, biodegradability, and minimal toxicity compared to synthetic counterparts (Uhumwangho *et al.,* 2015; Pandey *et al.,* 2013).

Previous studies have demonstrated the feasibility and advantages of mucoadhesive microspheres in gastro-retentive drug delivery systems (Dash *et al.,* 2010; Elsayed *et al.,* 2007). Research on similar systems, such as those containing acyclovir, carvedilol, and

amoxicillin, has highlighted formulation strategies, characterization techniques, and in vitro/in vivo evaluations crucial for optimizing drug delivery performance (Bhalekar *et al.,* 2009; Singh *et al.,* 2013; Verma *et al.,* 2003).

This paper aims to explore the formulation, design, and evaluation of mucoadhesive microspheres loaded with Lafutidine hydrochloride using natural polymers. By leveraging the advantages of natural polymers and mucoadhesive properties, this study seeks to enhance Lafutidine's bioavailability, prolong its gastric residence time, and improve patient compliance through reduced dosing frequency. The findings are expected to contribute to the development of effective gastro-retentive drug delivery systems tailored for optimal treatment outcomes in gastric disorders.

MATERIALS AND METHODS

Preparation of chitosan mucoadhesive microspheres of Lafutidine HCl

Chitosan microspheres were prepared by ionotropic gelation method (Sharma *et al.,* 2017).

Chitosan stock solution (1% w/v) was prepared by dissolving chitosan in acetic acid (5% v/v) at room temperature. The drug (10 mg) was dissolved in chitosan solution (5ml). 1% Sodium tripolyphosphate solution was prepared in water. Sodium tripolyphosphate solution was added drop wise with a 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.

Evaluation of mucoadhesive microspheres

Percentage Yield

The prepared microspheres (F1-F6) were collected and weighed for each formulation code (Priyadarshini *et al.,* 2014). 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 Lafutidine HCl in each formulation was calculated according to procedure given below (Priyadarshini *et al.,* 2014). 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 282nm.

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 282nm (Labindia 3000+ spectrophotometer) as reported by Berthold *et al.,* (1996). 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 (Malvern particle size analyser**)** 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 (Dhanaraju *et al.,* 2009).

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 (Thejeswini *et al.,* 2014).

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.

Mucoadhesion testing by ex vivo wash-off test:

The mucoadhesive property of the microspheres was evaluated by an in vitro adhesion testing method known as the wash-off method. Freshly excised pieces of the intestinal mucosa (2×2cm) from sheep were mounted on to glass slides (3×1inch) with cyanoacrylate glue. Two glass slides stood allied with a seemly backing. Almost 20 microspheres remain spread onto each wet rinsed tissue specimen and proximately advanced the backing was hung onto the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was run, the tissue specimen was particular a relaxed, steady up-and-down movement in the test fluid at 37°C enclosed in a 1 L vessel of the machine. At the end of 30 minutes, at the end of 1 hour, and at hourly intervals up to 10 hours, the machine was stopped and the number of microspheres still adhering to the tissue was counted. The test was performed at intestinal pH (pH7.4 phosphate buffer (Nighute *et al.,* 2009).

***In-vitro* drug release studies**

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 282nm 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 Lafutidine HCl.

RESULTS AND DISCUSSION

The formulation and evaluation of chitosan microspheres loaded with Lafutidine HCl present promising advancements in drug delivery technology aimed at improving treatment efficacy for gastric disorders. The study's findings, as depicted in Tables 2 to 7 and Figures 1 to 3, underscore several important aspects to the development of effective gastro-retentive drug delivery systems.

Firstly, the formulation process demonstrated varying yields among formulations, with F3 exhibiting the highest yield at 74.65%, indicating efficient production and reproducibility of chitosan microspheres. This high yield is essential for scalability and cost-effectiveness in pharmaceutical manufacturing (Table 2). Simultaneously, entrapment efficiency results (Table 3) revealed that formulation F3 also boasted the highest percentage of Lafutidine HCl encapsulation at 73.25%, ensuring maximal drug loading within the microspheres. This parameter is pivotal for optimizing therapeutic efficacy by maintaining adequate drug concentration at the target site over an extended period.

Regarding stability, the microspheres demonstrated robust performance in simulated gastric fluid (0.1 N HCl), as evidenced by the maintenance of high transmittance levels over 12 hours for formulation F3 (Table 4). This stability profile is indicative of the microspheres' ability to withstand acidic environments, crucial for ensuring drug integrity and sustained release kinetics in the stomach.

Moreover, the physical characteristics of the microspheres were evaluated through particle size analysis (Figure 1) and zeta potential measurements (Figure 2). Formulation F3 exhibited optimal particle size distribution suitable for gastro-retentive applications, promoting prolonged gastric residence time and enhanced drug absorption. The favorable zeta potential of F3 indicated sufficient surface charge, facilitating strong mucoadhesive interactions with gastric mucosa, which is vital for achieving prolonged drug retention and localized therapeutic effects.

The scanning electron microscope image (Figure 3) further validated the uniform morphology and spherical shape of optimized formulation F3, confirming successful microsphere fabrication. This structural integrity contributes to the controlled and sustained release of Lafutidine HCl, critical for achieving consistent therapeutic outcomes.

In vitro drug release studies (Table 6) demonstrated that Lafutidine HCl released from chitosan microspheres (F3) exhibited sustained release profiles over 12 hours in simulated gastric fluid, contrasting with the rapid release of plain drug. This sustained release pattern aligns with zero-order kinetics and the Pappas plot model (Table 7), indicating controlled drug release mechanisms that could potentially enhance bioavailability and reduce dosing frequency, thereby improving patient compliance and therapeutic efficacy.

Table 1: Formulations of chitosan mucoadhesive microspheres

S. No.	Formulation Code	Lafutidine HCl (mg)	Chitosan (mg)	Sodium tripolyphosphate (mg)
1.	F1	10	100	500
2.	F2	10	150	500
3.	F3	10	200	500
4.	F4	10	100	750
5.	F5	10	150	750
6.	F6	10	200	750

Table 2: Percentage yield for different formulation

S. No.	Formulation	Percentage yield* (Mean ± S.D)
1	F1	64.58±0.15
2	F2	66.85±0.23
3	F3	74.65±0.32
4	F4	69.98±0.45
5	F5	71.12±0.65
6	F6	68.87±0.52

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

Table 3: Entrapment efficiency for different formulations

S. No.	Formulation	% Entrapment Efficiency* (Mean ± S.D)
1	F1	62.25±0.25
2	F2	65.45±0.32
3	F3	73.25±0.14
4	F4	66.98±0.65
5	F5	69.98±0.11
6	F6	67.55±0.33

***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	76.65	53.32	33.32
2	F2	65.58	48.85	22.41
3	F3	72.25	36.65	11.12
4	F4	74.45	45.65	22.14
5	F5	69.98	42.12	21.41
6	F6	65.56	36.65	15.65

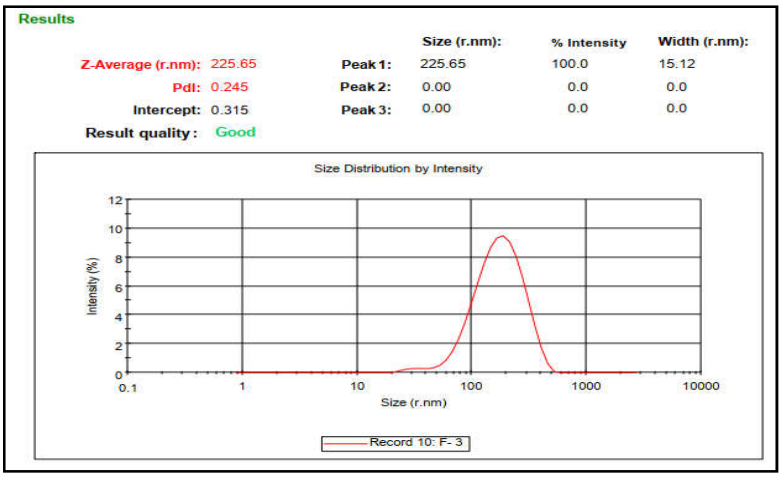

Figure 1: Particle size data of chitosan microspheres (F3)

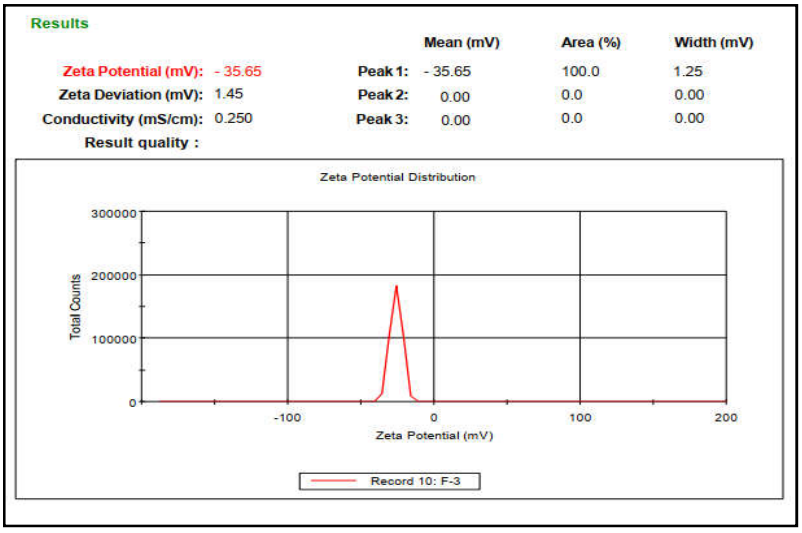

Figure 2: Zeta potential data of chitosan microspheres (F3)

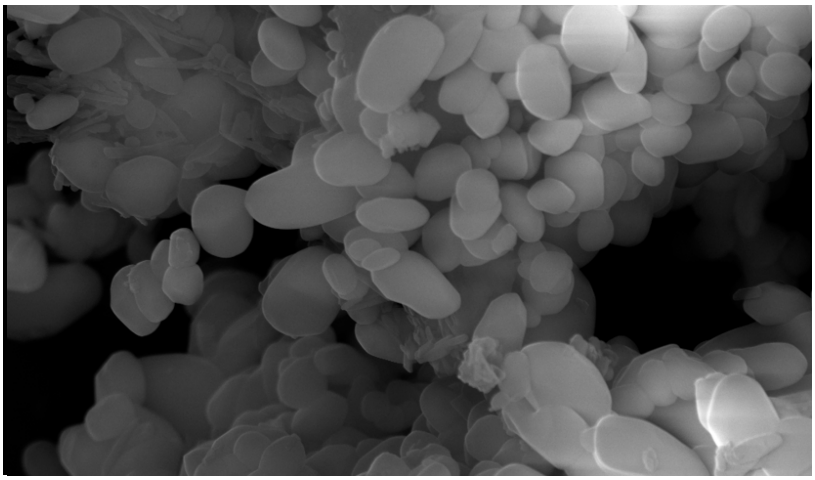

Figure 3: Scanning Electron Microscope of optimized formulation (F3)

Table 5: Results of mucoadhesion testing by ex vivo wash-off test

Formulation Code	% Mucoadhesive strength
F1	65
F2	70
F3	75
F4	63
F5	69
F6	70

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

S. No.	Dissolution medium	Time (hrs)	% Cumulative Drug Release	
			Plain drug	Chitosan microspheres
1	SGF (pH 1.2)	1	24.65	9.12
2		2	55.65	16.65
3		3	72.23	24.85
4		4	-	31.52
5		5	-	38.85
6		6	-	46.65
7		7	-	55.74
8		8	-	68.98
9		9	-	76.65
10		10	-	88.45
11		12	-	97.74

***Simulated gastric fluid (SGF)**

Table 7: Regression analysis data of microsphere formulation

Formulation	Zero order	First order	Pappas plot
F3	$R^2 = 0.9925$	$R^2 = 0.8116$	$R^2 = 0.9952$

CONCLUSION

In conclusion, the comprehensive evaluation of chitosan microspheres loaded with Lafutidine HCl highlights their potential as effective gastro-retentive drug delivery systems. The study's systematic approach in formulation optimization, characterization, and performance evaluation underscores the importance of these microspheres in advancing pharmaceutical strategies for the treatment of gastric disorders. Future research may focus on further refining formulation parameters, conducting extensive pharmacokinetic and pharmacodynamic studies, and exploring clinical applications to translate these promising findings into clinical practice.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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