International Journal of Pharmaceutics and Drug Research
ISSN: 2347-6346
Available online at http://ijpdr.com

Original Research Article

FORMULATION AND CHARACTERIZATION FLURBIPROFEN SUSTAINED RELEASE MUCOADHESIVE MICROSPHERES USING NATURAL POLYMERS

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***Article History:**

Received: 20/04/2026
Revised: 11/05/2026
Accepted: 25/05/2026

ABSTRACT

The present study was aimed at the formulation and characterization of Flurbiprofen sustained release mucoadhesive microspheres using chitosan as a natural polymer. Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID) widely used in the management of pain and inflammation; however, its conventional dosage forms require frequent administration and may produce gastrointestinal side effects. To overcome these limitations, mucoadhesive microspheres were developed to achieve prolonged gastric residence time and sustained drug release. The microspheres were prepared using suitable formulation techniques and evaluated for percentage yield, entrapment efficiency, stability in acidic medium, particle size, zeta potential, and in vitro drug release. The percentage yield of different formulations ranged from 68.74% to 76.65%, while entrapment efficiency ranged from 67.78% to 73.32%. Among all formulations, F3 showed the highest percentage yield and entrapment efficiency. Stability studies in 0.1 N HCl demonstrated that the microspheres maintained satisfactory integrity under acidic conditions. Particle size and zeta potential analysis confirmed the formation of stable microspheres with suitable physicochemical properties. In vitro drug release studies revealed that the plain drug exhibited rapid release, whereas chitosan microspheres showed sustained drug release over a period of 12 hours. The optimized formulation (F3) demonstrated 98.85% cumulative drug release at 12 hours. Release kinetic studies indicated that the optimized formulation followed zero-order release kinetics. The sustained release behavior was attributed to the mucoadhesive and gel-forming properties of chitosan. The results of the study suggest that chitosan-based mucoadhesive microspheres are promising carriers for sustained delivery of Flurbiprofen, offering prolonged drug release, improved stability, and potential enhancement in therapeutic efficacy and patient compliance.

Keywords: Flurbiprofen, Mucoadhesive microspheres, Chitosan, Sustained release, Natural polymers, Drug entrapment efficiency, In vitro drug release, Zero-order kinetics, Oral drug delivery system.

INTRODUCTION

Oral drug delivery remains the most preferred and widely accepted route of administration due to its convenience, patient compliance, cost-effectiveness, and ease of manufacturing (Jain, 2019). However, conventional oral dosage forms often exhibit limitations such as frequent dosing, fluctuating plasma drug concentration, reduced bioavailability, and poor patient adherence, especially in the treatment of chronic inflammatory disorders (Homayun *et al.*, 2019).

Sustained release drug delivery systems have therefore gained considerable attention as they are capable of maintaining therapeutic drug levels for prolonged periods, reducing dosing frequency, minimizing side effects, and improving patient compliance.

Among the various sustained release approaches, mucoadhesive microspheres have emerged as an effective and promising drug delivery system (Md *et al.,* 2012). Mucoadhesive microspheres possess the ability to adhere to the mucosal surface of the gastrointestinal tract, thereby prolonging gastric residence time and enhancing drug absorption. The microsphere-based system also provides controlled and sustained drug release, protects the drug from degradation, and improves bioavailability (Singh *et al.*, 2012). The use of mucoadhesive polymers further enhances intimate contact between the dosage form and the mucosal membrane, resulting in improved therapeutic efficacy.

Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID) widely used in the management of pain, inflammation, rheumatoid arthritis, osteoarthritis, and musculoskeletal disorders (Richy *et al.*, 2007). It acts by inhibiting cyclooxygenase enzymes and reducing prostaglandin synthesis. However, Flurbiprofen possesses a relatively short biological half-life and requires repeated administration to maintain therapeutic plasma concentrations (Wang *et al.*, 2020). Prolonged use of conventional Flurbiprofen formulations may also cause gastrointestinal irritation, ulceration, and other adverse effects. Therefore, development of a sustained release mucoadhesive delivery system for Flurbiprofen can help maintain controlled drug release, reduce dosing frequency, minimize gastrointestinal side effects, and improve therapeutic outcomes.

Natural polymers have gained increasing importance in pharmaceutical formulation development due to their biocompatibility, biodegradability, non-toxicity, cost-effectiveness, and eco-friendly nature (Basem *et al.,* 2026). Natural polymers such as sodium alginate, chitosan, guar gum, xanthan gum, pectin, and gum acacia exhibit excellent mucoadhesive and gel-forming properties, making them suitable candidates for microsphere formulation (Nanda *et al.,* 2025). These polymers can effectively control drug release, improve stability, and enhance retention of the dosage form at the absorption site.

Mucoadhesive microspheres prepared using natural polymers offer several advantages including prolonged gastrointestinal residence time, enhanced drug absorption, improved bioavailability, site-specific delivery, and reduced systemic side effects (Rajput *et al.,* 2010). Various techniques such as ionotropic gelation, solvent evaporation, spray drying, and emulsion cross-linking are employed for the preparation of microspheres depending on the nature of the drug and polymers used.

The present study is therefore aimed at the formulation and characterization of Flurbiprofen sustained release mucoadhesive microspheres using natural polymers. The developed microspheres will be evaluated for various physicochemical parameters including particle size, percentage yield, drug entrapment efficiency, swelling index, mucoadhesive strength, surface morphology, and in vitro drug release behavior. The study is expected to provide an effective sustained release drug delivery system capable of

improving the therapeutic efficacy and patient compliance associated with Flurbiprofen therapy.

MATERIALS AND METHODS

Material

Flurbiprofen was used as the model drug for the preparation of sustained release mucoadhesive microspheres. Chitosan was utilized as the natural mucoadhesive polymer for microsphere formulation. Sodium tripolyphosphate (TPP) was used as a cross-linking agent. Acetic acid was employed for dissolving chitosan, while hydrochloric acid and simulated gastric fluid (SGF, pH 1.2) were used during stability and dissolution studies. All other chemicals and reagents used in the study were of analytical grade and obtained from standard commercial sources.

Methods

Preparation of mucoadhesive microspheres of Flurbiprofen using natural polymers

Chitosan-based mucoadhesive microspheres of Flurbiprofen were prepared using the ionotropic gelation method. A 1% chitosan solution was made by dissolving chitosan in 5% acetic acid. Flurbiprofen (10 mg) was added to 5 ml of this solution. Separately, 1% sodium tripolyphosphate (TPP) solution was prepared in water. TPP was added dropwise to the chitosan-drug solution under magnetic stirring, leading to microsphere formation via ionic cross-linking. The microspheres were filtered, washed with distilled water, air-dried for 24 hours, and then oven-dried at 40°C for 6 hours. Six formulations (F1–F6) were prepared using varying amounts of chitosan (100–200 mg) and TPP (500–750 mg) (Sharma *et al.*, 2017).

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:

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

Entrapment Efficiency

Amount of Flurbiprofen in each formulation was calculated according to procedure (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 244nm.

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 244nm (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℃ in triplicate (Thejeswini *et al.,* 2014).

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 formula:

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

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

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

$$\textbf{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X}100$$

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

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

***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 (Higuchi, 1963; Korsmeyer *et al.,* 1983). 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 244nm 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 Flurbiprofen.

RESULTS AND DISCUSSION

The present study was carried out to formulate and characterize Flurbiprofen-loaded sustained release mucoadhesive microspheres using chitosan as a natural polymer. The formulated microspheres were evaluated for percentage yield, entrapment efficiency, stability in acidic medium, particle size, zeta potential, in vitro drug release, and release kinetics in order to assess their suitability as a sustained release drug delivery system.

The percentage yield of the prepared microspheres ranged from 68.74% to 76.65%, indicating satisfactory production efficiency of the formulation method. Among all formulations, F3 exhibited the highest percentage yield (76.65%), suggesting efficient cross-linking and better polymer-drug interaction during microsphere preparation. Variations in percentage yield among formulations may be attributed to differences in polymer concentration, viscosity, and process conditions affecting microsphere formation and recovery.

Entrapment efficiency is an important parameter that determines the amount of drug successfully incorporated within the microspheres. The entrapment efficiency of all formulations ranged from 67.78% to 73.32%. Formulation F3 showed the highest entrapment efficiency (73.32%), which may be due to the optimum concentration of chitosan providing effective encapsulation and minimizing drug diffusion into the external medium during preparation. Higher polymer concentration generally enhances the viscosity of the polymeric solution, resulting in improved drug entrapment within the microspheres.

The stability study of chitosan microspheres in 0.1 N HCl demonstrated that the microspheres maintained structural integrity in acidic conditions for prolonged periods. The gradual reduction in percentage transmittance over time indicated swelling and sustained stability of the microspheres in gastric pH conditions. Formulation F3 showed comparatively better stability characteristics, suggesting that chitosan effectively protected the drug and maintained microsphere integrity under acidic conditions. This property is important for oral sustained release formulations intended for gastric retention.

Particle size analysis of the optimized formulation (F3) indicated the formation of microspheres within a suitable size range for sustained drug delivery. Uniform particle size distribution contributes to consistent drug release behavior and improved formulation stability. Zeta potential analysis revealed adequate surface charge on the microspheres, indicating good physical stability and reduced aggregation tendency. The positive surface charge observed in chitosan microspheres may also contribute to enhanced mucoadhesion due to interaction with negatively charged mucosal surfaces.

The in vitro drug release study demonstrated a significant difference between the release profile of plain Flurbiprofen and the chitosan microspheres. The plain drug exhibited rapid release, with more than 65% drug release within 3 hours, whereas the microsphere formulation showed controlled and sustained release over 12 hours. Formulation F3 exhibited an initial slow release in simulated gastric fluid followed by gradual and prolonged drug release, reaching 98.85% release at 12 hours. The sustained release behavior may be attributed to the swelling and gel-forming properties of chitosan, which retard drug diffusion and prolong drug release from the polymeric matrix.

Release kinetic analysis indicated that the optimized formulation followed zero-order kinetics with a high regression coefficient value ($R^2 = 0.991$), suggesting a constant and controlled drug release pattern independent of drug concentration. The lower regression coefficient observed in the Korsmeyer–Peppas model suggested that the release

mechanism was predominantly controlled by matrix diffusion and polymer relaxation. The sustained release profile observed in the formulation is advantageous for reducing dosing frequency and maintaining therapeutic drug concentration for extended periods.

The results of the study demonstrated that chitosan-based mucoadhesive microspheres are effective carriers for sustained delivery of Flurbiprofen. Among all formulations, F3 showed the most promising characteristics in terms of percentage yield, entrapment efficiency, stability, and sustained drug release behavior. The developed microspheres may therefore serve as a promising oral sustained release drug delivery system capable of improving therapeutic efficacy, reducing gastrointestinal side effects, and enhancing patient compliance in the treatment of inflammatory disorders.

Table 1: Formulation of mucoadhesive microspheres using natural polymers

S. No.	Formulation Code	Flurbiprofen (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	70.12±0.25
2	F2	73.25±0.36
3	F3	76.65±0.14
4	F4	72.25±0.52
5	F5	69.39±0.63
6	F6	68.74±0.50

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

Table 3: Entrapment efficiency for different formulations

S. No.	Formulation	% Entrapment Efficiency* (Mean ± S.D)
1	F1	68.85±0.85
2	F2	69.98±0.65
3	F3	73.32±0.74
4	F4	68.85±0.32
5	F5	69.98±0.85
6	F6	67.78±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	74.45	52.25	16.65
2	F2	76.65	48.85	22.25
3	F3	78.12	34.65	10.25
4	F4	70.32	52.23	24.45
5	F5	74.65	52.23	18.85
6	F6	71.54	66.65	19.98

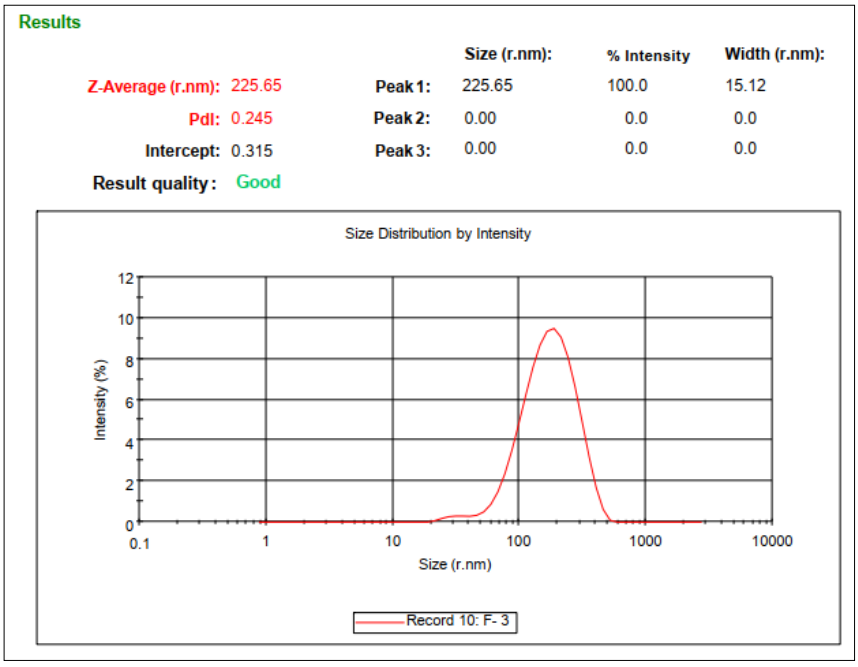

Figure 1: Particle size data of chitosan microspheres (F3)

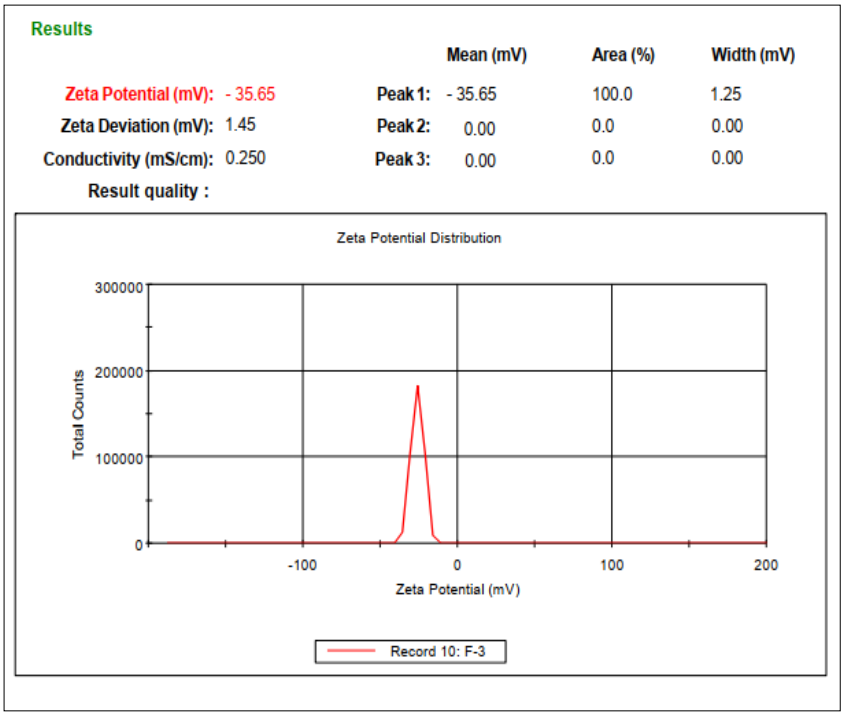

Figure 2: Zeta potential data of chitosan microspheres (F3)

Table 5: Cumulative % drug release of Flurbiprofen 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	23.32	4.85
2		2	58.89	6.98
3		3	65.78	16.65
4		4		28.85
5		5		32.25
6		6		44.65
7		7		59.98
8		8		65.58
9		9		73.32
10		10		85.45
11		12		98.85

***Simulated gastric fluid (SGF)**

Table 6: Regression analysis data of microsphere formulation

Formulation	Zero order	First order	Pappas plot
F3	$R^2 = 0.991$	$R^2 = 0.890$	$R^2 = 0.486$

CONCLUSION

The present study successfully developed Flurbiprofen-loaded sustained release mucoadhesive microspheres using chitosan as a natural polymer. The prepared microspheres showed satisfactory percentage yield, entrapment efficiency, acidic stability, particle size distribution, and sustained drug release properties. Among all formulations, F3 demonstrated the best performance with the highest yield, drug entrapment, stability, and controlled drug release over 12 hours. Release kinetic analysis indicated zero-order drug release behavior, confirming sustained and concentration-independent release. Chitosan-based mucoadhesive microspheres proved to be a promising oral sustained release delivery system for Flurbiprofen, with potential to improve therapeutic efficacy, reduce dosing frequency, and enhance patient compliance.

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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