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Development And Characterization Colon Targeting Microspheres Of Anti-Inflammatory Drug Felbinac

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ABSTRACT

The present study aimed at developing and characterizing colon-targeted chitosan microspheres of Felbinac, a non-steroidal anti-inflammatory drug (NSAID), to achieve site-specific drug release for the treatment of inflammatory bowel conditions. Microspheres were prepared using the ionotropic gelation method, employing chitosan as the primary polymer and sodium tripolyphosphate as the cross-linking agent. Six formulations (F1–F6) were evaluated for flow properties, percentage yield, entrapment efficiency, particle size, surface charge (zeta potential), and in vitro drug release. Among the tested batches, formulation F5 demonstrated the best characteristics, with high entrapment efficiency (76.65%), good flow properties, and favorable particle size. In vitro drug release studies conducted under simulated gastrointestinal conditions revealed that uncoated chitosan microspheres showed premature drug release, whereas Eudragit S100-coated microspheres significantly minimized drug release in acidic environments and provided sustained release in colonic pH, reaching 89.98% at 12 hours. Drug release kinetics of F5 followed a first-order model with a non-Fickian diffusion mechanism. Stability studies confirmed that the optimized formulation remained physically and chemically stable over three months. The findings suggest that Eudragit-coated chitosan microspheres of Felbinac provide an effective platform for colon-specific drug delivery, potentially enhancing therapeutic outcomes and minimizing systemic side effects in the treatment of colonic inflammatory diseases.

Keywords: *Felbinac, colon-targeted drug delivery, chitosan microspheres, ionotropic gelation, Eudragit S100, pH-sensitive release, inflammatory bowel disease, controlled release, entrapment efficiency, in vitro drug release.*

1. INTRODUCTION

Inflammatory bowel diseases (IBDs), such as ulcerative colitis and Crohn's disease, are chronic inflammatory conditions of the gastrointestinal (GI) tract that significantly affect patients' quality of life. These disorders primarily affect the colon and rectum, necessitating localized drug delivery systems that can release therapeutic agents directly at the site of inflammation, thereby minimizing systemic side effects and improving treatment efficacy (Sinha & Kumria, 2001).

Colon-targeted drug delivery systems (CTDDS) are specifically designed to deliver drugs to the colon, either for local action in the treatment of colonic diseases or for systemic absorption of poorly bioavailable drugs. Among the various approaches, the use of biodegradable polymeric microspheres has gained attention due to their ability to protect the drug from premature degradation and ensure controlled release at the target site (Vandamme & Ellis, 2004).

Felbinac, a non-steroidal anti-inflammatory drug (NSAID), exhibits potent anti-inflammatory and analgesic properties. It is commonly used for the treatment of musculoskeletal disorders and has shown potential benefits in managing inflammation associated with IBD when delivered directly to the colon (Okabe et al., 1990). However, oral administration of Felbinac is limited by poor colonic bioavailability and potential gastric irritation, which can be overcome by formulating colon-targeted drug delivery systems.

Microspheres are multiparticulate drug delivery systems that offer several advantages, including uniform distribution in the GI tract, reduced dosing frequency, and improved patient compliance (Singh et al., 2015). For colon-specific delivery, polymers such as Eudragit S100 and Eudragit L100, which are pH-sensitive, are frequently employed. These polymers remain intact in the acidic environment of the stomach and dissolve at higher pH levels, typically encountered in the distal small intestine and colon (Chourasia & Jain, 2004).

The present study focuses on the development and characterization of Felbinac-loaded microspheres using pH-dependent polymers to achieve site-specific drug release in the colon. The formulation was optimized and evaluated for particle size, drug entrapment efficiency, surface morphology, in-vitro drug release, and release kinetics, to ensure effective delivery and sustained therapeutic action at the site of inflammation.

2. MATERIAL AND METHODS

Material

The materials used for the formulation of colon-targeted microspheres of Felbinac included both active pharmaceutical ingredients and excipients sourced from reputable suppliers. Felbinac was obtained as a gift sample from Pharmaceutical Company. Chitosan, used as a biodegradable polymer for microsphere formation, was procured from HiMedia Laboratories Pvt. Ltd., Mumbai. Sodium tripolyphosphate, a cross-linking agent, was supplied by Loba Chemie, Mumbai. Buffer salts such as disodium hydrogen phosphate and dipotassium hydrogen orthophosphate were obtained from S.D. Fine Chem. Ltd., Mumbai, to maintain the pH for various studies. Organic solvents like methanol, ethanol, and chloroform were sourced from Qualigens Fine Chemicals, Mumbai, while sodium hydroxide and hydrochloric acid were procured from Chempure Speciality Chemicals and Thomas Baker, Mumbai, respectively, for pH adjustment and analytical purposes. Surface morphology of the microspheres was analyzed using a Scanning Electron Microscope (SEM) from JEOL Japan (Model 6000).

Methods

Preparation of colon targeting microspheres of Felbinac

Chitosan microspheres containing Felbinac were prepared using the ionotropic gelation method, a widely adopted technique for encapsulating drugs in natural polymers due to its simplicity, mild processing conditions, and ability to form stable microspheres without the use of harsh chemicals or high temperatures. Initially, a **chitosan stock solution (1% w/v)** was prepared by dissolving chitosan in **1% v/v acetic acid** under room temperature conditions, with continuous stirring to ensure complete solubilization of the polymer. In the next step, **Felbinac (50 mg)** was incorporated into this chitosan solution by thorough mixing to ensure uniform dispersion of the drug within the polymer matrix. Separately, a **1% sodium tripolyphosphate (TPP) solution** was prepared in distilled water. TPP acts as a cross-linking agent that interacts with the positively charged amino groups of chitosan through ionic interactions, leading to the formation of a gel matrix. This TPP solution was then **added dropwise** into the drug-loaded chitosan solution using a syringe under continuous magnetic stirring. The slow and controlled addition of TPP promoted uniform cross-linking and microsphere formation. The resulting suspension was stirred for **30 minutes** to allow sufficient time for microsphere formation and stabilization. The formed microspheres were then **filtered** and gently **rinsed with distilled water** to remove any unreacted materials or loosely bound surface drug. The microspheres were **air-dried for 24 hours** to allow gradual evaporation of surface moisture, followed by **oven drying at 40°C for six hours** to ensure complete removal of residual moisture, yielding dry, free-flowing chitosan microspheres suitable for further characterization and evaluation (Sharma et al., 2017).

Table 1: Formulations of chitosan microspheres prepared

Sr. No.	Formulation Code	Felbinac (mg)	Chitosan (mg)	STPP (mg)
1.	F1	50	250	500
2.	F2	50	250	750
3.	F3	50	250	1000
4.	F4	50	500	500
5.	F5	50	500	750
6.	F6	50	500	1000

Coating of chitosan microspheres

Microspheres were coated with Eudragil S-100 (ES) using solvent evaporation method. Microspheres (50 mg) were dispersed in 10 mL of coating solution prepared by dissolving 500 mg of eudragit S-100 in ethanol: acetone (2:1) to give 5:1 (coat: core ratio). This organic phase was then poured in 70 mL of light liquid paraffin containing 1% wt/vol Span 80. The system was maintained under agitation speed of 1000 rpm at room temperature for 3 hours to allow for the evaporation of solvent. Finally, the coated microspheres were filtered, washed with n-hexane, and dried in desiccators (Priyadarshini et al., 2014).

Evaluation of microspheres

There are many formulations and process variables involved in mixing step and all these can affect characteristics of blend produced, bulk density, true density and percent compressibility index have been measured which are given in table.

Bulk density

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Procedure:- A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml gm/ml, by the formula:

Bulk density = Bulk Mass/ Bulk Volume

Compressibility index (Carr's index):

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material. It can be calculated as per given formula:

$$\text{Tapped density} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} x100$$

Hausner ratio

It indicates the flow properties of the powder and it can be measured by the ratio of tapped density to bulk density.

Hausner ratio = Tapped density / Bulk Density

Percentage Yield

The prepared microspheres F1-F6 were collected and weighed from each formulation. 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 Felbinac in each formulation was calculated according to procedure given below (Berthold et al., 1996): 10 mg of chitosan microspheres from each batch were accurately weighed. The powder of chitosan microspheres were dissolved in 10 ml 7.4 pH Phosphate Buffer and centrifuge at 1000 rpm. This supernatant solution is than 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 7.4 pH phosphate buffer. The supernant was analyzed for drug content by measuring the absorbance at 242.0nm.

Measurement of mean particle size

The mean particle size of the microspheres was determined by Photo 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 microspheres 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 microspheress was measured on a zeta sizer (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).

***In-vitro* Release Studies**

***In vitro* drug release in gastrointestinal fluids of different pH**

The in vitro drug release study of the prepared Felbinac-loaded chitosan microspheres was conducted to evaluate the release profile and effectiveness of the colon-targeted delivery system. The study was performed using a **USP Type I (basket) dissolution test apparatus**, which provides consistent agitation and temperature control. A **weighed quantity of microspheres equivalent to 30 mg of Felbinac** was encapsulated in a hard gelatin capsule and placed in the basket of the dissolution apparatus. The dissolution medium used was **900 ml,** and the temperature was maintained at **37±0.2°C,** simulating physiological conditions. The apparatus was operated at a **rotation speed of 100 rpm** to ensure uniform mixing and effective drug release. To mimic the varying pH conditions encountered throughout the gastrointestinal tract, a **step-wise pH change protocol** was followed using different simulated fluids over a six-hour period. In the **first hour, simulated gastric fluid (SGF, pH 1.2)** was used to simulate stomach conditions. During the **second and third hours**, a **mixture of**

SGF and simulated intestinal fluid (SIF, pH 4.5) was used, representing the upper intestinal transit. From the **fourth to fifth hour**, the pH was adjusted to **6.8,** simulating the conditions of the small intestine, and from the **sixth hour onward**, the pH was increased to **7.4,** which corresponds to the colonic environment.

At predetermined time intervals, **aliquots of the dissolution medium were withdrawn** and replaced with an equal volume of fresh, pre-warmed medium to maintain sink conditions and constant volume. The withdrawn samples were made up to 5 ml with the corresponding dissolution medium and analyzed **spectrophotometrically at 242.0 nm** using a UV-visible spectrophotometer. The cumulative amount of Felbinac released was determined by referencing a pre-constructed **standard calibration curve of Felbinac**, and the percentage drug release was calculated for each time point. This pH-dependent release study was essential in evaluating whether the microspheres could withstand the acidic gastric environment and release the drug predominantly in the colonic pH, thereby achieving the desired **site-specific drug delivery** for effective management of inflammatory bowel conditions (Higuchi; 1963, Korsmeyer; 1983, Peppas; 1989).

3. RESULTS AND DISCUSSION

The present study focused on the development and evaluation of colon-targeted chitosan microspheres of Felbinac, with the objective of delivering the drug specifically to the colon for effective management of inflammatory conditions such as inflammatory bowel disease (IBD). The microspheres were prepared using the ionotropic gelation method, and various formulations (F1–F6) were assessed for physicochemical and in-vitro performance parameters.

The flow behavior of the prepared microspheres was evaluated through bulk density, tapped density, compressibility index, and Hausner ratio (Table 2). Among the formulations, F2 showed the best flow properties with a compressibility index of 18.35% and a Hausner ratio of 1.225, indicating fair to good flow. Most formulations exhibited acceptable flow characteristics, though formulations F4 to F6 showed slightly higher compressibility indices (>23%), which may indicate some degree of inter-particle friction.

The production yield ranged from 68.85% to 78.85%, with formulation F5 showing the highest yield (Table 3). Entrapment efficiency (EE), which reflects the ability of the polymer matrix to encapsulate the drug, was also highest in F5 (76.65%) and lowest in F1 (65.58%) as shown in Table 4. The improved EE in F5 could be attributed to optimal polymer-to-drug ratio and effective cross-linking with sodium tripolyphosphate, minimizing drug loss during processing.

Particle size analysis (Figure 1) of the optimized formulation F5 revealed nanoscale microspheres, which can enhance mucosal adhesion and colon targeting. The zeta potential data (Figure 2) confirmed sufficient surface charge, indicating good stability of the microsphere suspension by preventing aggregation due to repulsion forces.

Drug release profiles were significantly affected by the pH of the dissolution medium and the type of formulation (Table 5). Uncoated chitosan microspheres exhibited an initial burst release, with about 13.25% of the drug released in simulated gastric fluid (pH 1.2) during the first hour, followed by progressive release in subsequent media, reaching nearly complete release (99.02%) at 12 hours. In contrast, Eudragit S100-coated microspheres demonstrated effective pH-dependent protection, with minimal drug release in acidic and slightly acidic conditions and a controlled release in the colonic pH (7.4), reaching 89.98% at 12 hours. This indicates that Eudragit S100 coating significantly improved the site-specific drug delivery to the colon by resisting premature drug release in the upper GIT.

Regression analysis (Table 6) of formulation F5 showed that the drug release best followed **first-order kinetics** ($r^2 = 0.9511$), suggesting that the release rate was concentration-dependent. The Higuchi model and Korsmeyer–Peppas model also provided relevant insights, with Peppas $r^2 = 0.8902$ indicating a non-Fickian diffusion mechanism, where both diffusion and erosion could be involved in drug release.

Stability data over a 3-month period (Table 7) confirmed that the optimized formulation F5 remained physically stable with consistent appearance and acceptable changes in particle size and entrapment efficiency. Although slight reductions in %EE were observed, the values remained within acceptable pharmaceutical limits. No physical degradation or discoloration was noted under both refrigerated (4°C) and room temperature (25–28°C) conditions, indicating that the microspheres were stable for at least three months.

Table 2: Result of flow properties of prepared Felbinac microspheres

F. Code	Bulk density(gm/cm^3)	Tapped density(gm/cm^3)	Compressibility index	Hausner ratio
F1	0.325	0.412	21.117	1.268
F2	0.347	0.425	18.353	1.225

F3	0.342	0.432	20.833	1.263
F4	0.352	0.462	23.810	1.313
F5	0.341	0.452	24.558	1.326
F6	0.338	0.448	24.554	1.325

Table 3: Percentage Yield for Different Formulation

Formulation code	Percentage Yield (%)
F1	68.85±0.25
F2	73.32±0.32
F3	75.45±0.15
F4	72.23±0.22
F5	78.85±0.36
F6	70.12±0.45

Table 4: Entrapment Efficiency for Different Formulation

Formulation code	Entrapment Efficiency of prepared microspheres
F1	65.58±0.32
F2	70.23±0.15
F3	73.32±0.33
F4	71.15±0.25
F5	76.65±0.18
F6	68.85±0.36

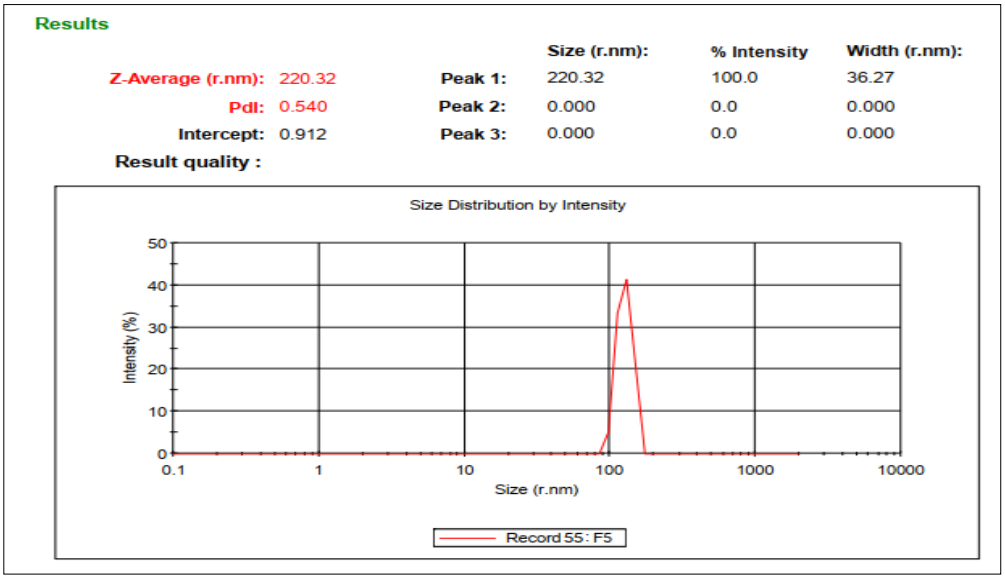

Figure 1: Particle size data of chitosan microspheres (F5)

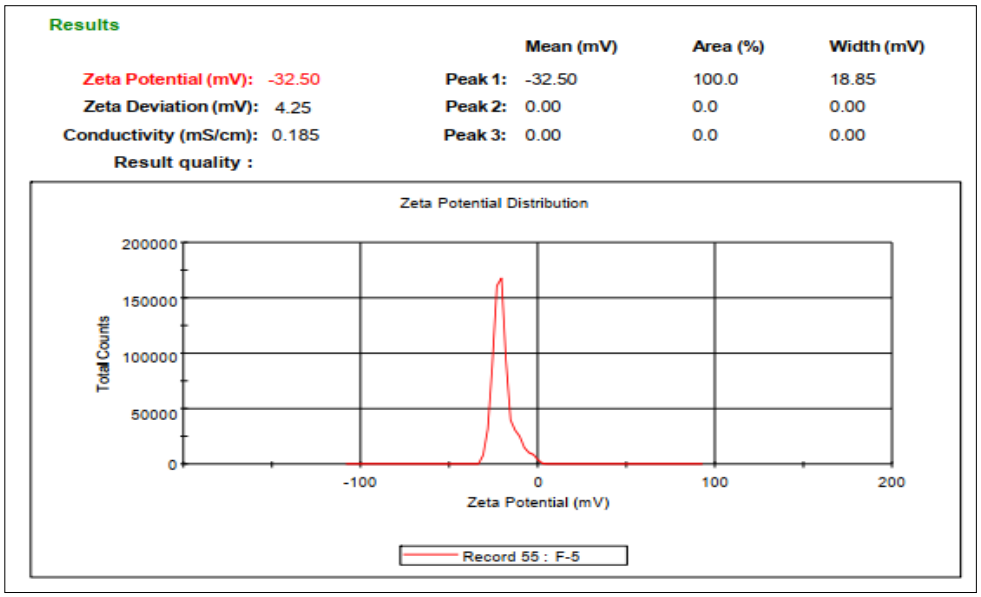

Figure 2: Zeta potential data of chitosan microspheres (F5)

Table 5: Cumulative % drug release of Felbinac from plain and Eudragit S100 coated microspheres at different pH

S. No.	Dissolution medium	Time (hrs)	% Cumulative Drug Release	
			Chitosan Microspheres	Eudragit S100 Coated Microspheres
1	SGF (pH 1.2)	1	13.25	1.12
2		2	29.98	1.65
3	SGF+SIF(pH 4.5)	3	36.65	1.95
4		4	45.58	3.25
5		5	55.65	8.85
6	SIF (pH 6.8)	6	68.85	12.23
7		7	73.32	26.65
8	SIF (pH 7.4)	8	78.85	48.85
9		9	89.98	62.23
10		10	93.32	73.36
11		12	99.02	89.98

Table 6: Regression Analysis Data of microspheres Formulation

Formulation	Zero order	First order	Higuchi plot	Pappas plot
F5 (r^2)	0.8959	0.9511	0.7932	0.8902

Table 7: Characterization of stability study of Optimized formulation F5

Characteristic	Time (Month)					
	1 Month		2 Month		3 Month	
Temperature	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C
Average particle size (nm)	210.25	245.65	215.65	255.45.65	220.32	269.98
% EE	75.32	73.15	73.18	72.22	72.15	70.15
Physical Appearance	Normal	Normal	Normal	Normal	Normal	Normal

4. CONCLUSION

In Conclusion, formulation F5 emerged as the optimized batch based on superior entrapment efficiency, yield, controlled drug release, and physical stability. The use of Eudragit S100 as a pH-sensitive coating polymer effectively restricted drug release in the upper gastrointestinal tract and enabled targeted delivery to the colon. This approach offers a promising strategy for delivering Felbinac to the colon for the treatment of localized inflammatory conditions, potentially improving therapeutic outcomes and minimizing systemic side effects.

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