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Formulation and Evaluation of Chronothetapeutic beads using Antiasthematic agent Montelukast Sodium

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ABSTRACT

This study explores the development of oral controlled release systems for Montelukast sodium aimed at treating nocturnal asthma. Utilizing multiparticulate systems like chitosan and sodium alginate beads, the formulations maintain therapeutic drug concentrations over extended periods. Characterization confirmed the drug's integrity through melting point, UV scanning, and FTIR spectroscopy. Beads were created with varying drug-to-polymer ratios, achieving encapsulation efficiencies of 25.17% to 78.28%. Chitosan-based formulations exhibited superior mucoadhesion due to its positive charge. In vitro drug release studies demonstrated sustained release with a lag time of up to 6 hours in Eudragit S-100 coated beads, following zero-order kinetics. Stability studies indicated formulations remained stable at 40°C and 75% humidity for three months. The results indicate that these chronotherapeutic beads effectively deliver Montelukast sodium, optimizing drug release for patients with nocturnal asthma and enhancing therapeutic efficacy and compliance.

1. INTRODUCTION

Oral controlled release drug delivery systems offer several advantages over conventional immediate release formulations. They deliver drugs at a controlled rate, maintaining therapeutic concentrations in the bloodstream for extended periods. Multiple unit dosage forms, like microspheres and beads, are increasingly popular for oral drug delivery due to their uniform drug distribution in the gastrointestinal tract, optimal absorption, reduced local irritation, and elimination of unwanted polymer retention. Beads, which are spherical particles ranging from 15 nm to 2 mm, contain dispersed drug particles and allow for sustained or multiple release profiles with minimal side effects. They enhance bioavailability, increase surface area for absorption, and provide greater safety compared to single unit forms. In chronotherapeutics, multiparticulate systems are favored for their predictable gastric emptying, flexible release patterns, and improved bioavailability, making them suitable for time-controlled drug administration when a lag time is required1[-2].

Chronotherapeutics involves the strategic delivery of medications in varying amounts over time, considering factors like disease rhythms (chronopathology) and the pharmacological effects of drugs (chronopharmacology). This approach optimizes drug delivery patterns, doses, and timing to enhance efficacy and reduce adverse effects.

1.1 CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM (CDDS)

Controlled release formulations can be divided into subgroups of rate-controlled release, delayed-release and pulsed-release formulations[4,5,6]. Delayed-release formulations include time-controlled release and site-specific dosage forms. When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms[7,8]. By timing

drug administration, plasma peak is obtained at an optimal time and the number of doses per day can be reduced. Saturable first-pass metabolism and tolerance development can also be avoided. Various technologies to develop time controlled peroral drug delivery systems have been extensively studied in recent decades[9,10].

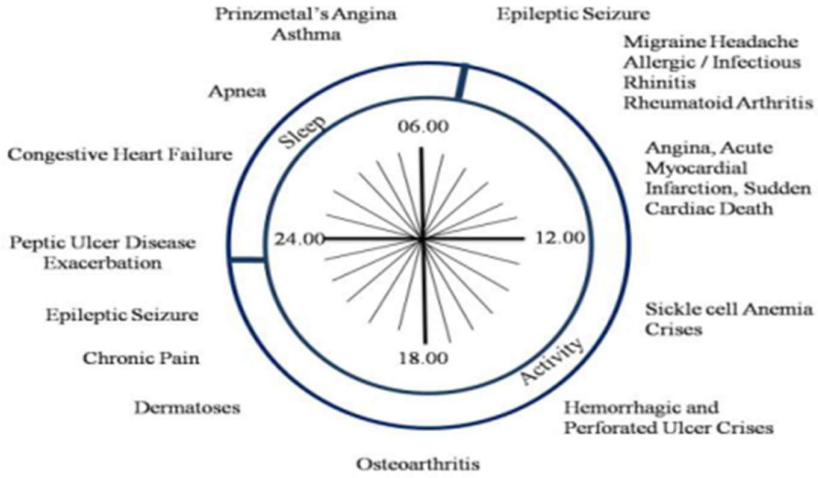

Fig. No. 1: The circadian pattern of diseases.

2. MATERIALS

1. MATERIALS

Montelukast Sodium(Glenmark Generics Ltd. Goa),Chitosan 81% Deacylated (Evonik Rhoem Pharma,Germany), Eudragit S100, (Evonik Rhoem Pharma,Germany) , Sodium Alginate(Loba ChemiePvt. Ltd. Mumbai.) , Hydrochloric Acid (HCl), (Loba ChemiePvt. Ltd. Mumbai), Potassium Chloride (KCl) (Loba ChemiePvt. Ltd. Mumbai),Dihydrogen Potassium Phosphate (KH_2PO_4)(Loba ChemiePvt. Ltd. Mumbai),Sodium Hydroxide (NaOH) (Loba ChemiePvt. Ltd. Mumbai), Sodium Lauryl Sulphate(Loba ChemiePvt. Ltd. Mumbai), Potassium Bromide (KBr)(Loba ChemiePvt. Ltd. Mumbai).

3. Preformulation Parameters

3.1 Characterization of drug, polymer, excipient and physical mixture using fourier transfer infrared spectroscopy.

Method:

The potassium bromide disc containing drug Montelukast sodium, polymers and their physical mixture were prepared to record the spectrum in the range of 4000 to 500 cm^{-1} by using FTIR spectrophotometer (Model no.84005 Shimadzu Asia Pacific Pvt. Ltd., Singapore).

Observation:

Table No 1: FTIR Spectral Analysis of Montelukast Sodium

Drug	Frequency (cm^{-1})	Assignment
Montelukast sodium	3300	Tertiary Hydroxyl group
	1700	Carboxylic Acid
	2900	Aromatic C-H

4.DIFFERENTIAL SCANNING CALORIMETRY (DSC).

Thermal analysis was carried out using differential scanning calorimeter (DSC Mettler Toledo DSC 821^e, Japan). The samples were placed in an aluminium sealed pan and preheated to 200˚C. The sample was cooled to room temperature and then reheated from 40 to 600˚C at a scanning rate of 10˚C/min.

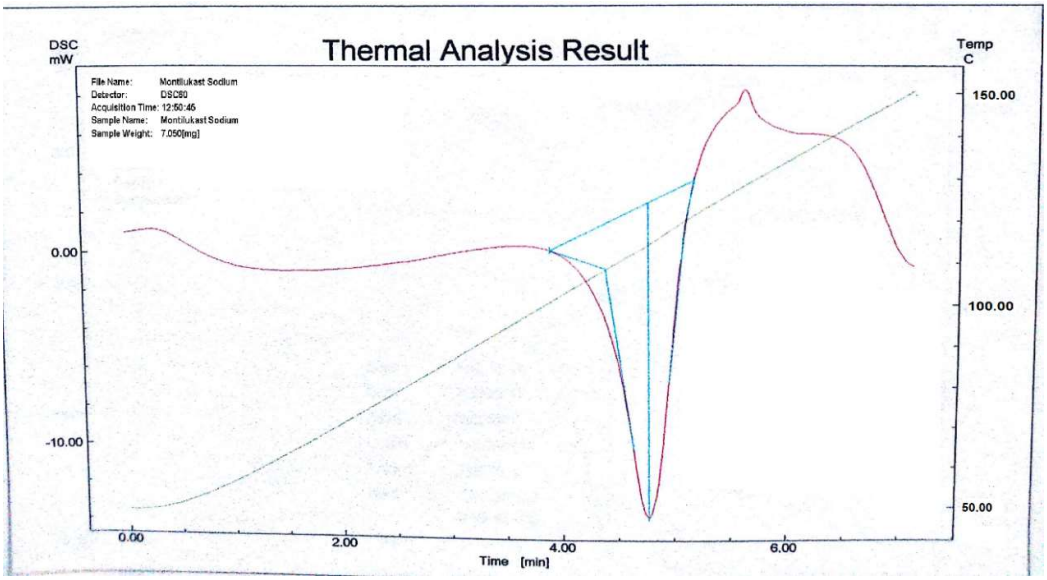

Figure No. 3: DSC Thermogram of Montelukast Sodium.

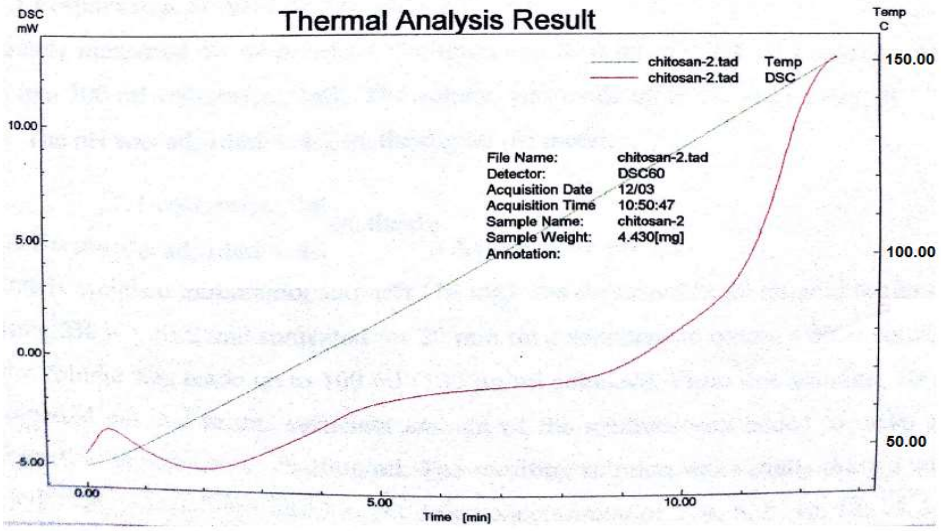

Figure No. 4: DSC Thermogram of Chitosan 81% Deacylated.

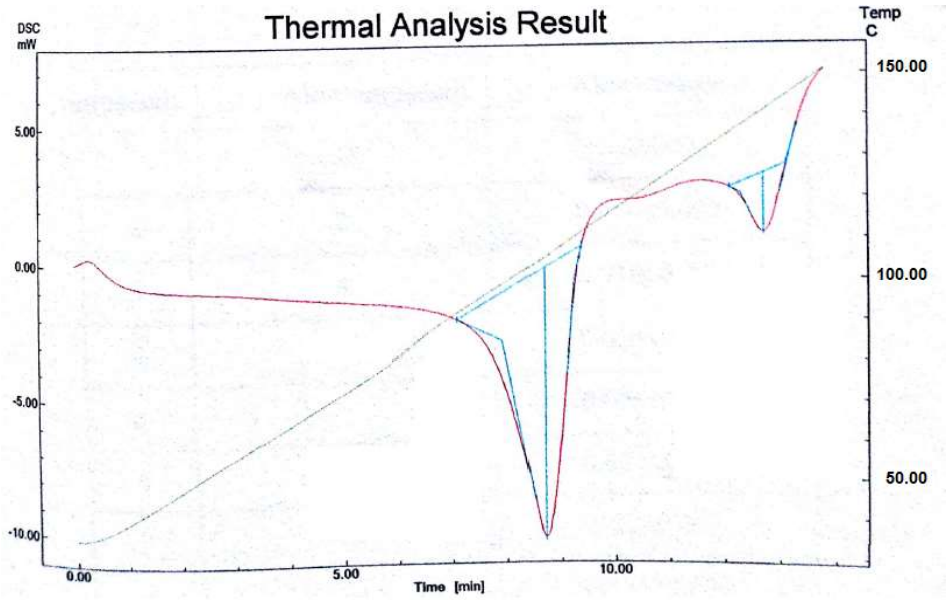

Figure No. 5: DSC Thermogram of physical mixture of Montelukast Sodium, Chitosan 81% Deacylated Polymer and Eudragit S-100 Polymer.

1. **U.V SPECTROPHOTOMETRIC STUDIES**

1. **UV Spectral analysis of Montelukast**

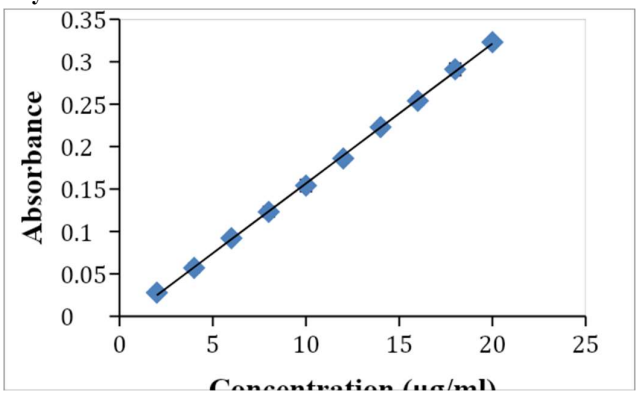

Fig. No. 6: Standard Calibration Curve of Montelukast Sodium in Acid Buffer pH 1.2.

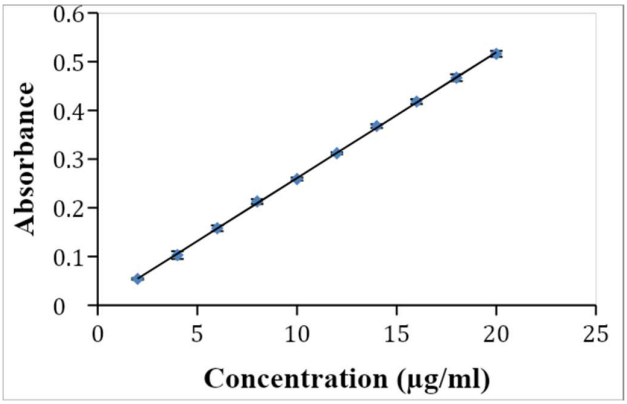

Fig. No. 7: Standard Calibration Curve of Montelukast Sodium in Phosphate Buffer pH 6.8.

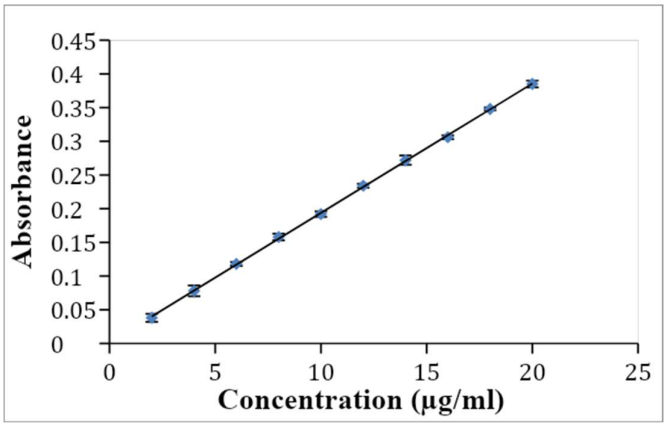

Fig. No. 8: Standard Calibration Curve of Montelukast Sodium in Phosphate Buffer pH 7.4

4.2 PREPARATION OF BEADS.

The beads were prepared by ionotropic gelation technique reported by Behin SR *et al*. Chitosan was dissolved in acetic acid 1%v/v solution at the concentration of 2.0% w/v using gentle magnetic stirring. On complete solution, an accurately weighed quantity of drug was added and dispersed uniformly. The dispersion was sonicated to remove air bubbles that have been formed during the stirring process, bubble free. Chitosan drug dispersion was added drop wise via a 18-guage hypodermic needle fitted with a 20ml syringe into 50 ml of Sodium tripolyphosphate solution (1,1.5,2 % w/v) and stirred for 30 min. After specified stirring time the gelled beads were separated by filtration and dried. Similar procedure was carried out for formulation of Montelukast sodium:sodium alginate. Sodium alginate was dissolved in deionized water at the concentration of 2.0% w/v using gentle magnetic stirring. On complete solution, an accurately weighed quantity of drug was added and dispersed uniformly. The dispersion was sonicated to remove air bubbles that have been formed during the stirring process, bubble free. Sodium alginate drug dispersion were added drop wise via a 18-guage hypodermic needle fitted with a 20 ml syringe into 50ml of calcium chloride solution (4,6,8 % w/v) and stirred for 30 min. After specified stirring time the gelled beads were separated by filtration and dried.

Different formulation were prepared by taking various concentration of drug: polymer ratio and by varying amount of crosslinking agent as shown in Table below

Table No. 2: Composition of formulations.

Formulations	Montelukast sodium : Chitosan	Solution of TPP (%w/v)	Montelukast sodium : Sodium alginate	Solution of $CaCl_2$ (%w/v)	Stirring Time (Min.)
F1	1 : 2	1	-	-	30
F2	1 : 2	1.5	-	-	30
F3	1 : 2	2	-	-	30
F4	-	-	1 : 2	4	30
F5	-	-	1 : 2	6	30
F6	-	-	1 : 2	8	30
F7	2 : 2	1	-	-	30
F8	2 : 2	1.5	-	-	30
F9	2: 2	2	-	-	30
F10	-	-	2 : 2	4	30
F11	-	-	2 : 2	6	30
F12	-	-	2 : 2	8	30

4.3 EVALUATION OF BEADS

4.3.1Loading Efficiency (LE) and Drug Encapsulation Efficiency (EE)

Accurately weighed 100 mg of beads were crushed in mortar and added to 100 ml of pH 7.4 Phosphate buffer. This mixture was stirred for 24 hours on magnetic stirrer and filtered through Whatman filter paper no. 42 and

analyzed spectrophotometrically at 243.40 nm.

$$\% \text{ Loading Efficiency} = \frac{\text{Weight of drug in beads}}{\text{Weight of drug loaded beads}} \times 100$$

$$\% \text{ Encapsulation Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Table No. 3: Loading Efficiency and Drug Encapsulation Efficiency of Batches F1 toF12.

Sr. No.	Batches	Theoretical Drug Loading	Loading Efficiency (%w/w)	Encapsulation Efficiency (%w/w)
1	F1	33.33	8.38 ± 0.43	25.17 ± 0.53
2	F2	33.33	17.85 ± 0.39	53.56 ± 0.52
3	F3	33.33	21.84 ± 0.48	65.53 ± 0.42
4	F4	33.33	10.86 ± 0.55	32.59 ± 0.33
5	F5	33.33	22.71 ± 0.59	68.15 ± 0.25
6	F6	33.33	25.15 ± 0.43	75.46 ± 0.34
7	F7	50	14.30 ± 0.47	28.61 ± 0.38
8	F8	50	34.28 ± 0.56	68.57 ± 0.45
9	F9	50	36.05 ± 0.53	72.71 ± 0.53
10	F10	50	17.27 ± 0.62	34.55 ± 0.54
11	F11	50	36.61 ± 0.65	73.22 ± 0.47
12	F12	50	39.14 ± 0.49	78.28 ± 0.52

***Each value represent the mean ± standard deviation (n=3).**

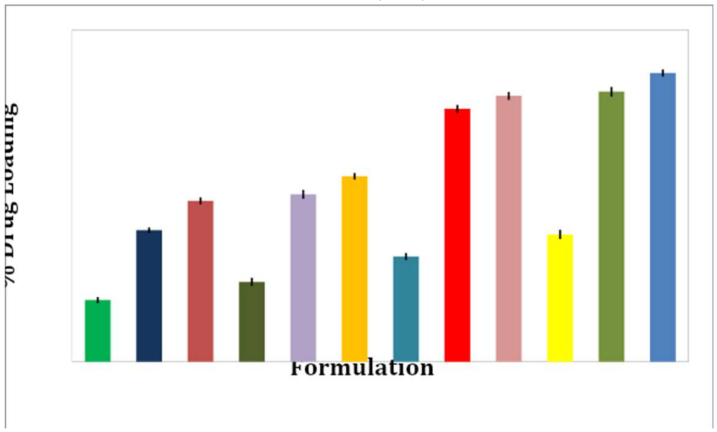

Fig. No.9: Loading Efficiency of Batches F1 to F12.

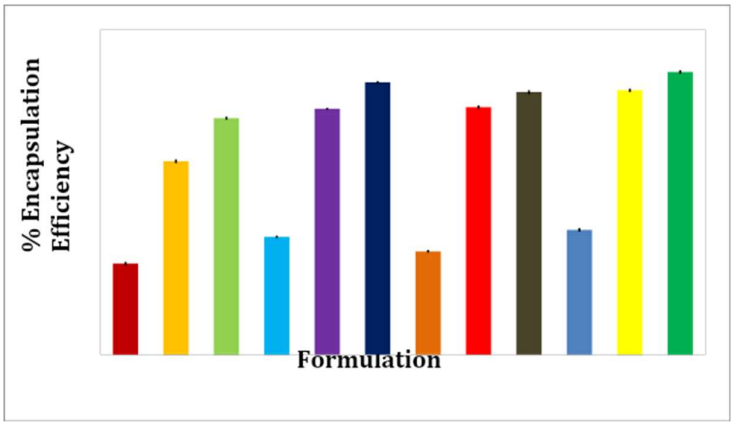

Fig. No.10: Drug Encapsulation Efficiency of Batches F1 to F12.

4.3.2 *IN VITRO* MUCOADHESION STUDY

In-vitro mucoadhesion studies were carried out using goat intestinal mucosa.The goat fresh intestinal mucosa was washed with physiologic saline at the rate (5 to 10 ml/min for 10 min, then 20 to 30 ml /min) by using peristaltic pump. After 15 min mucosa was held in inclined position, mucosa was cut in 10/4 cm and fixed to a glass slide and about 50 beads (N_0) hydrated with little amount of water dispersed on the mucosal surface and left for 20 min for interaction with mucosal surface. During this period whole system was placed in a constant humidity chamber which was adjust to 90% relative humidity. At the end the system was washed with pH 7.4 phosphate buffer at the rate of 22 ml/min using peristaltic pump. After 20 min beads detached from mucosa (N_s) were observed visually and percent mucoadhesion was calculated by following equation-

% Mucoadhesion = $(N_0 - N_s) \times 100/N_0$

Table No. 4: Percent Mucoadhesion of Formulations F1 to F12.

Sr. No.	Batches	% Mucoadhesion
1	F1	94 ± 0.542
2	F2	92 ± 0.125
3	F3	90 ± 0.452
4	F4	88 ± 0.365
5	F5	86 ± 0.412
6	F6	84 ± 0.245
7	F7	88 ± 0.354
8	F8	92 ± 0.745
9	F9	90 ± 0.325
10	F10	84 ± 0.425
11	F11	80 ± 0.563
12	F12	78 ± 0.481

***Each value represents mean ± standard deviation (n=3).**

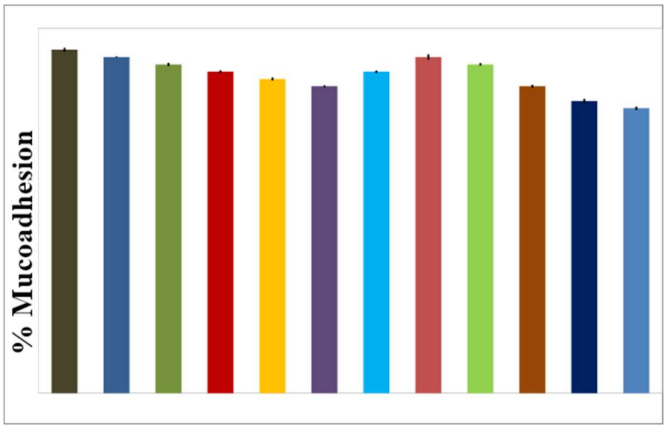

Fig. No.11: % Mucoadhesion of Formulations F1-F12.

4.3.3 SWELLING STUDY

The swelling index of beads is an indication of the capacity of beads to imbibe water and swell.

Method

Accurately weighed beads (40 mg) beads were placed in basket of USPXXX dissolution apparatus type I. The basket was immersed into 900ml of buffer and rotated at 50 rpm and maintained at 37±0.5 °C. After every 2 hours each basket was withdrawn, the beads were blotted to remove excess of water and immediately weighed. The swelling study was done in pH 1.2 acid buffers for first 2 hrs and subsequently in pH 6.8 phosphate buffers for next 3 hrs and then in pH 7.4 phosphate buffer upto 12 hrs. The percentage swellings of beads were calculated using following equation.

$$\% \text{ Swelling Index} = \frac{Wt - Wo}{Wt} \times 100$$

Where,

Wt = Weight of swollen beads; Wo = Weight of dried beads

Observation: The % swelling index of chitosan beads and sodium alginate beads are given inbelow

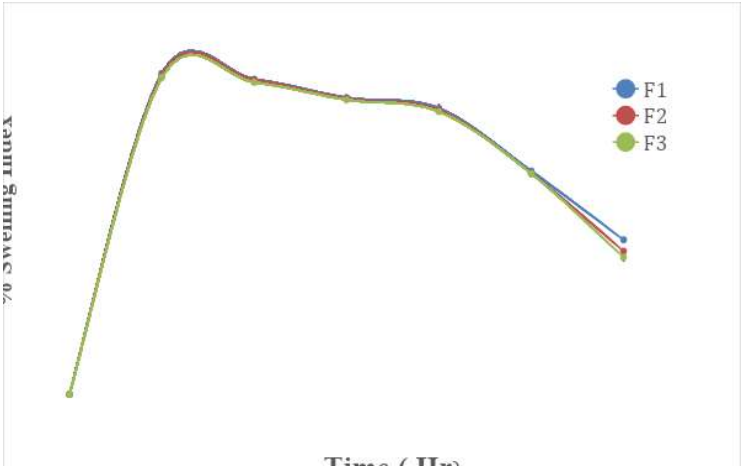

Fig. No. 12: % Swelling Index of Formulations F1 to F3.

Fig. No. 13: % Swelling Index of Formulations F4 to F6.

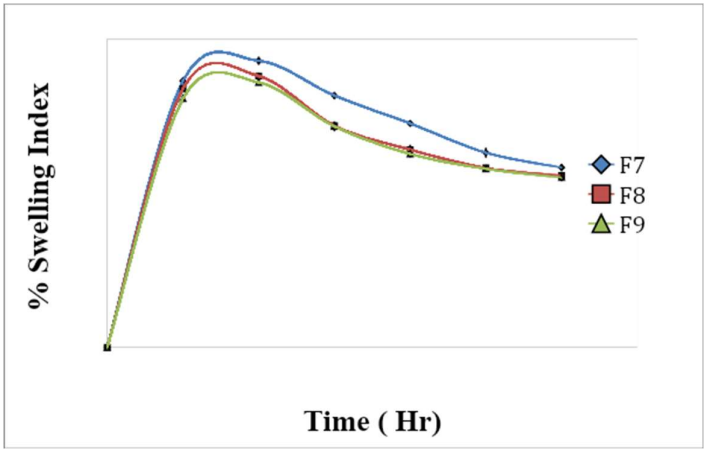

Fig. No. 14: % Swelling Index of Formulations F7 to F9.

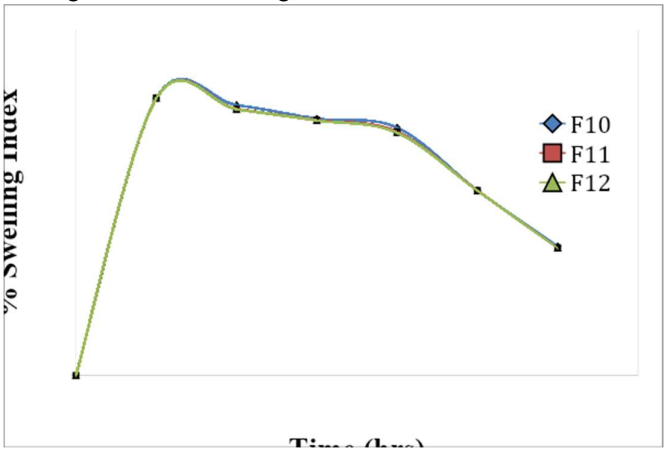

Fig. No. 15: % Swelling Index of Formulations F10 to F12.

4.3.4 PARTICLE SIZE ANALYSIS

The particle size was determined using Imaging System (Biowizard Software 4.1).

The diameter of about 200 beads was measured.

Observation: The mean particle diameter of beads is as shown in Table No. 12.

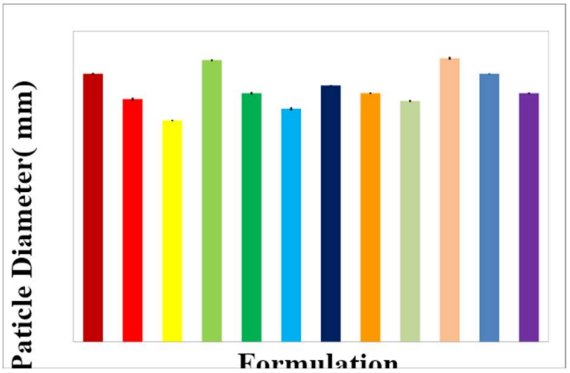

Fig. No. 16: Mean Particle Diameter of Formulations F1 to F12.

4.3.5*IN VITRO* DRUG RELEASE STUDY

In vitro dissolution study was carried out using USP Type I (Basket method) apparatus (Dissolution Test Apparatus Model No.DA-3 Veego Scientific Devices, Mumbai). In order to simulate the pH changes along the GI tract, three dissolution media acid buffer pH 1.2, phosphate buffer pH 6.8 and phosphate buffer pH 7.4 were sequentially used.

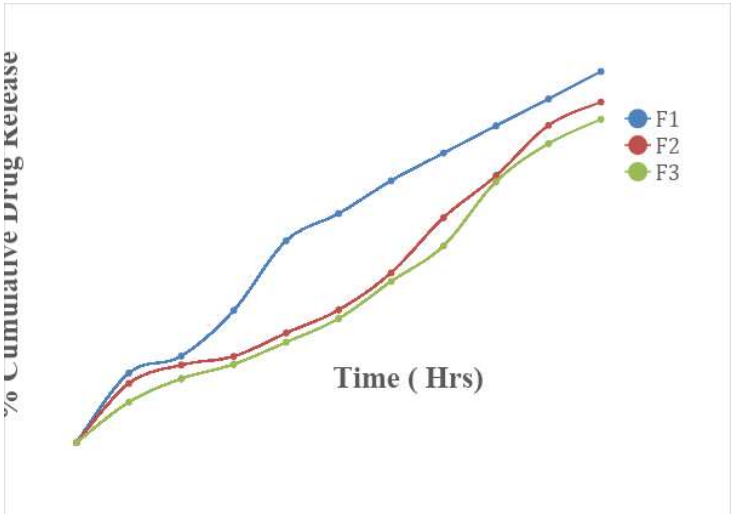

Fig. No. 17: *In vitro* Dissolution Study of Formulations F1, F2 and F3.

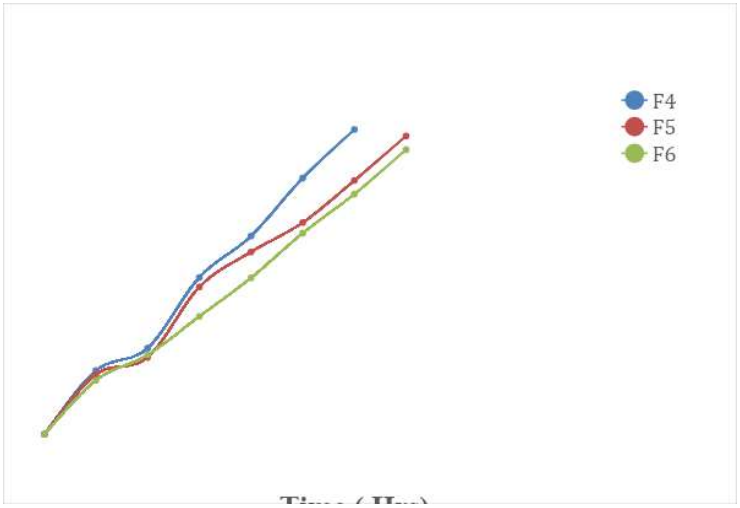

Fig. No. 18: *In vitro* Dissolution Study of Formulations F4, F5 and F6.

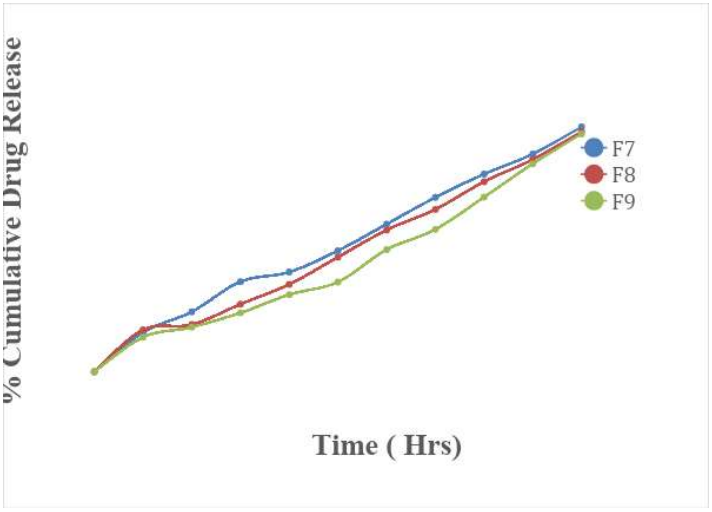

Fig. No. 19: *In vitro* Dissolution Study of Formulations F7, F8 and F9.

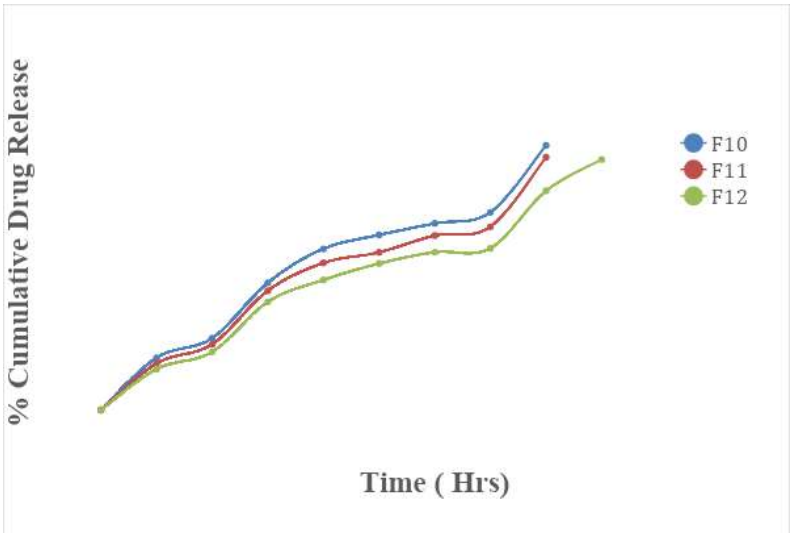

Fig. No. 20: *In vitro* Dissolution Study of Formulations F10, F11 and F12.

4.4 COATING OF BEADS

The enteric coating of beads of optimized batch F8 was performed by spray coating using Pharma R and D coater (Ideal Curves Pvt. Ltd., India)In brief coating solution was prepared by mixing Eudragit S-100 with acetone for 1hr using a stirrer. After an hour, triethyl citrate (TEC) 6%w/v was added and stirring was continued for 30 min. The solution was sprayed at an automizing air pressure of 2 bars. The coating was continued until the desired weight gain achieved. Coated beads with different film thickness were produced, quantified with total weight gain (%TWG), by varying amount of coating solution sprayed.

4.4.1 *In vitro* Drug Release Study of Coated beads

In-vitro dissolution studies were carried out using USP Type I (Basket method) apparatus (Dissolution Test Apparatus Model No.DA-3 Veego Scientific Devices, Mumbai). In order to simulate the pH changes along the GI tract, three dissolution media acid buffer pH 1.2, phosphate buffer solution pH 6.8 and pH 7.4 were sequentially used.

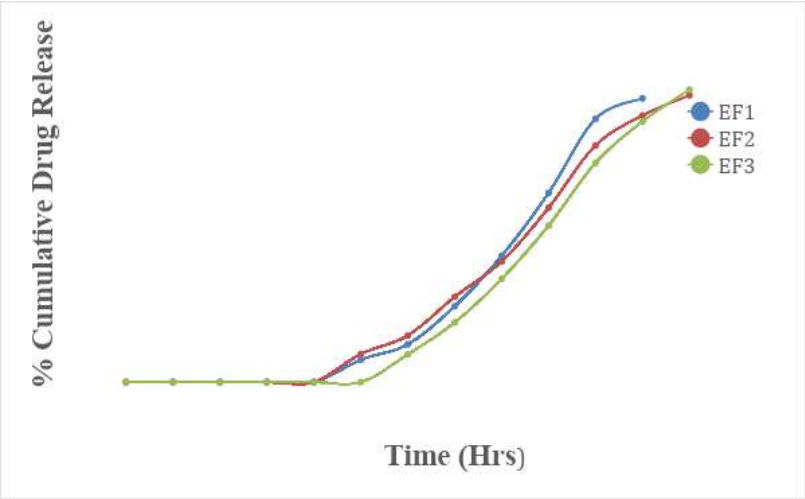

Fig. No. 21: *In vitro* Dissolution Study of Eudragit S-100 Coated Formulations EF1, EF2 and EF3.

1. Particle size analysis of coated beads:

The particle size was determined using Imaging System (Biowizard Software 4.1).

Table No. 5: Mean Particle diameter of formulations EF1 to EF3.

Sr. No.	Batches	Mean Particle Diameter (mm)
1	EF1	1.38 ± 0.004
2	EF2	1.42 ± 0.008
3	EF3	1.48 ± 0.005

*Each value represents the mean ±standard deviation (n=20).

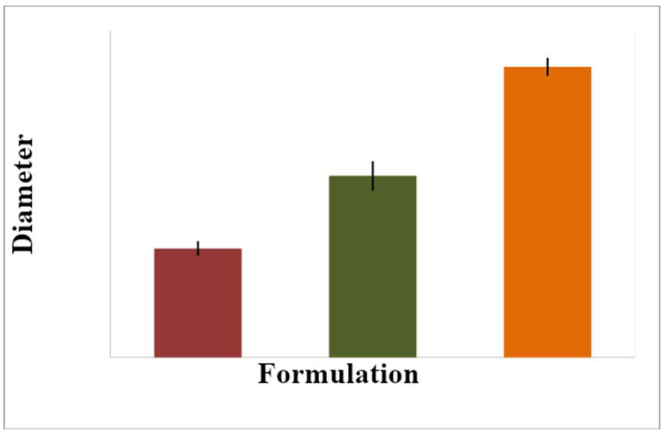

Fig. No. 22: Mean Particle Diameter of Formulations EF1, EF2 and EF3.

4.4.2 Scanning Electron Microscopy

Scanning electron microscopy was used to determine the surface morphology and the cross section view of coated and uncoated beads of batch F8 and EF3 respectively. The specimen was positioned on the sample holder so as to present a cross section and surface morphology of beads to the microscope. Samples were coated with gold and visualized under scanning electron microscope.JSM 6380A (JOEL, France) at North Maharashtra Jalgaon University, Jalgaon, Maharashtra. The beads were kept on the sample holder and the scanning electron micrographs are shown in figure.

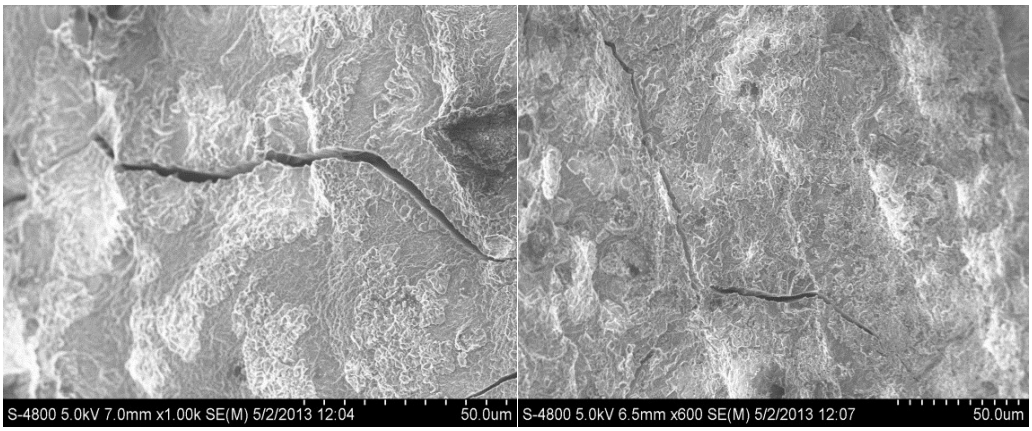

Fig. No. 23: SEM Photomicrographs of Uncoated Beads Formulation F8.

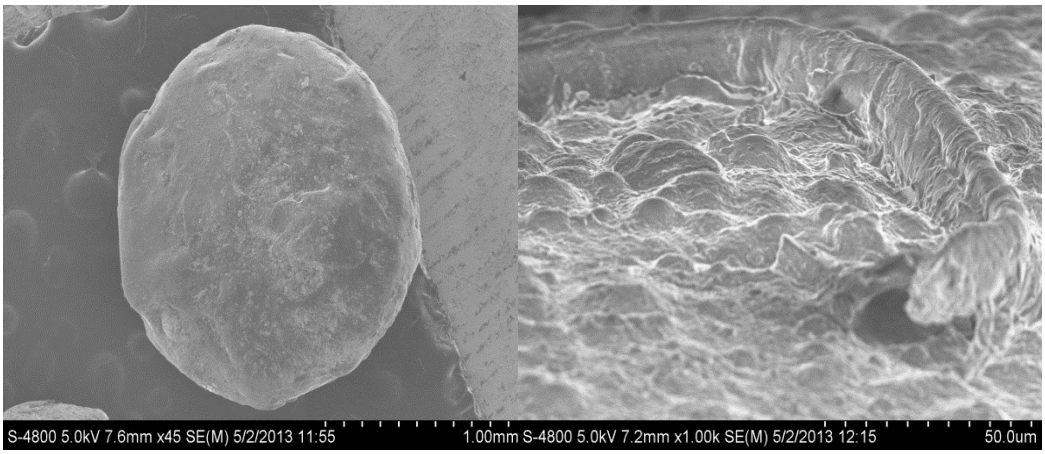

Fig. No. 24: SEM Photomicrographs of Coated Beads Formulation EF3.

4.5Treatment of dissolution data with different kinetic equation

To describe the kinetics of drug release from the Formulations, mathematical models zero-order, first order, Higuchi, Hixon-crowell, Korsmeyer-Peppas were used. The criterion for selecting the best fit model was chosen on the basis of the goodness fit test..

Observation:

The results of kinetic treatment applied to dissolution profile of optimized formulation EF3 is shown in below

Table No. 6: Kinetic Treatment of Data of Formulation EF3.

Variables	Zero Order	First Order	Hixon Crowell	Korsmeyer and Peppas	Higuchi Plot
R2 Value	0.994907	0.882610	0.969248	0.604023	0.938811
Slope	17.191428	0.285115	1.569576	1.134454	0.029298
Intercept	-3.3	0.569811	1.438205	-0.582183	0.348366

4.5.1 STABILITY STUDY

Stability study of an optimized formulation EF3 was carried out by storing the beads (wrapping in aluminum foil) at 40±2^{0}c and 75±5% relative humidity for 3 months. At an interval of 1 month, the beads were examined for *in-vitro* release data. The dissolution profile of formulation EF3 put under stability study is given in

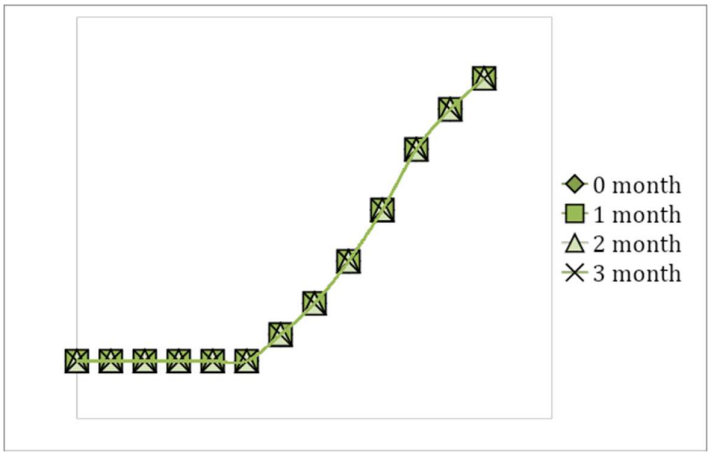

Fig. No. 25: *In-vitro* Dissolution Study of Formulation EF3

5. CONCLUSION

From the present study it can be concluded that chitosan beads containing Montelukast sodium were successfully prepared and coated with the pH sensitive polymer i.e. Eudragit S-100. Further it can also concluded that, the prepared chronotherapeutic beads of Montelukast sodium was found to be satisfactory in terms of release of the drug after a predetermined lag time i.e., 6 hrs and thus dosage form can be taken at bed time so that the content will be released in the morning hours. Lag time of formulation was modified by varying the coating levels of Eudragit S-100.

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