Research Article

DEVELOPMENT AND EVALUATION OF MONTELUKAST SODIUM COLON TARGETED MATRIX TABLETS BASED ON PULSATILE APPROACH FOR NOCTURNAL ASTHMA

Surender Verma[*1], Vinay Valecha[2], Shailendra Kumar Singh[3], Navneet Syan[4], Pooja Mathur[4]
[1] Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119, Haryana, India.
[2] B. S. Anangpuria Institute of Pharmacy, Faridabad-121001, Haryana, India.
[3] Department of Pharmaceutics, Guru Jambheshwar University, Hisar-125001, Haryana, India.
[4] Ganpati Institute of Pharmacy, Bilaspur, Yamunanagar-135102, Haryana, India.
*Corresponding author's E-mail: soni2pharma@rediffmail.com

Accepted on: 26-02-2011; **Finalized on:** 01-05-2011.

ABSTRACT

The aim of present study was to formulate and evaluate colonic pulsatile release matrix tablets of Montelukast sodium for time and site specific delivery based on chronotherepeutical consideration. Montelukast sodium is a leukotriene receptor antagonist especially used in the treatment of nocturnal asthma. Colon targeted matrix tablets of model drug were formulated by wet granulation method using different combinations of HPMC K4M and K15M along with varying amount of croscarmellose sodium. Formulations were enteric coated with polymers (Insta-moistshield™ and Instacoat simply enteric™) and evaluated for various *in vitro* tests such as hardness, friability, wt. variation, content uniformity, disintegration and dissolution. Surface morphological analysis of tablets was performed by scanning electron microscopy before and after dissolution. System was evaluated for drug release mechanism by applying zero, first, higuchi and peppas kinetic models. A criterion for selecting the most appropriate model was based on linearity. Effect of polymer concentration and superdisintegrant level was also investigated. Dissolution data revealed that formulations having HPMC K4M : K15M in ratio of 20 : 0 along with croscarmellose sodium at a level of 2.4% were optimized in terms of achieving the drug delivery system, consistent with the requirement of chronopharmaceutical drug delivery, providing release rate of more than 85% in 12h of duration. Drug release data fits well to zero order kinetics and mechanism of drug release was found to be combination of swelling and erosion.

Keywords: Chronotherapy, nocturnal asthma, release kinetics, superdisintegrant.

INTRODUCTION

Circadian rhythm is a self sustaining oscillation of endogenous origin characterized by period, level, amplitude and phase. Nearly all body functions such as metabolism, hormone production, sleep behavior, physiology shows prominent daily variation based on biological rhythm. Hence, the purposeful delivery of right concentration of medication to the targeted tissue based on its diurnal variation along with knowledge of variation determinants (Chronopathology, Chronopharmacology and its attributes) is called as chronotherapy. The discipline of chronotherapy in combination with targeted drug delivery systems (TDDS) has emerged as an effective tool for achieving optimized treatment outcomes in several acute and chronic disorders such as respiratory disorders, cardiovascular disorders, CNS disorders, gastrointestinal disorders, blood disorders, endocrine disorders, musculoskeletal disorders, genetic disorders[1-5].

The worsening of asthma symptoms at night time is known as nocturnal asthma which is characterized by circadian rhythm based changes in airway caliber, airway hyperactivity, airway inflammation and neuroendocrine system[1-4]. The ultimate aim in the design of an oral controlled release dosage form includes maintaining relatively constant therapeutic blood levels of the drug for a desired period, reduce dosing frequency, improve patient compliance and decrease incidences of adverse drug reactions[6].

Hydrophilic matrix system is widely used for the modification of drug release in oral therapy because of its simplicity in manufacture. In such a system, the drug release is controlled by a combination of several physical processes which include, but are not limited to, diffusion, polymer swelling, erosion and dissolution. Different cellulose derivatives or their combinations have been extensively used in the preparation of matrix tablets. Hydroxypropyl methyl cellulose (HPMC) is the most widely studied hydrophilic swellable matrix forming material for the preparation of modified drug release products. Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release, ease of compression, and its capability to accommodate high levels of drug loading[6-9].

Pulsatile release dosage form is one such type of system addressing chronotherapeutic needs by incorporating the concept of colonic drug delivery (site specific release). Though Colon targeting can be achieved through various drug delivery systems differing in their mechanism to target drugs such as pH sensitive systems, microbially triggered systems, timed release systems, osmotically controlled systems, pressure dependent systems but pulsatile release colon targeted systems gain more attention due to the requirement of chronotherapy based treatment[10-14]. After a lag time, the release of active ingredients from the pulsatile dosage form can be completed through a burst effect, releasing all the drug in

a short time period or it can be in a sustainable manner, releasing the drug for prolonged duration[15-17].

Thus the aim of this study was to formulate a pulsatile release colon targeted drug delivery system of Montelukast sodium for chronotherapy based treatment of nocturnal asthma. Montelukast sodium, an orally active drug, was utilized as model drug as it ameliorates broncho-constriction in asthmatic patient by binding to cystenyl leucotriene receptors (cysLT1 receptors present in human airways) with greater affinity than leucotrienes (LTD4) which are thousand times more potent than histamine and hence causes relief in asthmatic patient. The colonic drug delivery system comprises of two parts. The inner part is the core tablet having Montelukast sodium having combinations of time dependent polymers (HPMC K4M and K15M) with superdisintegrant (croscarmellose sodium). The outer part comprises of combination of seal coating polymer and enteric polymer (Insta-moistshield™ and Instacoat simply enteric™). This enteric coating was to minimize the drug release in the stomach region allowing intact tablet to enter into the small intestine. Now from this region onwards, it was the responsibility of the time dependent polymers to retard the release in the intestinal region exposing the content to colonic medium. *In vitro* dissolution studies were carried out by using sequential pH change method in acidic buffer of pH 1.2 followed by phosphate buffers of pH 7.4 and 6.8 simulating stomach transit time, intestinal transit time and colonic transit time of 2h, 3h and 7h respectively. Scanning electron microscopy of the formulations was also carried out before and after dissolution testing. The effects of the polymer concentration along with the superdisintegrant concentration were also studied. *In vitro* kinetic models were also applied to the dissolution results to predict the order and mechanism of drug release.

MATERIAL AND METHODS

Montelukast sodium was provided by Ranbaxy laboratories (Gurgaon, India) as a gift sample. HPMC K4M and HPMC K15M were kindly provided as gift sample by Colorcon Asia Pvt. Ltd. (Goa, India). Insta-moistshield™ and Instacoat simply enteric™ were kindly provided as gift sample by Ideal Cures Pvt. Ltd. (Panchkula, India). Croscarmellose sodium was gifted by Mapple Biotech. Pvt. Ltd. (Pune, India). All other reagents were of analytical grade and were purchased from S.D. Fine Pvt. Ltd. HPLC grade water and acetonitrile were procured from Merck Pvt. Ltd.

Preparation of core tablets

All the ingredients were weighed separately. Afterwards, drug was mixed with polymers (HPMC K4M and HPMC K15M), superdisintegrant (croscarmellose sodium 1.2% w/w and 2.4% w/w) and diluent (lactose monohydrate) in a mortar pestle followed by in a poly bag for 20 min. Mixed powder was granulated with polyvinylpyrollidone K-30 (10% w/w in isopropyl alcohol) to make dough mass. Granules were prepared and kept in a dark room for overnight drying. Flow properties of granules were determined in terms of angle of repose, compressibility index, and Hausner ratio. Granules obtained were mixed with accurately weighed quantity of glidant (talc) and lubricant (magnesium stearate) in 2:1 ratio. Tablets (each of 200 mg) were formulated on mini rotary tablet press (Fluid pack machinery) using 8 mm punch with a dissection in it. In this way six different formulations coded as F 41, F 42, F 51, F 52, F 61 and F 62 were formulated having different amount of synthetic polymers and superdisintegrant in them. The formula for tablet preparation is given in **[Table 1]**.

Enteric coating of core tablets

Now formulated matrix tablets were enteric coated by spray coating using Instacoat™ R&D coater machine to prevent the premature drug release in physiological environment of stomach. First of all seal coating solution was done with Insta-moistshield™ polymer up to a weight gain of 2-5% w/w (actually 3.5% w/w) on tablets. It provides moisture resistance property to the tablets and also serves as a barrier to prevent any interaction between the drug and enteric polymer. Afterwards, coating solution for Instacoat-simply enteric™ was used for enteric coating up to a weight gain of 30-40% w/w (actually 36.4% w/w). The formula for preparing the coating solutions and parameters for adjusting the coating process are provided in **[Table 2] [Table 3]**.

Table 1: Composition of pulsatile release matrix tablets of Montelukast sodium for colon targeting

Ingredients	F 41	F 42	F 51	F 52	F 61	F 62
Montelukast sodium	10.4	10.4	10.4	10.4	10.4	10.4
HPMC K4M + K15M (20% w/w total)	(40 + 0)	(40 + 0)	(30 + 10)	(30 + 10)	(10 + 30)	(10 + 30)
Lactose monohydrate	121.6	119.2	121.6	119.2	121.6	119.2
PVP K-30 (10%w/w)	20	20	20	20	20	20
Croscarmellose Sodium	2.4 (1.2%)	4.8 (2.4%)	2.4 (1.2%)	4.8 (2.4%)	2.4 (1.2%)	4.8 (2.4%)
Talc	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2
Total weight	200	200	200	200	200	200

*All the quantities are expressed in milligrams

Table 2: Composition of coating solution of Instacoat simply enteric™ and Insta-moistshield™

Characteristics	Instacoat simply enteric™	Insta-Moistshield™
Solvent system	Organic type	Organic type
Reconstitution level	10% w/w	5% w/w
Formulation components	Instacoat (ISE-10001): 100 g	Insta-moistshield : 40 g
	Iso propyl alcohol : 900 g	Iso propyl alcohol : 266 g
		Methylene chloride : 494 g

Table 3: Coating parameters for adjusting the coating process

Parameters	Working Conditions
Coating pan size	12" conventional with 3 baffles
Batch size	1.00 kg tablets
Coating Pan speed	25 to 30 rpm
Spray gun type	Bullows 630 with 1.2 mm nozzle
Atomization pressure	2 kg/cm^2
Spray rate	10 to 15 gm/minute
Inlet air temperature	60 to 65 ^oC
Tablet bed temperature	35 to 40 ^oC
Pre warming	10 to 15 minutes at slow rpm
Post drying	20 to 30 minutes at slow rpm

Method of analysis by HPLC and preparation of standard curve

Drug was analyzed by validated HPLC method and analysis was carried out by using C18 symmetry column (Eclipse XDB - C18, 4.6 x 150 mm, 5 µm) with mobile phase consisting of 0.05M potassium dihydrogen phosphate buffer (pH of 3.5 ± 0.1) adjusted with dilute orthophosphoric acid) and acetonitrile in ratio 30:70 with a flow rate of 2 ml per min. and injection volume of 10 µl, analyzing content at 345 nm by standard variable wavelength detector[18]. Standard plots were made to find out the concentration of drug in the samples. Drug equivalent to the prescribed dose i.e. 10 mg was accurately weighed and a standard stock solution of 100µg/ml was prepared. A series of standard solutions were obtained by diluting the stock solution to 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml and 12µg/ml. Another standard curve was plotted by obtaining the standard solutions having concentrations of 100µg/ml, 200µg/ml, 400µg/ml, 800µg/ml and 1600µg/ml. All the volumetric flasks were wrapped with aluminium foil and stored in dark because Montelukast shows fast degradation in presence of light. Calibration curve was drawn between area of injected volume of samples and concentration of injected sample to obtain regression equations which will be used to quantify the amount of drug in the dissolution sample and to analyze drug content uniformity.

STUDY OF IN-PROCESS QUALITY CONTROL (IPQC) PARAMETERS

Evaluation of granules

Granules prepared by wet granulation method were evaluated for bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose.

Uniformity of weight

Twenty tablets were weighed individually on electronic weighing balance (Afcoset, Gujarat) and their average weight was also calculated. Weight variation was calculated and was compared with I. P. standards.

Hardness of tablets

Five tablets from each formulation batch were selected randomly and their crushing strength (kg/cm^2) was determined using Pfizer hardness tester (Afcoset, Ambala).

Friability

Twenty preweighed tablets from each formulation were placed in Roche Friabilator (Electrolab Friabilator USP EF-1W), Mumbai for carrying out friability. Apparatus was run on 25 rpm for 4 min. Then tablets were taken out, dedusted and weighed again. Friability of tablets was calculated from the formula:

$$\text{Percentage Friability} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}}$$

Content uniformity test

Three tablets from each formulation were tested for content uniformity test. Each tablet was individually triturated and dissolved in 100 ml of methanol. Afterwards, solution was filtered through 0.22 µm membrane filters and drug content was determined by HPLC analysis at 345 nm by standard variable wavelength detector as described earlier. Area of the injected solution was used to calculate content uniformity utilizing standard plot.

Disintegration test

Disintegration test was performed on each formulation

for checking intactness of enteric coat. Electrolab disintegration apparatus, ED-2L (Mumbai) was used and I.P. method for enteric coating testing was followed. Six tablets of each formulation were tested for disintegration. Tablets were firstly tested in 0.1N HCL for 2h (simulating gastric transit time) to see the damage to the coat. Afterwards, tablets were tested in the phosphate buffer pH 7.4 (simulating intestinal pH) till the coating dissolved. Temperature in each case was kept at 37 ± 0.5 °C. Disintegration time was reported in min.

Scanning electron microscopy (SEM)

Surface morphology of the coated matrix tablets of Montelukast sodium based pulsatile tablets were examined using Hitachi S-3400N scanning electron microscope (Japan) with image analysis system. Prior to analysis, samples were gold sputter coated with to render them electrically conductive. Samples were analyzed before dissolution and after dissolution.

***In vitro* drug release studies**

The ability of the formulated tablets to retard the drug release in the physiological environment of the stomach and small intestine was assessed by conducting drug release studies in simulated stomach and simulated intestinal pH respectively. *In vitro* dissolution studies were performed for the pulsatile release matrix tablets using USP dissolution apparatus II (paddle type, Electrolab tablet dissolution apparatus), 50 rpm, thermostatically maintained at temperature 37 ± 0.5°C, with dissolution medium of 900 ml having 0.1% of sodium lauryl sulphate in it. In order to simulate the pH change along the gastrointestinal tract, the tablets were studied in pH 1.2 acidic buffer (900 ml) for 2h pertaining the average gastric emptying time of stomach. Then the tablets were tested in pH 7.4 buffer (900 ml) for 3h, mimicking small intestinal transit time. At predetermined time interval, samples of 10 ml were taken, filtered through 0.22µm membrane filter and drug content was determined by HPLC method as described earlier. After that same formulations were tested in the dissolution medium having phosphate saline buffer of pH 6.8 for simulation of the colonic medium. Dissolution study was carried out for duration of 7h to complete overall 12h of the dissolution study. All the conditions for the *in vitro* drug release study were same as used in earlier case and drug content was also determined by the same method.

Release kinetics analysis

To establish the order and mechanism of drug release, dissolution data of all the formulations were fitted to four different kinetic models named as zero order model, first order model, higuchi model and koresmeyer peppas model. The model for best fit was predicted from the value of r^2. The value which was closer to 1 was selected as the best fit model for the drug release. The n value which is the slope of the curve obtained from the peppas model describes the mechanism of drug release[15, 19].

RESULTS AND DISCUSSION

In present study, our plan was to formulate drug delivery system for chronotherapy based treatment of nocturnal asthma. The granules for the purposed formulations were evaluated for their physical characteristics like bulk density, tapped density, compressibility index, Hausner ratio, and angle of repose respectively. The results of the bulk density and tapped density ranged from 0.278 to 0.355 and 0.321 to 0.438 respectively and the compressibility index (%) ranged from 12.77 to 19.40. The value for hausner ratio and angle of repose was found to be 1.14 to 1.24 and 19.11 to 22.99. The results obtained from the preformulation studies were indicating good flow ability of granules [**Table 4**].

All the formulations were seems to pass the test for weight variation, hardness, friability, thickness, and content uniformity as average value for these parameters were found to be within the official limit [**Table 5**].

The intactness of coat in acidic medium and in phosphate buffer was determined by disintegration test. To prevent premature release, it was planned to apply an enteric coat consisting of Insta-moistshield™ (seal coat) and Instacoat-simply enteric™. Due to light sensitivity of the drug, it was necessary to use polymer having red iron oxide to prevent degradation of the drug by providing color to it. From the results it was clearly found that for all the formulations, coat remained intact for 2h in the acidic media preventing the drug release completely and gets dissolved in the phosphate buffer at a time period of around 90 to 110 min. The tablets of each formulation batch subjected to drug content uniformity by HPLC method at 345 nm by standard variable wavelength detector. The tablets were found to be containing 97.10 % to 100.20 % of Montelukast sodium; these indicate uniformity of drug content.

Table 4: Properties of granules of matrix tablet prepared from HPMC K4M and 15M

Sr. No.	Batch code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index	Hausner's ratio	Angle of repose
1	**F 41**	0.353	0.438	19.40	1.24	21.69
2	**F 42**	0.355	0.438	18.94	1.23	22.99
3	**F 51**	0.278	0.322	13.66	1.16	19.11
4	**F 52**	0.280	0.321	12.77	1.14	20.24
5	**F 61**	0.342	0.419	18.37	1.22	22.20
6	**F 62**	0.350	0.418	16.26	1.19	20.21

Table 5: Physical characteristics of pulsatile release matrix tablets of Montelukast sodium

Batch code	Weight (uncoated tablets) (mg)	Weight (coated tablets) (mg)	Hardness (uncoated tablets) (kg/cm^2)	Hardness (coated tablets) (kg/cm^2)	Friability (%)	Disintegration Time (min.)	Content Uniformity (%)
F 41	200.10 ± 1.29	279.76 ± 2.91	6.8 ± 0.07	8.64 ± 0.11	0.18	225.16 ± 2.78	97.10 ± 0.556
F 42	200.05 ± 1.36	279.71 ± 2.93	6.74 ± 0.15	8.58 ± 0.08	0.16	216.35 ± 3.01	98.83 ± 0.568
F 51	199.05 ± 1.19	280.38 ± 3.84	7.08 ± 0.13	8.96 ± 0.18	0.19	224.65 ± 1.87	100.2 ± 0.642
F 52	200.25 ± 1.48	281.09 ± 2.66	7.1 ± 0.2	8.96 ± 0.09	0.2	219.76 ± 3.50	98.86 ± 0.950
F 61	200.15 ± 1.56	280.19 ± 2.15	7.36 ± 0.15	8.92 ± 0.19	0.13	231.18 ± 2.87	99.43 ± 0.680
F 62	200.20 ± 1.64	279.33 ± 2.35	7.62 ± 0.11	8.90 ± 0.16	0.15	230.82 ± 2.25	99.13 ± 0.208

All values are shown in mean ± S.D.

The tablets weight variation was found under prescribed limits. This showed that prepared tablets were uniform in weight & percentage drug content. From the scanning electron micrographs, it was clear that the surface of the tablets after coating with enteric polymers appears intact and homogeneous before dissolution testing as shown in **Fig. 1 (a)**. It was undoubtedly seen from micrographs that after dissolution of the tablets, there appears a number of deep fractures (cracks), irregular cavities along with pores formation due to the burst effect of superdisintegrant leading to erosion of tablets and hence providing pathway for easy penetration of dissolution medium into the interior of tablet for diffusion of drug **Fig. 1 (b)**. Hence Scanning electron microscopy was also found to be helpful in predicting the drug release mechanism indirectly.

Figure 1: Scanning electron micrographs of coated matrix tablets of optimized batches F 42

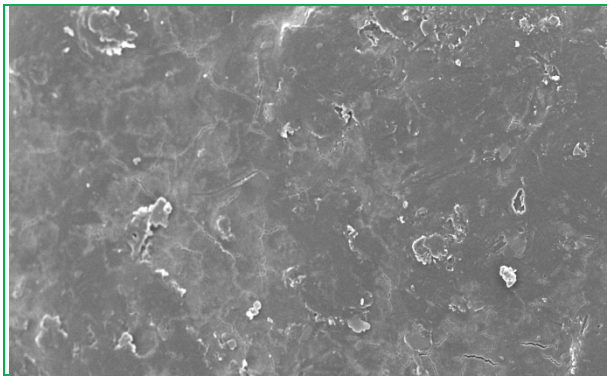

Figure 1(a) before dissolution

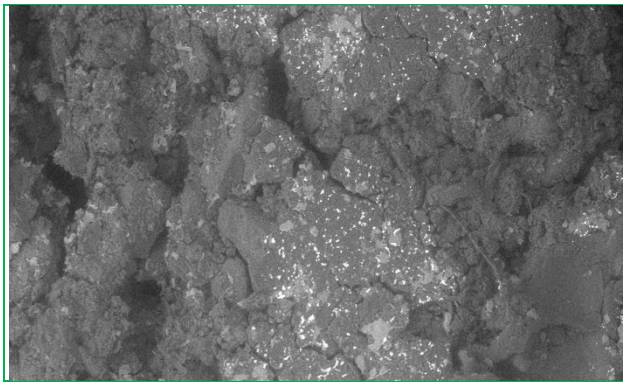

Figure 1(b) after dissolution

In vitro drug release study

Formulations were first tested in dissolution medium of pH 1.2 simulating the physiological environment of the stomach. Dissolution samples were analyzed by HPLC method showed absence of drug in the samples. This was in agreement with the disintegration test results confirming the effectiveness of the enteric polymer allowing no drug release form the formulations. Afterwards, the same formulations were tested in phosphate buffer of pH 7.4 simulating the environment of the small intestine. From the dissolution results, cumulative % drug release in 3h of dissolution testing in medium simulating intestinal conditions was found to be 17.05% in F 41, 19.45% in F 42, and 16.63% in F 51, 17.58% in F 52 followed by 12.01% in F 61 & 14.48% in F 62.

Drug release from the polymer matrix containing HPMC K4M and HPMC K15M follows pathway of polymeric hydration, swelling followed by diffusion of the drug particles. However, this also depends upon the solubility of drug. Sometimes erosion of the polymer matrix became the predominant pathway for drug release than the diffusion of drug particles. Drug release from the tablets in the preliminary phase of dissolution study was attributed to the drug present on the surface of the matrix tablets. The results obtained were in agreement with the fact that formulations having higher percentage of HPMC K15M as a matrix former show much more retardation of drug release as compared to the formulations having lower percentage of HPMC K15M. Formulation F 61 and F 62 show least amount of drug release in dissolution study illuminating the effect of HPMC K15M concentration in the formulations. Presence of HPMC K15M forms a much more viscous layer around the tablet allowing less seepage of fluid into the tablet to prolong the drug release. Higher concentration of HPMC K15M provides gel layer which was more viscous as compared to that formed by lower concentration of HPMC K15M. The delay in drug release can be attributed to the time taken by the combination of polymers between transitions from glassy state to rubbery state. Instead of higher concentration of HPMC K15M in the formulations F 61 and F 62, drug release values were almost nearer to the release values obtained from formulations F 51 and F 52 which were having lower

concentration of HPMC K15M. The reason behind this was correlated to the higher molecular weight of the polymer. Owing to higher molecular weight, polymer chains were also bulkier in nature requiring more time for their unwinding by solvent molecules leading to delay in instant swelling of the polymer. This delay was responsible for the higher drug release from the formulations having higher concentration of HPMC K15M.

Afterwards, results obtained from the dissolution study of formulations in colonic pH 6.8 were also evaluated. In the 6th h of dissolution study, drug release was found to be 34.45% in F 41, 40.57% in F 42, and 30.23% in F 51, 31.94% in F 52 followed by 25.18% in F 61, 26.94% in F 62. Results of the initial hour of dissolution in colon concluded that instead of the presence of superdisintegrant (croscarmellose sodium) in the formulations the cumulative percentage drug release from all the formulations was not high. This was in conformity of the fact that initial drug release from the formulations depends upon the time taken by polymers for transition from glassy to rubbery state along with the amount of superdisintegrant in the formulation. As it was clear from the dissolutions results that formulations having higher amount of superdisintegrant shows higher drug release as compared to that having lower amount of superdisintegrant. After 12 h of dissolution study, the cumulative percentage drug release was found to be 91.25% in F 41, 96.53% in F 42 and 83.54% in F 51, 90.21% in F 52 followed by 66.40% in F 61, 70.44% in F 62. From the results shown in **table 6** and **fig. 2**, an increase in the drug release was noticed in each formulation. This augment in drug release can be attributed to the rubbery transition of polymer matrix which allows greater seepage of the dissolution fluid into the matrix of tablets and allowing drug dissolution and diffusion[20]. These results were also in correlation with the amount of superdisintegrant present in the formulation. After coming in contact with the dissolution fluid, superdisintegrant swells and burst, allowing pore formation and cavity formation in the matrix of tablets, providing drug release to occur at faster rate.

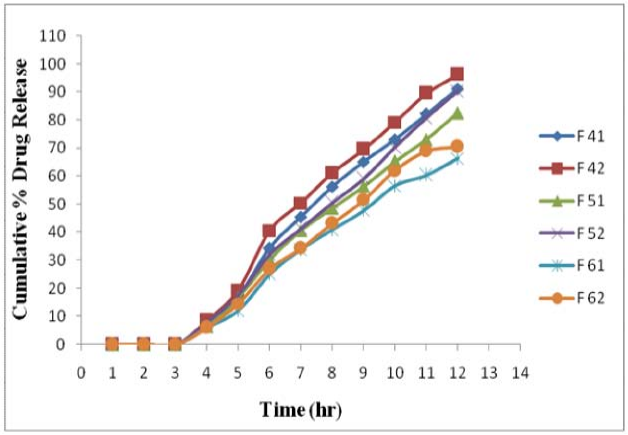

Figure 2: Dissolution release profile curve for pulsatile release matrix tablets of Montelukast sodium

From results of our study, it was obvious that formulation F 42 achieved more than 95% of the drug release in the required time period and is best fitted to be called as optimized formulations for the chronotherapy based treatment of nocturnal asthma.

Table 6: Cumulative % drug release data of pulsatile release matrix tablets of Montelukast sodium

Time (h)	Cumulative % drug release at pH 6.8					
	F 41	F 42	F 51	F 52	F 61	F 62
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	6.65	8.58	6.45	7.85	6.02	6.12
5	17.05	19.45	16.63	17.58	12.01	14.48
6	34.45	40.57	30.23	31.94	25.18	26.94
7	45.45	50.42	40.55	41.33	33.91	34.38
8	56.23	61.07	48.57	50.58	40.87	43.17
9	65.14	69.57	56.39	59.22	47.80	51.54
10	73.11	79.25	65.24	70.35	56.50	62.09
11	82.12	89.45	73.04	80.80	60.40	68.96
12	91.25	96.53	82.54	90.21	66.40	70.44

Effect of polymer type and concentration on the drug release behavior

From the results of *in vitro* dissolution studies, it was clear that drug release depends upon the type of polymer and concentration of polymer. Drug release was found to be higher in case of formulations based on HPMC K4M. HPMC K15M being more viscous in nature as compared to HPMC K4M forms a very viscous gel layer which will reduce the seepage of dissolution fluid into the core of tablets and leading to sustained drug release. Delay in drug release was also owing to the enormous swelling potential of HPMC K15M which led to increase in diffusion path length. Dissolution results in pH 6.8 medium were also in correlation with above explanation as drug release was 91.25% in F 41, 82.54% in F 51 and 66.40% in F 61 while it was 96.53% in F 42, 90.21% in F 52 and 70.44% in F 62. Effect of polymer concentration can clearly be seen in the **fig. 3 (a, b)**.

Figure 3 (a), 3 (b): Effect of HPMC K4M and 15M concentration on drug release from matrix tablets of Montelukast sodium

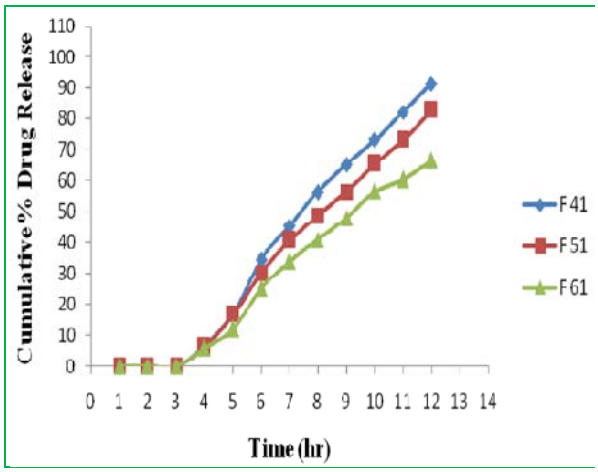

Figure 3 (a)

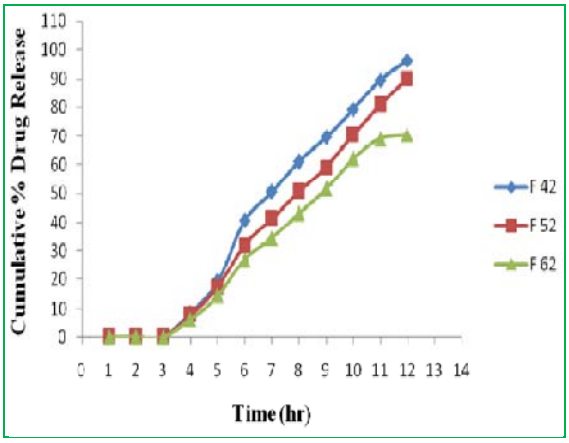

Figure 3 (b)

Effect of superdisintegrant concentration on drug release behavior

Formulations having higher concentration of croscarmellose sodium showed greater drug release as compared to that having lower concentration in the matrix of tablets. This was also clear from the comparison between dissolution results of formulations F 41 and F 42, F 51 and F 52 followed by F 61, F 62 in dissolution medium of 6.8. The reason for increased drug release in formulations containing higher amount of superdisintegrant was attributed to the formation of pores and cavities in the matrix of tablets. Seepage of the dissolution medium in the matrix of tablets allows rapid swelling of tablet to provide burst effect. Swelling of the tablet depends upon the concentration of superdisintegrant in the formulation; higher amount of superdisintegrant provides higher swelling. After some time, this swelling leads to the formation of pores and cavities in the tablet through which drug can leach out from the matrix. Scanning electron micrographs of matrix tablets after dissolution testing in pH 6.8 were also in correlation with the formation of pores and cavities. But presence of rate controlling hydrophilic polymers do not allows drug to be released at rapid rate and sustained the release of drug from the matrix of tablets. Due to this reason Formulations F 42, F 52, F 62 provides higher drug release than formulation F 41, F 51, F 61. Effect of superdisintegrant concentration can clearly be seen in Fig. 4 (a,b,c).

Figure 4 (a), (b), (c): Effect of croscarmellose concentration on drug release from matrix tablets of Montelukast sodium

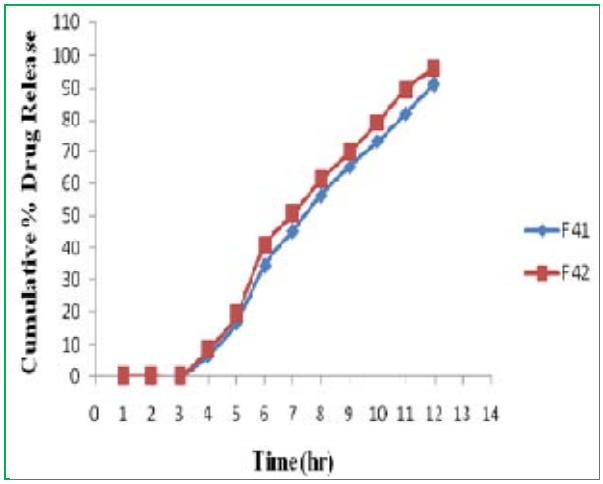

Figure 4 (a)

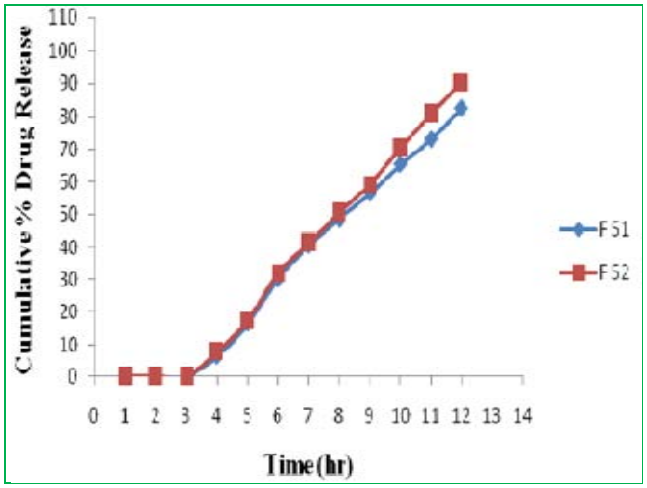

Figure 4 (b)

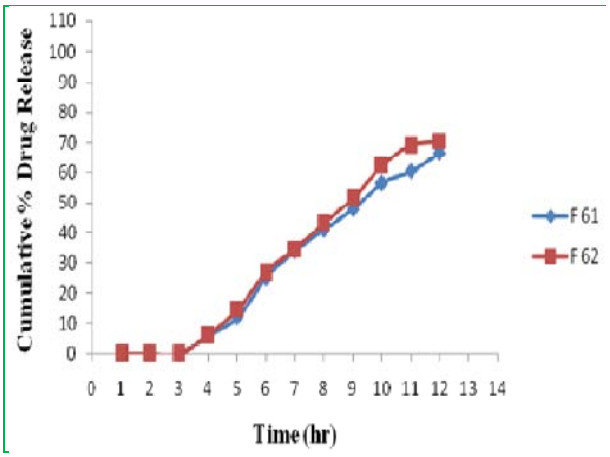

Figure 4 (c)

Statistical kinetic modeling

Dissolution data of all the formulations of pulsatile release tablets was fitted to zero order model, first order model, higuchi model and koresmeyer peppas model. From the results of the data fitting provided in **table 7**, the best linearity was shown by zero order models giving value of r^2 much closer to one. So the drug release was said to follow zero order drug release kinetics. After predicting the order of drug release, mechanism of drug release was determined by value of "n" which was equal to the value of slope given by the equation of line obtained by fitting the data to koresmeyer peppas model. Value of "n" was found to lie between 0.68-0.98 indicating anomalous behavior (also called as non-fickian diffusion) as a mechanism of drug release. This consists of phenomenon of diffusion and erosion of polymer matrix. This mechanism of drug release was also in agreement of presence of superdisintegrant in the formulations which causes tablets to degrade due to burst effect of superdisintegrant.

Table 7: value of r^2 and n obtained after fitting dissolution data to various kinetic models

Formulation Batch Code		Zero Order Kinetics	First Order Kinetics	Higuchi Kinetics	Koresmeyer Peppas Kinetics
F 41	r^2 value	**0.9986**	0.9427	0.9785	0.9920
	Rate constant value	0.1867	0.0021	5.274	**n value**-0.77
F 42	r^2 value	**0.999**	0.8898	0.9891	0.9864
	Rate constant value	0.1936	0.0031	5.460	**n value**-0.68
F 51	r^2 value	**0.9989**	0.9627	0.9930	0.9960
	Rate constant value	0.1712	0.0016	5.363	**n value**-0.81
F 52	r^2 value	**0.9951**	0.9506	0.9945	0.9997
	Rate constant value	0.1848	0.0022	5.234	**n value**-0.73
F 61	r^2 value	**0.9954**	0.9934	0.9930	0.9979
	Rate constant value	0.1591	0.0012	4.504	**n value**-0.98
F 62	r^2 value	**0.9989**	0.9617	0.9856	0.9989
	Rate constant value	0.1699	0.0016	4.781	**n value**-0.79

CONCLUSION

From the study, it was concluded that the novel pulsatile dependent colon targeted drug delivery system could be effectively formulated using combination of time dependent hydrophilic polymers (HPMC K4M & HPMC K15M) along with croscarmellose sodium as superdisintegrant in the matrix of tablets, followed by enteric coating with a pH dependent enteric polymers. From the results of *in vitro* dissolution study, formulation F 42 was found to be optimized in terms of achieving the drug delivery system, consistent with the requirement of chronopharmaceutical drug delivery, providing drug delivery rate of more than 80% in 10-12h of duration. Concentration of HPMC K15M along with that of croscarmellose sodium was found to be predominating factor for sustained effect of drug from the matrix of tablets, controlling lag time as well as drug release rate simultaneously. Enteric coating of the formulations was valuable in obtaining gastro resistant system, providing maximum release in colonic region. Scanning electron micrographs were also in agreement with fact that drug release depends upon the intactness of the enteric coat along with the presence of croscarmellose sodium in the polymer matrix. Drug release kinetics of this system best corresponds to zero order and the mechanism of drug release as calculated from n value obtained from koresmeyer peppas model was found to be anomalous behavior (combination of diffusion and erosion). So the formulated drug delivery system was found to be promising in order to achieve the chronotherepeutic based treatment of nocturnal asthma.

Acknowledgement: The authors greatly acknowledge Ranbaxy Laboratories, Colorcon Asia Pvt. Ltd., Instacoat (Ideal Cures Pvt. Ltd.) and Mapple Biotech Pvt. Ltd. for providing free gift samples. The authors acknowledge Center for Pharmaceutical Nanotechnology, NIPER for carrying out the scanning electron microscopy of formulated batches. Authors are also thankful to Mr. Ankit Jain for his help during HPLC analysis of samples.

REFERENCES

1. Smolensky MH, Lemmer B, Reinberg AE. Chronobiology and chronotherapy of allergic rhinitis and bronchial Asthma. Advanced Drug Delivery Reviews, 59, 2007, 852-882.
2. Smolensky MH, Peppas NA. Chronobiology, drug delivery and chronotherepeutics. Advanced Drug Delivery Reviews, 59, 2007, 828-851.
3. Youan BBC. 2004. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery. Journal of Controlled Release, 98, 2004, 337-353.
4. Janugade B, Patil SS, Patil VS, Lade DP. Pulsatile drug delivery system for chronopharmacological disorders: An overview. Journal of Pharmacy Research, 2(1), 2009, 1-12.

5. Nayak UY, Shavi GV, Nayak Y, Averinen RK, Mutalik S, Reddy SM, Gupta PD, Udupa N. Chronotherapeutic drug delivery for early morning surge in blood pressure: A programmable delivery system. Journal of Controlled Release, 139, 2009, 125-131.
6. Khairuzzaman A, Ahmed SU, Savva M, Patel NK. Zero-order release of aspirin, theophylline and atenolol in water from novel methylcellulose glutarate matrix tablets. International Journal of Pharmaceutics, 318, 2006, 15-21.
7. Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled release dosage forms. International Journal of Pharmatech Production Manufacturing, 5, 1984, 1–9.
8. Deshapande Rhodes CT, Shah NH. Controlled release drug delivery systems for prolonged gastric residence: an overview. Drug Development and Industrial Pharmacy 22, 1996, 531–539.
9. Gil EC, Colarte AI, Bataille B, Pedraz JL, Rodriguez F, Heinamaki J. Development and optimization of a novel sustained release dextran tablet formulation for propranolol hydrochloride. International Journal of Pharmaceutics, 317, 2006, 32-39.
10. Valentine IC, Richard AK, Basit AW. Drug delivery to colon. The drug delivery company reports spring summer, 2004, 27-30.
11. Jain A, Jain SK. Perspective of biodegradable natural polysaccharides for site specific delivery to colon. Journal of Pharmacy & Pharmaceutical Sciences, 10(1), 2007, 86-128.
12. Rathod S, Ram A, Thiru G. Colon targeted pulsatile drug delivery: A review, Pharmainfo.net, 5(2), 2007, 1-8.
13. Singh BN. Modified-release formulations for colonic delivery. Recent patents on drug delivery and formulations, 1, 2007, 53-63.
14. Qureshi AI, Cohen RD. Mesalamine drug delivery: do they really make difference. Advanced drug delivery reviews, 57, 2005, 281-302.
15. Goyal A, Shukla P, Srivastava AK. Factors influencing drug release characteristics from hydrophilic polymer matrix tablets. Asian journal of pharmaceutical and clinical research, 2(1), 2009, 93-98.
16. Arora S, Ahuja A, Ali J, Baboota, Qureshi J. Pulsatile drug delivery system: An approach for controlled drug delivery. Indian Journal of Pharmaceutical Sciences, 68(3), 2006, 295-300.
17. Belgamwar VS, Gaikwad MV, Patil GB, Surana S. Pulsatile drug delivery systems. Asian Journal of Pharmaceutics, 2(3), 2008, 141-145.
18. Alsarra IA. Development of a stability-indicating HPLC method for the determination of Montelukast in tablets and human plasma and its applications to pharmacokinetic and stability studies**.** Saudi Pharmaceutical Journal, 12(4), 2004, 136-143.
19. Shoaib HM, Tazeen J, Merchant HA, Yousuf RI. Evaluation of drug release kinetics from Ibuprofen matrix tablets using HPMC. Pakistan Journal of Pharmaceutical Sciences, 19(2), 2006, 119-124.
20. Sung KC, Nixon PR, Skoug JW, Roburt JT, Gao P, Topp EM, Patel MV. Effects of formulation variables on drug and polymer release from HPMC based matrix tablets. International Journal of Pharmaceutics, 142, 1996, 53-60.

About Corresponding Author: **Mr. Surender Verma**

Mr. Surender Verma is currently working as Assistant Professor in the Deptt. of Pharmaceutics at the Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India. His main area of research includes, colon targeted drug delivery, optimization in floating and mouth dissolving drug delivery systems. He has eight national and international papers published in various journals.