WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 14, 1130-1151. Research Article ISSN 2277– 7105

FORMULATION, DEVELOPMENT AND EVALUATION OF CHRONOMODULATED DRUG DELIVERY SYSTEM OF MONTELUKAST SODIUM FOR THE TREATMENT OF NOCTURNAL ASTHMA

Kale Aparna*

Department of Pharmaceutical Chemistry, Matoshree Radha College of D. Pharmacy Akole.

Article Received on
20 Sept. 2020,

Revised on 10 October 2020,
Accepted on 30 October 2020

DOI: 10.20959/wjpr202014-19012

***Corresponding Author**
Kale Aparna
Department of Pharmaceutical Chemistry, Matoshree Radha College of D. Pharmacy Akole.

ABSTRACT

The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity. The main objective is to find out the circadian rhythm, that is, a suitable indicator that will trigger the release of the drug from the device. It can be concluded that oral chronotropic drugs help in various drug delivery problems such as extensive first pass metabolism, chronotropic behaviour of the diseases and nocturnal dosing thereby increasing the patient compliance and is the future of the drug delivery systems. The Objective of this study is to design and characterize chronomodulated drug delivery system containing Montelukast Sodium, which can be targeted to colon in a pH and time dependent manner, to modulate the drug level in synchrony with the circadian rhythm of nocturnal asthma patients. In the present research work, developed novel dosage forms by using chronopharmaceuticalapproach. this dosage form, taken at bedtime with a programmed start of drug release after 4 to 5 hours, can prevent the nocturnal asthma in patients.

KEYWORDS: Circadian rhythm, Chronomodulated, Time dependent drug delivery, Nocturnal asthma.

Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure.[1] Chronopharmacology is the science that considers the

variations in the pharmacological actions of various drugs over a period of time.[2] The review addresses the approaches to this sub-discipline, calls attention to potential disease-targets, and identifies existing technologies, hurdles and future of chropharmaceuticals. Chronopharmaceuticals coupled with nanotechnology could be the future of DDS, and lead to safer and more efficient disease therapy in the future.[3,4]

The Chronopharmaceutical Drug Delivery System (ChrDDS) has emerged during the last decade as a possible drug delivery system against several diseases, which may lead to the creation of a sub-disciple of pharmaceutics to be explored called 'chronopharmaceutics'.[5,6] Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches in real time the biological requirement of a given disease therapy.[7,8,9]

The main goal of chronotherapeutics is to match the timing of treatment with the intrinsic timing of illness.[10] Optimum therapy is given when the right amount of drug is delivered to the correct target organ at the most appropriate time. If symptoms of a disease are varied the circadian rhythms also varied the drug release.[11]

MATERIALS AND METHODS

The material were used is Montelucast sodium (SBP Pharma, pune), Hard gelatin capsule shells ARI Pharmatech (nashik), The all excipient of (Lobacheme) were used from laboratory. These are Starch (potato), Microcrystaline cellulose, Crosscarmellose sodium, Sodium alginate, Hydroxyl propyl methyl cellulose, Xanthum Gum, Eudragit S-100, Magnesium stearate, and Polyvinyl pyrollidone k 30, Formaldehyde, NaOH, Hcl, Potassium Permangnate, Ethanol (99.9%)s were used analytical grade. The equipment used were Tablet Dissolution Apparatus (Electrolab), Digital Weighing Balance (Schimadzu), Hot Air Oven (Digital) (Scientific), U V Spectrophotometer (Schimadzu), Mono Quartz Distillation Unit (Borosil), Spray Dryer (Labultima), Friabilator (Labin), Disintegration Test Apparatus (Electrolab), Extruder And Spheroniser (Cornimach), Hardness Tester (Pfizer), Mechanical Shaker (Pritec), FT-IR(Bruckner), Vernier Caliper Scale, Dissolution Test Apparatus (Electrolab), Stability Chamber (Thermolab).

Preformulation study

Preformulation studies were performed for the obtained sample of drug for identification and compatibility studies.

Identification and Characterization of drug

Organoleptic characteristics: The organoleptic characteristics of Montelukast Sodium such as color, odor, and taste were studied. Color of drug was found to be pale yellow. Drug was found to be slightly bitter in taste.

Melting point

Melting point of drug Montelukast Sodium was determined by capillary method. The temp at which drug goes in the liquid state was consider as a melting point of Montelukast Sodium. Practically it was found that drug get melts at135ºC. Reported melting point of the drug Montelukast Sodium is 135.5ºC.

FT-IR spectra

FT-IR spectra of Montelukast Sodium were taken on IR spectrophotometer by simply placing small amount of drug in powder form on selenium bromide crystal. FT-IR spectra of Montelukast Sodium was found as shown in fig 1.

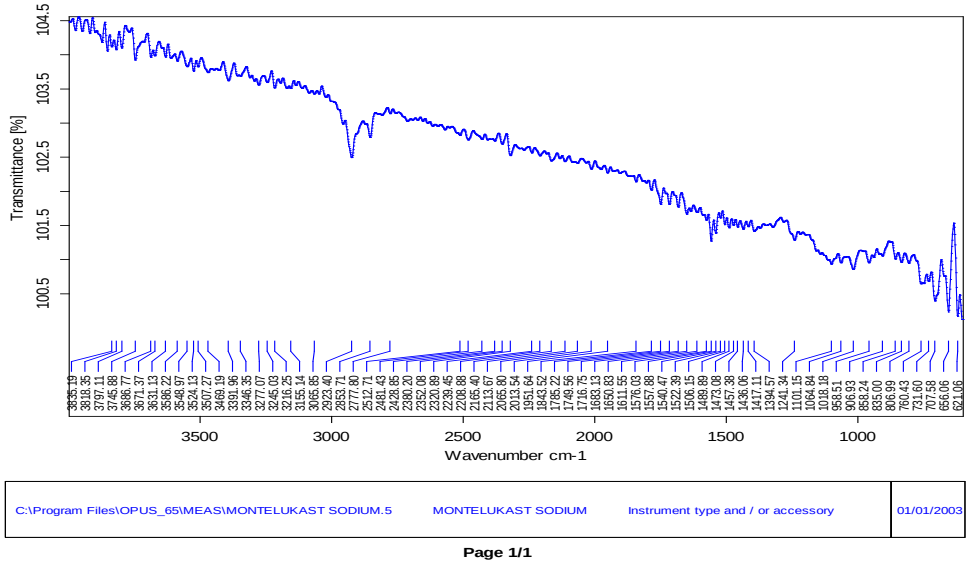

Fig. 1: IR Graph for montelukast sodium.

Differential scanning calorimetry (DSC)

The thermal curve of MKS showed no endothermic peak as shown in fig 2 which confirms that MKS is amorphous in nature. There was no extra peak appeared in thermogram of drug-polymer mixture which confirms no interaction or change in polymorphic nature of MKS. This is also confirmed by Fourier transform infrared (FTIR) spectroscopy study.[12,13,14,15]

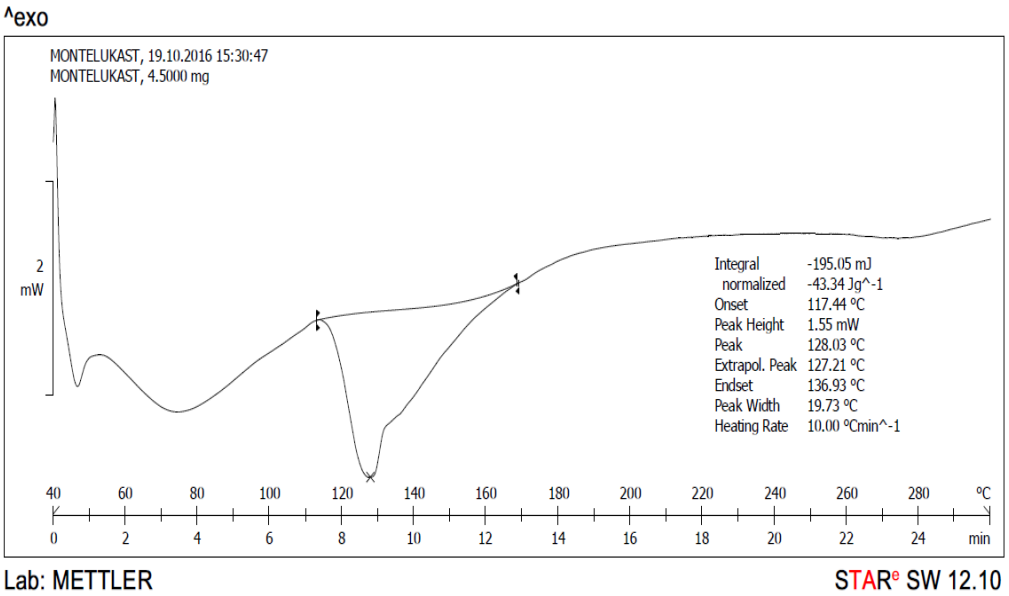

Fig. 2: Differential scanning calorimetry (DSC).

Drug-Excipients compatibility study

A compatibility study was carried out with potential formulation excipients to determine drug-excipients interaction. All the physical mixtures of drug and excipients in 1:1 ratio were kept under compatibility study for 14 days at 55°C in glass vials sealed. The physical mixtures was taken in same ratio as that of actual formulation ratio and were observed physically for:

- Caking,
- Liquefaction,
- Discoloration, and
- Odor or gas formation.

Physical observations for any change in appearance were recorded.[16]

Formulation and Development

Montelukast sodium core pellets

Pellets were prepared by using extrusion and speronisation technique. Drug Montelukast Sodium, spheronising agent Microcrystalline Cellulose, Crosscarmellose Sodium, Starch were mixed well to form uniform blend. PVP K30 solution (5%) was added slowly in a powder mixture to form dump mass. Then this dump mass were passed through the sieve no.20. Then extruded material was subjected to spheronization at different speed and time. Formula for montelukast sodium pellets given in Table 1.[17,18,19]

Table 1: Formulation of montelukast sodium core tablet.

Sr. no	Ingredients	Amount (% W/V)
1	Drug	10
2	Micro Crystalline Cellulose	40
3	Starch	45
4	Crosscarmellose sodium	5
5	Pvpk30 (5% W/V)	Q.S

The formulation trial were taken with combination of MCC and Cross carmellose Sodium. The pellets were made by extrusion and spheronisation method as given in Table 2. The pellets were formulated by using the factorial design. the batches were prepared F1-F9 as shown in Table 3.

Table 2: Process parameters for optimization of extrusion and spheronisation.

Speed For Spheronisation (RPM)	Time For Spheronisation (Minutes)
500	15
850	15
1600	10

Table 3: Formulation of factorial design batches from f1-f9.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Montelukast Sodium(mg)	10	10	10	10	10	10	10	10	10
MCC (mg)	30	30	30	40	40	40	50	50	50
Crosscarmellose Sodium (mg)	3	4	5	3	4	5	3	4	5
Starch (mg)	57	56	55	47	46	45	37	36	35
PVP K30 (5%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total Weight(mg)	100	100	100	100	100	100	100	100	100

Evaluation of montelukast sodium core pellets

The pellets were analyzed for the parameters such as bulk density, tapped density, compressibility index, Hausner's ratio and the drug content results were found to be within the limits.[20]

In-vitro % drug RELEASE sudy of drug pellets

From experimental trial batches it was concluded that the % cumulative drug release of the drug was upto a considerable time period of 1 hour' by Trial batches F8. As trial batch F8 showed drug release 96.99 near about 100% in 1hours, expectable drug release profile at different time interval as compared to other batches. So, Batch F8 considered as optimized batch for the further incorporation into chronomodulated capsule.[21] The fig 3 shows the drug release of batch F1-F5 and fig 4 shows the in vitro drug release of batch F6- F9 study.

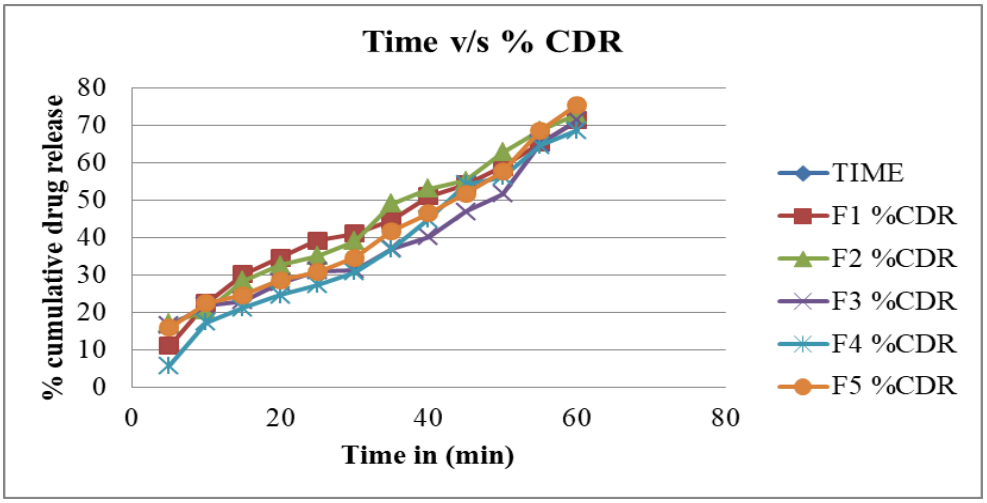

Fig. 3: *In-vitro%* drug released study of Pellet formulation F1-F5.

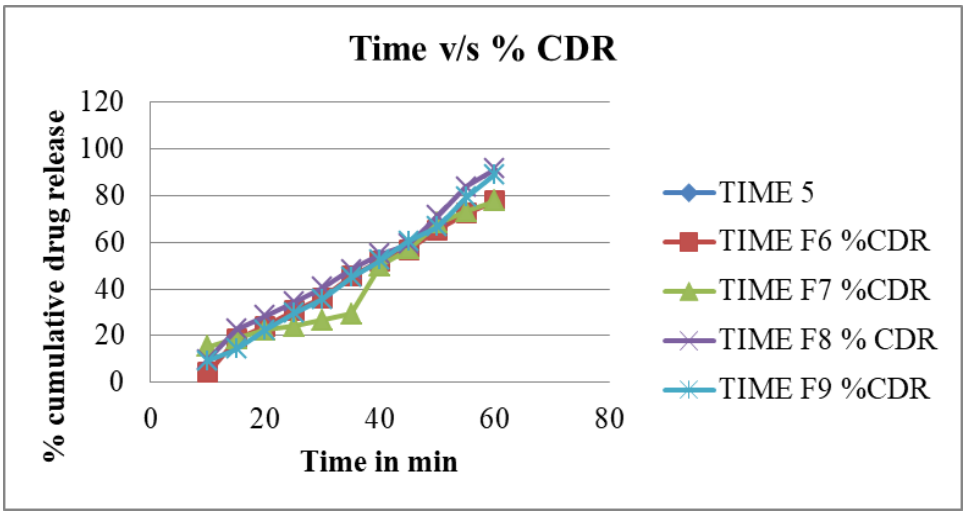

Fig. 4: *In-vitro%* drug released study of Pellet formulation F6-F9.

Formulation of hydrogel tablet plug

Direct compression method was used to prepare the erodible tablet plug. The compositions of different the erodible tablet plugs used were as shown in Table 4. The plug ingredients and Mannitol were mixed for 10 minutes. Magnesium stearate (2%) was added to the previous mixture and further blended for 5 minutes and compressed using rotary tablet press (Jaguar (JM-D-4-8) tablet machine by using 6mm punch.

Table 4: Composition of different hydrogel tablet plug of hpmc k4m and xanthum gum as lag time modifiers for the chronomodulated drug delivery systems of montelukast sodium.

	HPMC K4M (mg)	Xanthum Gum (mg)	Mannitol (mg)	Magnesium Stearate (%)	Total weight (mg)
HPT1	40	-	28	2	70
HPT2	50	-	28	2	80
HPT3	60	-	28	2	90
XGT1		40	28	2	70
XGT2		50	28	2	80
XGT3		60	28	2	90

Preparation of hydrogel tablet plug

Selection of plug material

Capsule containing the drug were then plugged with different hydrogel plugs of polymer at different concentration like Xanthum Gum and HPMC K4M.the lag time of Xanthum Gum and HPMC K4M shown in table no 5 as per result of plug opening time selected plug material HPMC K4M shows good plug opening time (4 to 4.5 h) which is suitable for the drug release. Xanthum Gum shows plug opening time 5.5 -6 hrs shown in table 6 which is not suitable due to higher plug opening or lag time. Therefore HPMC K4M selected as a plug material for design of pulsincap. HPMC K4M was selected as a plug material for the formulation of modified pulsincap dosage form plug was made by direct compression tablet machine using 6 mm tablet punch. HPMC K4M evaluated for the swelling index and flow properties.

Table 5: Plug opening time of hpmc k4m.

Material	Weight of Plug(Mg)	Plug opening time(Min)
HPMC K4-M	70	240
HPMC K4-M	80	270
HPMC K4-M	90	300

Table 6: Plug opening time of xanthum gum.

Material	Weight of plug (Mg)	Plug opening time (Min)
Xanthum Gum	70	330
Xanthum Gum	80	360
Xanthum Gum	90	390

Swelling index

Hydrogel plugs of HPMC K4M and Xanthum Gum were taken of weights 70mg, 80 mg and 90 mg and kept immersed in three different pH conditions. Plugs were taken out carefully at 2, 4,6 hours and their weights were determined accurately shown in Table 7 and graphical presentation of swelling index shown in fig 5.

Table 7: Swelling index of hpmc k4m.

Material	Swelling index(%)		
HPMC	pH 1.2	pH 6.8	pH7.4
K4-M	76%	80%	82%

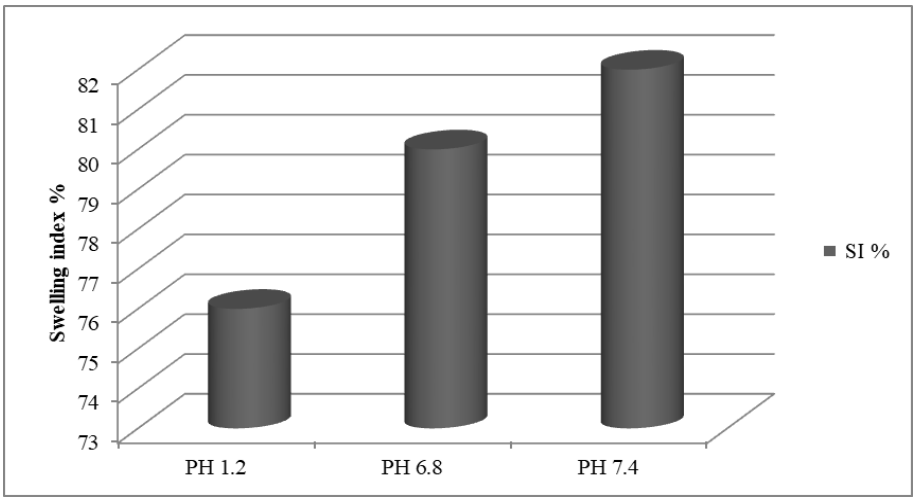

Fig. 5: Swelling Index of HPMC K4M In pH 1.4, pH 6.8, pH 7.4.

Physicochemical characterization of hydrogel plug

Hydrogel Plugs were studied for hardness, friability, weight variation and lag time. HPMC K4M selected for the plug material the flow properties of HPMC K4M shown in Table 8.[22,23,24]

Table 8: Flow properties of hpmc k4m.

Parameter	Result
Bulk Density(g/ml)	0.66
Tapped Density(g/ml)	0.76
Angle Of Repose	36.58
Carr's Index (%)	13.15(Good)
Hausner's Ratio	1.15(Good)

Formulation design

Preparation of crossed-linked gelatin capsule

Formaldehyde treatment

The '2' sized hard gelatin capsules (approximately 100 in number) were taken. The bodies of the capsules were then placed one wire mesh, which was kept in a desiccator. An aliquot of 25ml of 15% v/v formaldehyde was taken into a bottom of desiccator and a pinch of potassium permanganate was added to it to generate formalin vapours. The reaction was carried out for 12 hours. After which the bodies were removed and dried at 50° C for 30 minutes to ensure completion of reaction between gelatin and formaldehyde vapour. The bodies were dried at room temperature to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated caps and stored in a air tight container.[25,26,27]

Test for formaldehyde treated capsule

Physical test

Identification attributes

The size '2'capsules chosen were clear transperent body and cap. They were lockable type, odorless, soft and sticky when touched with wet hand. After treating with formaldehyde, there were no significant changes in the capsules except for the stickiness. The body of the capsule was hard and non-sticking even when touched with wet hand.[28,29]

Visual defects

Among 100 capsules body which were treated with formaldehyde, about 15 to 20 of them were found to be shrunk or distorted into different shapes due to the complete loss of moisture. Such bodies were discarded.[30]

Dimensions

Variation in dimension between formaldehyde treated and untreated capsules were studied before and after formaldehyde treatment, usingvernier caliper.

Solubility test for formaldehyde treated capsules

The empty hard gelatin capsule was stirred vigorously in 100ml of dissolutionmedium were taken in 250 ml beaker, with magnetic stirrer. The dissolution medium was1.2 pH, 6.8 pH and 7.4pH phosphate buffer. The time at which the capsule dissolves s forms a soft mass was noted.

Chemical test

Qualitative test for free formaldehyde

Standard formaldehyde solution

Dilute a suitable volume of formaldehyde solution with water to give a solution containing 20 µg/ml of formaldehyde. Sample solution 25 formaldehyde treated bodies were cut into small pieces and taken into a beaker containing distilled water (40 ml). This was stirred for 1hrs with a magnetic stirrer, to solubilize the free formaldehyde. The solution was filtered into a 50 ml volumetric flask, washed with distilled water and volume was made up to 50 ml with washings.

Procedure

To 1 ml of sample solution in a test tube, add 4 ml of water and 5 ml of acetyl acetone solution, place the test tube in a water bath at 40^{o}C for 40 min, at the same time reference solution is placed in the same manner using 1 ml of standard formaldehyde solution. The sample solution is not more intensely colored than the standard solution inferring that less than 20 µg/ml of free formaldehyde is present in 25 capsules body.[31,32,33]

Formulation of modified pulsincap drug delivery system

Formaldehyde treated hard gelatin capsules of 'size 2' were chosen for the formulation. The bodies and caps separated manually. Pellets of Montelukast Sodium 100 were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the Montelukast Sodium pellets were then plugged with different polymers like HPMC K4M, Xantham Gum at different concentrations viz. 70mg, 80mg and 90 mg. The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution. The treated capsules were completely coated with Eudragit S-100 to prevent variable gastric emptying. Coating was repeated until an 8-12% increase in weight obtained.% weight gain of the capsules before and after coating was determined. Dip coating method was followed to develop the pulsincap. The capsules were alternatively dipped in 5% CAP solution and dried. Coating was repeated until an expected weight gain 8-12% was obtained.[34,35,36,37,38]

Evaluation of modified pulsincap

Plug opening time

Plug opening time is the total time period after which the plug is ejected out of the capsule body and the drug releases immediately. Plug opening time was determined visually using

phosphate buffer pH7.4 in a 100 ml beaker. The plug opening time at different time interval were recorded. Results of preliminary trial formulations are showed in table 9. From the lag time determination study of the trial formulations, it was found that from all the formulations trial shows the plug opening time of about 4.5 hrs. The Graphical presentation of plug opening time shown in fig.6. Photographic images of plug opening time at different time points Shown in fig 7. From the plug opening time determination study it was observed that at 120 min entericcoatig of capsule will get removed and the cap of the capsule will get dissolved completely in pH 7.4 buffer. At different time interval capsule plug swells slowly. After 250 min it get swell completely and the formaldehyde treated capsule remain intact in the buffer solution.[39,40,41,42]

Table 9: Plug opening time of modified pulsincap by using selected concentration of eudragits-100 and hpmc k4m as a plug material.

Formulation Trial	Plug OpeningTime In pH 7.4(Min)
Trial 1	275
Trial 2	260
Trial 3	270
Trial 4	265

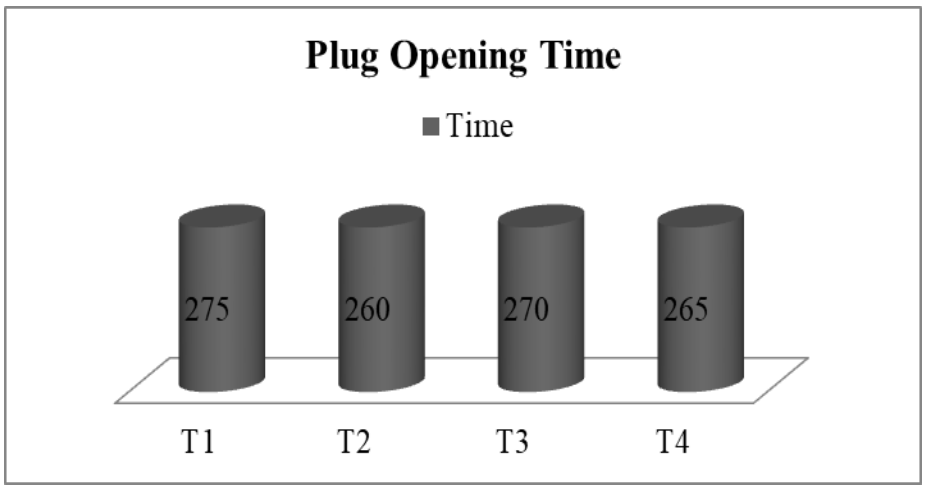

Fig. 6: Plug opening time of chronomodulated capsule.

At 30 Min	At 60 Min
	

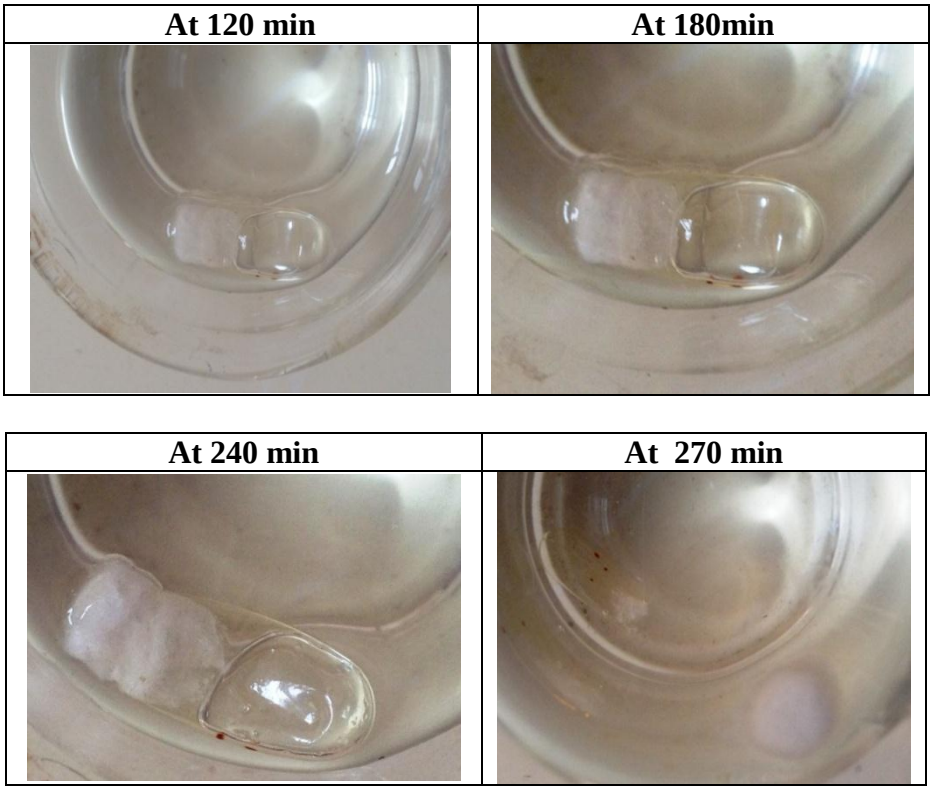

Fig.7: Photographic images of plug opening time at different time points.

Coating of modified pulsincap

A dipping method

The size "2" capsules were selected and then capsule were coated with 3% of EudragitS-100 solution using the dipping method. Coating was also done by using coating solutions oh 2,3,4,5% of Eudragit S-100 grades in concentration by dissolving Eudragit S-100 in acetone and isopropyl alcohol (1:1). Coated capsules were then air-dried overnight and kept aside for 1 day. The experiments were carried out in 100 ml beakers in an incubator shaker to maintain a speed of 100 rpm and temperature of 24^0C, using various pH mediums such as simulated gastric (pH 1.2) and intestinal pH6.8) fluids.

Thickness of eudragit S-100 Coating

The thickness of the Eudragit S-100coating was measured using Vernier Caliper. It was expressed in mm.

Disolution study of chronomodulated capsule

In vitro release profile of chronomodulated capsule dissolution studies were carried out by using USP II dissolution test apparatus (paddle method). Capsule was tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not

float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 6.8 and 7.4 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hours (since the average gastric emptying time is 2 hrs), then removed and the fresh pH 6.8 phosphate buffer saline (PBS) was added. After 3 hours (average small intestinal transit time is 3 hours), the medium was removed and colonic fluid pH 7.4 buffer was added for subsequent hours. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5^{o}C.10 milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 285 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.[43,44,45,46]

Formulation of chronomodulated drug delivery system

The basic design is based on the Pulsincap technology and consisted of formaldehyde treated insoluble hard gelatin capsule body filled with Montelukast Sodium and sealed with a hydrogel tablet plug of HPMC K4M. The entire device was enteric coated by Eudragit S-100, so as to prevent the variable gastric emptying time. The optimized formula of montelukast sodium pellets for incorporation into the capsule shown in table 10. Also the Composition Batch F1- F9 of chronomodulated drug delivery system filled of Montelukast Sodium pellets shown in table 11.In vitro % drug release study shown in Table 12. Dissolution study were taken of these batches and %CDR is givens as shown below in table 13.

Table 10: Optimized formula of montelukast sodium pellets for further incorporation into the capsule.

Sr. no.	Ingredients	Amount (% W/V)
1	Montelukast Sodium	10
2	Micro Crystalline Cellulose	50
3	Starch	36
4	Crosscarmellose Sodium	4
5	Pvpk 30 (5% W/V)	Q.S

Table 11: Composition of chronomodulated drug delivery system filled of montelukast sodium pellets.

Code	Weight of Empty Capsule (Mg)	Weight of Pellets (Mg)	Weight of Tablet Plug (Mg)	Total Weight of Capsule (Mg)	Weight After Enteric Coating (Mg)
F1	61.03	100	70.28	231.31	242.06
F2	61.07	100	70.56	231.63	241.12
F3	61.08	100	70.42	231.64	246.15
F4	61.01	100	70.54	231.55	245.21
F5	61.03	100	70.62	231.65	241.22
F6	61.05	100	70.30	231.35	244.23
F7	61.05	100	70.42	231.47	246.19
F8	61.07	100	70.38	231.45	243.18
F9	61.06	100	70.42	231.48	245.32

Table 12: *In-vitro* %drug release of various formulations of drug pellets.

Dissolution Time(Min)	%CDR of Pellet Formulation Batches F1-F9								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	11.09	17.27	16.54	5.81	16	4.18	15.45	9.81	9.27
10	22.48	20.54	21.81	17.33	22.53	18.40	18.70	22.82	14.28
15	30.24	28.58	23.13	21.27	24.60	24.20	22.56	28.60	22.51
20	34.69	32.67	27.88	24.59	28.65	30.80	24.05	34.49	29.51
25	39.27	35.07	31.02	27.35	30.85	36.33	26.80	40.73	35.59
30	41.14	39.10	31.42	30.83	34.69	45.48	29.38	48.44	44.92
35	44.62	49.14	37.15	36.87	41.82	51.94	49.94	54.88	52.29
40	51.02	53.07	40.21	44.94	46.45	56.74	57.08	59.13	60.56
45	54.18	55.29	46.97	54.29	51.77	65.33	68.07	71.36	66.47
50	58.94	62.78	51.60	56.59	57.65	72.34	73.10	83.67	79.26
55	65.36	68.68	65.28	64.61	68.62	77.68	77.69	91.45	89.04
60	71.43	72.92	71.43	68.70	72.55	88.65	89.02	96.99	91.68

Table 13: In vitro %drug release of f1 to f9 formulation of chronomodulated capsule device.

Dissolution Time(Min)	%CDR of Formulation Batches F1-F9								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
30	8.15	9.52	7.89	9.23	7.56	4.23	8.45	8.21	6.67
60	8.30	9.62	9.21	10.96	8.96	9.36	18.70	10.20	8.16
90	9.41	10.21	10.98	11.20	9.23	13.56	12.56	13.21	11.15
120	11.21	11.23	12.65	11.65	11.58	13.86	13.05	16.9	12.93
150	14.16	12.62	15.27	12.36	16.32	15.36	16.82	20.00	14.74
180	14.89	13.62	16.78	14.75	16.95	15.48	26.98	21.10	14.93
210	15.36	15.69	20.36	25.63	17.63	16.94	19.94	23.70	15.45
240	60.12	65.32	74.20	60.23	60.45	56.74	74.08	75.20	70.91
270	74.20	81.23	84.23	75.49	81.77	85.33	89.07	88.11	90.83
300	89.20	90.20	91.58	88.56	95.65	94.34	93.10	98.20	96.41

Drug release kinetic study

The in vitro drug release study (% CDR) of final formulation of chronomodulated capsule shown in fig 8 and fig. 9.

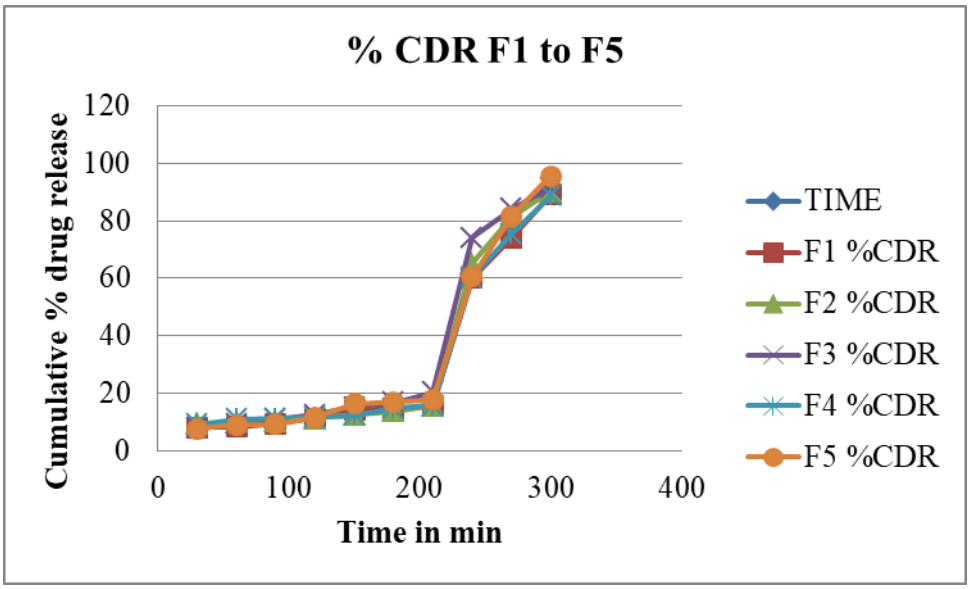

Fig. 8: *In-vitro%* drug released study of capsule formulation F1-F5.

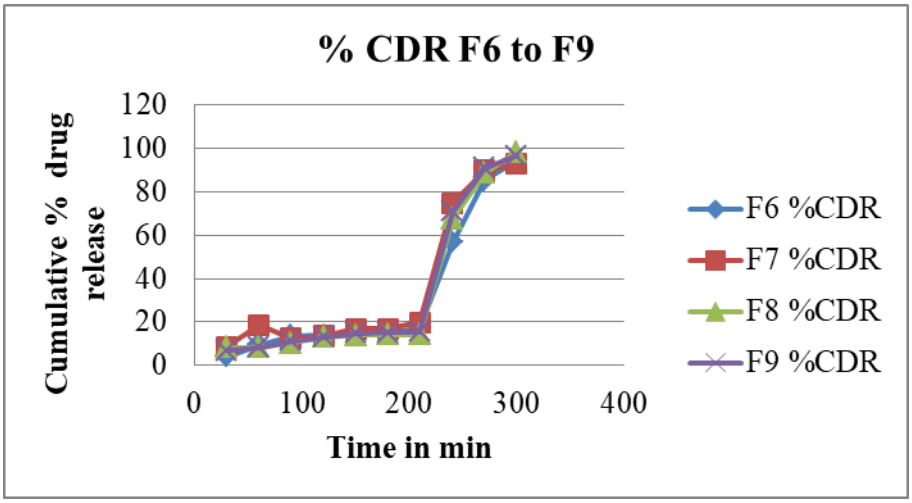

Fig. 9: *In-vitro%* drug released study of capsule formulation F6-F9.

Drug release kinetics study: Drug release kinetic study were studied by zero order, first order, higuchi model, and corsemayer peppas model as shown in fig 10,11,12,13 respectively. In the present study, the drug release was analyzed by PCP Disso Version 3 software to study the kinetics of drug release mechanism. Putting all data (Table 14) in different release kinetics models and comparing the coefficient of determination (R^2), it was found that the release data Zero order model have higher (0.793) correlation coefficient so this was considered to be the best model.[47]

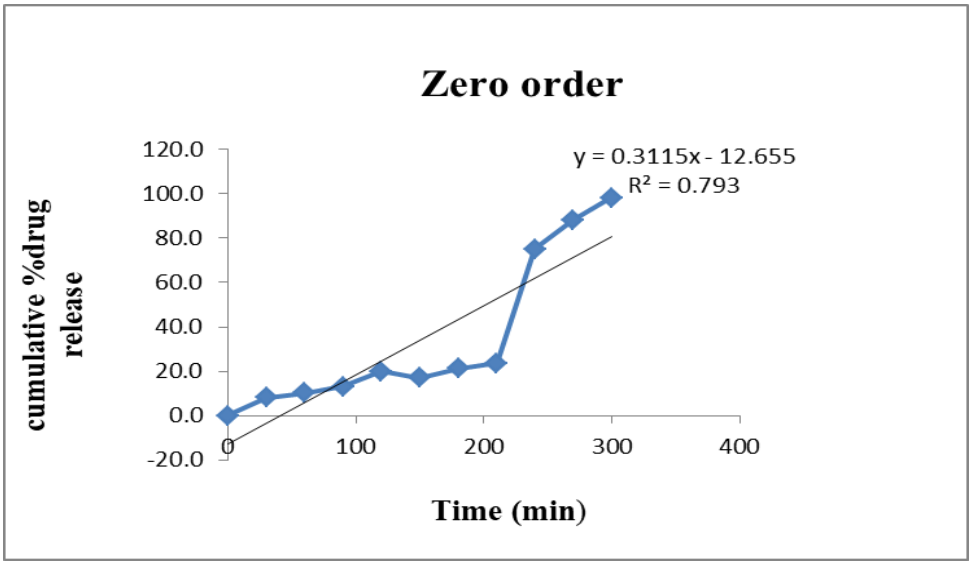

Fig. 10: Graphs of drug release zero order kinetic models.

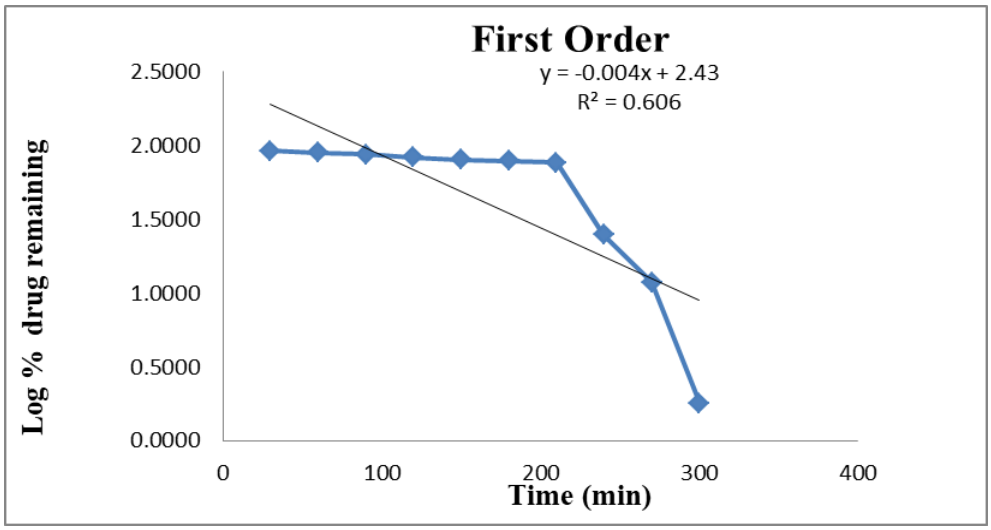

Fig. 11: Graphs of drug release first order kinetic models.

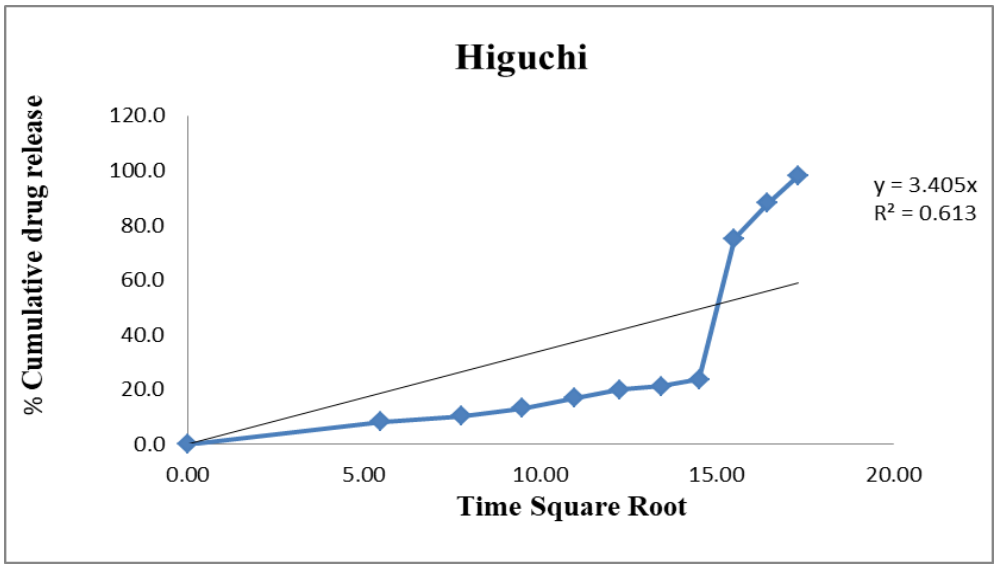

Fig. 12: Graphs of drug release kinetic higuchi model.

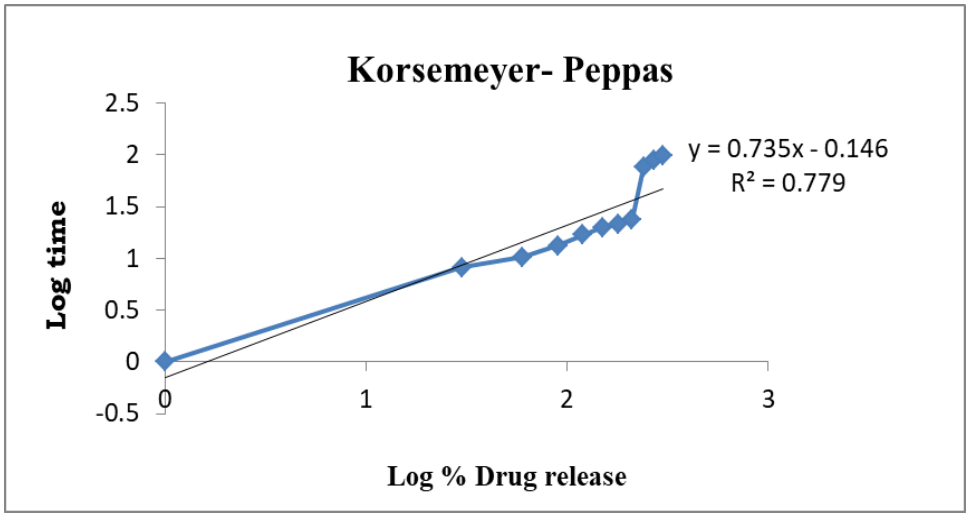

Fig. 13: Graphs of drug release kinetic korr peppas semay model.

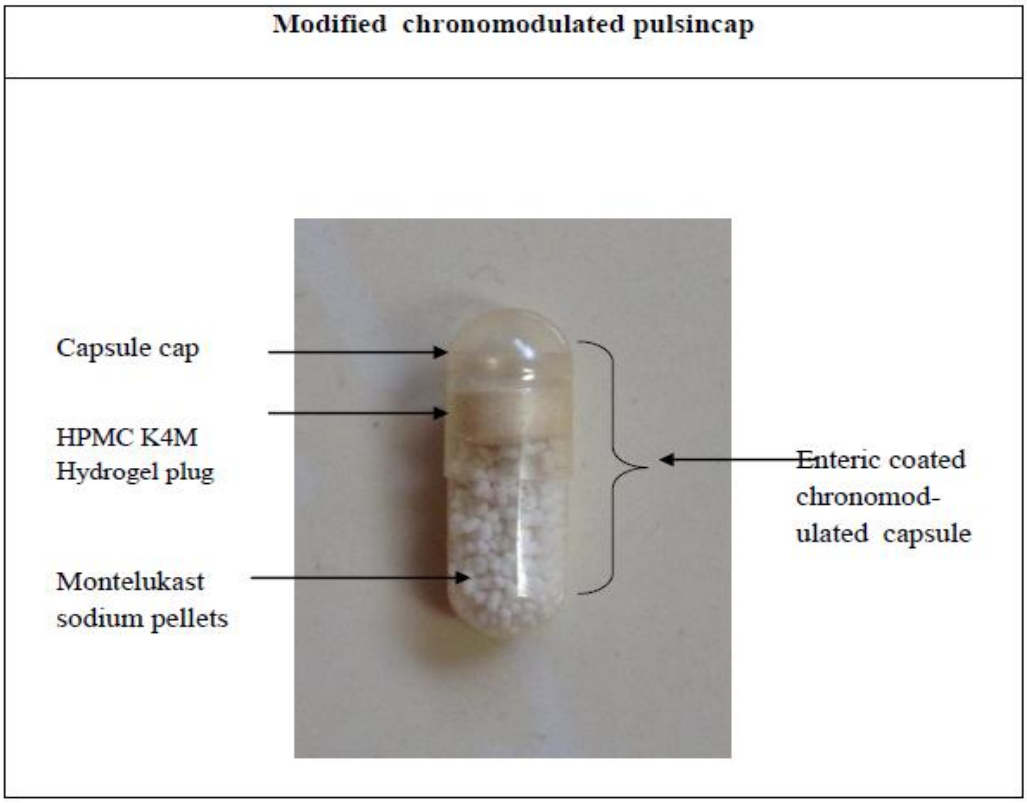

Fig. 14: Photographic image of modified chronomodulated capsule device.

Table 14: kinetic model value.

Model	R^2
Zero order	0.793
First order	0.606
Higuchi Model	0.613
Korsmayer peppas model	0.779

RESULT AND DISCUSSION

The present study was aimed at exploring the feasibility of time and chronomodulated drug delivery system of Montelukast sodium to modulate the drug level in synchrony with the circadian rhythm of nocturnal asthma. The Preformulation studies like melting point, Diffrential Scannig Colorometry and UV-analysis of Montelukast sodium were found to comply with official standards. The FTIR Spectra revealed that there was no interaction between the polymers and drug. The solubility studies of empty gelatin capsule bodies, which were cross linked with formaldehyde treatment, revealed that they are intact for 24 hrs, and hence suitable for colon targeting. The pellets prepared by the Extrusion and Spheronisation process at the speed 1600 rpm at the time 10 minutes. The in-vitro drug release of drug pellets were carried out in 1.2, 6.8,7.4 pH for 1 hour. The hydrogel plug is prepared by using polymer like HPMC K4M.it can be used to delay the release until the formulation reaches the colon and thereafter its release in the colon. Formaldehyde treatment given to the chronomodulated capsule to make impermeable and the solubility study of capsule carried out. it shows that the capsule remain intact for 24 hrs. The plug opening time of formaldehyde treated capsule is carried out in 7.4 buffer solution at different time interval. These capsule were enteric coated by 3% Eudragit S-100 to avoid variable gastric emptying time. The drug release of capsule was carried out in 1.2, 6.8,7.4 pH for 5 hour it shows drug release upto 98.20%. Thus in the present study, it was proved that the novel chronomodulated technology could be most ideal to modulate the drug level in synchrony with the circadian rhythm of Nocturnal asthma and this technique was far more superior than the available conventional dosage form of Montelukast Sodium in terms of patient compliance, efficiency, simplicity, reproducibility and easy scale-up.

ACKNOWLEDGEMENTS

I sincerely acknowledge Amrutvahini college of pharmacy, Sangamner for providing all the facility and environment to work. i would also like to thank SBP Pharma, pune for providing montelukast sodium drug and, ARI Pharmatech (nashik) for providing hard gelatin capsule shells.i would also like to thank matoshree radha college of D pharmacy, Akole. for providing technical facility.

REFERENCES

1. Pavol Š. Introductory Chapter: Chronobiology - The Science of Biological Time Structure, Chronobiology - The Science of Biological Time Structure, 2018.

2. Robert D, Steven AB, Frederic G. Chronopharmacology: New Insights and Therapeutic Implications. Annu Rev Pharmacol Toxicol, 2014; 6: 1-25.
3. Mullaicharam B.A Review on Chronopharmaceutical Drug Delivery System Sci, 2013; 4(3): 200-209.
4. Anil KP, Betty P. Chronopharmaceuticals: Hype or Future of Pharmaceutics .Curr Pharm Des, 2011; 17(15): 1512-6.
5. Bi-Botti CY.Chronopharmaceutical Drug Delivery Systems: Hurdles, Hype or Hope? Adv Drug Deliv Rev, 2010; 62(9-10): 898–903.
6. Mullaicharam AR. A Review On Chronopharmaceutical Drug Delivery System Research J of Pharmaceutical, Biological and Chemical Sci, 2013; 4(3): 200-210.
7. Neeraj S, Nisha, Vivek G, Parina G, Sukhbir S. Chronopharmaceutical Drug Delivery System-A Guided Therapy.Res J Pharm. App Sci., 2013; 3(4): 84-87.
8. Sunitha MR, Neerudu SR, Muhammad FH, Chronopharmaceutical Drug Delivery Systems: Present Scenario. J of Pharmacy Res, 2012; 5(9): 4840-4844.
9. Subhashis D, Vijay GK, Debarshi D, Swetha D, Niranjan BM. Chronopharmaceutics as A Novel Approach for Clinically Relevant Drug Delivery System. Res J of Pharmaceutical Dosage Forms and Tech, 2012; 4(6): 309-317.
10. Amitha S,Selvam T.Review On Chronotherapy :A Review on Novel Drug Delivery System.J Pharm Sci Bioscientific Res, 2016; 6(5): 646-653.
11. Sunny B, Bhushan K, Sachin M. Oral Chronotherapeutics: Future of Drug Delivery Systems Int J of Scientific Study, 2014; 2(4).
12. L. Lachman H. Liberman, The Theory And Practice of Industrial Pharmacy, Cbs Publishers And Distributors, Special Indian Edition, 2009; 171-195.
13. M. Aulton, Pharmaceutics: The Science of Dosage Form Design, Churchill Livingstone, 2: 113-137.
14. Indian Pharmacopoeia Six Edition, Ministry of Health and Family Welfare, The Indian Pharmacopeia Commission, Ghaziabad, 2010; 162,170.
15. Indian Pharmacopoeia Six Edition, Ministry of Health and Family Welfare, The Indian Pharmacopeia Commission, Ghaziabad, 2010; 1704.
16. Srilakshmi N, Rani PS, Das AD, Formulation Development and Evaluation of Press Coated Tablets of Montelukast Sodium. Int J of Advance Pharm Biotech, 2015; 1: 45-55.
17. Muley S, Nandgude T, Poddar S, Extrusion–Spheronization A Promising Pelletization Technique: In-Depth Review, Asian J of Pharm Sci, 2016: 684–699.

18. Srilakshmi N, Rani PS, Das AD, Formulation Development and Evaluation of Press Coated Tablets of Montelukast Sodium. Int J of Advance Pharm Biotech, 2015; 1: 45-55.
19. Mohd AH, Srinivasa AR, Abhinetri V, Avula Hariom PR. Design and In-Vitro Evaluation of Multiparticulate Drug Delivery System of Terbutaline Sulphate for The Treatment of Nocturnal Asthma Department of Pharmaceutics, Der Pharmacia Lettre, 2012: 4(6): 1777-1785.
20. Amit MG, Umesh D, Shivhare BS. Different Aspects of Pellets Formulation and Their Evaluation. Int J of Pharmaceutical and Phytopharmacol Res, 2015; 4(6): 331-336.
21. Nikolett K, Oliver L, Judit D, Kristóf K, Miléna L, István A. Evaluation of Drug Release From Coated Pellets Based on Isomalt, Sugar, And Microcrystalline Cellulose. Inert Cores, 2010; 11(1): 383–391.
22. Amit B, Chowdary KPR, Shobharani RH, Lakshmi NB. Formulation and Evaluation of Chronopharmaceutical Drug Delivery of Theophylline For Nocturnal Asthma. Int J Pharm Pharm Sci, 2011; 3(2): 183-185.
23. Gangane PS, Mahajan NM, Mahajan UN, Shende MV, Pawde GN. Formulation and Evaluation of Chronomodulated Pulsincap Therapeutic System For Early Morning Surge In Blood Pressure.Indian J of Novel Drug Delivery, 2016; 8(4): 225-230.
24. Pandey JK, Indira MY, Misra G. Preparation and Evaluation of Pulsatile Drug Delivery of Lovastatin. Int. J. Pharm Sci Rev Res, 2015; 32(1): 182-187.
25. Ofner CM, Zhang YE, Jobeck VC, Bowman BJ. Crosslinking Studies in Gelatin Capsules Treated with Formaldehyde and In Capsules Exposed to Elevated Temperature and Humidity. J Pharm Sci, 2001; 90(1): 79-88.
26. Parepalli S. Hemalatha, Venkata S, Suggala S. Formulation Development and In-Vivo Radiographic Studies of Diltiazem Hydrochloride Loaded Floating Capsules Prepared by Modified Pulsincap Technology. Int J Pharmaceutical Sci Res, 2019; 10(5): 2550-2564.
27. Rama KM, Prameela RV. Design and Characterization of Pulsatile Drug Delivery of Budesonide .Int J of Pharm, Chemical and Biological Sci, 2017; 7(3): 240-246.
28. Omkar AP, Indrajeet SP, Vishal VB, Dheeraj SR, Mangesh AB, Somnath DB. Formulation and Evaluation of Valsartan Pulsincap Drug Delivery System for Treatment of Hypertension. Asian J of Pharmacy and Tech, 2018; 8(2): 65-70.
29. Sai KV, Narasimha RN, Mahalakshmi GS. Design and Development of Press Coated Prasugrel Hydrochloride Tablets for Pulsatile Drug Delivery System. Res J of Pharm, Biological and Chemical Sci, 2014; 5(1): 1056-1064.

30. Sreejan M, Krishnaveni V, Sai PK, Satyavathi K, Bhojaraju P, Madhubabu. Design and Evaluation of Chronotherapeutic Delivery of Terbutaline Sulphate by Pulsincap Technology. Int J of Drug Delivery Tech, 2017; 7(1): 75-82.
31. Indrajeet SP, Omkar AP, Girish Chandra RM, Manoj MN. Development and Evaluation of Telmisartan Pulsatile Drug Delivery By Using Response Surface Methodology Asian J. Phar Res, 2018; 8(4): 205-214.
32. Vipul P P, Moinuddin M. Soniwala. Studies on Pulsincap Formulation of Aceclofenac and Serratiopeptidase for Treatment of Inflammatory Disorders. J of Chemical and Pharmaceutical Res, 2015; 7(12): 750-762.
33. Chandra S.Formulation and Evaluation of Atorvastatin as Pulsatile Drug Delivery System by Using Pulsincap. Tech J. Pharm. Sci. & Res, 2019; 11(8): 2820-2826.
34. Madhuri A, Anusha, Vaidehi D. Formulation and Evaluation of Chronomodulated Drug Delivery of Montelukast Sodium. Glob J Pharmaceu Sci, 2017; 1(1): 1-8.
35. Sokar M, Hanafy A, Elkamel A, El-Gama S. Design of Chronomodulated Drug Delivery System of Valsartan: In Vitro Characterization Ind J Pharm Sci, 2015; 77(4): 470-477.
36. Mohd JQ, Javed A, Sanjula B, Alka A,Chitneni M. Chronomodulated Drug Delivery System of Salbutamol Sulphate For The Treatment of Nocturnal Asthma. Trop J of Pharm Res, 2014; 13(1): 17-22.
37. Piyush P, Dinesh P, Anil B, Deepak C, Rambabu S, Vivek B. Formulation and Evaluation of Chronomodulated Floating Drug Delivery System of Famotidine. Ind Pharm Sci, 2011; 36: 167-180.
38. Sona S. Chaudhary, Hetal K. Patel, Punit B. Parejiya, And Pragna K. Shelat Chronomodulated Drug Delivery System Of Urapidil For The Treatment Of Hypertension Int J Pharm Investig, 2015; 5(2): 107–113.
39. Manjula BV, Divyasri CH, Shravya CH, Maniteja Y. Formulation and Evaluation of Pulsatile Drug Delivery System of Lisinoprel.J of Drug Delivery and Therapeutics, 2019; 9(2): 76-82.
40. Mathew P, Jacob BM: Development and Evaluation of Chronomodulated Pulsincap Drug Delivery System of Ketoprofen. Int J Pharm Sci Res, 2018; 9(4): 1462-77.
41. Jitendra KP, Indira MY, Gitanjali M.Preparation and Evaluation of Pulsatile Drug Delivery of Fluvastatin Sodium. Asian J Pharm Clin Res, 2016; 2(9): 348-35.
42. Gayatri CP, Madhabhai MP. Developing a Modified Pulsincap System. Pharm Tech Europe, 2009; 21(11).

43. Kalyani VKB, Murthy TEGK. Formulation and Evaluation of Modified Pulsincap Drug Delivery System for Chronotherapeutic Delivery of Montelukast Sodium. Res. J. Pharm. Dosage Form. and Tech, 2014; 6(4): 225-229.
44. Swati CJ, Pravin SP, Gajanan JC.Formulation and Evaluation of Modified Pulsincap Drug Delivery System of Rizatriptan Benzoate. Int J Pharm Pharm Sci, (6)5: 48-52.
45. Dasharath MP, Rushiraj HJ, Chhagan NP.Design and Evaluation of Colon Targeted Modified Pulsincap Delivery of 5-Fluorouracil According to Circadian Rhythm Int J Pharm Investig, 2011; 1(3): 172–181.
46. Tarun G, Arsh C, Ankit G, Neetu K, Govind S. Pulsatile Drug Delivery Systems: Pulsincap System. J of Pharm, 2012; 2(2): 338-339.