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FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF MONTELUKAST

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ABSTRACT

Aim of the present work was to formulate and evaluate an oral pulsatile drug delivery system to achieve timed release of Montelukast, based on Chronopharmaceutical approach for the treatment of Asthma. Pulsatile drug delivery system is capable of delivering drug when and where it required most. Time-delayed tablets, designed to release drug after a predictable lag time, are intended for oral chronotherapy. The basic design consists of a core tablets prepared by direct compression method. The tablets were coated with an swellable layer containing Metolose, Karaya gum. The prepared pulsatile tablets were evaluated for the drug content, thickness and *in-vitro* release profile, etc. *In-vitro* release profiles of pulsatile device during six hours studies were found to have very good sustaining efficacy. During the first five hours it shows minimum drug release and at the end of six hours immediate release was observed. Increasing the level of the rupturable layer increased mechanical strength and retarded the water uptake and thus prolonged the lag time. Stability studies proved that coating of tablets seems to decrease the effect of temperature and moisture on the degradation of montelukast. The programmable pulsatile release has been achieved from tablet over a 7-8 hr period, consistent with the demands of chronotherapeutic drug delivery.

KEYWORDS: Pulsatile drug delivery system; Montelukast, Sodium starch glycolate, Ludiflash, Crosscarmellose sodium, Metolose, and Karaya gum.

INTRODUCTION

A pulsatile dosage form, taken at bed time with a programmed start of drug release in the early morning hours, can prevent this. By timing drug administration, plasma peak is obtained, at an optimal time. Number of doses per day can be reduced. When there are no symptoms there is no need of drugs. Saturable first pass metabolism and tolerance development can also be avoided.[1]

PULSATILE DRUG DELIVERY SYSTEMS[2,3]

In this century, the pharmaceutical industry is caught between pressure to keep prices down and the increasing cost of successful drug discovery and development. In the form of an NDDS or Chronic DDS, an existing drug molecule can "get a new life" thereby increasing its market value and competitiveness and extending patent life.

Among modified- release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsative) and site-specific delivery of drugs.[4] In particular, systems for delayed release are meant to deliver the active principle after a programmed time period following administration[5] These systems constitute a relatively new class of devices the importance of which is especially connected with the recent advances in chronopharmacology[6,7] It is by now well-known that the symptomatology of a large number of pathologies as well as the pharmacokinetics and pharmacodynamics of several drugs follow temporal rhythms, often resulting in circadian variations. Therefore, the possibility of exploiting delayed release to perform Chronotherapy is quite appealing for those diseases, the symptoms of which occur mainly at night time or in the early morning, such as bronchial asthma, angina pectoris and rheumatoid arthritis. The delay in the onset of release has so far mainly been achieved through osmotic mechanisms, hydrophilic or hydrophobic layers, coating a drug- loaded core and swellable or erodible plugs sealing a drug containing insoluble capsule body.[20]

Delivery systems with a pulsatile pattern are receiving increasing interest for the development of dosage forms, because conventional systems with a continuous release are not ideal. Most conventional oral controlled release drug delivery systems release the drug with constant or variable release rates. A pulsatile release profile is characterized by time period of no release (lag time) followed by a rapid and complete release.

MATERIALS[8]

Montelukast (Dr. Reddy's), Ludiflash(Narmada fine chemicals), Crosscarmellose sodium(Narmada fine chemicals), Sodium starch glycolate(Narmada fine chemicals), MCC(Narmada fine chemicals), Talc(Narmada fine chemicals), Magnesium stearate(Narmada fine chemicals), Metolose(Narmada fine chemicals), Karaya gum(Narmada fine chemicals).

Formulation of Compressed Tablets of Montelukast

The methodology adopted includes:

1) Preparation of core tablets of Montelukast.

2) Coating of the core tablets.

1. Formulation of core tablet of Montelukast[9]

Table 1: Formulation of core tablet of Montelukast.

Material	F1	F2	F3	F4	F5	F6	F7	F8	F9
MONTELUKAST (mg)	10	10	10	10	10	10	10	10	10
Ludiflash (mg)	3	5	7	-	-	-	-	-	-
SSG(mg)	-	-	-	3	5	7	-	-	-
CCS (mg)		-	-	-		-	3	5	7
MCC (mg)	75	73	71	75	73	71	**75**	73	71
Talc (mg)	4	4	4	4	4	4	4	4	4
Magnesium stearate(mg)	6	6	6	6	6	6	6	6	6

The inner core tablets were prepared by using direct compression method as per the developed formulation table which was shown above. Accurately weighed amounts of Montelukast sodium, MCC, Ludiflash, Crosscarmellose sodium, Sodium starch glycolate, talc were dry blended for about 15min followed by addition of magnesium stearate. The mixture was then further blended for 10 min. Now the resultant powder blend was manually compressed using punching machine and finally the core tablet was obtained.

Formulation of Compression Coated Tablets of Montelukast.[10]

Table 2: Composition of compression coated tablets.

Formulation	P1F6	P2F6	P3F6	P4F6	P5F6	P6F6
Core tablet	100	100	100	100	100	100
Metolose	400	-	200	125	150	250
Karaya gum	-	400	200	275	250	150
Total weight	500	500	500	500	500	500

The optimized core tablets were coated with coating ingredients like metolose, karaya gum. Now accurately weighed amount of barrier layer material was transferred into a 16 mm die then the core tablet was placed manually at the center. The remaining amount of the barrier layer material was added into the die and compressed. Compression of tablets wsa done in rotary compression tablet machine using 16.4X8mm flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties.

Evaluation of Preformulation Parameters[12]

1. Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Where, h and r are the height and radius of the powder cone respectively.

Table 3: Angle of repose value - flow significance.

S. No.	Angle of repose(θ)	Type of flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

2. Determination of Bulk density and Tapped density

20 g of the granules (W) from each formula were introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 Sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulae.

Bulk density = W / V_O

Tapped density = W / V_F

Where, W = weight of the granules, V_O = initial volume of the granules, V_F = final volume of the granules after tapping.

3. Hausner's Ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density/Bulk density.

Table 4: Hausner's Ratio - flow significance.

Sr. No.	Hausner's Ratio	Property
1.	0-1.2	Free flowing
2.	1.2-1.6	Cohesive powder

4. Compressibility index (Carr's Index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.

$$CI = \frac{(Tapped\ Density - Bulk\ Density)}{Tapped\ Density} \times 100$$

Table 5: Carr's index value - flow significance.

Sr. No	Carr's Index	Properties
1	5-12	Free flowing
2	12-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Evaluation of Core tablet[13]

1. Weight variation

20 tablets weighed individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the Table given below.

Table 6: USP Wt. variation test limits.

Sr. No.	Average weight of tablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	>324	5

2. Tablet hardness

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2.5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

3. Friability

20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

% Friability = $$\frac{Initial\ weight\ of\ tablet - Final\ weight\ of\ tablets}{Initial\ weight\ of\ tablet} x100$$

4. Tablet thickness

Thickness was measured using digital Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.

5. Content Uniformity

At random 20 tablets were weighed and powdered. The powder equivalent to 10 mg of drug was weighed accurately and dissolved in 100ml of buffer used. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whattman's filter paper No.41. Then the serial dilutions were carried out. The absorbance of the diluted solution was measured at 286 nm. The concentration of the drug was computed from the standard curve of the Montelukast in 6.8 phosphate buffer.

6. Disintigration time

The test for disintegration was carried out in Electrolab USP disintegration test apparatus. The time taken for the complete disintegration of the 6 tablets was noted and average disintigration time was calculated.

7. In-vitro Dissolution studies

In-vitro dissolution study of core and coated tablets of Montelukast was carried out using Electrolab TDT-08L USP dissolution test apparatus. 6.8 phosphate buffer solution was used as dissolution medium. The apparatus was set at 50 rpm and $37^0c \pm 0.2^0$. 5 ml of sample was withdrawn for required time intervals. Samples withdrawn for 1hr. at 5 min. time interval were analyzed by UV spectrophotometer using buffer solution as blank.

EVALUATION OF PULSATILE DRUG DELIVERY SYSTEMS[16]

1. Test for thickness

Thickness of coated Montelukast tablet formulations was determined by using digital Vernier calipers. 3 tablets of each type of coated formulation were determined for thickness and average thickness of the formulation was determined. Similarly the thickness of the coating on the formulation was determined by deducting the thickness of core tablets from thickness of the coated formulation.

2. *In-vitro* Dissolution studies

Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50 rpm and 37±0.5°C has usually been conducted in different buffers for different periods of time. The ability of the coats/carriers to remain intact in the physiological environment of the stomach and small intestine is generally assessed by conducting drug release studies in 0.1N HCL for 2 hours (mean gastric emptying time) and in pH 6.8 phosphate buffer for remaining hours (mean small intestinal transit time) using USP dissolution test apparatus. The samples were withdrawn at regular intervals and analyzed by UV Spectrophotometer (Shimadzu UV/Vis 1800). Dissolution tests were performed in triplicate.

3. Stability Studies

The formulation of optimized was selected for the study and formulations were packed in amber-colored bottles tightly plugged with cotton and capped. They were exposed to 40ºC temp and 75% RH for 30 days. At regular intervals, the tablets were taken in 100 ml of pH 6.8 buffer and were shaken for 1 hr. The resultant solutions were filtered, properly diluted and estimated spectrophotometrically by keeping pH 6.8 buffer as blank. % drug remained undecomposed was checked for both core and coated tablets.

RESULTS AND DISCUSSION

1. UVSpectral analysis of Montelukast

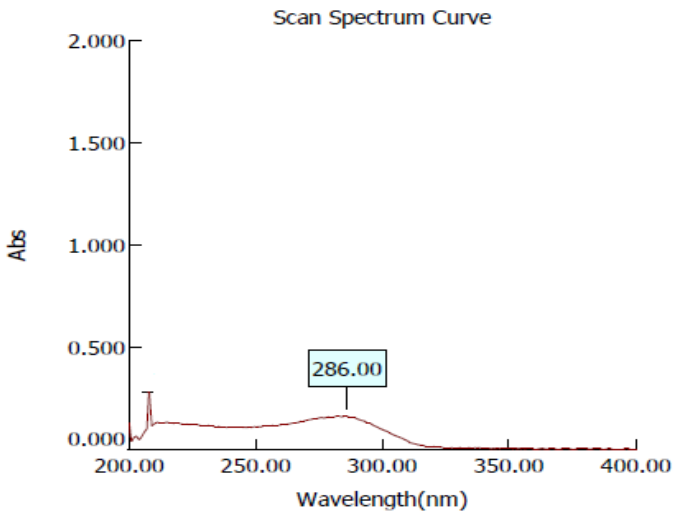

Fig. No. 1: UV Spectrum of Montelukast.

2. Calibration curve of Montelukast in pH 1.2 &pH 6.8 buffer solution

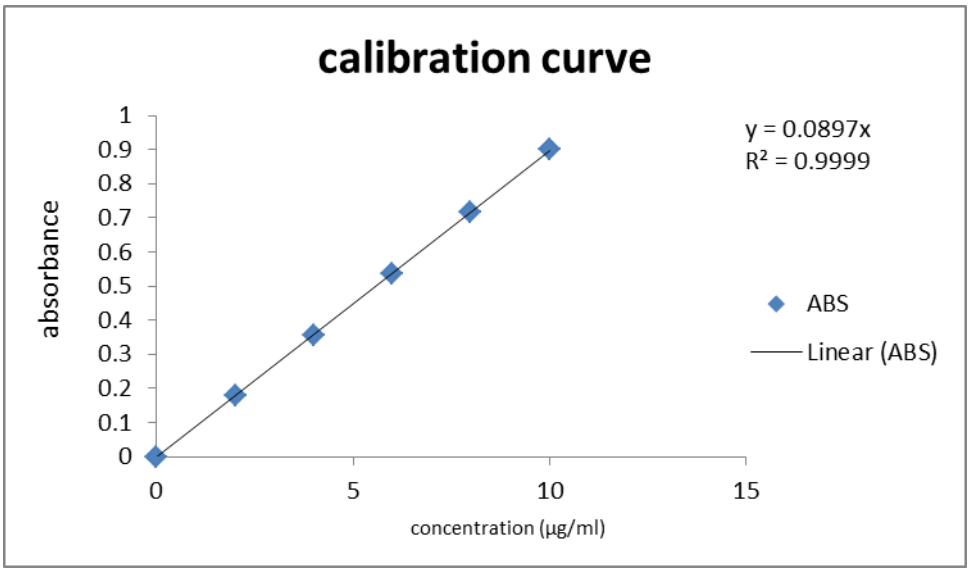

Figure 2: Calibration curve of Montelukast in pH 1.2 buffer solution

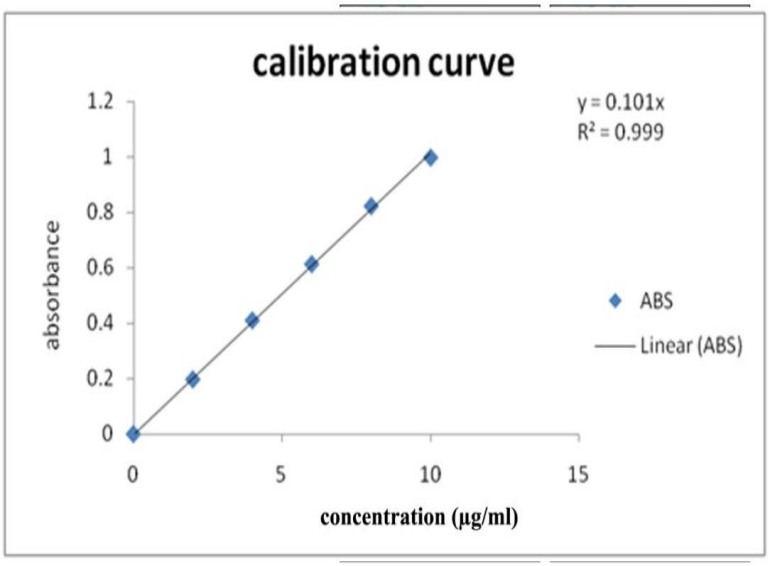

Figure 3: Calibration curve of Montelukast in Phosphate buffer pH 6.8.

Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

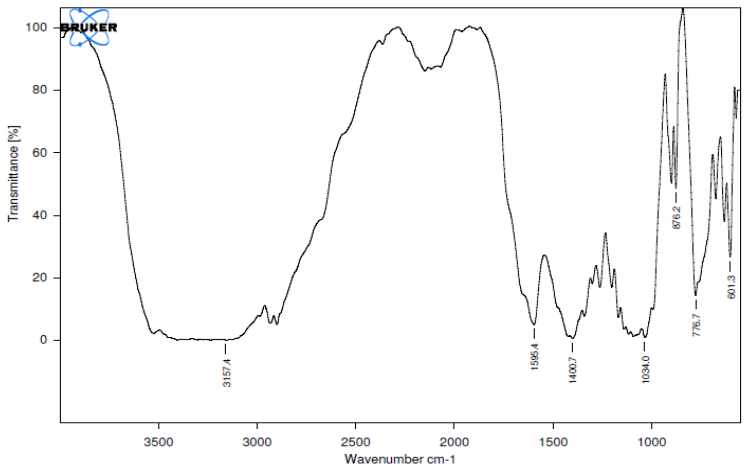

Figure 4: FTIR Spectrum of Montelukast pure.

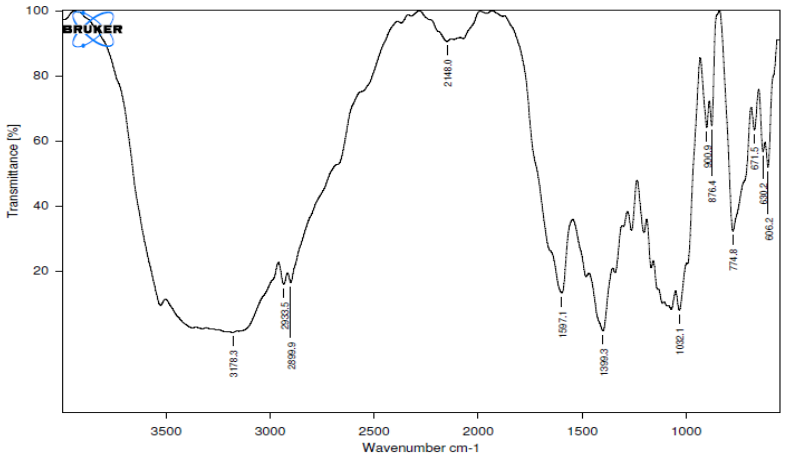

Figure 5: FTIR Spectrum of Montelukast best formulation.

Micrometric Properties of Powder Blend

Table 7: Micromeretic properties of core tablet of Montelukast.

Formula	Micrometric properties of powder blend				
	Angle of Repose (θ) ±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml) ±SD	Carr's Index. (%)±SD	Hausner's ratio±SD
F1	27.20±0.36	0.412±0.018	0.476±0.019	13.44±0.15	1.155±0.021
F2	28.41±0.23	0.403±0.024	0.465±0.016	13.33±0.11	1.153±0.034
F3	23.77±0.22	0.410±0.032	0.473±0.026	13.31±0.25	1.153±0.033
F4	24.85±0.56	0.398±0.024	0.446±0.030	10.76±0.22	1.120±0.020
F5	24.68±0.27	0.387±0.017	0.440±0.026	12.04±0.16	1.136±0.014
F6	29.85±0.22	0.421±0.013	0.483±0.022	12.83±0.25	1.147±0.028
F7	27.44±0.22	0.411±0.012	0.478±0.018	14.01±0.13	1.163±0.032
F8	27.96±0.44	0.402±0.032	0.455±0.025	11.64±0.17	1.131±0.037
F9	26.74±0.32	0.410±0.024	0.463±0.026	11.44±0.25	1.129±0.014

DISCUSSION

Pre-compression parameters were conducted for all formulation blends and were found to be satisfactory. Bulk density was found in the range 0.387 -0.421 g/cm^2 and tapped density in the range of 0.440 to 0.483 g/cm^2. Using these two density factors Hausner's ratio and compressibility index was calculated. The powder blend of all formulations had Hausner's ratio less than 1.16 which indicates better flow property and compressibility index between 10.76 to 14.01 which indicates fair flowability property.

The fair flowability property of the powder blend was also evidenced with angle of repose between 23.77 to 29.85 which is below 40 indicating good flowability

Post Compression Parameters of Core Tablet

Table 8: Post compression parameters of core tablet.

Formula	Post compression parameters of core tablet				
	Weight variation(%)	Hardness (kg/ cm^2)	Thickness (mm)	Friability (%)	Disintegration time(sec)
F1	1.31	4.02	3.32	0.89	86
F2	0.83	4.85	3.45	0.74	72
F3	1.03	4.78	3.52	0.52	68
F4	0.88	4.96	3.63	0.40	98
F5	0.68	4.87	3.41	0.78	74
F6	1.1	4.21	3.74	0.53	57
F7	0.99	4.36	3.65	0.63	61
F8	0.87	4.12	3.41	0.96	48
F9	0.33	4.52	3.52	0.14	26

DISCUSSION

Weight Variation Test

The percentage weight variations for all formulations were given. All the formulated (F1 to F9) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test

The measured hardness of tablets of all the formulations ranged between 4.02-4.96 kg/ cm^2. This ensures good handling characteristics of all batches.

Disintegration test for core tablets

It was found between 26-98 seconds ensuring that all the cores of different formulations were rapid disintegrating type.

Friability Test

The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable.

Evaluation of Physical Parameters of Compressed Tablets of Montelukast

Table 9: Evaluation of Physical Parameters of compressed tablets of Montelukast.

Formula	% Weight Variation	Weight variation (mean ± SD, mg)	Hardness (mean ± SD)	Friability (%)	Thickness (mm)
P1F9	0.35	498.25±11.35	5.56±0.5	0.28	5.10
P2F9	0.37	498.11±09.68	5.78±0.18	0.36	5.21
P3F9	0.71	496.45±08.59	5.60±0.19	0.12	5.09
P4F9	0.55	497.23±08.36	5.42±0.18	0.48	5.22
P5F9	0.33	498.31±11.57	5.52±0.5	0.69	5.16
P6F9	0.15	499.25±07.23	5.11±0.19	0.78	5.08

Weight Variation Test

The percentage weight variations for all formulations were given. All the formulated (P1F9 to P6F9) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test

The measured hardness of tablets of all the formulations ranged between 5.11-5.78 kg/ cm^2. This ensures good handling characteristics of all batches.

Thickness

The measured thickness of tablets of all the formulations ranged between 5.08-5.22 mm. This ensures good handling characteristics of all batches.

Friability Test

The % friability was less than 0.78 % in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity

Table 10: Content uniformity of different core tablet formulae (F1 to F9).

Formulation code	Drug content
F1	98.30±0.89
F2	97.23±1.02
F3	98.07±0.78
F4	99.12±0.49
F5	97.20±0.15
F6	98.59±0.97
F7	97.69±1.23
F8	98.89±1.30
F9	99.63±1.05

DISCUSSION

The percentage of drug content for F1 to F9 was found to be between 97.20% and 99.63%. It complies with official specifications.

Table 11: Content uniformity of different coated tablet formulae (P1F9 to P6F9).

Formulation code	Drug content
P1F9	98.06±0.05
P2F9	96.23±0.87
P3F9	97.44±0.41
P4F9	96.36±1.20
P5F9	97.10±0.85
P6F9	99.60±0.55

DISCUSSION

The percentage of drug content for P1F9 to P6F9 was found to be between 96.23% and 99.60%. It complies with official specifications.

DISSOLUTION STUDIES

Table 12: Cumulative percent drug release of core Montelukast tablets (F1 to F9).

TIME (min)	Cumulative % drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	20.26	22.33	25.54	24.41	29.96	32.52	33.20	38.58	42.32
10	39.20	42.02	47.74	38.56	45.12	48.57	51.01	59.65	64.47
15	48.87	52.30	60.33	53.30	58.87	63.30	72.36	80.84	82.25
20	63.32	67.74	75.50	69.65	70.11	79.98	84.87	96.97	99.69
25	79.78	81.23	85.88	80.12	83.56	87.10	97.65	--	--
30	86.63	91.20	97.89	91.22	96.89	98.87	--	--	--
45	95.54	99.45	--	99.07	--	--	--	--	--

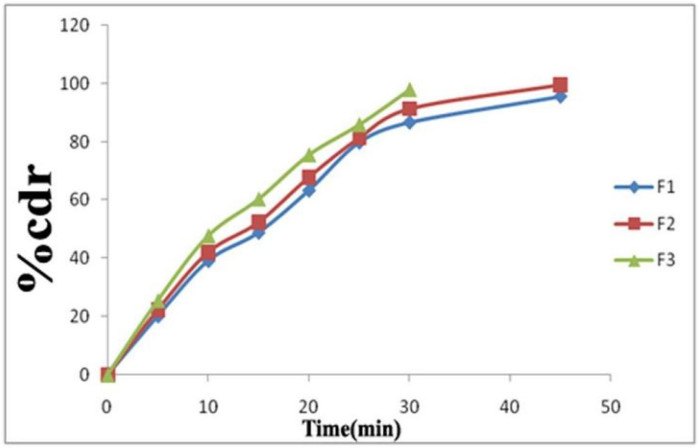

Figure 6: Cumulative percentage drug release of core formulation F1, F2, F3.

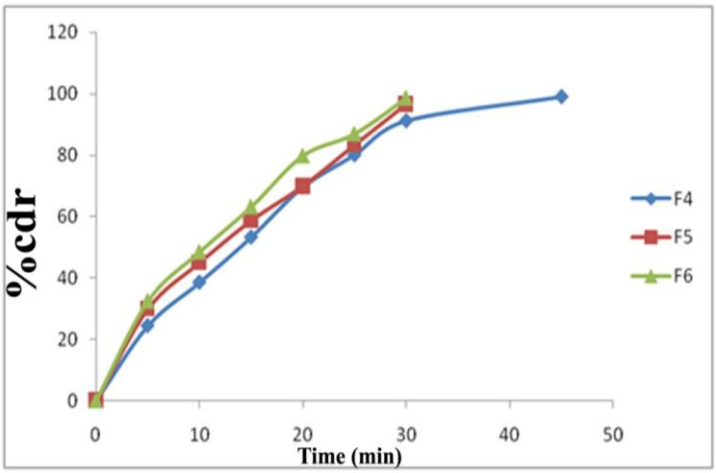

Figure 7: Cumulative percentage drug release of core formulation F4, F5, F6.

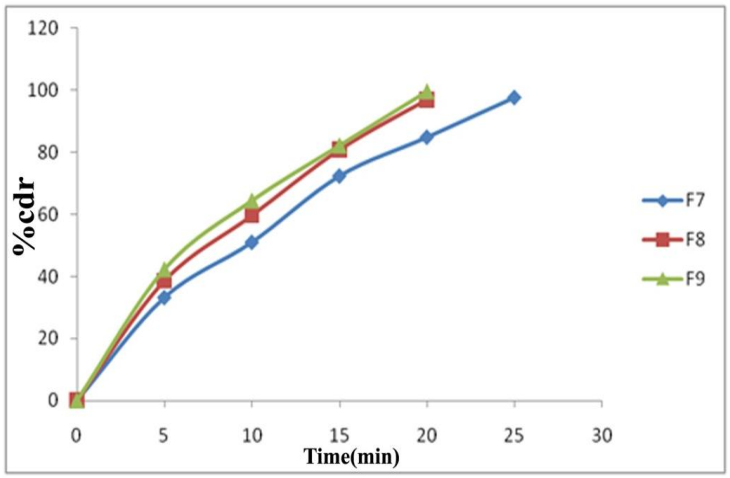

Figure 8: Cumulative percentage drug release of core formulation F7, F8, F9.

Dissolution studies for coated tablets

Table 13: Cumulative % drug release of coated tablets (P1F9 to P6F9).

Time(hrs)	P1F9	P2F9	P3F9	P4F9	P5F9	P6F9
0	0	0	0	0	0	0
1	0.88	0.77	0.65	0.28	0.12	0.36
2	2.87	1.42	3.55	1.07	0.97	2.56
3	6.45	5.87	8.74	11.03	1.58	10.23
4	22.30	13.28	20.31	30.47	3.36	22.33
5	33.02	18.12	31.23	47.36	8.99	46.58
6	41.20	47.75	42.03	59.57	49.98	67.87
7	59.87	68.68	55.06	75.17	78.80	76.99
8	74.89	90.02	69.63	94.20	98.77	89.65

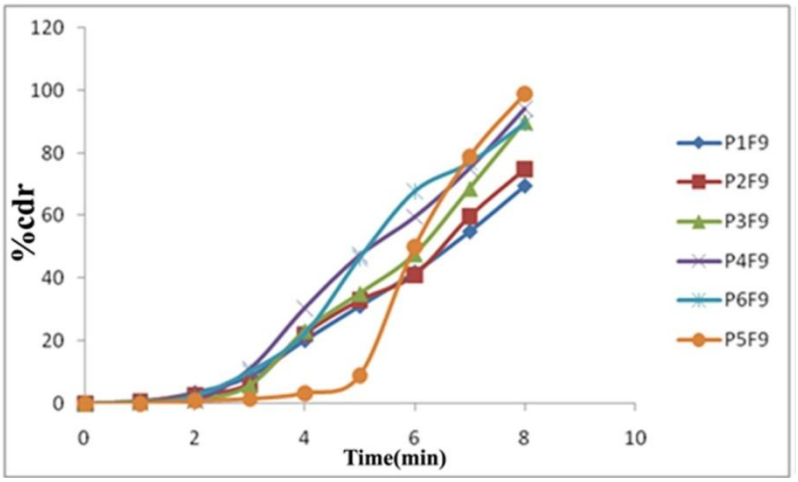

Figure 9: Cumulative percentage drug release of coated formulations P1F9 –P6F9.

DISCUSSION

Invitro dissolution studies were performed for all the core formulations (F1-F9) of that Formulation containing CCS shows best drug release within 20 mins. By selecting F9 as optimized formulation now core tablet was coated using Metolose and Karaya gum as polymers. Among all of the coated tablets (PIF9-P6F9), formulation containing combination of Metolose and Karaya gum in the ratio of 1.5:2.5 (P5F9) has shown betterlag time for drug release ie., upto 5hrs. showing less than 10% release in 5hrs and showing immidiate release after 5hrs. Hence it was selected as optimized formulation.

Drug release kinetics of coated tablet

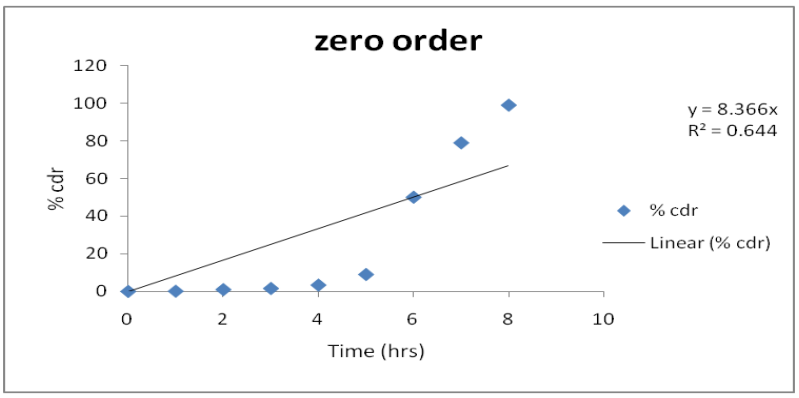

Figure No. 10: Zero order release plot for optimized formulation (P5F9).

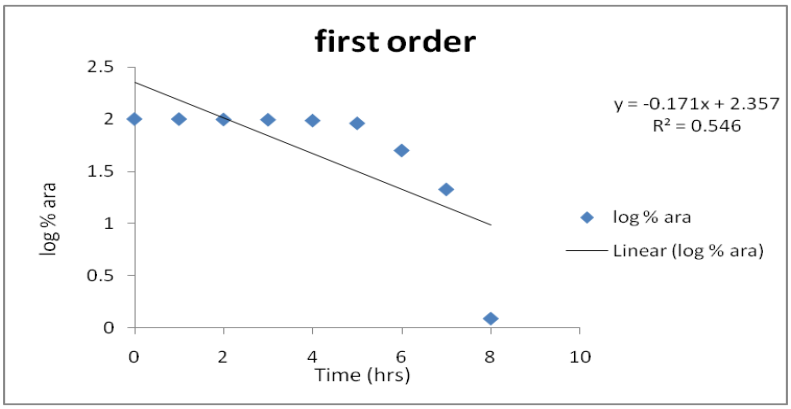

Figure 11: First Order release plot for optimised formulation (P5F9).

DISCUSSION

Optimised formula shows zero order drug release kinetics studies.

STABILITY STUDIES

RESULTS

Table 14: Results of Stability Studies.

Time in Days	% Drug Content in Core Tablets	% Drug Content in Coated Tablets
0	99.63	99.60
10	99.67	99.65
20	99.71	99.63
30	99.65	99.59

DISCUSSION

For the optimized formulation stability studies were also conducted and finally basing on results we can say that the prepared optimised formulation is a stable formulation.

CONCLUSION

A satisfactory attempt was made to develop Pulsatile drug delivery system of Montelukast. The coating given by the combination of Metalose & Karaya gum in the ratio of 1.5: 2.5 is very much suitable for the development of pulsatile drug delivery system for Monteleukast and can be successfully used as a time dependent modified chronopharmaceutical formulation. Thus pulsatile drug delivery system can be considered as one of the promising formulation technique for chronotherapeutic management of asthma.

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