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Formulation and Evaluation of Pulsatile Drug Delivery System of Anti-Asthmatic Drug

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ABSTRACT

Aim of the present work was to formulate and evaluate an oral, time controlled drug delivery system to achieve timed release of Montelukast sodium, for the treatment of nocturnal asthma. An asthmatic attack mainly takes place early in the morning. Time controlled delivery system is capable of delivering drug when and where it is required most. Time-delayed tablets, designed to release drug after a predictable lag time, are intended for oral chronotherapy. A time dependant pulsed release system consisting of a core surrounded by coat layer of different ratios of swellable erodible hydrophilic layer HPMC K100M and rupturable hydrophobic layer Eudragit L 100 and Eudragit S 100 were prepared. These pulsatile tablets were evaluated for the drug content, thickness and in-vitro release profile, etc. and two optimized formulation were selected and subjected to further studies. .

Keywords: Pulsatile drug delivery ,time controlled drug delivery; Chronotherapeutics; Circadian rhythm; Nocturnal asthma; Montelukast sodium; Eudragit L 100:Eudragit S 100; HPMC K100M.

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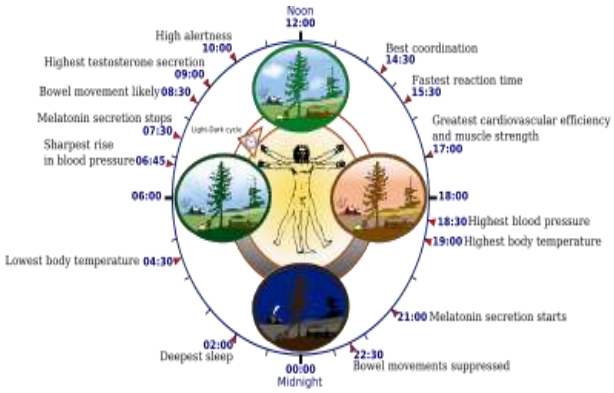
INTRODUCTION

Pulsatile drug delivery system:

Pulsatile system is gaining a lot of interest as it is increasing patient compliance by providing time- and site-specific drug delivery. there by providing special and temporal delivery. Pulsed or pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off-release period. Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions.



NECESSITIES OF PULSATILE DDS:

1.first pass metabolism:

Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

2. Biological tolerance:

Drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin, salbutamol sulphate.

3. Special chronopharmacological needs:

Circadian rhythms in certain physiological functions are well established. It has been recognized **t**hat many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

4. Local therapeutic need:

For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

5. Gastric irritation or drug instability in gastric fluid:

Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (eg, peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting.

6. Extended day time or night time activity

7. Lower daily cost to patient due to fewer dosage units are required in therapy

8. Reduction in dose size and dosage frequency and also side effects.

Merits:

1. Predictable, reproducible and short gastric residence time
2. Less inter- and intra-subject variability
3. .Improve bioavailability
4. Limited risk of local irritation
5. No risk of dose dumping
6. Flexibility in design
7. Improve stability

Demerits:

1.Lack of manufacturing reproducibility and efficacy

2.Large number of process variables

3.batch manufacturing process.[1]

MATERIALS AND METHOD

Montelukast Sodium was received as a gift sample from Microlab Ltd. Bangalore , HPMC K100M was received from Alembic Pvt. Ltd. Vadodara ,Eudragit S-100,and Eudragit L- 100 was obtained from East West college of pharmacy Bangalore ,Sodium Lauryl Sulphate, Lactose Monohydrate was taken from S.D. Fine chem. Ltd., Mumbai ,Micro crystalline cellulose, Croscarmellose Sodium was received from Alembic Pvt. Ltd. Vadodara.

PREFORMULATION STUDIES

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients

1.Angle of repose

The angle of repose, which signifies the flow properties of powder blends was determined by the funnel method. The accurately weighed powder blend was taken in a funnel. The height of the

funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of powder. The powders were allowed to flow through the funnel freely onto a clean surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\text{Tan } \theta = {}^{h}/_{r}$$

where h is the height of powder cone and r is the radius of the powder con

2.Bulk density and tapped density

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. Both bulk density (BD) and tapped bulk density (TBD)of powder blends were determined using the following formulae.

BD = Weight of the powder/Volume of the powder

TBD = Weight of the powder/Tapped volume of the powder

3.Carr's compressibility index

The compressibility indices of the formulation blends were determined using following Carr's compressibility index formula.

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

4.Hausner ratio

Hausner ratio is the ratio between tapped density and bulk density.

$$Hauser's\ ratio = \frac{Tapped\ \ Density}{Bulk\ \ Density}$$

Hausner ratio less than 1.25 indicates good flow properties while Hausner ratio greater than 1.5 shows poor flow of powder. Hausner's ratio between 1.25 to 1.5 can be improved by addition of glidants[2].

5. Formulation of core tablets by direct compression

The inner core tablets were prepared by using direct compression method. The powder mixtures of Montelukast sodium, Lactose (lactochem), croscarmellose sodium (Ac-DiSol) ingredients were dry blended for 20 min. followed by addition of magnesium Stearate. The mixtures were then further blended for 10 min., 100mg of resultant powder blend was manually compressed using tablet pushing machine (Rimek mini press-1) with a 6.3 mm punch and die to obtain the core tablet. Tablets of Montelukast sodium were formulated by incorporating diluents such as lactose and other excipients like croscarmellose sodium and magnesium stearate etc. dry blend o

the powder were prepared. The core tablets were further coated with HPMC, Eudragit and lactose, starch as diluents.

Table 1: Formula for the Core Tablet

Sl.No	Ingredients	core(mg)
1	Montelukast sodium	10.2
2	Croscarmellose sodium	5
3	Microcrystalline cellulose	83
4	Magnesium stearate	2
Total Weight		**100**

POST COMPRESSION PARAMETERS OF THE CORE TABLET

Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.

Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Method

6 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.

Percentage friability was calculated by using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \text{ X } 100$$

Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.[3]

Content Uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 10.4mg Montelukast sodium was weighed accurately and dissolved in 100ml of 0.5% of Sodium Lauryl Sulphate (SLS) in water. The solution was sonicated for 15-20mins. The undissolved matter was removed by filtration through Watt man No.41 filter paper and dilutions were carried out. The absorbance of the diluted solutions was measured at 345.5 nm. The concentration of the drug was computed from the standard curve of the Montelukast sodium in 0.5% of SLS in water.[4,3]

Formulation of Core tablet and Coat Tablets:

the ingredients used in preparing the core tablets and various formulation Compositions containing EudragitL-100 and Eudragit S 100 ,HPMC K100M were prepared i.e. formulation from F1 to F12 different compositions were weighed and dry blended at about 10 min. and used as press-coating material to prepare press-coated pulsatile tablets by direct compression method. Press coated tablets of Montelukast sodium was developed with different concentration.

Development of Press-coated tablets

The core tablets were press-coated with 200 mg of mixed Blend as given in Table.5 100mg of barrier layer material was weighed and transferred into a 9.54 mm die then the core tablet was placed manually at the center. The remaining 100 mg of the barrier layer materiel was added into the die, so that the core tablet get covered by the barrier layer completely and compressed by tablet punching machine (Rimek mini press-1). The total weight of the tablet would be 300 mg.Post compression parameters of Press-coated tablets like weight variation, tablet hardness, friability, tablet thickness, content uniformity and in-vitro evaluation of press-coated tablets were done in a similar manner as that of the core Post compression parameters of Press-coated tablets like weight variation, tablet hardness, friability, tablet thickness, content uniformity and in-vitro evaluation of press-coated tablets were done in a similar manner as that of the core tablets

Evaluation of Press-coated tablets

Effect of hardness on optimized formulation:

Coated tablets were given the different hardness (3 to 6 kg/cm2) and effect of hardness on lag time was determined similarly to the method used for in-vitro drug release studies.

10. Swelling studies

Core tablets were press-coated with the different ratios of polymers and HPMC used as a swelling agent was observed and swelling index was determined. Swelling effect on lag time and release behavior was observed. A known weight of a tablet was placed in 0.5% of SLS and

allowed to swell for the required period of time at 37ºC ± 0.5ºC in the dissolution apparatus (Dissolution Tester USP 2).A tablet was periodically removed and blotted with filter paper; then their change in weight (after correcting for drug loss) was measured until attainment of equilibrium. The swelling ratio (SR) was then calculated using the following formula.

SR=WF-WI/WI*100

Where SR= swelling ratio, WF = weight of the tablet after swelling, WI= initial weight of the tablet.

11. Rupture studies

The Rupture test on press-coated tablets was carried out using USP II (paddle) apparatus at 50 rpm and 37±0.5°C of 0.5% of SLS in water maintained as the dissolution medium. Rupture time of the coated tablet was determined.[5]

RESULTS AND DISCUSSION

The prepared powder blend was of the different formulations was evaluated for angle of repose, loose bulk density, tapped density, compressibility index and Hausner's ratio. The prepared matrix tablet were evaluated for thickness, weight variation, hardness, friability, drug content, in vitro drug dissolution studies and stability studies. All the studies were performed in triplicate.

Characterization of powder blend

The powder blend prepared for compression of matrix tablets were evaluated for their flow properties. Angle of repose was in range of 22.75 to 29.11 which indicates good flow of all formulations. The bulk density was in range of 0.342 to0.414 g/cm^3. The tapped density was in range of 0.364 to0.480 g/cm^3, which indicates that the powder was not bulky. The Carr's Index was found to be in range of 6.21 to 13.33, which indicates good flow for all formulations except few. Hausner ratio was found to be in range of1.02 to 1.15, these values indicates that the prepared blend exhibited good flow properties.

Table 2: Preformulation characteristics of coat layer

Batch	Bulk density (w/v)	Tapped density (w/v)	Hausner's ratio	Carr's index	Angle of repose (θ)
F1	0.342	0.364	1.14	12.53	22.75
F2	0.416	0.480	1.15	13.33	24.14
F3	0.395	0.452	1.14	12.61	25.31
F4	0.367	0.390	1.02	5.90	25.39
F5	0.361	0.409	1.13	11.74	29.11
F6	0.352	0.397	1.13	11.34	28.14
F7	0.413	0.443	1.07	6.77	25.34
F8	0.414	0.477	1.15	6.21	24.34
F9	0.394	0.451	1.14	12.64	27.21

Table 3: Post compression parameters of press-coated tablets

Batch	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Wt. variation	Friability (%)	drug content(%)
F1	9.45±0.003	5.26±0.342	5-6	299.45±2.811	0.231	98.90±0.501
F2	9.45±0.004	5.33±0.031	5-6	300.01±0.910	0.144	99.81±0.312
F3	9.45±0.003	5.30±0.024	5-6	300.02±1.741	0.088	99.42±0.402
F4	9.45±0.004	5.31±0.003	5-6	299.44±1.140	0.289	98.56±0.300
F5	9.45±0.003	5.29±0.257	5-6	298.89±2.007	0.216	97.59±0.046
F6	9.45±0.003	5.29±0.269	5-6	300.01±1.119	0.192	98.78±0.251
F7	9.45±0.002	5.30±0.031	5-6	299.60±1.818	0.177	99.40±0.310
F8	9.45±0.002	5.31±0.027	5-6	299.55±0.973	0.176	99.12±0.411
F9	9.45±0.005	5.32±0.152	5-6	298.90±0.993	0.184	98.50±0.052

Evaluation of Pulsatile tablets

The results of physicochemical properties are shown in table. The thickness was measured by vernier caliper and was ranged between 5.26±0.342 to 5.32±0.152 for all formulations. The weight variation for different formulations was found 298.90±0.993 to 300.01±0.910. The hardness of tablet is indicative of crushing strength to withstand handling during packaging and transportation. The hardness of the tablet was measured by Monsanto tester and was controlled between 5-6 kg/cm^2. Another measure of a tablet's strength is friability. Conventional tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the % friability of formulations was below 1%, indicating that the friability was within the prescribed limits, which is an indication of good mechanical resistance of the tablet. Drug uniformity for all formulations was found to be above 97.59±0.046 to 99.81±0.312 All the tablet formulations showed good pharmacotechnical properties.

The drug release could be modified by adjusting the ratio of these two polymers in combination. When a tablet comes in contact with the dissolution media, water influx was through the highly permeable rupturable hydrophobic layer (Eudragit L,S) which leads to swelling and erosion of hydrophilic layer (HPMC K100M). HPMC K100M forms a very viscous gel layer which will reduce the seepage of dissolution fluid into the core tablets and thereby retards the drug release. When HPMC K100M swells to a maximum extent, it expands and creates pores on the surface facilitating the dissolution media to enter into a reservoir (core). Core containing croscarmellose sodium as a superdisintegrant and swelling in nature develops a pressure from inside the reservoirs finally leading to rupture of the coat layer. In-vitro dissolution studies revealed that there was no drug release until the coat ruptures.

In vitro drug release studies

The in vitro dissolution studies of all formulations of pulsatile drug delivery tablets of were carried out in first 2hrs in 0.1N HCl and remaining 0.5% of SLS in water. The results of in vitro dissolution studies of all formulations are shown in table 3.

F1 contained eudragit L is 100mg and lactose 100mg was found to be 92.06% 2ndhrs ,F2 Eudragit S is 100mg and HPMC E15 100mg was found to be 94.26% at 1st hr .it indicates low viscosity of polymer,F3 contained eudragit S and lactose is 100mg and 100mg 89.09% at 1sthr,F4 contained eudragit S 200mg was found to be 91.28% at 4thhr ,F5 contained eudragit L is 100mg and S is 100mg was found to be 89.15% at 3rdhr. and F6 contained HPMC E15 is 100mg and Eudragit L is 100mg was found to be 96.48% at 2nd hr. F7 contained Eudragit L 200mg was found to be 93.54% at 3rd hr , F8 contained HPMC K100M is 20mg and Eudragit L is 50 mg Eudragit S is 50mg and stach is 125mg was found to be 93.46% at 7thhr .the % drug release is increased with decreases the polymer concentration,F9 contained HPMC K100M is 30mg Eudragit L is 50mg and Eudragit S is 50mg and starch is 70mg was found to be 93.24% at 9thhr it indicates the % drug relese time is incresed with the increses the polymer concentration.

Table 4: *in-vitro* dissolution of coated tablets F1 to F9

Medium	**First 2 Hrs 0.1N Hcl Remaining with 0.5% of SLS in Water**					**RPM**	**50**			
Method	**Test Apparatus USP II(Paddle)**					**Volume**	**900 ml**			
Batch	**Cumulative Percentage Release(CPR) TIME (H)**									
	0.5	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
F1	30.25	62.84	92.06	91.26	91	-	-	-	-	-
F2	46.87	94.26	93.56	-	-	-	-	-	-	-
F3	49.41	89.09	88.63	88.01	-	-	-	-	-	-
F4	28.44	60.88	88.65	91.28	91.08	-	-	-	-	-
F5	25.48	55.84	70.50	89.15	89	-	-	-	-	-
F6	31.48	52.31	92.04	92.36	-	-	-	-	-	-
F7	18.62	35.16	62.42	93.54	88.26	-	-	-	-	-
F8	0.004	1.428	5.58	13.25	18.47	30.11	77.30	93.46	93.2	-
F9	0.005	1.245	2.36	5.47	15.26	25.74	52.97	71.69	86.41	91.06

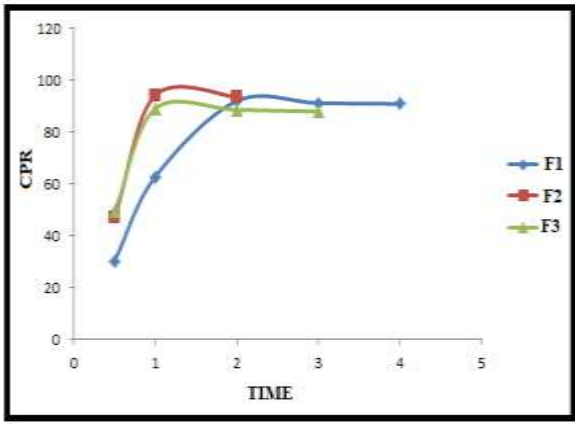


Figure 1:% Drug Release of F1,F2,F3

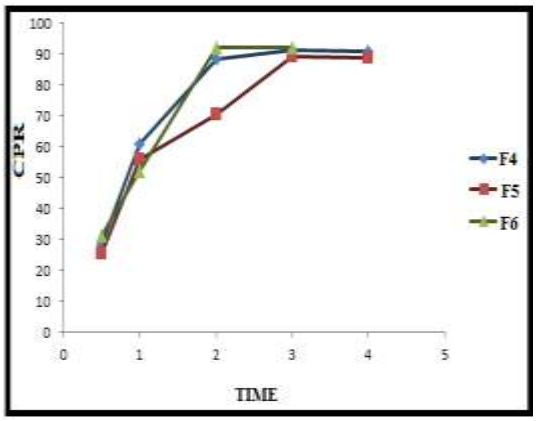


Figure 2:% Drug Release of F4,F5,F6

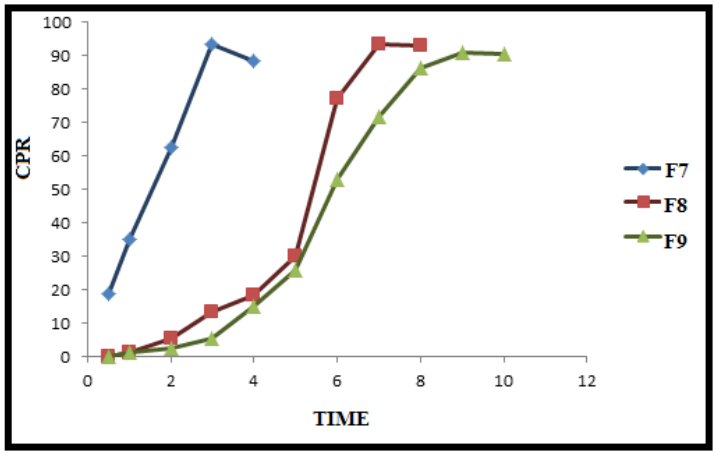


Figure 3:% Drug Release of F7,F8,F9

CONCLUTION:

Pulsatile drug delivery tablet of Montelukast sodium was easily prepared using combination of HPMC K100M, Eudragit L 100 , Eudragit S 100 with Direct compression method was used to overcome stability problems by avoiding heat as well as moisture during formulation of tablets.Preformulation and post-formulation parameters (Table 2, 3) were found to be good meeting the requirements for pulsatile drug delivery release formulations.

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