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Research article

Development and Evaluation of Pulsatile Drug Delivery System containing Montelukast Sodium by Press Coated Tablet using natural Polysaccharides

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Abstract

The aim of the study was to develop press coated time release tablets of montelukast, to achieve the time controlled disintegrating or rupturing function with a distinct predetermined lag time and produce sustained drug delivery released to suite the chronotherapeutics of the disease i.e., bronchial asthma.The tablets, each consisting of a core and a coat, were prepared using compression coating technique. The core tablet was then coated with a natural polymers such xanthan gum, guar gum and mixture of it respectively. Fourier transform infra-red (FTIR) spectrometry, differential scanning calorimetry (DSC), were applied to investigate the drug-excipients compatibility of the formulation and the studies revealed no chemical interactions between drug and polymers used.Stability studies also were performed for 3 months at 40°C and 55°C at 75% RH as per ICH guidelines for optimized formulation and it was found to be stable. The effect of formulation composition on the barrier layer comprising both polymers, excipients on the lag time of drug release was investigated. It was observed that when compared with all other formulations developed, formulation P5F3 shows great ideal in pulsatile drug delivery. The release data from the formulation was found to fit in peppas model with R^2 of 0.983.

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Press-coated tablet, lag time, Diffusion, pulsatile drug delivery, bronchospasm, Erosion,

INTRODUCTION

Pulsatile drug delivery system is the type of drug delivery system, where the delivery device is capable of releasing drug after predetermined time-delay (i.e. lag time) known as pulsatile drug delivery system. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release"[1] Diseases, such as cardiovascular, asthma, peptic ulcer, arthritis etc follow the body's circadian rhythm. Coordination of biological rhythms and medical treatment is called chronotherapy while chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases and peptic ulcer disease. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Approximately two-thirds of asthmatics suffer from night time symptoms. In a large study involving 8,000 asthmatics it is observed that, 75% awakened one night per week, 64% awakened 3 nights per week and 39% had their sleep disturbed on a nightly basis. The patients who self-characterized their asthma as mild, 26% had nightly awakenings and 53% of asthma deaths occurred during the night time hours[2], these cases, therapy should be modified to achieve an effective drug level at the required time, that is, taken at bedtime with a programmed start of drug release in early morning hours, could offer a more effective therapy than a typical controlled release drug delivery system, provided that the most appropriate drugs are administrated. This can be achieved by adapting a pulsatile drug delivery system of a suitable drug. The press-coating technique by direct compression offers such drug delivery system and also has advantages over liquid coating as it does not involve the use of solvents, requires a relatively short manufacturing process, and allows greater weight gain to the core tablet. However, the requirement for reliable and reproducible central positioning of the core tablet within press-coated tablet is a major challenge for large scale industrial manufacturing. The main objective of the study was to develop a time controlled release formulation based on a press-coating technique using rate controlling natural polymers and montelukast sodium as a model drug. The intention was to maintain a lag time of 4 – 6 hrs, as the symptoms of asthma are experienced in the early morning hours. The incorporation of drug as an immediate release formulation in the core is proposed to provide the drug to the patient at the right time of asthmatic risk.

MATERIALS AND METHODS

Materials

Montelukast Sodium from Chandra Labs, Hyderabad, Microcrystalline cellulose from Degussa India Pvt. Ltd., Mumbai, Cross povidone, Sodium starch glycolate, Lactose monohydrate, Croscarmellose sodium, Magnesium stearate and Sodium lauryl sulphate were from S.D. Fine Chem. Ltd., Mumbai, Xanthan gum and Guar gum were from L.R. Sisco Research Lab.Pvt. Mumbai.

Pre-compression evaluation

Micromeritic properties[3]

Flowability of the pre-compression mixture of core tablet was performed by measuring the angle of repose by fixed funnel method. A measured amount of the powder was allowed to flow through the funnel fixed at a constant height (h=2.5 cm) and mean diameter (2r) of the powder pile was measured. The bulk density (BD) and tapped bulk density (TBD) of pre-compression mixture was determined using bulk density apparatus (Electro Lab, India) from 3 independent analyses. Carr`s index and Hausner`s ratio were calculated using BD and TBD values.

Methodology

Stage1. Formulation of rapid release core tablets (RRCTs) by direct compression[4]

The inner core tablets were prepared by using direct compression method as per formulation variable shown in Tab1. Powder mixtures of montelukast sodium, microcrystalline cellulose (MCC, Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol), Sodium starch glycolate, crospovidone, lactose monohydrate ingredients were dry blended for 20 min followed by addition of magnesium stearate. The mixtures were then further blended for 10 min. 150mg of resultant powder blend was manually compressed using hydraulic press at a pressure of 1 ton, with a 9mm punch and die to obtain the core tablet.

Stage 2. Formulation of mixed blend for barrier layer

The various formulation compositions containing Xanthan gum and Guargum as shown in tab 2 were weighed dry blended at about 10 min. and used as press-coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Stage 3.Preparation of press-coated tablets (PCT)

The optimized core tablets were press-coated with 300mg of mixed blend/granules as given in Tab 2, 150mg of barrier layer material was weighed and transferred into a 13mm die then the core tablet was carefully placed manually at the center. The remaining 150mg of the barrier layer materiel was added into the die and compressed at a pressure of 5 tons for 3min using hydraulic press.

Tab 1. Formulation variables of core montelukast sodium tablets

	Formulation code								
Formulation	**F 1**	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**	**F7**	**F8**	**F9**
Montelukast	10	10	10	10	10	10	10	10	10
Microcrystalline Cellulose	64.5	62.2	60	64.5	62.2	60	64.5	62.2	60
Lactose Monohydrate	64.5	62.2	60	64.5	62.2	60	64.5	62.2	60
Crospovidone	9	13.5	18	-	-	-	-	-	-
Croscarmellose Sodium	-	-	-	9	13.5	18	-	-	-
Sodium starch Glycolate	-	-	-	-	-	-	9	13.5	18
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Total weight	150	150	150	150	150	150	150	150	150

Tab 2. Formulations of montelukast sodium press coat tablets

	Formulation code				
Formulation	**P1**	**P2**	**P3**	**P4**	**P5**
Xanthan gum	300	-	150	225	75
Guar gum	-	300	150	75	225
Total weight	300	300	300	300	300

Physicochemical parameters of core tablets and press coated tablets

The tablets were checked for weight variation[5], wetting time. Tablet thickness was measured using a micrometer (Mitutoyo, 103-260, Japan). Hardness of tablets was determined using a hardness tester (model: TH-16, China). Friability was determined using a Roche friabilator (Erweka Apparatebau GmbH, Germany) for core tablets and press coated tablets individually. Drug content uniformity was determined by dissolving 10mg equivalent amount from the crushed core tablets placed in 100 ml volumetric flask and dissolved in 0.5% SLS solution and 5 ml is taken and diluted with 0.5% SLS solution upto 100 ml. The absorbance of the solution was measured at 342 nm using UV/VIS spectrophotometer (Corporation-BL-220H) using a reference to a standard calibration curve of the drug (r^2 = 0.998). The experiments were performed in triplicate and the average values ± standard deviations (SD) were reported.

Swelling index for press coated tablets[6]

The tablets were weighed and placed in Petri dish containing 10ml of Distilled water. At specified time intervals, remove the tablets and lightly bottled with tissue paper to remove excess water and weighed.

Swelling index (%) = [Ws-Wd / Wd] 100

Where Ws is weight of swollen tablet at time 't' and Wd is the weight

FT-IR Study

The compatibility between drug and polymers was detected by IR spectra (Corporation, Japan). The pellets were prepared on KBr-press. The spectra were recorded over the wave number range of 4000 to 500 cm^{-1}.

DSC Study

Thermogram were obtained by using a differential scanning calorimeter at a heating rate of 10°C/min over a temperature range of 50-300 °C. The sample was hermetically sealed in an aluminium crucible.

Dissolution rate study of rapid release core tablets (RRCT)[7]

Dissolution rate studies of Montelukast sodium from all formulations was performed using dissolution rate testing apparatus with paddle. The dissolution fluid was 900ml of phosphate buffer pH 7.2. The test was performed at a speed of 50rpm and at a temperature of 37±0.5°C. Samples of dissolution medium (5ml) were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted and assayed for Montelukast sodium by measuring absorbance at 346 nm. The dissolution experiments were conducted in triplicate.

In Vitro Dissolution Study of PCT

The release of montelukast from the press-coated tablet was accomplished

In-vitro release study was carried out (USP dissolution test apparatus Type-II Paddle type) using 900 ml of Distilled water with 0.5% SLS a. The paddles are rotated at 50 rpm. The medium was set at 37 ± 0.5^0 C. Aliquot (5 ml) of the solution was collected from the dissolution apparatus hourly and was replaced with fresh dissolution medium. The withdrawn samples were analyzed by an UV spectrophotometer at 342 nm.

Mechanism of drug release[8]

The mechanism of release was determined by fitting the release data into various kinetic equations such as Zeroorder, First-order, Higuchi, and Korsemeyer-Peppas and finding the R^2 values of the release profile corresponding to each model.

Stability studies[9]

The stability study of the selected formulations was carried out according to ICH guidelines at 40±2°C/75 ±5% RH for three month by storing the samples in stability chamber.

RESULTS AND DISCUSSION

Compatibility studies by FTIR and DSC analysis

FTIR spectrum of pure montelukast is characterized by the exhibited peak at 3366.88cm-1 and 2923.68 cm-1 due to N-H stretching and saturated alkane respectively[10]. The presence of characteristic peaks of drug in the FTIR spectra of physical mixture (Drug: Polymer) and formulation indicates the absence of chemical interaction between the drug and the polymers employed in the study. The results are shown in Fig 1.

DSC scans of the montelukast sodium press coated tablet and it pure drug are presented in Fig 2. The thermogram of Montelukast exhibited an endothermic peak at 67.5°C corresponding to its melting point range[11]. The thermograms of formulation does not show profound shift in peaks, suggesting that drug has almost same melting point in its formulation. Hence it was concluded that drug had not interacted with the polymer, which indicates compatibility.

Pre-compression parameters

Powder blends used for preparing rapid release core tablets were evaluated for angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index and the results are shown in table 3. The values for angle of repose, Hausner's ratio, and compressibility index were found to be in good correlation, indicating that all formulations possess good flow property and compressibility.

Tab 3. Evaluation of directly compressible blends of core tablet

Formulation Code	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose
F1	0.41±0.11	0.501±0.04	1.99±0.22	16.57±1.20	32±2.0
F2	0.42±0.10	0.51±0.03	1.21±0.23	17.45±1.40	36±2.0
F3	0.44±0.70	0.49±0.03	1.13±0.18	11.60±1.50	30±2.0
F4	0.45±0.90	0.52±0.02	1.15±0.15	13.46±1.20	27±1.0
F5	0.41±0.11	0.49±0.05	1.19±0.16	16.29±2.20	42±2.0
F6	0.42±0.13	0.51±0.04	1.21±0.28	17.44±3.20	36±1.0
F7	0.43±0.10	0.49±0.03	1.16±0.90	13.82±1.40	31±1.0
F8	0.39±0.90	0.47±0.06	1.20±0.80	17.02±1.80	29±2.0
F9	0.41±0.80	0.46±0.07	1.18±0.19	16.40±0.90	26±1.0

Tab 4. Evaluation of Formulations of rapid release core tablet

	Physical parameter for core tablet					
Formulation Code	**Weight variation (%)**	**Hardness (Kg/cm²)**	**Thickness (mm)**	**Friability (%)**	**Disintegration time (min)**	**Wetting time(sec)**
F 1	1.65±0.7	64±.150	2.5±0.15	0.70±0.04	4.00±0.5	52±2.1
F 2	1.57±0.6	54.2±.21	2.3±0.20	0.55±0.34	3.30±0.5	55±2.0
F 3	1.42±0.4	54.3±.34	2.4±0.67	0.62±0.05	1.00±0.2	56±4.0
F 4	1.54±0.5	64.1±.31	2.2±0.81	0.54±0.67	1.30±0.5	48±6.0
F 5	1.18±0.2	34.3±.45	2.4±0.56	0.62±0.49	2.12±0.4	48±8.0
F 6	1.35±0.3	44.4±.45	2.0±0.34	0.57±0.34	1.30±0.3	50±3.0
F 7	1.44±0.5	64.2±.35	2.3±0.68	0.55±0.23	2.45±0.4	51±5.0
F 8	1.23±0.6	54.3±.34	2.4±0.45	0.62±0.34	0.30±2.1	50±7.0
F 9	1.48±0.6	74.4±.87	2.0±0.67	0.52±.034	1.45±0.0	54±3.0

Tab 5. Physical evaluation for press coated tablets

Parameter	**P1F3**	**P2F3**	**P3F3**	**P4F3**	**P5F3**
Weight variation (%)	1.65±0.12	1.57±0.09	1.42±0.80	1.54±0.67	1.18±0.12
Hardness (Kg/cm^2)	6.5±0.98	6.70±0.76	6.6±0.45	7.2±0.45	7.1±0.23
Thickness (mm)	6.5±0.67	6.45±0.87	6.4±0.34	6.0±0.23	6.1±0.56
Friability %	0.7±0.10	0.55±0.09	0.62±0.06	0.54±0.05	0.62±0.07
Swelling index%	280±18.0	100±8.0	130±9.0	180±12.0	250±16.0

Tab 6 .Shows Dissolution Rate of Montelukast Sodium from rapid release core Tablets

Formulation	**Cumulative percentage drug release from core tablet**						
	Time in minutes						
	05	10	15	20	30	45	60
F1	36.1±1.2	42.4±0.9	56.0±1.9	58.3±2.5	78.4±2.9	81.4±2.1	90.2±1.3
F2	32.1±0.9	41.5±1.2	66.4±2.1	81.7±2.6	84.6±2.3	91.8±3.2	105.4±0.2
F3	40.3±0.8	60.8±1.3	73.5±1.6	83.9±3.2	97.7±3.1	-	-
F4	25.6±0.6	36.2±1.5	49.8±1.9	55.1±2.6	68.9±3.2	80.7±4.3	90.6±0.8
F5	27.4±0.5	40.9±1.6	52.9±1.8	59.5±2.8	73.3±3.6	78.9±3.3	91.8±3.2
F6	30.7±0.8	42.3±1.6	50.2±0.9	58.8±2.7	67.6±1.7	74.4±2.5	89.12±0.2
F7	22.9±0.5	37.6±1.9	49.4±1.4	59.3±2.9	67.8±0.9	78.8±1.5	86.1±.31
F8	24.3±0.9	36.6±1.8	51.7±1.7	62.2±3.01	71.9±1.8	82.2±0.2	92.3±0.9
F9	27.6±0.4	41.5±1.9	48.4±2.1	57.7±2.3	72.2±0.4	78.9±0.9	86.5±0.8

Characterization of rapid release core and press coated tablet

The rapid release core tablets were tested for diameter, thickness, hardness, friability, tensile strength, drug content uniformity and results are presented in table 4. Diameter, thickness, and hardness were found to be within acceptable limit. The friability was <1%, indicating good mechanical resistance of the tablet.

In Vitro dissolution of rapid release core tablets

The drug content of all the formulations was found to be existed between 90 and 100% within the USP limits as per the drug content. The invitro disintegration time were found to be very less for F8 and wetting time for F4 & F5 formulation that is 1minute and 48 Sec respectively and the results of the dissolution profiles of all the formulations were represented in table 6 and figure 1. F3 shows 98 % of drug release within 30 minutes upon contact with dissolution medium, irrespective to it disintegration time and wetting time shows better dissolution profile when compared to remaining formulations.

In Vitro dissolution of press coated tablets

The formulation of P5F3 showed only 11% of drug release upto 4h and 92% of drug release was found within 9h.However, P4F3 showed 42% of drug release within 4h and 95% of drug release upto 10h,nearly half of the dose was released within 4h and shows <4h lag time. The results are presented table 7.All press coated formulations showed pulsatile release behavior with distinct lag time upto 3h and further the release of the drug was in sustained pattern. Negligible amount of drug was released during initial hours of lag time was supposed to be due to loose matrix on barrier layer at the time of swelling, possibly reason for the minor amount leakage of the drug. From all above the formulations, the press coated tablet prepared with 75 and 225mg of xanthan gum and guar gum respectively showed good deal with pulsatile drug delivery due to more lag time and dissolution rate. The release data from the formulation was found to fit in peppas model with R^2 of 0.983.

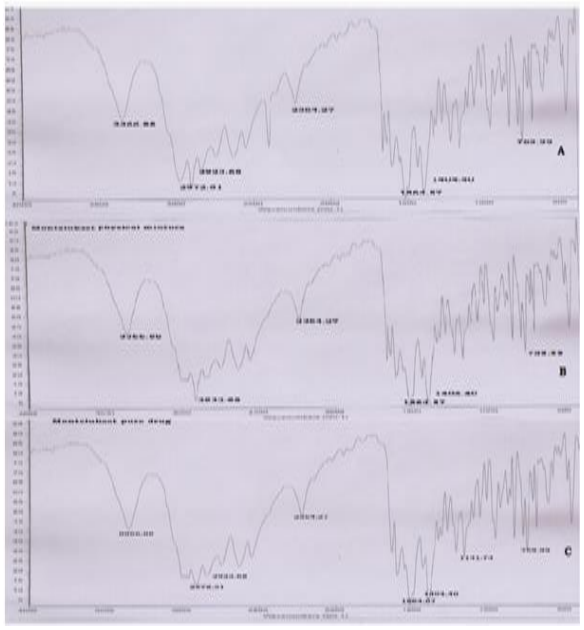

Fig 1. FTIR spectra of: (a) montelukast sodium; (b) physical mixture of drug &

excipients; (c) montelukast rapid release core tablet

Tab 7. Cumulative Release Rate Profiles of Montelukast Sodium from Press Coated Tablets

Cumulative percentage drug release from press coated tablets

	Formulations code				
Time in hrs	**P1F3**	**P2F3**	**P3F3**	**P4F3**	**P5F3**
1	02.2±0.3	04.4±0.50	05.6±0.7	04.8±0.40	03.3±0.5
2	05.4±0.2	09.1±0.30	11.6±0.8	09.3±0.60	07.6±1.1
3	10.6±4.8	12.2±1.10	28.6±1.2	24.7±1.17	09.7±1.2
4	13.7±0.1	13.4±0.40	40.2±1.3	42.6±1.15	11.9±1.1
5	19.4±1.1	22.8±1.40	59.8±0.5	57.4±2.10	28.4±1.2
6	28.6±1.1	34.6±1.18	79.2±2.1	73.6±0.60	43.2±1.1
7	34.9±0.9	37.4±1.13	82.3±2.1	79.6±2.40	55.1±0.8
8	43.8±1.1	46.2±1.14	90.3±1.1	89.7±0.90	70.9±1.1
9	55.7±1.1	57.9±0.90	90.4±1.1	92.6±3.10	83.4±3.1
10	65.5±0.6	73.2±1.14	90.6±4.1	95.2±1.19	92.8±3.8

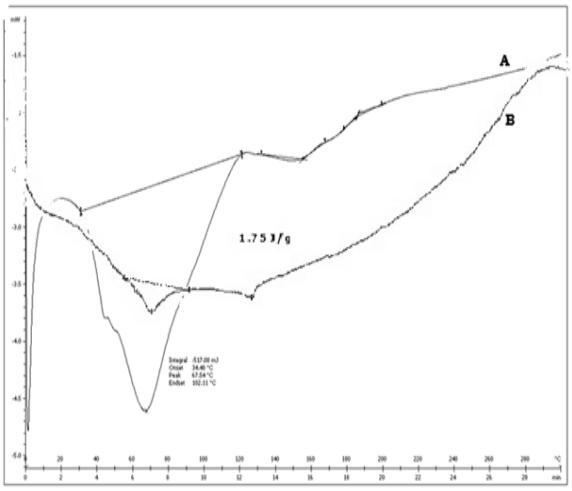

Fig 2. DSC thermograms of: (a) montelukast sodium pure; (b) montelukast press coated tablet.

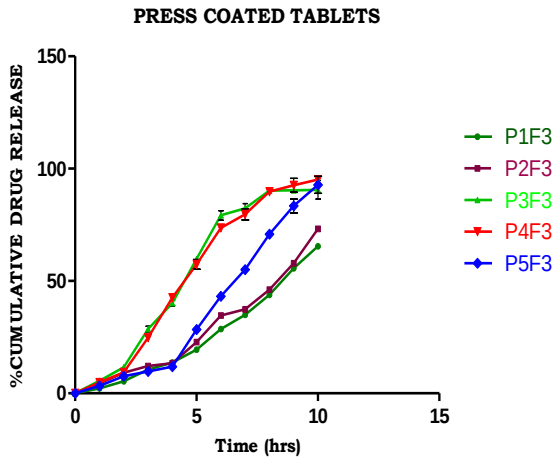

Fig 3. Dissolution comparison plot for press coated tablets

CONCLUSION

Press coated time release tablets of montelukast sodium can be obtained using direct compression technique. Xanthan gum and guar gum mixture provide sufficient lag time for timed release of montelukast sodium useful for chronopharmacotherapy of asthma. The results of in vitro dissolution tests indicate that amount of polymer in the formulation affects the drug release rate. These results also show that the *in vitro* lag time before drug release could be used to predict the in vivo lag time of drug release. Thus, press coated time-release formulations that control the plasma drug concentrations by design show promise as timed release drug delivery systems.

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