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FORMULATION AND *IN VITRO* EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF MONTELUKAST SODIUM BY PRESS COATED TABLETS 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 sodium alginate, guar gum and mixture of it respectively. Fourier transform infra-red (FTIR) spectrometry, differential scanning colorimetry (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 40ºC and 55ºC 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 P5F2 shows great ideal in pulsatile drug delivery. The release data from the formulation was found to fit in peppas model with R^2 of 0.938.

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

INTRODUCTION

PULSATILE DRUG DELIVERY SYSTEM

The oral route of drug delivery is typically considered the favoured and the most user friendly means of drug administration having the highest degree of patient compliance, as a result of which much effort are aimed to identify orally active candidates that would provide reproducible and effective plasma concentrations *in vivo* (Charman&Charman, 2003). Traditionally, drug delivery systems have focused on constant/sustained drug output with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance can also be expected for the controlled/sustained release drug delivery systems, compared to immediate release preparations (Burnside et al., 2003) However, in the field of modern drug therapy, growing attention has lately been focused on pulsatile delivery of drugs for which conventional controlled drug-release systems with a continuous release are not ideal.

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired.

Necessity of Pulsatile Drug Delivery Systems: There are many conditions and diseases where sustained release formulations do not show good efficacy so these conditions demand the release of drug after a lag time in, in other words it is required that the drug should not release at all during the initial phase of dosage form administration. In such cases Pulsatile DDS is applicable.

1. Many body functions follow circadian rhythm, i.e., their activity increases or decreases with time. A number of hormones like rennin, aldosterone, and cortisol show daily as well as timely fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion.
2. Severity of diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension is time dependent. Sharp increase in asthmatic

attacks during early morning hours have been reported by Dethlefsan and Repges such a condition demands supplement of drug at particular time rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug as a burst after the time of administration (during morning hours), would be ideal in this case. Same is true for preventing heart attacks in the middle of the night and the morning stiffness typical of people suffering from arthritis.

3. Drugs like Salbutamol sulphate produce biological tolerance and hence demand for a system that will prevent their continuous presence at the site of action as this tends to reduce their therapeutic effect.

4. Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting. These conditions can be satisfactorily handled by enteric coating, and in this sense, enteric coating can be considered as a pulsatile drug delivery system.

5. To achieve localized action at distal organs of GIT such as colon for drugs used in ulcerative colitis (e.g. Sulfasalazine) the drug release needs to be prevented in the upper two-third portion of the GIT.

6. The drugs that undergo extensive first-pass metabolism (ß-blockers) and those that are characterized by idiosyncratic pharmacokinetics or pharmacodynamics resulting in reduced bioavailability, altered drug/metabolite ratios, altered steady state levels of drug and metabolite, and potential food-drug interactions require delayed release of the drug to the extent possible.

All of these conditions demand for an efficiently programmed drug delivery system releasing the right amount of drug at the right time.

This can be achieved by Pulsatile Drug Delivery Systems. A pulsatile drug delivery system is characterized by a rapid drug release after a predetermined lag time that is an interval of no drug release.

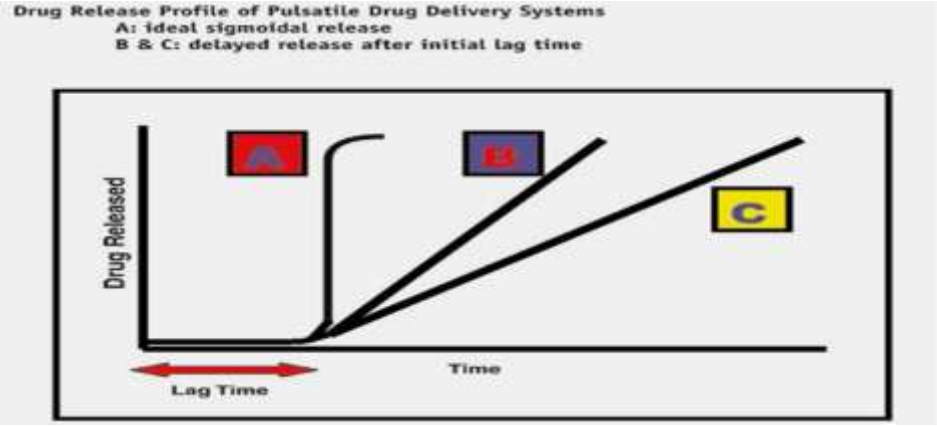

Fig 1. The drug release profile of pulsatile drug delivery system

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Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems".

In these systems, there is rapid and transient release of a certain amount of drug molecules within a short time period immediately after a predetermined off release period ,i.e lag time(Survase& Kumar, 2007). Lag time is defined as the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredient begins to get released from the dosage form(Ayres, 2004).

Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, microflora activated systems etc. which can be designed as per the physiology of disease and properties of the drug molecule (Survase& Kumar, 2007). The pulsatile release of an active agent is desirable when treating diseases that require drug delivery in a manner to maintain therapeutic levels albeit circadian rhythms(Ting & Hsiao, 2004).

A large body of literature can be found on oral pulsatile drug delivery systems, which have been accepted as potentially useful to the chronotherapy of some common diseases, such as bronchial asthma, hypertension, angina pectoris, allergic rhinitis and osteo-/ rheumatoid-arthritis with mainly night or early morning symptoms(Aithal et al., 2006).

Table 1: Diseases requiring Pulsatile Drug Delivery

Disease	Chronological Behaviour	Drugs used
Peptic Ulcer	Acid secretion in high in the afternoon and at night	H2 blockers
Asthma	Precipitation of attacks during night or at early morning hour	β 2 agonist, Antiasthmatics
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blocker, ACE inhibitors, β blockers etc.
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Diabetes Mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate
Hypercholesterolimea	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors

Advantages of Pulsatile drug delivery system

1. Extended day time night time activity.
2. Reduce side effects.
3. Reduced dosage frequency.
4. Reduction in dose size.
5. Improved patient compliance.
6. Lower daily cost to patient due to fewer dosage unit are required .
7. Drug adapts to suit cardiac rhythms to body function or disease.
8. Drug targeting to specific site like colon.
9. Protecting of mucosa from irritating drugs.

Disadvantages of Pulsatile drug delivery system

1. Multiple manufacturing steps in case of Multiparticulate drug delivery system.
2. Low drug load.
3. Incomplete release.
4. In vivo variability in single unit pulsatile drug delivery system.
5. Drug dose manipulation in case of child and elder patients is not possible.
6. Immediate withdrawal of drug is not possible.

Table 2: Marketed Technologies of pulsatile drug delivery system

Technology	Mechanism	Proprietory name and dosage form	API	Disease	Reference
CODAS®	MultiparticularPh dependent system	Verelan® PM; XL release capsule	Verapamil HCL	Hypertension	(Panoz& Geoghegan,1989)
DIFFUCAPS®	Multiparticulate system	Innopran®; XL Tablets	Verapamil HCL, Propranolol HCL	Hypertension	(Percel et al., 2002)
Three dimen-Externally TheirForm®	Externally regulated system	TheirForm®	Diclofenac HCL	Inflammation	(Katstra et al., 2000)
PulsincapTM	Rupturable	PulsincapTM	Dofitilide	Hypertension	system (Stevens et al., 2002)

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, 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.

OBJECTIVE OF THE STUDY

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

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, Sodium lauryl sulphate and Talc from S.D. Fine Chem. Ltd., Mumbai, Sodium Alginate from L.R. Sisco Research Lab.Pvt. Mumbai.

Methods

(1) Preparation of dilution medium:

For the preparation of dilution medium firstly 7.4pH Phosphate buffer was prepared. The prepared buffer was sonicated for few minutes for obtaining uniform solution. Further 0.5% Sodium Lauryl Sulphate was mixed uniformly.

(2) Preparation of Standard Montelukast Sodium Solution:

About 10mg of Montelukast Sodium pure drug was weighed accurately and transferred into 10ml volumetric flask. The volume was made up to 10ml using ethanol to obtain a solution that has a concentration equal to 1 mg/ml standard solution.

Procedure for construction of calibration curve

To a series of 10ml volumetric flasks, carefully transferred aliquots of standard drug solution (0.2to 1.0 ml, 10µg/ml) and the volume was made with the diluents. The instrument was for photometric mode and the absorbances of each solution were recorded at 287.3nm against the blank diluents. Calibration curve was constructed by Taking absorbances on ordinates and concentration of the standard Montelukast Sodium on abscissa.

Procedure for Assay

To a cleaned 10ml volumetric flask transferred afew ml of sample solution of Montelukast Sodium and the volume was made with the diluents.Absorbance of the resulting solution was recorded at 287.3nm against its corresponding blank prepared in a similar manner except adding the substance being analyzed. The concentration of Montelukast Sodium present in the tablet dosage form was computed from its calibration curve.

Micromeritic properties

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

The inner core tablets were prepared by using direct compression method as per formulation variable shown in Tab3. 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 Sodium Alginate and Guargum as shown in Tab 4 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 4, 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.

Table 3: Formulation variables of Rapid release core tablets of montelukast sodium

Formulation	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)
Montelukast	10	10	10	10	10	10
Microcrystalline Cellulose	62.3	61.5	62.2	61.5	62.2	61.5
Lactose monohydrate	65.7	61.5	65.7	61.5	65.7	61.5
Crospovidone	10	15	-	-	-	-
Croscarmellose sodium	-	-	10	15	-	-
Sodium starch Glycolate	-	-	-	-	10	15
Magnesium Stearate	2	2	2	2	2	2
Total Weight	150	150	150	150	150	150

Table 4: Formulation of Montelukast sodium press coated tablets.

Formulation	P1(mg)	P2(mg)	P3(mg)	P4(mg)	P5(mg)
Sodium alginate	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, 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 (ErwekaApparatebau 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

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.

$$\text{Swelling index (\%)} = [Ws\text{-}Wd / Wd]\ 100$$

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 10ºC/min over a temperature range of 50-300 ºC. The sample was hermetically sealed in an aluminium crucible.

Dissolution rate study of rapid release core tablets (RRCT)

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. 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

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

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

RESULTS AND DISCUSSION

Solubility: Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

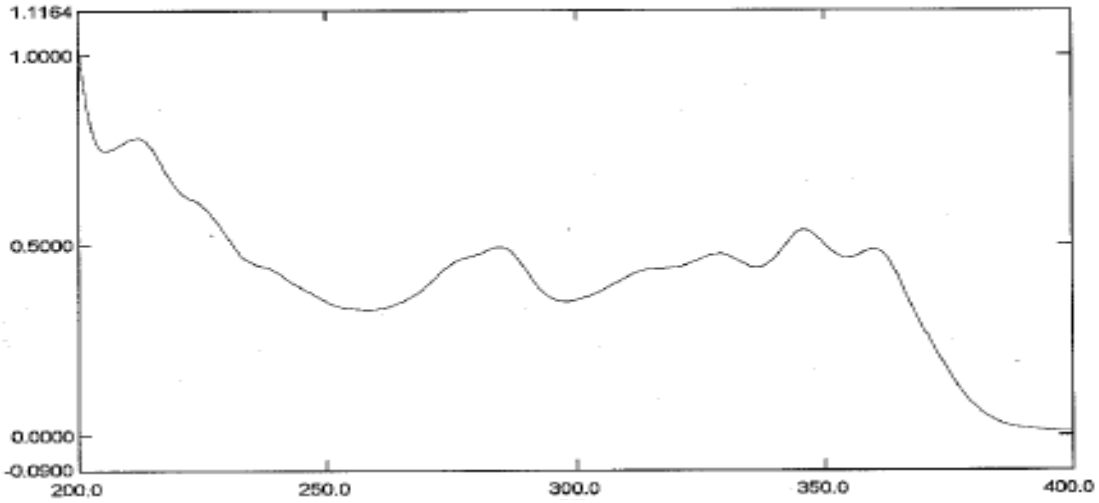

Fig 2: UV Spectrum of Montelukast sodium

Table 5: Mean absorbance values and statistical data of the calibration curve for the estimation of montelukast sodium

S.No	Concentration(µg/ml)	Mean Absorbance* ± S.D
1	2	0.0776 ± 0.00046
2	4	0.1466 ± 0.00011
3	6	0.2136 ± 0.00013
4	8	0.2816 ± 0.00026
5	10	0.3506 ± 0.00029

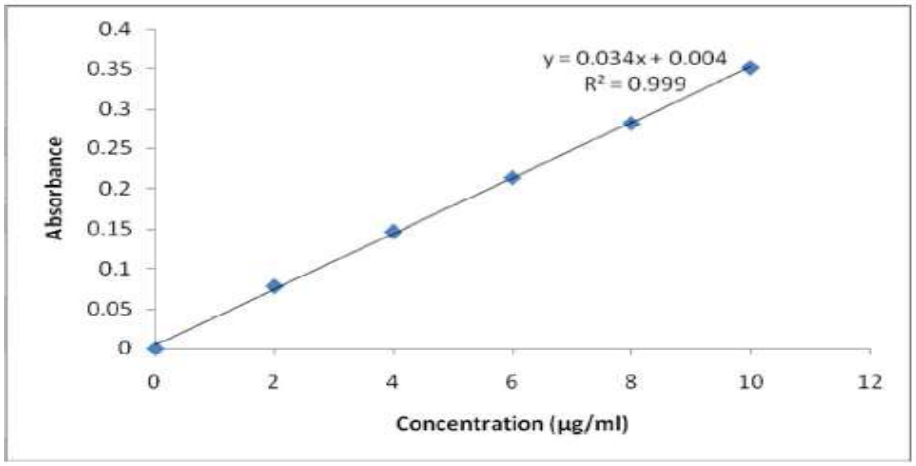

Fig 3: Calibration curve of montelukast sodium

Table 6: Optical Characteristics of Proposed Method

Parameter	Montelukast values
Linearity range (µg/ml)	2-100µg/ml
Regression equation (Y*)	y = 0.004 + 0.034x
First regression coefficient (b)	0.034
Intercept (a)	0.004
Standard deviation of the intercept (Sa)	$1.27 * 10^{-2}$
Correlation coefficient	0.999
Standard error of estimation	$3.5 * 10^{-3}$
Limit of Detection (LOD)	1.234
Limit of Quantification(LOQ)	3.735

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. 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 4.

SC scans of the montelukast sodium press coated tablet and it pure drug are presented in Fig 5. The thermogram of Montelukast exhibited an endothermic peak at 67.5ºC corresponding to its melting point range. 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.

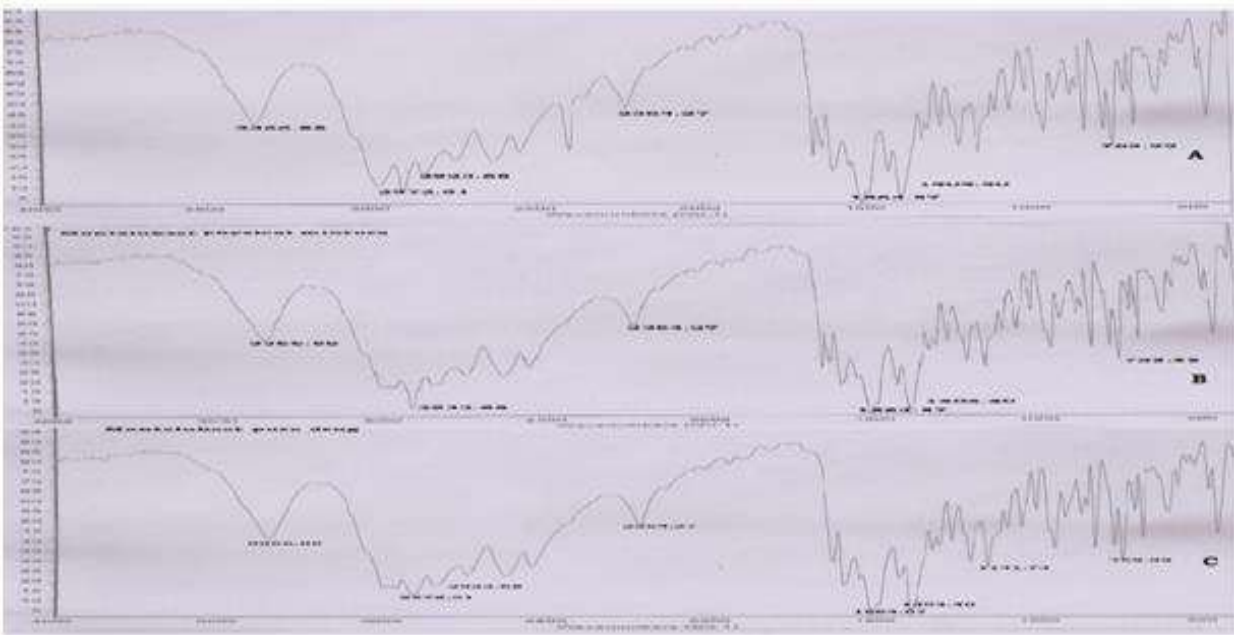

Fig 4: FTIR spectra of: (a) montelukast sodium; (b) physical mixture of drug & excipients; (c) montelukast rapid release core tablet.

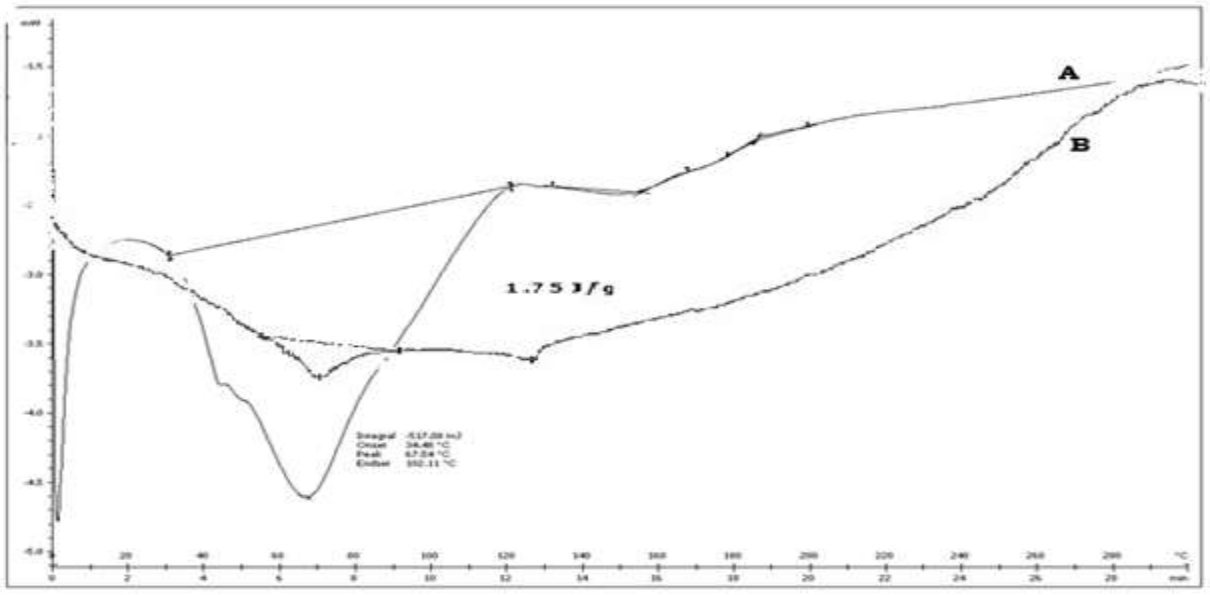

Fig 5. DSC thermograms of: (a) montelukast sodium pure; (b) montelukast press coated tablet.

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 7. 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 7: Evaluation of directly compressible blends of core tablet

Formulation code	Bulk Density (g/cm^3) ±SD	Tapped Density(g/cm^3) ± SD	Hausner's ratio± SD	Carr'sIndex (%)±SD	Angle of repose(Degrees) ± SD
F1	0.39±0.90	0.47±0.06	1.20±0.80	17.02±1.80	29±2.0
F2	0.44±0.70	0.49±0.03	1.13±0.18	11.60±1.50	25±2.0
F3	0.41±0.80	0.46±0.07	1.18±0.19	16.40±0.90	26±1.0
F4	0.42±0.10	0.51±0.03	1.21±0.23	17.45±1.40	28±2.0
F5	0.45±0.90	0.52±0.02	1.15±0.15	13.46±1.20	27±1.0
F6	0.41±0.11	0.501±0.04	1.99±0.22	16.57±1.20	30±2.0

Tab 8: Evaluation of Formulations of rapid release core tablet

Formulation Code	Weight variation (%)±SD	Hardness (Kg/cm^2) ±SD	Friability (%) ±SD	Thickness (mm) ±SD	Disintegration time (min) ±SD	Wetting time (sec) ±SD
F1	1.24±0.5	6.42±0.35	0.56±0.35	2.1±0.71	1.32±0.4	48±6.0
F2	1.43±0.3	5.53±0.33	0.62±0.05	2.4±0.20	1.10±0.5	56±4.0
F3	1.19±0.2	4.34±0.35	0.54±0.22	2.2±0.58	2.56±0.2	48±8.0
F4	1.53±0.4	5.32±0.21	0.53±0.65	2.5±0.25	3.30±0.4	50±3.0
F5	1.64±0.7	3.53±0.45	0.55±.032	2.0±0.87	1.45±0.7	54±3.0
F6	1.49±0.6	5.42±.21	0.61±0.50	2.3±0.35	2.12±0.3	54±3.0

Tab 9: Physical evaluation for press coated tablets

Parameter	Weight variation (%)±SD	Hardness (Kg/cm^2) ±SD	Thickness (mm) ±SD	Friability (%)±SD	Swelling index(%) ±SD
P1F2	1.65±0.12	6.5±0.98	6.5±0.67	0.7±0.10	280±18.0
P2F2	1.42±0.80	6.6±0.45	6.4±0.34	0.62±0.06	130±9.0
P3F2	1.54±0.67	7.2±0.45	6.0±0.23	0.54±0.05	180±12.0
P4F2	1.57±0.09	6.70±0.76	6.45±0.87	0.55±0.09	100±8.0
P5F2	1.18±0.12	6.9±0.23	6.1±0.56	0.62±0.07	240±16.0

Tab 10: Shows Dissolution Rate of Montelukast Sodium from rapid release core Tablets

FormulationCode	Cummulative % drug release of rapid release core tablet Time in minutes						
	05	**10**	**15**	**20**	**30**	**45**	**60**
F1	23.6±0.6	34.2±1.5	48.8±1.9	56.1±2.6	70.9±3.2	80.7±4.3	91.6±0.8
F2	40.3±0.8	58.8±1.3	75.5±1.6	84.9±3.2	98.7±3.1	-	-
F3	21.9±0.5	35.6±1.9	48.4±1.4	57.3±2.9	69.8±0.9	76.8±1.5	89.1±0.31
F4	26.6±0.4	39.5±1.9	46.4±2.1	59.7±2.3	76.2±0.4	80.9±0.9	90.5±0.8
F5	29.1±0.9	40.5±1.2	65.4±2.1	80.7±2.6	88.6±2.3	96.8±3.2	104.4±0.2
F6	25.3±0.9	34.6±1.8	49.7±1.7	64.2±3.01	73.9±1.8	84.2±0.2	94.3±0.9

Characterization of rapid release core and press coated tablet

The rapid release core tablets were tested for diameter, thickness, hardness, friability, tensile strength and results are presented in table 8 and 9. 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 *in-vitro* disintegration time were found to be very less for F2 and wetting time for F4 & F5 formulation that is 50 sec and 54 Sec respectively and the results of the dissolution profiles of all the formulations were represented in table 10. F2 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 P5F2 showed only 12% of drug release upto 4h and 93% of drug release was found within 10h.However, P4F3 showed 42% of drug release within 4h and 94% of drug release upto 10h,nearly half of the dose was released within 4h and shows <4h lag time. The results are presented Table 11.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 Sodium alginate 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 0.938.

Table 11: Cumulative percentage drug release from press coated tablets

Time (hrs)	P1F2	P2F2	P3F2	P4F2	P5F2
1	03.2±0.3	05.4±0.50	04.6±0.7	06.8±0.40	02.2±0.5
2	06.4±0.2	10.1±0.30	12.6±0.8	10.3±0.60	06.6±1.1
3	9.6±4.8	14.2±1.10	29.6±1.2	25.7±1.17	09.7±1.2
4	13.7±0.1	18.4±0.40	42.2±1.3	43.6±1.15	12.9±1.1
5	20.4±1.1	24.8±1.40	61.8±0.5	58.4±2.10	29.4±1.2
6	29.6±1.1	35.6±1.18	79.2±2.1	75.6±0.60	44.2±1.1
7	33.9±0.9	38.4±1.13	83.3±2.1	81.6±2.40	59.1±0.8
8	45.8±1.1	48.2±1.14	90.3±1.1	90.7±0.90	71.9±1.1
9	56.7±1.1	59.9±0.90	90.6±1.1	92.6±3.10	85.4±3.1
10	68.5±0.6	75.2±1.14	90.8±4.1	94.2±1.19	93.8±3.8

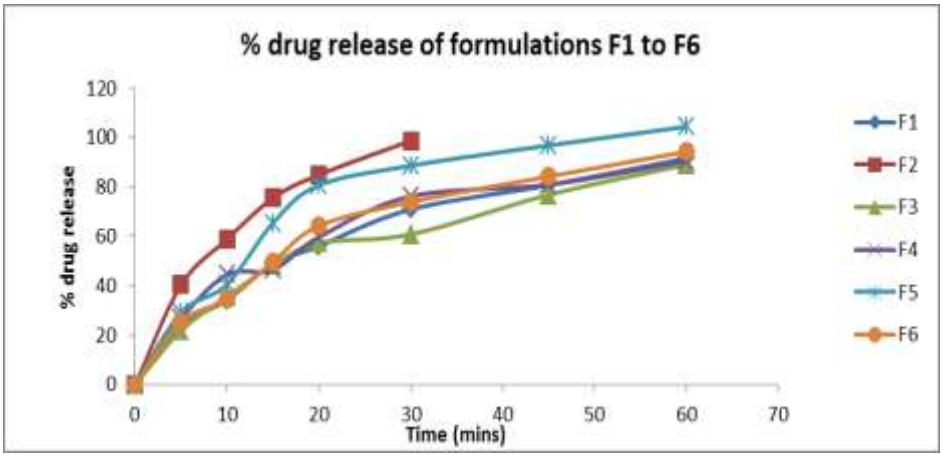

Fig 6: % drug release of Rapid release core tablets of formulation F1 to F6

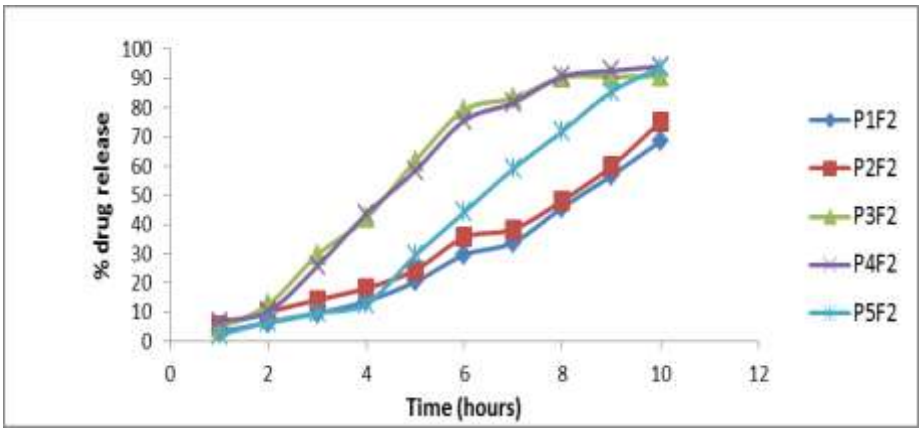

Fig 7: Dissolution comparison plot for press coated tablets

Table 12: Kinetic modeling of montelukast sodium formulation P5F2

S.no	Time (hrs)	CDR	Log CDR	Log t	SQRT t	% drug retained	Log % drug retained
1	**0**	**0**	**-**	**-**	**0**	100	**2**
2	1	2.2	0.342423	0	1	97.8	1.990339
3	2	6.6	0.819544	0.30103	1.41421	93.4	1.970347
4	3	9.7	0.986772	0.477121	1.73205	90.3	1.955688
5	4	12.9	1.11059	0.60206	2	87.1	1.940018
6	5	29.4	1.468347	0.69897	2.23607	70.6	1.848804
7	6	44.2	1.645422	0.778151	2.44949	55.8	1.746634
8	7	59.1	1.771587	0.845098	2.64575	40.9	1.611723
9	8	71.9	1.856729	0.90309	2.82843	28.1	1.448706
10	9	85.4	1.931458	0.954243	3	14.6	1.164353
11	10	93.8	0.972203	1	3.16228	6.2	0.792392

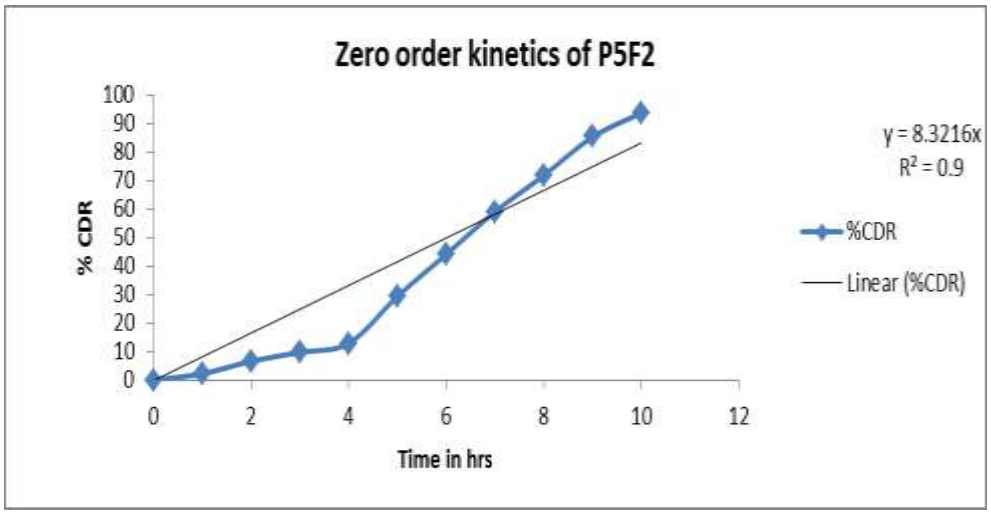

Fig 8: Graph of zero order kinetics of formulation P5F2

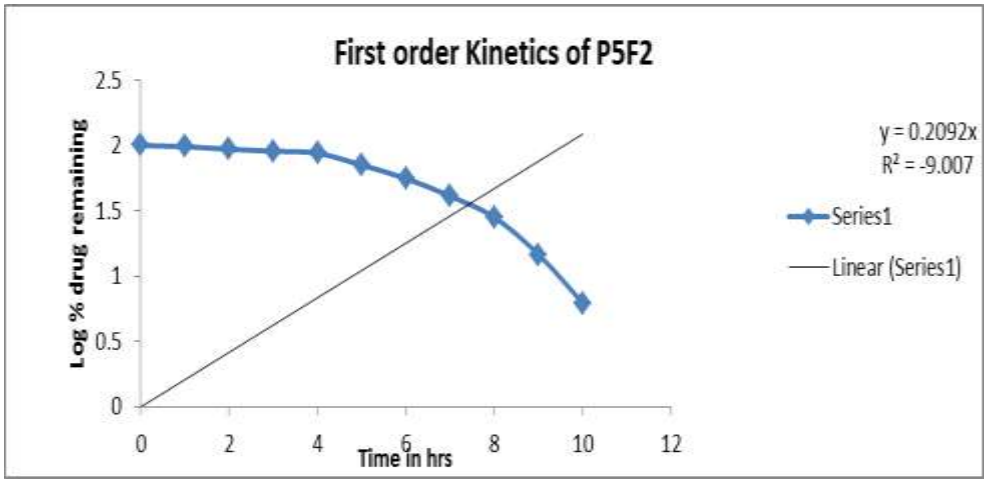

Fig 9: Graph of First order kinetics of formulation P5F2

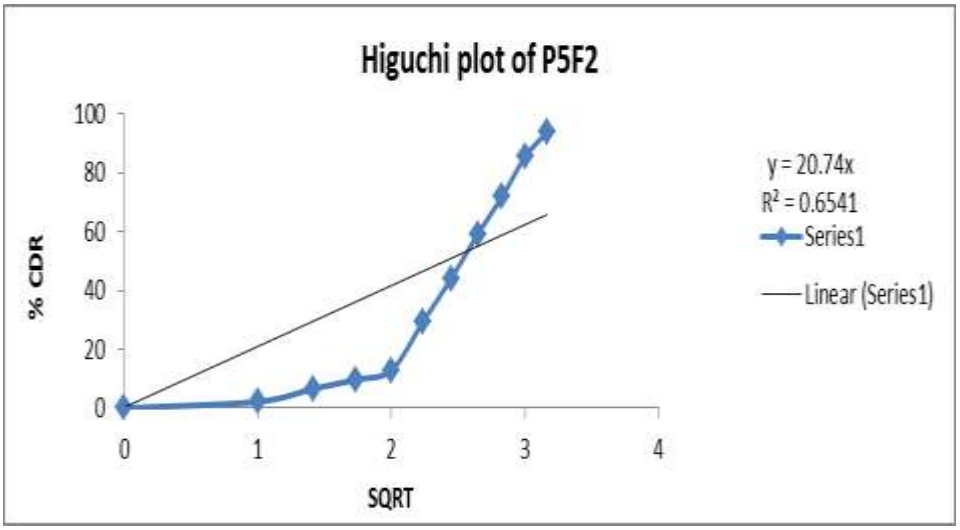

Fig 10: Higuchi plot of formuation P5F2

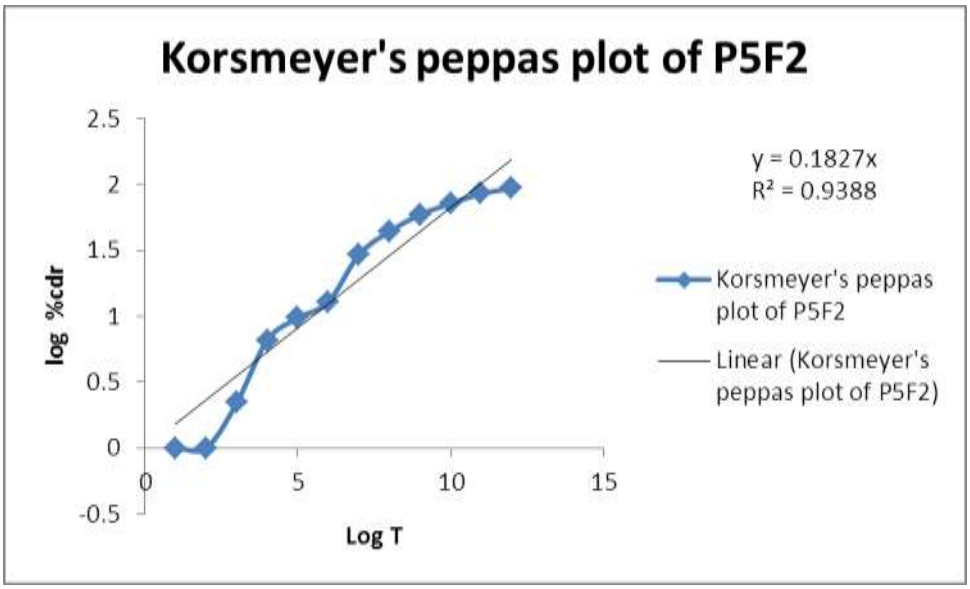

Fig 11: Graph of Korsmeyer's peppas of P5F2

From the study of release kinetics we can jusify that the best formulation P5F2 may follow zero order kinetics and Korsmeyer'speppas model.

FUTURE PERSPECTIVES

Now a day's pulsatile drug delivery is gaining popularity. The prime advantage in this drug delivery is that drug is released when necessity comes. As a result chance of development of drug resistance which is seen in conventional and sustained release formulations can be reduced. Furthermore, some anticancer drugs are very toxic. These drugs give hazardous problems in conventional and sustained release therapies. Now many FDA approved chronotherapeutic drugs are available in the market. This therapy is mainly applicable where sustained action is not required and drugs are toxic.

Key point of development of this formulation is to find out circadian rhythm i.e. suitable indicator which will trigger the release of drug from the device. Another point is absence of suitable rhythmic biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in rhythmic manner. Regulatory is another big question. In preapproval phase it is sometimes difficult to show chronotherapeutic advantage in clinical settings. In postapproval phase causal recreational drug abuse along with on a much larger scale, by the criminal diversion of these modified formulations for profit have arisen problems. The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow an approval of a drug to go forward while exercising some restrictions.

Many researches are going on the pulsatile drug delivery to discover circadian rhythm with suitable device in the world. In future this delivery will be a leading way to deliver therapeutic agents due to its some unique characters like low chance of dose dumping, patient compliance and the above factors.

CONCLUSION

Press coated time release tablets of montelukast sodium can be obtained using direct compression technique. Sodium Alginate 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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