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

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ABSTRACT

The main aim of the given research was to develop and assess the chrono-modulated drug delivery of Montelukast. Sodium when taken at bedtime releases the maximum amount of the drug in the morning hours after a predetermined time delay (lag time of 5-6 h). Various nocturnal asthma symptoms like chest tightness, shortness of breath, cough, and wheezing can be prevented when histamine concentration peak level coincided with the greatest degree of bronchoconstriction when asthma condition is more prevalent. In this research work core-coat tablets were prepared by press coating technique containing synthetic polymers like HPMC K4M and ethyl cellulose and natural polymers like xanthan and guar gum. The FT-IR spectra of montelukast sodium with different polymers showed no shift in peak, indicating absence of interaction. Pre-compression studies such as bulk density, tapped density, angle of repose and assay were evaluated for the prepared formulation. The post-compressions studies such as weight variation, thickness, friability, hardness, disintegration time, drug content and *in-vitro* dissolution studies. All the prepared formulations were within the standard pharmacopeia limit. The formulation (F3) containing HPMC K4M and ethyl cellulose (1:1) manifested the finest dissolution (99.96%) maximum release at the early morning hours.

INTRODUCTION

Oral controlled drug delivery systems are the most common form of controlled drug delivery systems which release the drug with constant or variable release rates. Indeed, these systems optimize drug efficacy and reduce adverse effects. Indeed, reduced dosing frequency and improved patient compliance can be achieved using controlled drug delivery systems, compared to immediate release preparations.

Conventionally, in oral controlled drug delivery systems, the release of the drug commences, as soon as the dosage form is administered. In addition, there are some specific conditions for which conventional release pattern is not suitable as it requires some sort of timed release of therapeutic agents at specific sites. Therefore, there is a need to develop a system which is capable of releasing drugs after predetermined time delay or lag time and maintain constant drug release for specified time. These drug deliveries are generally known as pulsatile drug delivery systems (PDDS), sigmoidal release systems or time-controlled systems.

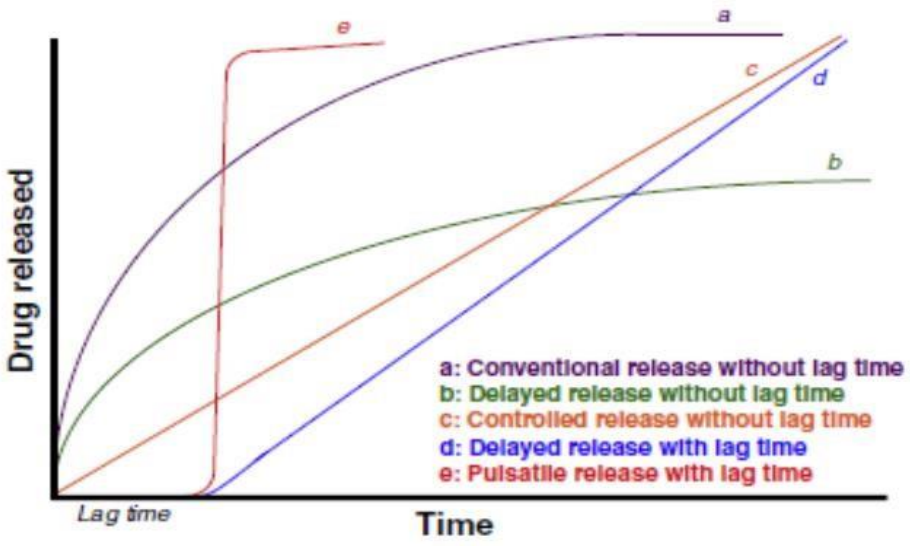

Figure 1: Different release patterns for various pharmaceutical dosage forms.

1. Pulsatile drug delivery system

The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time. Such systems are also called time-controlled as the drug released is independent of the environment. These

systems are designed in a manner that the drug is available at the site of action at the right time in the right concentration.

Circadian Rhythm:

Circadian rhythms are self-sustaining endogenous, exhibiting periodicities of about one day or 24 h. normally circadian rhythms are synchronized according to the body's pacemaker clock located in suprachiasmic nucleus of hypothalamus. The physiology and biochemistry of a human body is not same everyday but variable in a predictable manner as defined by the timing of the peak and trough of each of the body's circadian processes and functions.

There are many documents that verify that more chances of heart attacks occur during the early morning time, as levels of cortisol and blood pressure are high in early morning and low in the night. Indeed, nocturnal asthma increased responsiveness in early morning and there is a sudden surge of gastric acidity in the mid night. Moreover, high cholesterol synthesis occurs at night than in the daytime. All these events associated with the circadian rhythms, gives the importance for designing time specific drug delivery which is very important.

Need of Pulsatile Drug Delivery System

Many body functions follow circadian rhythm, i.e. their activity increases or decreases with time. 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 the stomach, gastric emptying, and gastro-intestinal blood transfusion.

Gastric emptying, Acid secretion cholesterol synthesis, and gastrointestinal blood transfusion may alter with circadian rhythm.

Chronopharmacotherapy of diseases which shows circadian rhythms in their path physiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.

Drugs undergo extensive first-pass metabolism that is easily given by pulsatile drug delivery system.

Lag time is essential for those drugs undergoing acidic degradation (e.g. peptide drugs) that irritate the gastric mucosa or induce nausea and vomiting.

Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon, the drug release should be prevented in the upper two-thirds portion of the GIT.

Advantages of Pulsatile Drug Delivery System.

- It extended day time or night time activity.
- Less side effects.
- Less dose size and dosing frequency.
- Good patient compliance.
- Improve bioavailability
- Drug adapts to suit circadian rhythms of body functions or diseases.
- It targets specific site like colon.
- It protects mucosa from irritating drugs.
- Drug loss is prevented by extensive first-pass metabolism.

Disadvantages of Pulsatile Drug Delivery System:

- Lack of manufacturing reproducibility and efficacy
- More formulation Process
- Expensive
- Need of advanced technology with an advance instrument
- In-vivo variability in single unit pulsatile drug delivery system

Table 1: Circadian rhythm and the manifestation of clinical disease

Diseases	Chronological Behaviour	Drugs Used
Cardiovascular Diseases	Increased onset of sudden cardiac death in first 3 hours after awakening	Cardiovascular Drugs
Asthma	Exacerbation is more common during the sleep period & attacks after midnight or at early morning hours	β2-agonist, Antihistamines
Allergic rhinitis	Bad in the morning/upon rising	Antihistamines
Rheumatoid arthritis	Morning pain/ night pain	NSAIDs
Hormone secretion	Growth hormone and melatonin produced at night testosterone and cortisol in the morning hour	Corticosteroids
Angina Pectoris	NSAIDs, Glucocorticoids Chest pain and ECG changes more common in morning time	Anti-angina drugs
Hypercholesterolemia	Cholesterol synthesis is usually more during the night than day time	HMG CoA reductase inhibitors
Myocardial Infraction	Incidence is higher in the early morning	Cardiovascular agents
Diabetes mellitus	Increased blood sugar level after meal	Sulfonylurea, Insulin
Peptic ulcer disease	Acid secretion is high in afternoon and at night	H2 blockers
Sudden cardiac death	Incidence is higher in the morning after awakening	--

Classification of Pulsatile Drug Delivery System:

Pulsatile drug delivery systems can be broadly classified into three classes; they are:

1) Time-controlled pulsatile drug delivery

2) Stimuli-induced pulsatile drug delivery

3) Externally regulated pulsatile drug delivery

ASTHMA

Asthma is the most common long-term inflammatory disease of the airways of the lungs which is characterized by variable and recurring symptoms, reversible airflow obstruction, and easily triggered bronchospasms. Symptoms include episodes of wheezing, coughing, chest tightness, and shortness of breath. These may occur a few times a day or a few times per week. In some cases, swelling in the airways can prevent oxygen from reaching the lungs hence oxygen cannot enter the bloodstream or reach vital organs. Therefore, people who experience severe symptoms need urgent medical attention.

Causes and Triggers

- Pregnancy
- Obesity
- Allergies
- Smoking tobacco
- Environmental factors
- Stress, genetic factors and hormonal factors

Hence asthma can affect people of any age, and the symptoms can range from mild to severe in most cases, effective treatment is available that can help a person live a full and active life with asthma.

CLASSIFICATION OF ANTIASTHMATIC

1. Bronchodilators

- β- Sympathomimetic: Salbutamol, Terbutaline, Ephedrine, Salmeterol
- Methylxanthines: Theophylline, Aminophylline
- Anticholinergic: Ipratropium bromide, Tiotropium bromide

2. Leukotriene antagonists: Montilukast, Zariflukast
3. Mast cell stabilizers: sodium cromoglycate, Ketotifen

4. Corticosteroids

- Systemic: Hydrocortisone, Prednisolone
- Inhalation: Beclomethasone dipropionate, Budesonide

5. Anti-IgE antibody: Omalizumab

MONTELUKAST SODIUM

Montelukast sodium is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT1 receptor. Montelukast sodium is a hygroscopic, optically active, and white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Mechanism of action: Montelukast selectively and competitively blocks the cysteinyl leukotriene 1 (CysLT1) receptor and prevents binding of the inflammatory mediator leukotriene D4 (LTD4). Inhibition of LTD4 activity results in inhibition of leukotriene-mediated inflammatory events including migration of eosinophil and neutrophils, adhesion of leukocytes to vascular endothelium, monocyte and neutrophil aggregation, increased airway edema; increased capillary permeability; and bronchoconstriction. The CysLT1 receptor is found in a number of tissues including spleen, lung, placenta, small intestine, and nasal mucosa, and in a variety of cell types including monocyte/macrophages, mast cells, eosinophil, CD34-positive hemopoietic progenitor cells, neutrophils and endothelial cells.

Chronotherapeutic Management of Asthma:

Chronotherapeutics is the synchronization of medication levels in time with reference to need. It is based on importance of biological rhythms in the pathophysiology of medical conditions and uses the timing of medication to provide maximal efficacy and minimal toxicity. Pulsatile drug delivery system exposes drug only when it is actually required and subsequently, a lower dose can be sufficient for chronotherapy of asthma. The pulsatile-release dosage form can be taken at bedtime with a programmed start of drug release in the early morning hours, when the risk of asthma is higher.

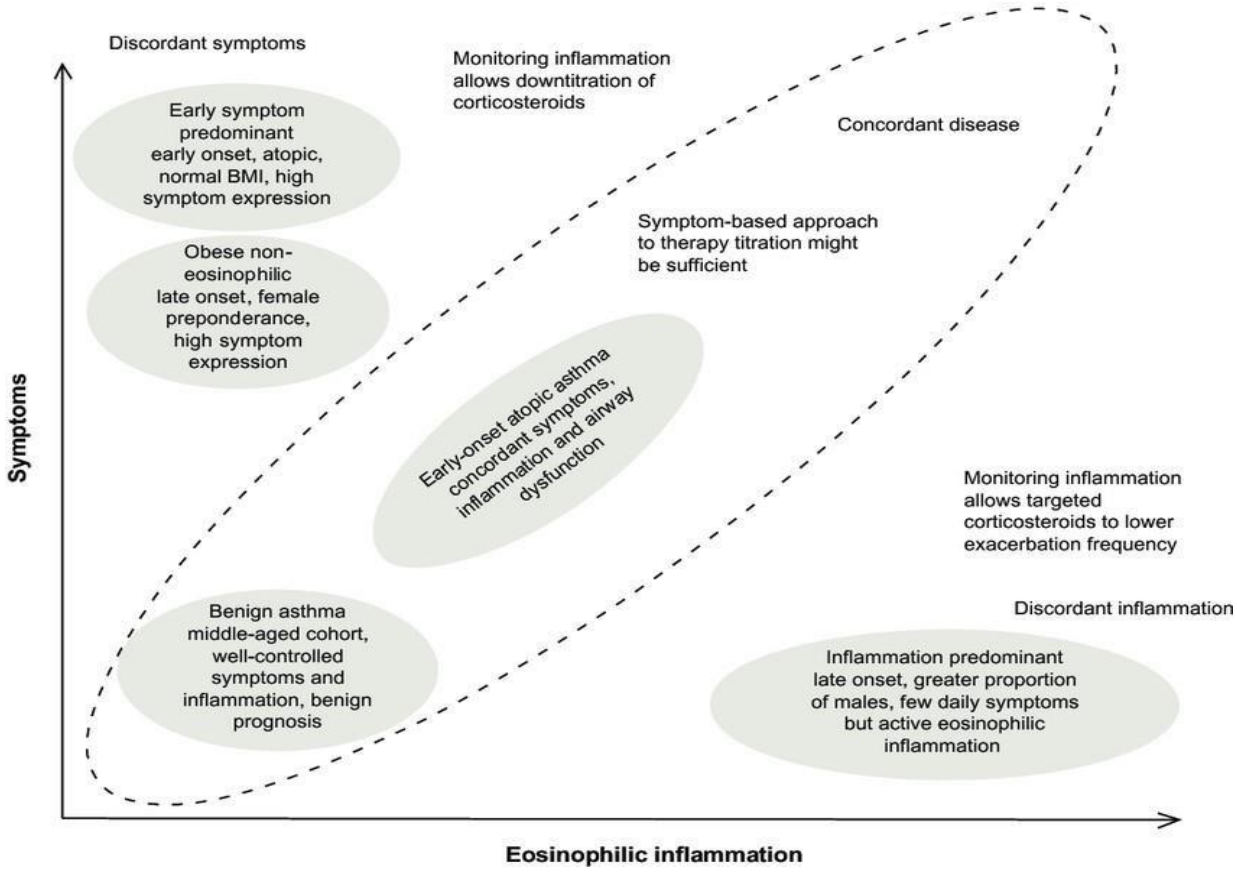

Figure 2: Clinical phenotypes of asthma

Asthma phenotypes can be integrated with distinct pathophysiological mechanisms to describe asthma endotypes that can be treated accordingly.

MATERIALS AND METHODOLOGY

Materials - Drug and Chemicals

The following materials and Laboratory Reagent (LR) were used as supplied by the manufacture. Distilled water was used in all experiments.

Table 2: List of Drugs and chemicals used

S.No.	Materials	Manufacturers/Suppliers
1.	Montelukast Sodium	Mopepen/Moregen Laboratories Ltd
2.	Sodium Starch Glycolate	Maruti Chemical/ K. kumar and Co.
3.	Cross povidone	Ashland Speciality/Everest distribution Pvt. Ltd.
4.	Cross carmellose Sodium	Indian Fine Chemicals, Mumbai
5.	Microcrystalline Cellulose	NB ENT/Drug Centre Delhi Pvt Ltd
6.	Talc	Neelkanth /Org Centre Delhi
7.	Magnesium stearate	Nice Chemicals, Kochi, Kerala
8.	HPMC K4M	Indian Fine Chemicals, Mumbai
9.	Ethyl Cellulose	Indian Fine Chemicals, Mumbai
10.	Xanthan Gum	Signet chemical corporation Pvt. Ltd
11.	Guar Gum	China/K.Kumar and Co.

DRUG PROFILE

Name: Montelukast Sodium

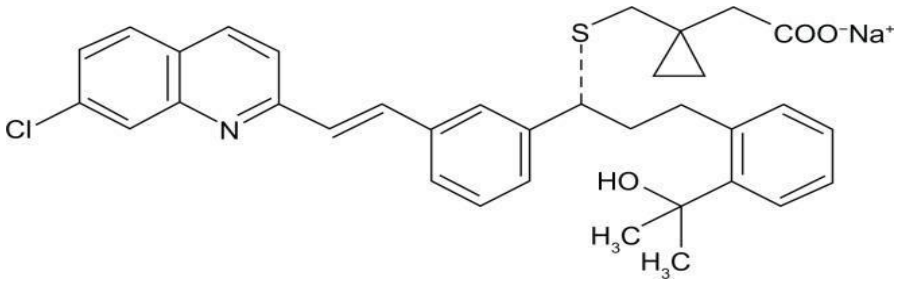

Figure 3: Structure of Montelukast Sodium

Molecular Formula: $C_{35}H_{35}ClNNaO_3S$

Molecular weight: 608.2 g/mol

IUPAC name: Sodium; 2-[1-[[(1*R*)-1-[3-[(*E*)-2-(7-chloroquinolin-2-yl) ethenyl] phenyl]-3-[2-(2-hydroxypropan-2-yl) phenyl] propyl] sulfanylmethyl] cyclopropyl] acetate

Category: Antiasthmatic

State: Solid and Montelukast sodium is a class I drug.

Colour: A white to off white powder.

Solubility: Freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Melting Point: 108-110 °C

Mechanism of action:

Montelukast sodium is a selective cysteinyl leukotriene receptor antagonist with anti-inflammatory and broncho-dilating activities. The CysLT1 receptor is found in a number of tissues including spleen, lung, placenta, small intestine, and nasal mucosa, and in a variety of cell types including monocyte/macrophages, mast cells, eosinophils, CD34positive hemopoietic progenitor cells, neutrophils and endothelial.

Cells. Montelukast selectively and competitively blocks the cysteinyl leukotriene 1 (CysLT1) receptor, preventing binding of the inflammatory mediator leukotriene D4 (LTD4). Inhibition of LTD4 activity results in inhibition of leukotriene-mediated inflammatory events include migration of eosinophils and neutrophils, adhesion of leukocytes to vascular endothelium, monocyte and neutrophil aggregation, increased airway edema, increased capillary permeability; and bronchoconstriction.

Absorption:

It has been observed that Montelukast is quickly absorbed by oral administration. The oral bioavailability of the drug is 64%. Furthermore, it seems that having a regular meal in the morning or even a high-fat snack in the evening does not affect the absorption of Montelukast.

Volume of distribution and Protein binding:

The steady-state volume of distribution for Montelukast is an average between 8 to 11 litres. It has been determined that the protein binding of Montelukast to plasma proteins exceeds 99%.

Metabolism

Montelukast is highly metabolized by the cytochrome P450 3A4, 2C8, and 2C9 is enzymes. It seems that the CYP2C8 enzymes play a significant role in the metabolism of the drug. Nevertheless, at therapeutic doses, the plasma concentrations of Montelukast metabolites are undetectable at steady state in adults and pediatric patients.

Route of elimination:

It has been reported that Montelukast and its metabolites are exclusively excreted in the bile and into the faeces.

Half-life

Plasma half-life of Montelukast varies from 2.7 to 5.5 h when observed in healthy young adults.

Clearance

The plasma clearance for Montelukast is an average of 45 mL/min when observed in healthy adults.

Toxicity

The adverse effects associated with overdosage of Montelukast include abdominal pain, somnolence, thirst, headache, and vomiting, psychomotor hyperactivity. The oral LD50 value determined for mice and rats is >5000 mg/kg. Montelukast has not been studied in pregnant women. Consequently, it should be used during pregnancy only if clearly needed. Additionally, as it is unknown whether Montelukast is excreted into human breast milk, there is also caution regarding the use of the medication in nursing mothers. The plasma half-life of Montelukast is somewhat prolonged in elderly patients.

Therapeutic use Treatment of asthma and seasonal allergic rhinitis.

Storage Store in well-closed container and protected from light.

Drug Interaction:

Table 3: Interaction of drugs with Montelukast Sodium

Drug	Interaction
Acetaminophen	The metabolism of Montelukast can be decreased when combined with acetaminophen
Acetohexamide	The metabolism of Montelukast can be decreased when combined with acetohexamide
Acetylsalicylic acid	The metabolism of Acetylsalicylic acid can be decreased when combined with Montelukast.
Abiraterone	The metabolism of Montelukast can be decreased when combined with abiraterone.

METHODOLOGY

Preformulation Studies of Raw Materials

Pre-formulation study is the first step in the development of the dosage form of a drug substance. It is defined as a phase of research and development, where the biopharmaceutical principles are applied to determine the physicochemical parameters of a new drug substance with a goal to design an optimum drug delivery system.

Melting Point determination

Melting Point of Montelukast Sodium was determined by open capillary method. The drug sample was filled into a capillary and was attached with thermometer and placed in an oil bath filled with liquid paraffin. The tube was heated and the temperature at which the drug melted was noted. This was performed thrice and the average value was calculated.

Bulk Density

- **Loose Bulk Density**

Accurately weighed 10 g of drug, was transferred into a graduated cylinder via a large funnel. The powder in the cylinder was leveled without compacting, and the unsettled apparent volume (V0) was noted. The apparent bulk density (g/ml) was calculated by the following formula;

Bulk density (BD) = Weight of powder/ Bulk volume (V0)

- **Tapped Bulk density**

The transferred 10 g of the drug into a graduated cylinder was mechanically tapped by raising the cylinder and allowing it to drop under its own weight using Bulk density apparatus. The density apparatus was set for 500 taps and after that, the tapped volume was measured and continued operation till the two consecutive readings were equal. The tapped bulk density in gm/ml was calculated by the following formula:

Tapped Density (TD) = Weight of powder / Tapped volume

Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it is packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100] / TD

Hausner's Ratio

Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The formula for Hausner's Ratio is as below:

Hausner's Ratio = TD/BD

Table 4: Effect of Carr's Index and Hausner's Ratio on flow property.

Carr's Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Angle of repose

The angle of repose of API powder was determined by the fixed funnel method. 4 g powder was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the conical pile of the blend. The blend was allowed to flow through the funnel freely onto the graph paper that is placed on a flat horizontal surface. The diameter of the base of the powder cone was measured and the angle of repose was calculated using the following equation.

$$\theta = \tan^{-1}(h/r)$$

Where, 'θ' = angle of repose

'h' = height of the powder cone

'r' = radius of the powder cone

Table 5 Effect of Angle of repose (θ) on Flow property

Angle of Repose (θ)	Type of Flow
< 20	Excellent
20-30	Good
30-34	Passable
>35	Very poor

Drug - Excipients Compatibility Studies

The infrared spectra of Montelukast Sodium and its mixture with excipients were recorded using a FT-IR spectrophotometer. The IR spectra of physical mixture were compared with that of Montelukast Sodium to check for any possible drug-excipients interaction.

Analytical Method

Analytical Method used in the determination of Montelukast Sodium

Spectrophotometric determinations were carried out on double-beam UV-Visible spectrophotometer with 1 cm quartz cell.

Determination of λ max

100 mg of Montelukast Sodium was accurately weighed and dissolved in 100 ml of 0.5% of SLS to get a stock solution of 1 mg/ml. Further, an aliquot was pipetted out and diluted suitably to get the concentration in the Beer's range and was scanned in the wavelength, region of 200-400 nm to record the wavelength of maximum absorption (λ max).

Methods

Preparation of dilution medium

For the preparation of dilution medium firstly 7.4 pH 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.

Preparation of Standard Montelukast Sodium Solution

About 10mg of Montelukast Sodium was weighed accurately and transferred into 10ml volumetric flask. The volume was made up to 10 ml using 0.5% of SLS to obtain a solution that has a concentration equal to 1 mg/ml standard solution. 20 ml of the primary stock solution was further diluted up to 200 ml to produce a secondary stock solution having concentration of 100 µg/ml.

Preparation of Montelukast Sodium Sample solution

Powder quantity equivalent to 10 mg was weighed accurately and transferred to 10ml volumetric flask. Further 20ml of the solution was diluted in 200ml volumetric flask using the dilution media.

Procedure for construction of calibration curve:

To a series of 50 ml volumetric flasks, carefully transferred aliquots of standard drug solution (1 to 6 ml) and the volume was made with the diluents to produce concentration as 2 to 12 µg/ml respectively. The absorbance of each solution was recorded at 345 nm against the blank. Calibration curve was constructed by taking absorbances on ordinates and concentration of the standard Montelukast Sodium on abscissa.

Formulation of Montelukast Sodium Press Coated - Tablets

Preparation of Montelukast Sodium core tablets:

- The core tablets of Montelukast Sodium were prepared by direct compression method.
- An accurately weighed quantity of Montelukast Sodium, Sodium Starch Glycolate, Crosspovide, Crosscarmellose Sodium and MCC were passed through 60# and mixed thoroughly by Spatulation method.
- Talc (2%) and Magnesium stearate (1%) were added into the blend and mixed in airtight plastic container for 5 min.
- The resultant powder blend was evaluated for pre-compression parameters and compressed into flat tablet by an 8 mm die and punches using rotary tablet compression machine.

Table 6: Composition of Montelukast Sodium Core Tablets (CT)

Name of the ingredients	Quantity (mg/ tablet)
Montelukast	10
Cross carmellose Sodium(CCS)	1.5
Sodium Starch Glycolate(SSG)	2
Cross povidone (CP)	2.5
Microcrystalline Cellulose(MCC)	32.5
Talc	1
Magnesium stearate	0.5
Total Weight (mg)	50

(**Note:** 10.4 mg of Montelukast Sodium is equivalent to 10 mg of Montelukast)

Preparation of press-coated tablets of Montelukast Sodium:

Table 7: Composition of outer shell coating materials.

Name of Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)
HPMC K4M	100	75	50	25	_	_	_	_	_	_	75
Ethyl Cellulose	_	25	50	75	100	_	_	_	_	_	_
Xanthum Gum	_	_	_	_	_	100	75	50	25	_	25
Guar Gum	_	_	_	_	_	_	25	50	75	100	_
Total	**100**	100	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Weight(mg)											
Name of Ingredients	**F12** (mg)	**F13** (mg)	**F14** (mg)	**F15** (mg)	**F16** (mg)	**F17** (mg)	**F18** (mg)	**F19** (mg)	**F20** (mg)	**F21** (mg)	**F22** (mg)
HPMC K4M	50	25	75	50	25	_	_	_	_	_	_
Ethyl Cellulose	_	_	_	_	_	75	50	25	75	50	25
Xanthum Gum	50	75	_	_	_	25	50	75	_	_	_
Guar Gum	_	_	25	50	75	_	_	_	25	50	75
Total Weight(mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

- The core tablets were press-coated with 100 mg of mixed blend of the polymers.
- 50 mg of barrier layer material was weighed and transferred into a 10 mm die cavity then the core tablet was placed manually at the centre.
- The remaining 50 mg of the barrier layer material was added into the die and compressed with 10 mm and evaluated for post compression parameters.

Evaluation of Prepared Tablets - Pre-Compression Studies

Bulk density and Tapped Density (g/ml)

Apparent bulk density (BD) and tapped density (TD) were determined by taking 10 gm of the bulk powder from each core tablet formulation.BD and TD were calculated using the following equations:

Bulk density (BD) = Weight of powder/ Bulk volume (V0)

Tapped Density (TD) = Weight of powder / Tapped volume (Vf)

Compressibility Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100] / BD

Hausner's Ratio

Hausner's Ratio was determined by Following Equation:

Hausner's Ratio = TD / BD

Angle of repose

The angle of repose of 4 g bulk powder for different core tablet formulations was determined by the fixed funnel method. Angle of repose was calculated using the following equation:

$$\tan\theta = h/r$$

Where, 'θ' = angle of repose, 'h' = height of the powder cone, 'r' = radius of the powder cone.

Post-Compression Studies:

- Shape and appearance:

The formulated tablets were visually observed for their shape and color.

- Uniformity of thickness:

The thickness of both core tablets and coated tablets was measured using a calibrated Vernier caliper. Three tablets of each formulation were picked randomly and dimensions were measured in mm and standard deviation was also calculated.

- Weight variation test:

The weight variation of tablet was determined by analytical weighing balance. Ten tablets were selected randomly from each batch and weighed individually. The average and standard deviation were then calculated. The specifications for weight variation and percentage deviation mentioned in Indian Pharmacopoeia are given in following table:

Table 8: Limits for Weight Variation (IP)

Average weight of a tablet	Percentage deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

Hardness test - Hardness of both core tablets and coated tablets was determined using a Monsanto hardness tester. Three tablets were randomly picked from each batch and hardness is expressed in kg/cm2. The mean and standard deviation were also calculated.

Friability test - Roche friabilator was used for friability test. Ten core tablets from each formulation were weighed (Winitial) accurately, placed in the friabilator and rotated at 25 rpm for a period of 4 min. Tablets were again weighed (Wfinal) and the percentage weight loss in tablets was determined using formula:

F %

% friability of the tablets less than 1% is considered acceptable.

Assay - 20 core tablets from each formulation were crushed. Powder equivalent to 100 mg of Montelukast Sodium was weighed accurately and dissolved in 100ml of methanol, shaken for ten minutes and filtered. 5 ml of this solution was taken in a 50 ml volumetric flask and volume was made up to the mark with methanol. Thus Montelukast Sodium of strength 100 µg/ml was obtained.

The solution was diluted suitably with methanol and drug content was analyzed at 345 nm against reagent blank.

Uniformity of Content - The content of active ingredient in each of 10 core tablets from each formulation taken at random was determined using the analytical method described in the assay to find out whether the individual contents are within limits set with reference to the average content of the sample**.**

In-vitro Disintegration test - The disintegration test for core tablets was carried by placing one tablet in each tube of the basket and the disc was dropped on tablet. The disintegrating apparatus was operated using simulated intestinal fluid (Phosphate buffer pH 6.8) maintained at 37±0.50 C as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute. The time taken for complete disintegration of the tablet with no mass remaining in the apparatus was measured and recorded. The experiment was carried out in triplicate for each formulation of core tablet.

In-vitro drug release studies of core tablets - Drug release studies of core tablets were carried out using a USP XXIII dissolution rate test apparatus (Apparatus 2, 50 rpm, 37±0.5° C) for 60 min in 0.5% SLS (900 ml). The samples were withdrawn at time intervals 5, 10,

20,30,40,50 and 60 min and directly analyzed for Montelukast Sodium content using UV spectrophotometer at 345 nm. Suitable volume of the dissolution media was added after each sample withdrawal to compensate loss.

In-vitro drug release studies of press-coated tablets - Drug release studies of press-coated tablets were carried out using a USP dissolution test apparatus (Apparatus 1, 50 rpm, 37 °C) for 2 h in simulated gastric fluid (0.1 N HCl, 900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with 0.5% SLS (900 ml) and tested for drug release up to complete drug release. The samples were withdrawn at time intervals of 60 min and directly analyzed for Montelukast Sodium content using UV spectrophotometer at 345 nm. A suitable volume of the dissolution media was added after each sample withdrawal to compensate loss.

Optimization of the barrier layer coating materials -Press-coated tablets with coating material formulation F1-F22 were analyzed for different post-compression parameters. The thickness and compositions of outer shell coating materials of the formulated press-coated tablets were optimized based on in-vitro drug release profile in simulated gastric and intestinal fluids. The formulation with barrier layer over the core tablet showing maximum drug release nearly after 6 h was selected as optimum coating material formulation.

Drug kinetic release

The cumulative amount of Montelukast Sodium release at different time intervals from the different formulations of tablets were fitted to zero order kinetics, first order kinetics, Hixson-Crowell Kinetics, Higuchi's model and korsmeyer-Peppas model to characterize mechanism of drug release.

Zero order release: Zero order release kinetics refers to the process of constant drug release from a drug delivery device. It describes the system in which the release rate is independent of its concentration. In its simplest form, zero-order release can be represented as:

$$Q = Q0 + K0t$$

Where, 'Q' is the amount of drug dissolved in time 't',

'Q0' is the initial amount of drug in solution, and

'K0' is the zero order release constant.

If the zero order drug release kinetic is obeyed, the plot of cumulative % drug release [Q] vs. time[t] will be straight line with a slope of K0 and an intercept at Q0.

First order release: This model has also been used to study absorption and/or elimination of drugs. The release of the drug which followed first-order kinetics can be expressed by the equation:

$$\frac{dC}{dT} = -K_1$$

The above equation can also be expressed as:

$$\text{Log } C = \log C^0 - \frac{K1t}{2.303}$$

Where, 'C' is the amount of drug dissolved in time 't',

'C0' is the initial amount of drug in the solution,

'K1' is the first order release constant

If the release pattern of drug follows first-order kinetics, then a plot of *log of cumulative drug remaining [log (C_0 - C)] vs. time[t]* will be straight line with a slope of $K_1/2.303$ and an intercept at t= 0 of $\log C_0$.

Hixson-Crowell Kinetics: Hixson and Crowell (1931) recognized that the particles' regular area is proportional to the cube root of its volume. They derived the

equation:

$$W_0^{1/3} - W_t^{1/3} = K_{HC}.\ t$$

Where; 'W0' is the initial amount of drug,

'W_t' is the amount of drug released at time 't', and

'K_{HC}' is the Hixson-Crowell rate constant.

If the Hixson-Crowell drug release kinetic is obeyed, the plot of *cube root of drug amount to be released [$W_0^{1/3}$ - $W_t^{1/3}$] vs. time[t]* will be a straight line with a slope of K_{HC} and an intercept at $W_0^{1/3}$.

Higuchi Model: Higuchi tried to relate the drug release rate to the physical constants based on simple laws of diffusion. Higuchi derived an equation to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion. The Fickion diffusion equation is:

$$\mathbf{Mt/M\infty = [2DS\varepsilon\ (A - 0.5S\varepsilon)]^{1/2} * t^{1/2}}$$

Where, Mt and M∞ = cumulative amount of drug release at time 't' and infinite time respectively.

'D' is the Diffusion coefficient,

'S' is Solubility,

'ε' is Porosity, and

'A' is the Drug content per cubic centimeter of matrix tablet.

Simplifying the equation;

$$\mathbf{Mt/M\infty = K_H * t^{½}}$$

Where, 'KH' is Higuchi release constant.

If the Higuchi model of drug release is obeyed, then a plot of *Mt/M∞ versus* $t^{1/2}$ will be a straight line with slope of K_H.

Krosmeyer-Peppas Model: Korsmeyer *et al.* (1983) derived a simple relationship that describes the fractional drug release is exponentially related to the release time. It adequately describes the release of drug from a polymeric system of slabs, cylinders and spheres, as expressed in following equation.

$$\mathbf{M_t / M_\infty = K\ t^n} \quad \text{or, } \mathbf{Log\ (Mt / M\infty) = log\ K + n\ log\ t}$$

Where, 'Mt / M∞' is fraction of drug released at time 't',

'k' is the rate constant, and

'n' is the diffusion exponent.

If the Krosmeyer-Peppas model of drug release is obeyed, then a plot of log cumulative % drug release [Log (M_t / M∞)] vs. log time [log t] will be a straight line. By incorporating the

first 60% of release data, mechanism of release can be indicated according to Korsmeyer where 'n' is the release exponent, indicative of mechanism of drug release.

Table 9: Different Drug Release Mechanisms as per Korsmeyer-Peppas Model

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Stability studies

Stability studies were done to understand how to design a product and its packaging such that product has appropriate physical, chemical and microbiological properties during a defined shelf-life when stored and used.

Tablet formulation was subjected to stability studies over a period of 3 months. The tablets were wrapped with aluminum foil and packed in amber colored screw capped and kept for the stability at 40 ˚C ±2 ˚C/75% RH ± 5%. Samples were taken after 3 month analyzed for the tablet parameters: colour, thickness, hardness, drug content, *In-vitro* disintegration time, and *In-vitro* dissolution profile. *In-vitro* drug release at 0 month and after 3 months of stability study was compared.

DRUG-EXCIPIENTS AND DRUG-POLYMER COMPATIBILITY STUDIES:

a) Montelukast Sodium (Pure Drug)

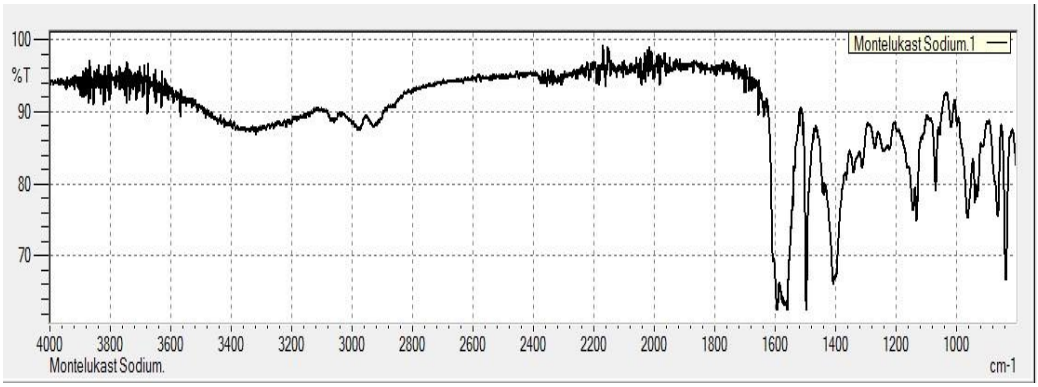

Figure 4: FT-IR Spectra of Montelukast Sodium + HPMC K4M

b)

Figure 5: FT-IR Spectra of Montelukast Sodium + HPMC

c) Crosspovidone

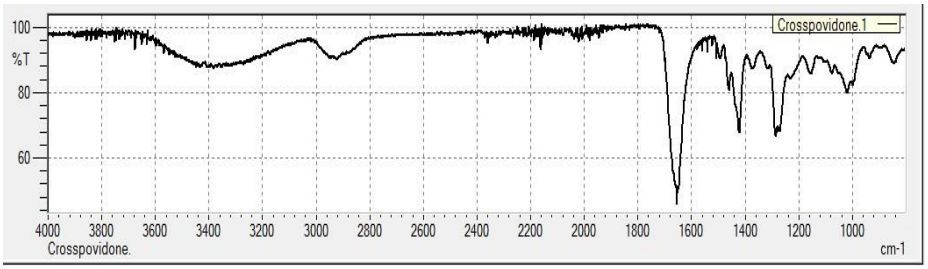

Figure 6: FT-IR Spectra of Crosspovidone

d) Montelukast Sodium +Sodium Starch Glycolate

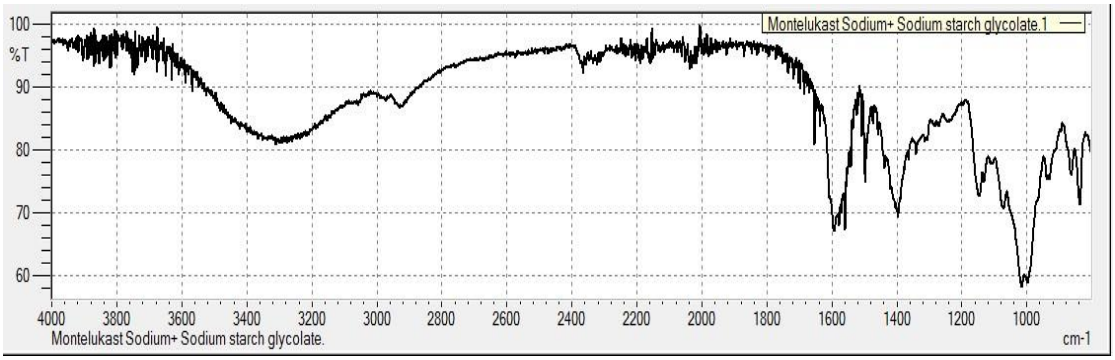

Figure 7: FT-IR Spectra of Montelukast Sodium+ Sodium Starch Glycolate

e) Montelukast Sodium+HPMC K4M +Ethylcellulose+Xanthan Gum+ Guar Gum

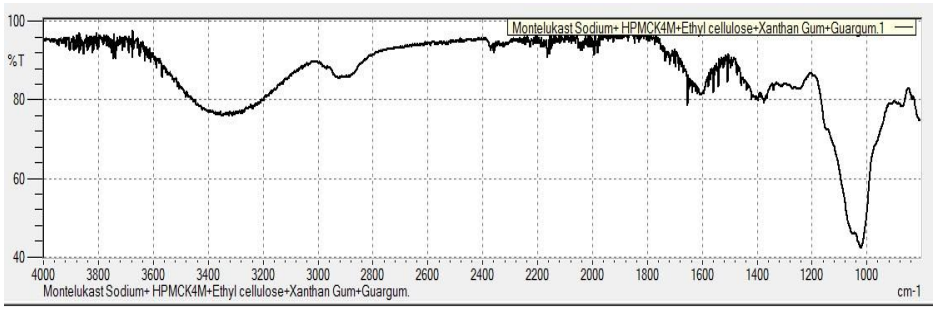

Figure 8: FT-IR Spectra of Montelukast Sodium + HPMC K4M + Ethylcellulose+Xanthan Gum+ Guar Gum

f) Montelukast Sodium + Xanthan Gum + Guar Gum

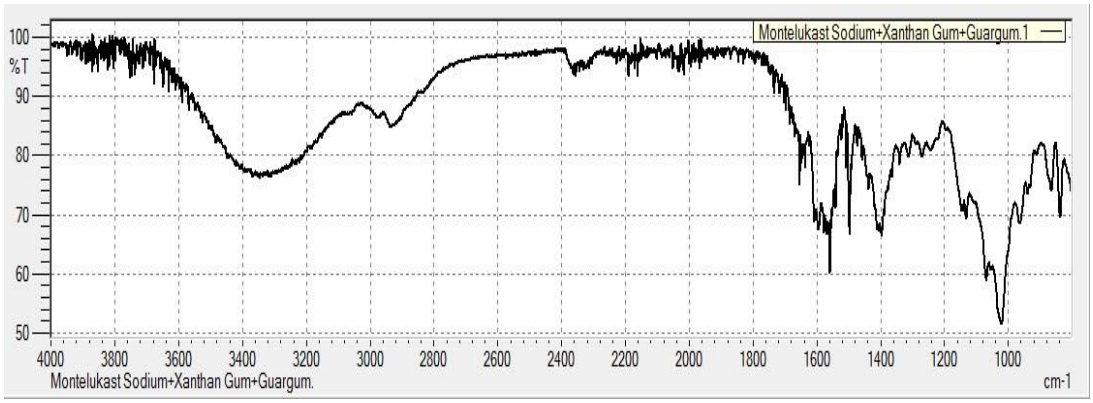

Figure 9: FT-IR Spectra of Montelukast Sodium+ Xanthan Gum + Guar Gum g) Ethycellulose

DISCUSSION

PREFORMULATION STUDIES

Melting point

The melting point of Montelukast Sodium was found to 109 ºC. So the sample complied with the pharmacopoeial standard and confirmed the identity and purity of the sample.

Solubility analysis

The solubility study confirmed that Montelukast Sodium is Freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Absorption maxima (λ max) of Montelukast Sodium

The λ max of Montelukast Sodium in 0.5 % SLS was found to be 345 nm.

Standard calibration curve of Montelukast Sodium

The standard calibration of Montelukast Sodium obeys Beer's law in the concentration range of 2-12 µg/ml in 0.5 % SLS. The curve showed linearity with slope value 0.0357 and regression coefficient 1. The calibration curve of Montelukast Sodium is shown in figure.

Drug and polymer compatibility studies

FTIR spectra of the drug and drug polymer did not show any major shifts of the characteristic peaks indicating drug and polymers (HPMC K4M, ethyl cellulose, xanthum gum, guar gum) are compatible. FTIR spectra of sample drug showed that the functional group frequencies were in the reported range indicating that the obtained sample of drug was pure are shown in table.

Evaluation of Prepared Core Tablets

Pre-Compression Studies:

Compressibility index and Hausner's ratio for powder blend for core tablets were found to be 20.93±1.72 and 1.26±0.028 respectively which indicate the flow property is passable. The angle of repose was found to be 25.64±0.41 showing good flow characteristics.

Post-Compression Studies:

Shape and appearance: The uncoated core tablet was white in color and round in shape.

Weight Variation: Prepared tablets were evaluated for weight variation and standard deviations from the average weight which was 49.98±0.92 mg. The average percentage weight variation was found to be within the prescribed pharmacopoeial limits of ±10%.

Tablet Thickness and Hardness: The hardness of the tablets was found to be 3.52±0.52 kg/cm2 and thickness was found to be 2.13±0.22 mm. The tablets possess good mechanical strength with sufficient hardness and thickness was almost uniform for all the tablets. Friability: The friability of the core tablets was found to be 0.62±0.05% as shown in table. The obtained results were found to be within the range (<1%) indicating tablets possess good mechanical strength.

Assay: The Percentage of drug content was found to be in 98.53±0.24 %. The results were within the limit (not < 90% and not > 110%) as specified in Indian pharmacopeia.

Drug Content Uniformity: The uniformity of drug content was determined on 5 individual tablets following the method of assay. None of the individual values obtained is outside the limits 85% to 115% of the average drug content, as specified in Indian pharmacopeia.

Disintegration Time: The disintegration time for core tablets was found to be 230±25 sec. The disintegration time is less due to three super disintegrants used in the formulation in suitable percentage. Thus, core tablet will undergo faster disintegration. The data is shown in table.

In-Vitro Drug Release Studies: The cumulative percentage drug released from core tablet formulation was studied at different time intervals. The use of super disintegrants Sodium Starch glycolate (4%), cross povidone (5%) and Crosscarmellose Sodium (3%) facilitated the formulation to release drug up to 99.72±1.15% at the end of 30 min.

Evaluation of Press-Coated Tablets of All Formulations

Pre-Compression Studies:

Pre-compression parameters performed on the polymers used for outer barrier layer of tablets, compressibility index and Hausner's ratio were found to be within the range of 16.16±0.76 to 25.35±1.75 and 1.19±0.01 to 1.33±0.03 respectively showing good to passable flow characteristics.

Post-Compression Studies:

Shape and appearance: The press-coated tablets of Montelukast Sodium were round biconvex and white in color.

Weight Variation: Prepared tablets of all formulations were evaluated for weight variation and standard deviation. All the formulated tablets (F1 to F22) passed the weight variation test, i.e., the average percentage weight variation was found to be within the prescribed Pharmacopoeial limits of ±7.5% as shown in the table.

Tablet Thickness and Hardness: The thickness in 3.06 ± 0.05 to 3.15 ± 0.11 mm and hardness in 6.33± 1.04 to 8.83 ± 1.05 kg/cm2 of the press-coated tablets from batch F1 to F22 was found as reported in table. The low standard deviation values indicate that the thickness

and hardness of all the formulations were almost uniform and also the tablets possess good mechanical strength with sufficient hardness.

In-Vitro Dissolution Studies: The dissolution profile for press-coated tablets from batch F1 to F22 is shown in table. Among all the formulations F3 has shown a maximum release 99.96±0.05 after the lag time of almost 6 h. The In-vitro drug release profile of F1 to F22 are shown in figure.

Optimization of the barrier layer coating material: Formulation F3, prepared by press-coating of the core tablet with the 100 mg barrier layer containing HPMC K4M and ethyl cellulose in ratio 1:1 provided maximum drug release after almost 6 h. So, F3 was selected as the optimized pulsatile tablet formulation among all the 22 formulations.

Drug Release Kinetics: The mechanism of drug release from the optimized press-coated tablet F3 was characterized by zero order kinetics, first-order kinetics, Higuchi's model and Korsmeyer-Peppas model plots. It was observed that the highest correlation coefficient (R^2) was found for zero-order kinetics, which indicates the drug release rate of the optimized press-coated tablets would be independent of its concentration. The drug release kinetics plot of F3 is shown in figure.

Table 10: Mathematical modeling and drug release

Formulation code	Kinetics Models							
	Zero order		Higuchi		Korsmeyerpeppas		First order	
	R^2	K0	R^2	KH	R^2	Km	R^2	K1
CT	0.9746	3.320	0.9743	141.02	0.9303	136.22	0.9756	-5.395
F3	0.5387	0.208	0.3438	35.34	0.5308	39.21	0.0257	0.1363

Stability Study:

The short-term stability study of the optimized formulation F3 was carried out for 90 days at 40 ± 2ºC / 75% RH ± 5%. The results of the stability are given in table. There was no significant change in colour and hardness, drug content and % CDR. 90 days of stability studies revealed that, there was no any significant degradation of the drug. The results were found to be satisfactory. The comparison graph of *in-vitro* drug release of formulation F3 is given in figure.

CONCLUSION

The lag time of almost 6 h was obtained by formulation of a pulsatile drug delivery system of Montelukast Sodium. The maximum drug release was obtained after 6 h. The core tablets were prepared by direct compression method using super disintegrants and press-coated tablets were prepared by using different concentrations of coating polymers of both natural and synthetic. The conclusions found by the studies are listed below:

1. The pure drug Montelukast Sodium was found to be compatible with the excipients and coating polymers by FTIR studies.

2. The Pre-compression parameters like Bulk density, tapped density, Angle of repose, Hausner's ratio and Carr's index of all the core-tablet formulations and coating polymers were found to be within the standard limits.

3. The obtained results from Post-Compression evaluation studies such as weight variation, hardness, thickness, friability, drug content, uniformity of drug content and in-vitro dissolution were found to be within the specified standards.

4. The fast disintegrating core tablets can be prepared by using super disintegrants.

5. Time controlled pulsatile release tablets can be prepared using press coating technique optimizing the ratio of polymers.

6. The drug release rate was found to be dependent upon the polymer coating ratio and nature of coating polymers.

7. The drug release was rapid and complete from barrier layer containing HPMC K4M and ethyl cellulose in 1:1 ratio as compared to other ratio.

8. The optimized core tablets followed first-order kinetics, which revealed that the drug release rate of the immediate-release core tablets is concentration dependent.

The optimized pulsatile tablets F3 followed Zero order kinetics, which revealed that the drug release rate of time-controlled pulsatile tablets is independent of drug concentration. Short-term stability studies for 3 months proved the integrity of the developed pulsatile tablets and showed that there were not much variations in colour, hardness, thickness and drug content even after the period of 90 days. The drug content of F3 was found to be 97.66 % after 3 months which was nearest to 99.66 % of original formulation drug content F3.

Future Perspective

The work can be extended to the in-vivo studies to conclude in-vitro and in-vivo corelation. Pulsatile drug delivery system can provide optimum therapeutic benefits by delivering drug according to the circadian cycle of the disease and as per the physiological need of the patient. The release of the drug, contained in core of the system can be modified to be released after different lag time, by coating with the suitable amount of polymers. PDDS is a novel drug delivery system promising health care technology and ensuring the better quality of treatment by delivering the drug at specific time when the medications require the most.

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