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FORMULATION AND EVALUATION OF MONTELUKAST SODIUM PULSATILE DRUG DELIVERY SYSTEM BY CORE IN CUP METHOD

D.Bhavani*, CH.S.Vijaya Vani, V.Uma Maheshwar Rao

Department of pharmaceutics, CMR College of pharmacy, Kandlakoya, Medchal Road, Hyderabad-501401, India.

ABSTRACT

The aim of present study is to Formulate and Evaluate Montelukast Sodium Pulsatile Drug Delivery system by Core in Cup method to mimic the circadian rhythm of the disease by releasing the drug with a distinct predetermined lag time of 7 hours. The basic design of the system consists of a rapid release core and controlled release coat. A combination of Hydroxy Propyl Methyl Cellulose and Ethyl Cellulose was used as a coating material for the tablet. Ten formulations (F1-F10) of the core were prepared by using CCS, SSG and CP as disintegrants in different proportions (5, 7.5 and 10%) to study the effect of variable concentrations of these on the characteristics of the formulation. Core blend was evaluated for Flow properties Hardness, Thickness, Friability and invitro drug release. Among the Ten formulations F9 containing CP (7.5%) as disintegrant showed a better drug release of 100% over 45minutes was selected .The core was coated with HPMC and EC with different polymer ratios (P1F9- P5F9). Among these P2F9 was optimized based on the lag time and percent of drug release (10.2% of drug release in 7 hours).

Key words: Hydroxy Propyl Methyl Cellulose, P2F9, Hardness, Thickness.

INTRODUCTION

Oral Route of Administration

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc., From immediate release to site specific delivery, oral dosage forms have really progressed.

Oral Dosage Form is the physical form of a dose of a chemical compound used as a drug or medication intended for administration or consumption by oral route. Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities, pharmaceutical formulations, mainly because of patient acceptance and convenience in administration of drugs that are administered orally, solid dosage forms represent the preferred class of product [1-2].

Advantages

1. It is convenient.
2. It is the cheapest available route.
3. It is easy to use.
4. It is safe and does not break skin barrier.
5. Administration usually does not cause stress.

Disadvantages

1. Less amount of drug reaches the target tissue.
2. It might cause gastric irritation.
3. It might cause discoloration of teeth e.g. iron causes staining.
4. In appropriate for patients with nausea and vomiting
5. Drugs may have unpleasant taste or odour
6. Inappropriate when gastrointestinal tract has reduced motility
7. Inappropriate if patient cannot swallow or is unconscious
8. Cannot be used before certain diagnostic tests or surgical procedures [3-5].

CONTROLLED DRUG DELIVERY SYSTEM

Controlled drug delivery systems have acquired a centre stage in the area of pharmaceutical R&D sector. Such systems offer temporal and spatial control over the

*Corresponding Author D.Bhavani E mail: dandubhavani1990@gmail.com

release of drug and grant a new lease of life to a drug molecule in terms of controlled drug delivery systems for obvious advantages of oral route of drug administration. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern is known as pulsatile release [6].

Traditionally, drug delivery has meant getting a simple chemical absorbed predictably from the gut or from site of injection. A second-generation drug delivery goal has been the perfection of continuous, constant rate (zero order) delivery of bioactive agents. However, living organisms are not zero order in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle in order to maximize desired and minimize undesired drug effects. Due to advances in chronobiology, chronopharmacology and global market constraints, the traditional goal of pharmaceutics (e.g. design drug delivery system with a constant drug release rate) is becoming obsolete.

However, the major bottle neck in the development of drug delivery systems that match circadian rhythms (chronopharmaceutical drug delivery system: ChrDDS) may be the availability of appropriate technology. The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify ChrDDS compared to the conventional drug administration approach.

These include asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases, hyper cholesterolemia, ulcer and neurological diseases [7].

If the organization in time of living system including man is born in mind, it is easy to conceive that not only must the right amount of the right substance be at right place but also this must occur at the right time. In the last decade numerous studies in animals as well as clinical studies have provided convicing evidence, that the pharmacokinetics and the drugs effect -side effects can be modified by the circadian time and the timing of drug application within 24 hrs of a day.

Circadian variation in pain, stiffness and manual dietry in patients with osteo and rheumatoid arthritis have been studied and has implication for timing anti rheumatoid drug treatment. Morning stiffness associated with pain at the time of awakening is a diagnostic criterion of the rheumatoid arthritis and these clinical circadian symptoms are supposed to be outcome of altered functioning of hypothalamic pitutary adrenocortical axis [8].

Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with peak pain and stiffness. A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutic system can also formulate pulsing cap method [9].

Drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of disease that have peak symptoms in the early morning such as nocturnal asthma, angina, arthritis.

Some orally administered drugs (E.g.Diclofenac, Theophyllin, Ibuprofen, Isosorbide) may exhibit poor uptake in the upper regions of GIT or degrade in the presence of GIT enzymes. Better bioavailability can be achieved through colon- specific drug delivery. Colonic targeting is also advantageous where delay in systemic absorption is therapeutically desirable [10].

Circadian rhythms and their implications

Circadian rhythms are self-sustaining, endogenous oscillation, exhibiting periodicities of about one day or 24 hours. Normally, circadian rhythms are synchronized according to the bodys pacemaker clock, located in the suprachiasmic nucleus of the hypothalamus.

The physiology and biochemistry of human being is not constant during the 24 hours, but variable in a predictable manner as defined by the timing of the peak and through of each of the bodys circadian processes and functions. The peak in the rhythms of basal gastric and secretion (pH-dependent) white blood cells (WBC), lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotrophic hormone (ACTH), follicle stimulating hormone (FSH), and leuteinizing hormone (LH), is manifested at specific times during the nocturnal sleep span. The peak in serum cortisol, aldosterone, testosterone plus platelet adhesiveness and blood viscosity follows later during the initial hours of diurnal activity. Hematocrit is the greatest and airway caliber the best around the middle and afternoon hours, platelet numbers and uric acid peak later during the day and evening. Hence, several physiological processes in humans vary in a rhythmic manner, in synchrony with the internal biological clock through a number of clinical trials and epidemiological studies, it has become evident that the levels of disease activity of number of clinical disorders have a pattern associated with the bodys inherent clock set according to circadian rhythms. Infect just as the time of day influences normal biologic processes, so it affects the pathophysiology of disease and its treatment [11-12].

Chronotherapeutic: Therapy in synchrony with biorhythms

Chronotherapy coordinates drug delivery with human biological rhythms and holds huge promise in areas of pain management and treatment of asthma, heart disease and cancer. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed chronotherapy [13].

Chronotherapeutics, or delivery of medication in concentrations that vary according to physiological need

at different times during the dosing period, is a relatively new practice in clinical medicine and thus many physicians are unfamiliar with this intriguing area of medicine. It is important that physicians understand the advantages of chronotherapy so that they can make well-informed decisions on which therapeutic strategies are best for their patients-traditional ones or chronotherapies [14].

The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time. In contrast, many side effects can be minimized if a drug is not given when it is not needed. Unlike homeostatic formulations, which provide relatively constant plasma drug levels over 24 hours, chronotherapeutic formulations may use various release mechanisms. e.g., time-delay coatings (Covera-HSTM), osmotic pump mechanisms (COER-24TM), and matrix systems (GeminexTM), that provide for varying levels throughout the major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules. In most cases, however, special drug delivery technology must be relied upon to synchronize drug concentrations to rhythms in disease activity [15-16].

Chronopharmaceutics

Chronopharmaceutics is a branch of pharmaceutics devoted to design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Ideally chronopharmaceutical drug delivery system (ChrDDS) should embody time-controlled and site specific drug delivery system.

Evidence suggests that an ideal ChrDDS should

- Be non-toxic within approved limits of use
- Have a real-time and specific triggering biomarker for a given disease state.
- Have a feed-back control system (ex: self-regulated and adaptive capability to circadian rhythm and individual patient to differentiate between awake-sleep status),
- Be biocompatible and biodegradable, especially for parentral administration,
- Be easy to manufacture at economic cost
- Be easy to administer to patients and enhances compliance to dosage regimen.

When treating human diseases, the overall goal is to cure or manage the disease while minimizing the negative impact of side effects associated with therapy. In this respect, chronopharmaceutics will be a clinically relevant and reliable discipline. If pharmaceutical scientists could delineate a formal and systemic approach to design and evaluate drug delivery system that matches the biological requirement.

Pulsatile drug delivery systems

New global trends in drug discovery and development

In this century, the pharmaceutical industry is caught between pressure to keep prices down and the increasing cost of successful drug discovery and development. The average cost and time for the development of a new chemical entity are much higher (app $500 million and 10-12 years) than those required to develop a novel drug delivery system (NDDS or ChrDSS) ($20-$50 million and 3 to 4 years). In the form of an NDDS or ChrDDs, an existing drug molecule can get a new life thereby increasing its market value and competitiveness and extending patent life.

Among modified-release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsatile) and site-specific delivery of drugs. In particular, systems for delayed release are meant to deliver the active principle after a programmed time period following administration.

These systems constitute a relatively new class of device, the importance of which is especially connected with the recent advances in chrono pharmacology. It is by now well-known that the symptomatology of a large number of pathologies as well as the pharmacokinetics and pharmacodynamics of several drugs follow temporal rhythms, often resulting in circadian variations. Therefore, the possibility of exploiting delayed release to perform chronotherapy is quite appealing for those diseases, the symptoms of which recur mainly at night time or in the early morning, such as bronchial asthma, angina pectoris and rheumatoid arthritis. The delay in the onset of release has so far mainly been achieved through osmotic mechanisms, hydrophilic or hydrophobic layers, coating a drug-loaded core and swellable or erodible plugs sealing a drug containing insoluble capsule body.

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

These dosage forms offer many advantages such as

- ✓ Nearly constant drug levels at the site of action.
- ✓ Avoidance of undesirable side effects.
- ✓ Reduced dose and
- ✓ Improved patient compliance.
- ✓ Used for drugs with chronopharmacological behaviour, a high first pass effect, the requirement.

The conditions that demand pulsatile release include:

- Many body functions that follow circadian rhythm i.e. their waxes and wanes with time. Ex: hormonal secretions.
- Diseases like bronchial asthma, myocardial infraction, angina pectoris, rheumatoid diseases, ulcer and hypertension display time dependence.
- Drugs that produce biological tolerance demand for a system that will prevent continuous present at the biophase

as this tend to reduce their therapeutic effect.

- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (ex: peptide drugs) irritate the gastric mucosa or induce nausea and vomiting.
- Targeting to distal organs of GIT like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.

All of these conditions demand for a time-programmed therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by pulsatile drug delivery system, which is characterized by a lag time that is an interval of no drug release followed by rapid drug release [1]. Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastrointestinal motility, etc. these time-controlled systems can be classified as single unit (tablet or capsule) or multiple unit (e.g., pellets) systems.

Single Unit Systems

Drug delivery systems with eroding or soluble barrier coatings

Most pulsatile delivery systems are reservoir devices coated with a barrier layer. The barrier dissolves or erodes after a specify lag period, after which the drug is released rapidly from the reservoir core. In general, the lag time prior to drug release from a reservoir type device can be controlled by the thickness of the coating layer.

E.g.The Time Clock® system and chronotropic® system consists of a drug containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release.

Drug delivery systems with rupturable coatings

In this the drug is released from a core (tablet or capsule) after rupturing the surrounding polymeric layer, caused by inbuilt pressure within the system. The pressure necessary to rupture the coating can be achieved with gas-producing effervescent excipients, osmotic pressure or swelling agents.

Capsular shaped systems

Several single unit pulsatile dosage forms with a capsular design have been developed. Most of them consist of an insoluble capsule body, containing the drug and a plug, which gets removed after a predetermined lag time because of swelling, erosion or dissolution. E.g., Pulsincap® system and Port® system The **Pulsincap®** system consists of a water-insoluble capsule body (exposing the body to formaldehyde vapor which may be produced by the addition of trioxymethylene tablets or potassium permanganate to formalin or any other method), filled with the drug formulation and plugged with a swellable hydrogel at the open end.

Upon contact with dissolution media or gastrointestinal fluid, the plug swells and comes out of the capsule after a lag time, followed by a rapid release of the contents. The lag time prior to the drug release can be controlled by the dimension and the position of the drug. In order to assure a rapid release of the drug content, effervescent agents or disintegrants were added to the drug formulation, especially with water-insoluble drug. Studies in animals and healthy volunteers proved the tolerability of the formulation (e.g., absence of gastrointestinal irritation).

In order to overcome the potential problem of variable gastric residence time of a single unit dosage forms, the Pulsincap® system was coated with an enteric layer, which dissolved upon reaching the higher pH regions of the small intestine.

The plug consists of

- Swellable materials coated with insoluble, but permeable polymers
  (e.g., Polymethacrylates)
- Erodible compressed materials
  (e.g., HPMC, Polyvinyl alcohol, Polyethylene oxide)
- Congealed melted polymers
  (e.g.,saturated polyglycoated glycerides or Glyceryl monooleate).

Methods for delayed drug delivery systems

1 pH-dependent delivery
2 Time dependent delivery
3 Pressure dependent delivery
4 Bacteria- dependent delivery

pH- Triggering Drug Delivery Systems

Use of pH-dependent polymers is based on the differences in pH levels throughout GIT. The polymers described as pH- dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. The principle group of polymers utilized for the preparation of colon targeted dosage forms has been the Eudragits (registered trademark of Rohm Pharma, Darmstadt, Germany), more specifically Eudragit L100 and S100 are copolymers of methacrylic acid and methyl methacrylate. The ratio of the carboxyl ester groups is approximately 1:1 in Eudragit L100 and 1:2 in Eudragit S100.

The polymers form salts and dissolve above pH 6 and 7 respectively. This approach is based on the assumption that gastrointestinal pH increases progressively from the small intestine to colon. In fact, the pH in the distal small intestine is usually around 7.5, while the pH in the proximal colon is closer to 6.The pH-sensitive delivery systems commercially available for mesalazine (5-aminosalicylic acid) (Asacol® and Salofalk®) and budesonide (Budenofalk® and Entocort®) for the treatment of ulcerative colitis and Chrons disease respectively.

Time-Dependent Delivery System

As discussed earlier, although gastric emptying tends to be highly variable, small intestinal transit times are less (3 h). So various attempts are made to prevent the release of drug until 3-4 h after leaving the stomach. These systems release their drug load after a pre-programmed time delay. To attain colonic release, the lag time should equate to the time taken for the system to reach the colon.

This time is difficult to predict in advance, although a lag time of five hours is usually considered sufficient, given that small intestinal transit time is reported to be relatively constant at three to four hours. The drug delivery systems, Pulsincap® and Time Clock® are time dependent formulations.

Pressure-Controlled Drug Delivery Systems

Gastrointestinal pressure has also been utilized to trigger drug release in the distal gut. This pressure, which is generated via muscular contractions of the gut wall for grinding and propulsion of intestinal contents, varies in intensity and duration throughout the gastrointestinal tract, with the colon considered to have a higher luminal pressure due to the processes that occur during stool formation. Systems have therefore been developed to resist the pressures of the upper gastrointestinal tract but rupture in response to the raised pressure of the colon. The system can be modified to withstand and rupture at different pressures by changing the size of the capsule and thickness of the capsule shell wall.

Microflora-Activated Drug Delivery Systems

The resident gastrointestinal bacteria provide a further means of effecting drug release in the colon. These bacteria predominantly colonize the distal regions of the gastrointestinal tract where the bacterial count in the colon is 1011 per gram, as compared with 104 per gramme in the upper small intestine. Moreover 400 different species are present. Colonic bacteria are predominantly anaerobic in nature and produce enzymes that are capable of metabolizing endogenous and exogenous substrates, such as carbohydrates and proteins that escape digestion in the upper gastrointestinal tract. Both prodrugs and dosage forms from which the release of drug is triggered by the action of colonic bacteria enzymes have devised. Enzymes produced by the colonic bacterial are capable of catalyzing a number of metabolic reactions, which includes reduction (of double bonds, nitro groups, azo groups, aldehydes, sulphoxides, ketones, alcohols, N-oxides and arsenic acid), hydrolysis (of glycosides, sulphates, amides, esters, nitrates and sulphonates), deamination, decarboxylation, dealkylation, acetylation, nitrosamine formation, heterolytic ring fission and esterification.

MATERIALS AND METHODS

Formulation Development

Formulation of core tablets by direct compression

- The inner core tablets were prepared by using direct compression method.
- As shown in Table powder mixtures of montelukast sodium, microcrystalline cellulose , cross-carmellose sodium (Ac-Di-Sol) ,SSG, crospovidone, SLS ingredients were dry blended for 20 min. followed by addition of Magnesium Stearate.
- The mixtures were then further blended for 10 min., 180mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with a 8mm punch and die to obtain the core tablet.

Formulation of Core in Cup Tablets by direct compression

As given in the table no, an impermeable coating cup consisting of Ethyl Cellulose was applied under the bottom and around the core tablet. The Ethyl cellulose powder (100 mg) was filled into a die of 12 mm diameter and then gently compacted to make a powder bed with a flat surface. The core tablet was carefully placed in the center of the powder bed, the die was filled with the remaining quantity of coating powder (60 mg) so that the surrounding surfaces of the core tablet were fully covered. On the top, hydrophilic polymer (HPMC) was added and the bed was compressed directly by using 12mm flat punch to produce the desired core-in-cup system.

CALIBRATION CURVE FOR MONTELUKAST

Construction of calibration curve (240 nm)

Standard solution

10 mg of Montelukast was dissolved in 10 ml 0.5 % of SLS solution to give a concentration of 1 mg/ ml (1000 µg/ml).

Stock solution

From standard solution take 5 ml of solution in 50 ml of 0.5 % of SLS solution to produce the 50 µg/ml concentration and take from the 50 µg/ml of the solution aliquots of 1, 2, 3, 4, and 5 ml of stock solution was pipette out in 10 ml volumetric flask. The volume was made up to mark with SLS solution to produce concentration as 5, 10, 15, 20, and 25 µg/ml of montelukast respectively. The absorbance of prepared solution of montelukast was measured at 240 nm in Shimadzu UV/visible 1700 spectrophotometer against 0.5 % of SLS solution as blank. The absorbance data for standard calibration curve are given in Table and plotted graphically as shown in the Figure. The standard calibration curve yields a straight line, which shows that drug obeys Beer's law in the concentration range 5 to 25 mcg/ml.

Discussion

the λ max of Montelukast Sodium was found to be 240nm because maximum abosorption has been obtained at this wavelength and the absorbance is within beer's lambert's law limits.

Discussion: The calibration was found to be linear with a regression value of 0.998.

RESULTS AND DISCUSSION

Drug-Excipient Compatibility Studies

The drug – excipient compatibility studies were carried out by FTIR.

Discussion

IR of Montelukast Sodium was determined by FTIR spectra. Physical mixture of drug and polymer was characterized by FTIR spectral analysis, from the results it was concluded that their was no interference of functional group as the principle peaks of Montelukast Sodium were found to be unaltered in the drug-polymer physical

mixtures, indicating they were compatible chemically for the best formulation.

EVALUATION

Micromeritic Studies

The tablets were studied for micromeritic properties and the values were tabulated as follows.

Discussion

The bulk density of the formulations F1 to F10 was found to vary between 0.423 to 0.485 gm/ml. Tapped density was found to be 0.501 to 0.593 gm/ml for formulations F1 to F10. Hausner's ratio was found to be 1.10 to 1.28 for the formulation of F1 to F10. The compressibilty's index was found to be 12.4 to 19.1% for formulation F1-F10. These values were found to be within pharmacopeia limits. The angle of repose of all the developed formulations F1 to F10 was found to be 24.30 to 29.82.

By observing the above micromeritic properties it was found that all the values of all formulations lie within pharmacopeial limits and tablet blend was found to have good flow properities.

In-Vitro Dissolution Studies

The dissolution studies were carried out according to the parameters mentioned above.

Based on the drug release within the required time period F9 was optimized and further formulated for montelukast core in cup.

Dissolution profiles for coated tablet P1F9, P2F9, P3F9, P4F9, P5F9

From the above core formulations **F9** was selected for core in cup by using different synthetic polymers (HPMC and ETHYL Cellulose in different ratios among which **P2F9** was optimized based on the lag time (10.2% in 7 hours) and percent of drug release.

Figure 1. Calibration curve of Montelukast Sodium in 0.5% SLS

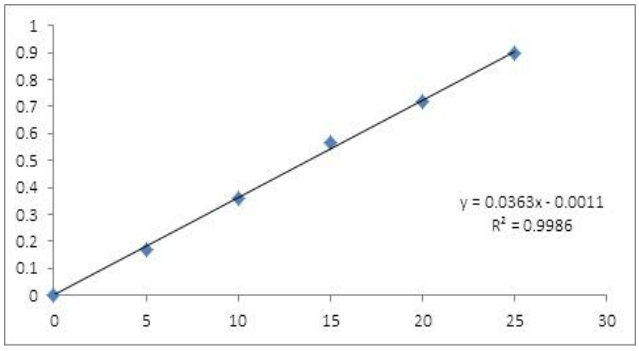

Figure 2. FTIR graph of Montelukast sodium

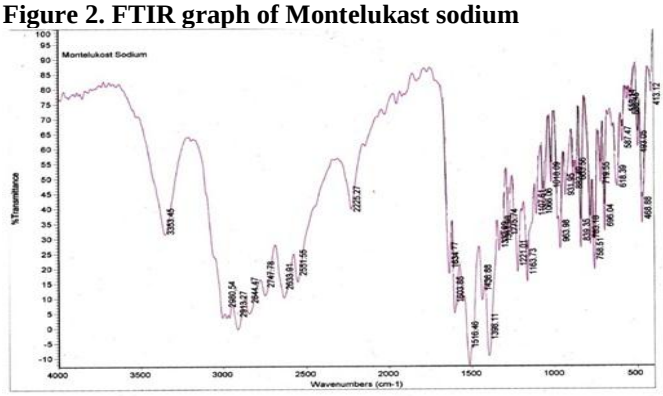

Figure 3. FTIR graph of Montelukast sodium core in cup optimized formulation

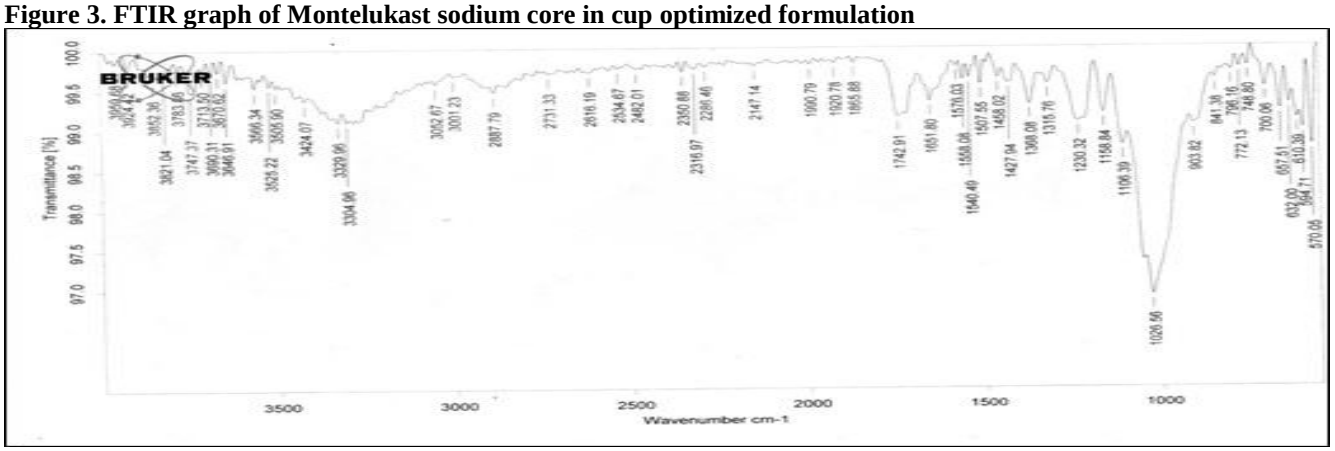

Figure 4. Dissintigration apparatus

Figure 5. Dissolution graph for core formulations of F1 to F10

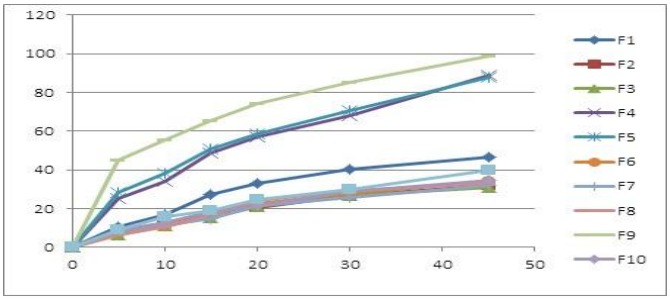

Figure 6. *In-Vitro* Drug Release of various Formulations for core in cup tablet

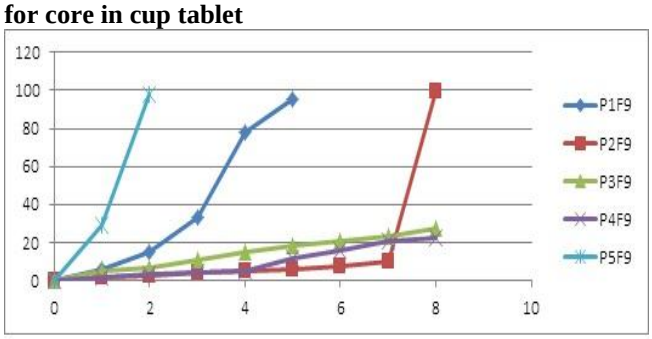

Figure 7. U.V.Spectrophotometer

Table 1. Formulation of Montelukast Sodium

Ingredients	F 1	F2	F 3	F 4	F5	F6	F7	F8	F9	F10
API	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10
Crospovidone	5%	--	--	7.5%	10%	--	--	--	7.5%	--
CCS	--	5%	--	--	--	10%	10%	--	--	10%
SSG	--	--	5%	--	--	--	--	10%	--	--
Magnesium stearate(1%)	1.8	1.8mg	1.8m	1.8mg	1.8mg	1.8mg	1.8mg	1.8mg	1.8mg	--
SLS (0.5%)	--	--	--	--	--	--	--	--	0.5%	0.5%
MCC	158.3	153.8	153.8	153.8mg	153.8	148.5mg	148.5mg	148.5mg	153.8mg	--
Aerosol	0.9mg	0.9mg	0.9mg	0.9mg	0.9mg	0.9mg	0.9mg	0.9mg	0.9mg	--
Total weight	180mg	180mg	180mg	180mg	180mg	180mg	18omg	180mg	180mg	180mg

MCC: Micro crystalline cellulose, CCS: Cross caramellose sodium,
SSG: Sodium starch glycolate, SLS: Sodium lauryl sulphate

Table 2. Composition of Montelukast Core in Cup Tablets

Core in Cup	P1 F9	P2 F9	P3 F9	P4 F9	P5 F9
HPMC	50	50	50	50	25
Ethyl cellulose	100	150	175	200	200

Table 3. Calibration curve data of Montelukast Sodium

S.No	Concentration	Absorbance
1	0	0
2	5	0.169
3	10	0.359
4	15	0.567
5	20	0.721
6	25	0.896

Table 4. Evaluation of Tablet blend

Formulation	Bulk Density (g/cc)	Tapped Density(g/cc)	Hausner ratio	Compressibility index (%)	Angle of repose (θ)
F1	0.464	0.574	1.23	19.1	29.47
F2	0.423	0.501	1.16	15.5	27.63
F3	0.456	0.542	1.22	15.8	25.54
F4	0.467	0.559	1.25	16.4	26.23
F5	0.485	0.593	1.10	18.2	27.21
F6	0.460	0.556	1.21	17.2	29.38
F7	0.478	0.575	1.24	16.8	28.46
F8	0.450	0.554	1.28	18.7	25.71
F9	0.442	0.537	1.27	17.6	29.82
F10	0.456	0.550	1.20	17.0	24.30

Table 5. Physical Evaluation Parameters for Core Tablets

S.NO	Formulation	Weight variation	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration Time	Drug content(%)
1.	F1	181±1.5	4±0.2	2.25±0.01	0.4±0.01	1 min±2 sec	82.14
2.	F2	180±1.5	4.2±0.1	2.22±0.03	0.55±0.02	1min 30sec±4sec	82.85
3.	F3	180±1.5	4.3±0.05	2.24±0.02	0.62±0.02	1min±3sec	85.71
4.	F4	179±0.5	4.1±0.17	2.24±0.03	0.54±0.01	30sec±2sec	70.2
5.	F5	178±1	4.3±0.05	2.24±0.03	0.62±0.005	32sec±2sec	82.85
6.	F6	180±0.5	4.4±0.05	2.20±0.02	0.57±0.01	1min 20sec±3sec	87.14

7.	F7	182±1.15	4.2±0.1	2.20±0.03	0.65±0.02	45sec±2sec	80.45
8.	F8	180±1.5	4.3±0.05	2.18±0.02	0.52±0.01	1min±2sec	82.23
9.	F9	180±1.5	4.4±0.05	2.26±0.05	0.54±0.005	35sec±1sec	99.28
10.	F10	179±1.5	3.8±0.05	2.21±0.02	0.4±0.02	1min 10sec±4sec	93.57

Table 5. *In-Vitro* Drug Release of various Formulations of core

Dissolution time(Min)	Core formulation code									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
5	10.5	8.4	6.5	25.4	28.1	7.4	8.2	6.4	45.2	8.4
10	16.8	12.4	11.3	34.2	38.2	10.5	11.4	10.4	55.4	12.5
15	27.1	17.6	15.4	48.8	50.6	16.6	14.6	16.7	65.6	18.6
20	32.8	20.5	21.0	56.9	58.8	22.5	21.4	24.0	74.0	21.7
30	40.4	26.6	26.5	68.0	70.4	27.6	25.6	29.5	85.2	29.0
45	46.8	32.0	30.8	88.7	87.8	33.8	31.8	32.8	98.7	34.7

Table 6. Composition of Montelukast Core in Cup Tablets

Core in Cup	P1 F9	P2 F9	P3 F9	P4 F9	P5 F9
HPMC	50	50	50	50	25
Ethyl cellulose	100	150	175	200	200

Table 7. Evaluation Parameters for Montelukast cup in core Tablets

S. No	Physical parameter	P1F9	P2F9	P3F9	P4F9	P5F9
1	**Weight variation**	332±2	351± 1.5	375± 1.5	401±1	375± 1.5
2	**Hardness (Kg/cm^2)**	6.5± 3.9	6.7± 2.9	6.8±3	6.2± 2.5	6.6± 3.2
3	**Thickness (mm)**	4.5± 2.8	4.6± 3.1	4.4± 3.4	4.4± 3.6	4.5± 3.4
4	**Friability %**	0.56± 0.02	0.55± 0.01	0.62± 0.03	0.54± 0.01	0.62± 0.02

Table 8. *In-Vitro* Drug Release of various Formulations for core in cup tablet

	Formulation code				
	P1F9	**P2F9**	**P3F9**	**P4F9**	**P5F9**
1	5.9	1.8	5	1.8	28.9
2	15	2.7	7	3.3	97.6
3	33.6	4.2	11	4.2	-
4	78.2	5.1	15	5.4	-
5	95.3	5.6	18.4	11.6	-
6	-	7.8	20.4	15.5	-
7	-	10.2	23.5	20.4	-
8	-	99.6	27.4	22.6	-

DISCUSSION

Montelukast sodium is a leukotriene receptor antagonist and is used in the treatment of ASTHMA. So, by increasing the lag time a pulsatile drug delivery system releases the drug during early hours when the patient takes the formulation at bed time. Thus, the patient compliance can be increased by pulsatile drug delivery. Pulsatile drug delivery was prepared by core in cup method to mimic the circadian rhythm of the disease by releasing the drug with a distinct pre-determined lag time of 7 hours. The basic design of the system consists of a rapid release core and controlled release coat. The inner core tablets were prepared by using direct compression method. All the

ingredients such as Montelukast Sodium, Microcrystalline Cellouse, Cross-Carmellose Sodium, Sodium Starch Glycolate , Crosspovidone, SLS where dry blended for 20 minutes followed by addition of Magnesium Stearate. The mixture was blended further 10 minutes. Ten formulations (F1-F10) of the core were prepared by using CCS, SSG and CP as disintegrants in different proportions (5, 7.5 and 10%) to study the effect of variable concentrations of these on the characteristics of the formulation. Core blend was evaluated for Flow properties Hardness, Thickness, Friability and invitro drug release. The drug (Montelukast Sodium) is compatible with all the excipients. All the parameters were in the optimum range. Among the Ten formulations F9 containing CP (7.5%) as disintegrant showed a better drug release of 100% over 45minutes was selected. 180mg of resultant powder blend was manually compressed at a pressure of 1 ton, with 8mm punch and die to obtain the core tablet. The core tablet was carefully placed at the centre of powder bed so that the surrounding surface of the core tablet were fully covered. On the top HPMC was added and the bed was compressed directly by using 12mm flat punch to produce the desired CORE - IN –CUP tablet. The core was coated with HPMC and EC with different polymer ratios (P1F9- P5F9). Among these **P2F9** was optimized based on the lag time and percent of drug release (10.2% of drug release in 7 hours).

CONCLUSION

It was concluded that Montelukast Sodium cup in core can be promising drug delivery system for pulsatile drug delivery as the drug releases after its lag time of 7hrs. So, that the early attacks of asthama can be prevented if the patient administers the formulation at the bed time and hence patient compliance can be increased.

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