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FORMULATION AND EVALUATION OF PRESS-COATED MONTELUKAST SODIUM TABLETS FOR PULSATILE DRUG DELIVERY SYSTEM

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ABSTRACT: An oral press-coated tablet was prepared by using direct compression and wet granulation methods to achieve the predetermined lag time. This press-coated tablet containing montelukast sodium in the inner core was formulated with an outer barrier layer by different compositions of hydrophobic polymer ethylcellulose and hydrophilic polymer low-substituted hydroxypropylcellulose. The effect of formulation composition on the barrier layer comprising both hydrophobic and hydrophilic excipients on the lag time of drug release was investigated. It was observed that lag time decreases with increasing concentration of low-substituted hydroxypropylcellulose. Press coated tablets coated by dry mixing and by wet granulation showed variations in lag time. As compared to dry mixed blend method wet granulation method gives less lag time.
KEYWORDS: Press-coated tablet, lag time, ethylcellulose, low-substituted hydroxypropylcellulose, pulsatile drug delivery.

INTRODUCTION:

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours.[1] Interestingly, the term circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle. Our circadian rhythm is based on sleep-activity cycle and is influenced by our genetic makeup and thereby affects our bodie's function throughout day and night (24-hour period). Circadian rhythm regulates many body functions in humans like metabolism, physiology, behavior, sleep pattern, hormone production.[2] There are number of conditions which show circadian pattern and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Diseases, such as cardiovascular, asthma, peptic ulcer, arthritis etc follow the body's circadian rhythm. Co-ordination of biological rhythms and medical treatment is called chronotherapy while chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.[3] Asthma is a chronic inflammatory disease of the airways, characterized by hyper responsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours.[4] The worsening of asthma at night, commonly referred to as nocturnal asthma (NA).A drug delivery system administered at bedtime but releasing drug during morning hours would be ideal in this case.[5] Nocturnal asthma is a variable exacerbation of the underlying asthma condition associated with increases in symptoms, need for medication, airway responsiveness, and/or worsening of lung function. Generally, a reduction in peak flow or forced expiratory volume in one second (FEV1) of at least 20% is implicit in this definition. Approximately two-thirds of asthmatics suffer from nighttime 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 nighttime hours.[6] The principles of chronobiology provide a framework for understanding nocturnal asthma. Chronobiology is the study of biological rhythms and their mechanisms. Every biological rhythm has a periodicity. Circadian rhythms have a periodicity of about 24 hours. It is well known that circadian rhythms influence disease processes and physiological events. For example, most myocardial infarctions occur in the early hours of the morning. Lung function (e.g., peak expiratory flow rate or FEV1) is usually highest at 4 PM and lowest at 4 AM the latter time is generally when asthma symptoms are most prevalent. Dethlefsen and Repges studied more than 3,000 asthmatic patients and demonstrated that more than 90% of their dyspneic episodes occurred during the nighttime hours. Based on these findings drug delivery and therapy should be modified to achieve an effective drug level at the required time. This can be achieved by adapting a pulsatile drug delivery system of a suitable drug. Consequently, the administration of a drug formulated in such a delivery system, i.e. 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.[7] Pulsatile drug delivery system is the one type of drug delivery system, where the delivery device is capable of releasing drug after predetermined time-delay (i.e. lag time) known as pulsatile drug delivery system.

Pulsatile drug delivery systems are gaining lot of interest and attention these days. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release."[8] Oral pulsatile administration could be useful for the treatment of certain diseases, such as asthma, gastric ulcer, hypertension, ischemic heart disease, arthritis, etc., which exhibit circadian rhythms. Pulsatile drug delivery denotes the capability of a controlled release preparation to deliver the drug at varying rates from very low to high over a desirable time. It also should be capable of releasing its drug content at either a predetermined time or at a specific site in the gastrointestinal tract. Press-coated tablets gained wide interest 'claiming some advantages over regular and (pan-) coated tablets, such as to protect hygroscopic, light-sensitive or oxygen-labile drugs from environmental-atmospheric ill effects or decomposition of acid-labile drugs by gastric fluids; to separate incompatible drugs from each other; to achieve a sustained release in that the drug in the core is embedded in waxes or fats constituting a depot; to protect the gastric mucosa from irritation by certain drugs by using enteric coating material in the outer press-coating granules; or to achieve intermittent release by incorporating one portion of drug in the core and the other in the coat, separated by a film-coat or a second press-coat. However, common drawbacks of the press-coating technique are the multi-step processes involved, and the requirement for reliable and reproducible central positioning of the core tablet within press-coated tablet (PCT), a major challenge for large scale industrial manufacturing. The lag time of drug release from PCTs depends upon the thickness and the composition of the barrier layer. Generally speaking, the thicker the barrier layer, the longer the lag time. The composition of the barrier layer controls the mechanism of effecting a lag time.[9] Shan-Yang et al has developed different technologies referring to tablet pulsatile release systems. Most of the tablet formulations are reservoir type devices with a barrier coating. Besides capsule-based pulsatile release systems, formulations, such as Pulsicap have also been developed. These systems consist of a water-impermeable or semi-impermeable capsule half with the drug formulation contained within the capsule and sealed by means of a hydrogel polymer plug. Contact of the dissolution media or gastrointestinal fluids with the barrier or the plug results to its removal or ejection followed by the rapid release of the drug. The aim of the present investigation was to develop and evaluate an alternative, simple, orally applicable one-pulse drug delivery system based on a press-coated tablet preparation. The PCT investigated in the current study consisting of a rapidly disintegrating core tablet press-coated by a barrier layer consisting of varying concentrations of low-substituted hydroxypropylcellulose (L-HPC) and Ethylcellulose (EC). L-HPC is a disintegrant and had been used to cause rapid disintegration of tablets. The other component of the barrier layer, EC, Ethylcellulose (EC) is a well-known water-insoluble polymer that has long been used as a rate-controlling membrane in medication dosage forms to regulate drug release. Although EC has also been added in tablet formulations to act as a retarding material, few papers have focused on the use of EC as a directly compressible excipient. It was postulated that when the barrier layer was exposed to dissolution media, the L-HPC particles swell and erode, a process which was retarded to varying degrees depending upon the quantity of EC present, demonstrating that manipulation of both components controls the erosion rate.

MATERIALS AND METHODS:

Materials:

Montelukast Sodium - model drug, microcrystalline cellulose (MCC, Avicel PH-102), ethylcellulose (Ethocel) low-substituted hydroxypropylcellulose (L-hpc, LH-31) were gifts from Cipla Pharma R & D (Mumbai, India). Cross-carmellose sodium (Ac-Di-Sol), magnesium stearate was purchased from Signet Chemical Corporation (Mumbai, India).

Polivinylpyrrolidone (PVP, K90) and Sodium Lauryl Sulphate (SLS) were gifts from Fine Chem. Industries (Mumbai, India). The colorant Erythrocin red was obtained as a gift from Flamingo Pharmaceuticals (Mumbai, India).

Formulation of core tablets by direct compression:
The inner core tablets were prepared by using direct compression method. As shown in Table 1 powder mixtures of montelukast sodium, microcrystalline cellulose (MCC, Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol) and erythrocin red ingredients were dry blended for 20 min. followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 100mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with a 9mm punch and die to obtain the core tablet.

Formulation of mixed blend for barrier layer:
As given in the Table 2 the various formulation compositions containing Ethylcellulose and L-HPC. That is from A1 to A7 different compositions were weighed dry blended at about 10 min. and used as press-coating material to prepare press-coated pulsatile tablets (A1Tab -A7Tab) respectively by direct compression method.

Formulation of granules for barrier layer:
A wet granulation process was used to prepare the barrier layer granules. The compositions of ethylcellulose and L-HPC as given in the Table 2 were wet granulated using polivinylpyrrolidone (PVP, K90) as binder. 10% granulating solvent system was made by dissolving PVP into hot water by continuous stirring. The dump mass was prepared and passed through sieve no.18 to obtain the granules. The granules were dried in hot-air oven at about 40^{o}C for 24 hours and stored in airtight container and used as press-coating material to prepare press-coated pulsatile tablets.

Preparation of press-coated tablets:
The core tablets were press-coated with 400mg of mixed blend/granules as given in Table 3. 200mg of barrier layer material was weighed and transferred into a 13mm die then the core tablet was placed manually at the center. The remaining 200mg of the barrier layer materiel was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press.

In vitro drug release study of core tablets:
The in vitro release pattern of core tablets was studied as per method given by Chaudhari S. P.[10] Release pattern was studied visually by taking images of the core tablets in a petri plate containing dissolution medium at the specific time intervals 0.5min, 1min, 1.5min, 2min, 2.5min and 3min. Also the sample was analyzed at 342nm using a UV spectrophotometer.

In vitro drug release study of press-coated tablets:
In-vitro dissolution studies of press coated tablets were performed at 37 ± 0.5 °C using 0.5% w/v aqueous solution sodium lauryl sulfate in USP II paddle method at 50 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh 0.5% sodium lauryl sulfate solution maintained at the same temperature. The samples were analysed at 342nm using a UV spectrophotometer. The lag time and percentage release was determined of the each formulation.

RESULTS AND DISCUSSION:

Design of Pulsatile release tablet:
The pulsatile drug delivery system consisted of inner core tablet containing drug reservoir and outer coating layer with combination of water insoluble polymer Ethylcellulose and water soluble polymer L-HPC. Ethyl cellulose was chosen because of its swelling and rupturable behavior. L-HPC was chosen because of its eroding behavior.

In Vitro dissolution of core tablets:
The core tablet shows 80 % of drug release within 9 minutes upon contact with dissolution medium, core tablet get erode and release the drug as given in Fig. 1.

In Vitro dissolution of press coated tablets:
All press coated tablet showed pulsatile release behavior with distinct lag time. Fig. 2 and 3 shows the dissolution profile of core tablet without barrier layer and press coated tablets. Incorporation of core tablet into press coated tablet produce a lag time prior to drug release. When the dissolution medium reaches the core after eroding or rupturing the outer barrier layer rapid drug release was observed. Press coated tablets A1Tab-A7Tab formulations showed distinct lag time as given Fig. 2. It showed that lag time decreases with increasing concentration of L-HPC. With Ethylcellulose alone showed highest lag time of four hours and with L-HPC alone showed lowest lag time of 45 min. this is probably because of mechanism of producing a lag time of this formulation was based upon the hydration of outer barrier layer or water penetration through outer barrier layer.[9] With the outer barrier layer being present when the dissolution medium reaches the core tablets preventing the rapid drug release. Ethylcellulose is semipermeable in nature, although it is naturally insoluble in water.[11] It penetrates the coating layer of the core tablet when used alone. After hydration of core, the drug was released. When ethylcellulose was used in combination with LHPC as a result of solubility of LHPC upon contact with dissolution medium LHPC hydrated and form compact with ethylcellulose. The hydrophobicity of ethylcellulose retards the hydration of LHPC. Therefore dissolution medium did not penetrate the outer coating layer, but the coating eroded slowly. The active erosion rate of outer barrier layer depends upon the composition of the formulation which determines the lag time of press coated tablets. The LHPC is responsible for active erosion of barrier layer as a characteristic of such disintegrants are absorption of water followed by swelling thus as the weight ratio of LHPC was increased, lag time decreases. Press coated tablets B1Tab-B7Tab formulations showed distinct lag time as given in Table No. It showed that lag time decreased with increasing weight ration of LHPC and decreasing Ethyl cellulose. With ethylcellulose alone showed highest lag time of two hours and with LHPC alone showed the lowest lag time of 30 min. the reason is as explained above. Press coated tablets coated by dry mixing and by wet granulation showed variations in lag time as given in Fig. 1 and 2. As compared with mixed blend method wet granulation

method gives less lag time. This may be because difference in hydration of outer barrier layer. The PVP which is used in wet granulation method is hydrophilic in nature[12] which achieves rapid hydration leads to rapid penetration of dissolution medium through outer barrier layer as compared with dry mixing method.

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Table 1: Formulations of core tablet.

Ingredients	**Quantity**
Montelukast Sodium	10mg
Microcrystalline Cellulose (MCC, Avicel PH-102)	q.s.
Cross-carmellose Sodium (Ac-Di-Sol)	5 %
Magnesium Stearate	10 %
Erythrocin Red	1 %
Total weight of tablet	**100mg**

Table 2: Formulations of barrier layers (400mg). EC: Ethyl cellulose, L-HPC: low-substituted hydroxypropylcellulose

EC: L-HPC (Percent Ratio)	100:0	87.5:12.5	75:25	50:50	25:75	12.5:87.5	0:100
Mixed blend	A1	A2	A3	A4	A5	A6	A7
Granules	C1	C2	C3	C4	C5	C6	C7

Table 3: Formulations of press coated tablets (500mg). MB: Mixed blend, G: Granules, EC: Ethyl cellulose, L-HPC: low-substituted hydroxypropylcellulose.

EC: L-HPC% ratio in MB/G	100:0	87.5:12.5	75:25	50:50	25:75	12.5:87.5	0:100
MB : Core tablet 400mg : 100mg	A1 Tab	A2 Tab	A3 Tab	A4 Tab	A5 Tab	A6 Tab	A7 Tab
G : Core tablet 400mg : 100mg	C1 Tab	C2 Tab	C3 Tab	C4 Tab	C5 Tab	C6 Tab	C7 Tab

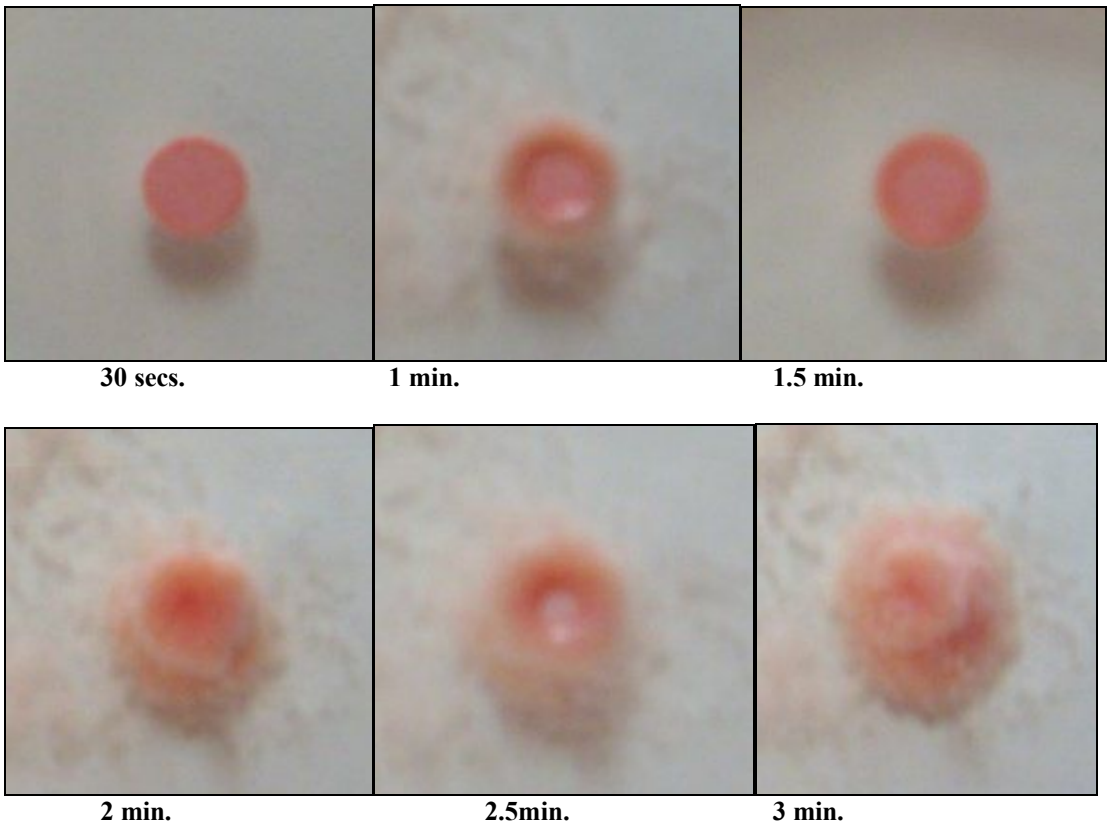

Fig. 1 Release pattern of Montelukast sodium.

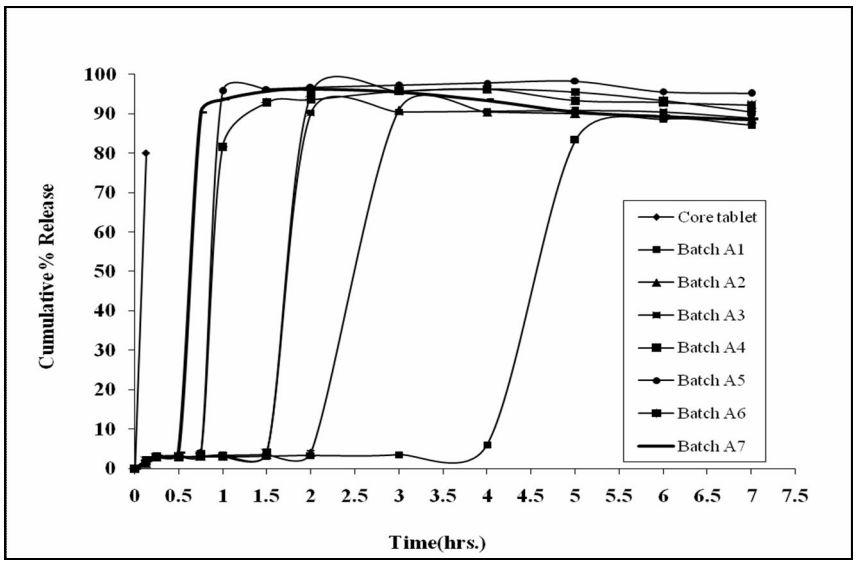

Fig. 2: In vitro drug release of montelukast sodium for tablets prepared by mixed blend.

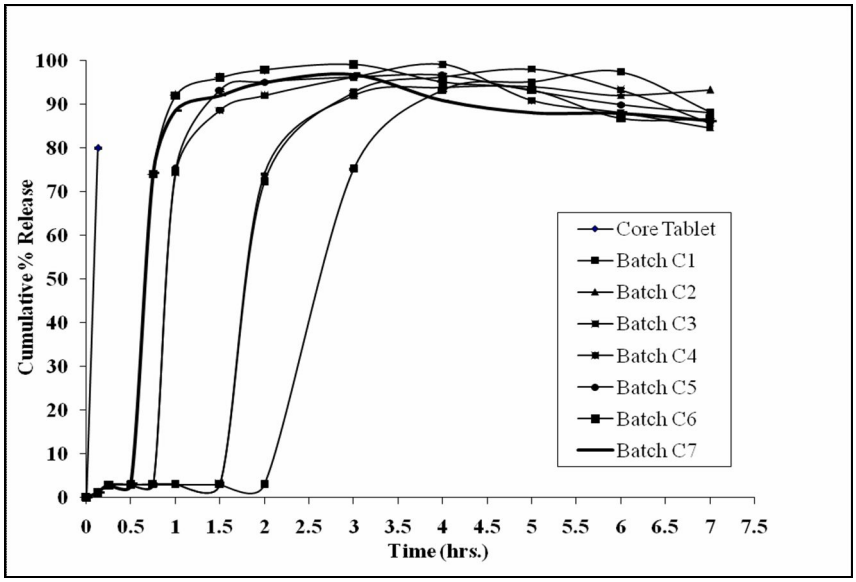

Fig. 3: In vitro drug release of montelukast sodium for tablets prepared by granules.

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