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Effect of Rupturable and Erodible Polymers in the Outer Shell of Press Coated Tablet.

Prashant S. Malpure*, P. Perumal, Avinash B. Gangurde
J. K. K. Nataraja College of Pharmacy, Komarpalayam, Dist-Namakkal, Tamilnadu, India.

Abstract
As a new oral chronopharmaceutical drug delivery system for asthma were developed by using press-coating technology. Tablets composed of an outer shell by using different rupturable and erodible polymers and their combination and core tablet containing Montelukast sodium as a model drug. Press coated tablets with different weight ratio of HPC (EXF) and Ethyl Cellulose (N22); as an outer coating shell and Starlac was used as filler binder in core tablet were examined for change in time lag and release pattern of Montelukast sodium. Press coated tablets were evaluated for thickness, hardness, friability, weight variation and in vitro dissolution test. The study showed different release pattern can be obtained from changing the coating composition. The results also showed that press coated tablets, comprising of a core tablet containing drug, an outer shell of different combinations of polymers, showed acid resistance and time-released functions on in vitro dissolution study.

Key Words
Oral drug delivery, hydroxy propyl cellulose (Klucel EXF), ethylcellulose (EC), press-coated tablet, chronopharmaceutical drug delivery system.

Introduction
The goal in drug delivery research is to develop formulations that meet therapeutic needs relating to particular pathological conditions. Up to late 1980's design of drug delivery systems governed by the homeostatic theory. This theory is based on the assumption of biological functions that display constancy over time. Research in chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of disease display circadian variations, drug release should also vary over time. Formulations should be justified by biopharmaceutical and pharmacokinetic study in order to choose the best hour for administration. Another point raised by circadian variation of physiological function is that drug pharmacokinetics can be time-dependent. Variations in physiological and pathophysiological functions in time, also need for variations of drug plasma concentration has brought a new approach to the development of drug delivery systems-chronopharmaceutical drug delivery. In chronopharmacotherapy, drug administration is synchronized with circadian rhythms. If the peak of symptoms occurs at daytime, a conventional dosage forms can be administrated just before the symptoms are worsening. If symptoms of the disease became worse during the night or in the early morning, the timing of drug administration and nature of the drug delivery system need careful consideration. In this case, modified-release dosage forms must be used. [1] The human body has many built-in rhythms known as biological clocks. Broadly, these can be classified as Ultradian, Circadian, Infradian and Seasonal. Ultradian cycles are shorter than a day, e.g. time taken for a nerve impulse to be transmitted. Circadian cycles last about 24 hours, e.g. sleeping and waking patterns. Infradian cycles are longer than a day, e.g. menstrual cycle. Recently, the role of these rhythms in fighting disease and responding to medication has come under study by researchers and scientists. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed Chronotherapy. To introduce the concept of chronopharmaceutics, it is important to define the concepts of chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. Biological rhythms are defined by a number of characteristics. The term "circadian" was coined by Franz Halberg from the Latin circa, meaning about, and dies, meaning day. Oscillations of shorter duration are termed ''ultradian'' (more than one cycle per 24 h).

***Corresponding Author:**
prashantmalpure@gmail.com

Oscillations that are longer than 24 h are ‘‘infradian’’ (less than one cycle per 24 h) rhythms. Ultradian, circadian, and infradian rhythms coexist at all levels of biologic organization.[2] Chronobiological studies have established circadian rhythm for almost all body functions. They are in synchrony with sleep-activity cycle of the individual. The rhythms tend to fall into two groups. In the first are those that peak during the daytime and are associated with the activity phase of the individual: body temperature, mental, physical and gastrointestinal activities, blood pressure, heart rate, secretion of adrenaline etc. The second group, where rhythms show a peak during nocturnal sleep, includes secretion of several hormones, among which are growth hormone, cortisol and melatonin. Beside the physiological functions, the pathological states of disease have also circadian rhythms. Results of several epidemiological studies demonstrate the elevated risk of different pathology during 24-hour cycle.[1] Based on the previous definitions “chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy”[3]. Ideally, chronopharmaceutical drug delivery systems (ChrDDS) should embody time-controlled and site-specific drug delivery systems. Advantages are safer, more effective and reliable therapeutic effect taking into account advances in chronobiology and chronopharmacology, system biology and nanomedicine. 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 (e.g. self-regulated and adaptative capability to circadian rhythm and individual patient to differentiate between awake-sleep status), be biocompatible and biodegradable, especially for parenteral administration, be easy to manufacture at economic cost, and be easy to administer in to patients in order to enhance compliance to dosage regimen.

Materials and methods

Materials

Montelukast sodium were gifted from Lupin Pharmaceuticals Ltd, Pune and used as a model drug. Starlac, Ac-Di-Sol®, Crosspovidone, Hydroxypropylcellulose (HPC-EXF), Ethyl cellulose were supplied from Signet chemicals, Mumbai; aerosil, magnesium stearate were supplied from S. D. Fine Chemicals Mumbai, India and Quinolline yellow was supplied from Colorcon Asia Ltd. Goa, India. All other chemicals and solvents were of analytical reagent grade.

Methods

Preparation of timed-release press-coated tablets

Preparation of core tablets

The inner core tablet was prepared by direct compression method using rotary tablet machine (Karnawati Rimek Minipress II) in order to perform different release pattern, depending upon different release mechanism involved. The powder mixture of Montelukast sodium, starlac®, Ac-Di-Sol®, and qunolline Yellow were dry blended first for 20 minutes followed by the addition of magnesium stearate and aerosil®. The powder mixture was further blended for 10 minutes. The resulting powder mixtures were compressed into tablets (average tablet weight 75 mg) using a rotary tablet machine equipped with 6 mm concave faced punch. Sufficient pressure was applied to keep the hardness 5 kg/cm^2. The core tablets were evaluated for tablet weight variation, thickness and diameter, hardness and friability etc.

Preparation of press - coated tablets

The Press-Coated tablet was prepared according to the method of Fukui E[4]. All the powder mixtures were previously passed through the sieve No. 44 and 200 mg of the powder mixture was used for the upper and lower shell. The press coating of tablets was performed using a rotary tablet machine. A half amount of the powder was filled into the die to make a powder bed, on the center of which was placed the core tablet manually. Then, the remaining half of the coating material filled in the die, and the contents were compressed under a sufficient compression force, using a concave punch 10 mm in diameter to keep the hardness of coated tablet 10 kg/cm^2. The total amount of upper and lower shell was 200 mg constant for all formulations.

In Vitro evaluation of timed-release press coated tablets

The test was carried out in a USP dissolution apparatus (Type II Paddle; Model-DT 60, Veego, India) at 100 rpm and temperature 37 ± 0.5^{0}C. 1.2 pH phosphate buffer (1st fluid; simulated gastric fluid) was used as dissolution medium for first 2 hr and 6.8 pH phosphate buffer (2nd fluid; simulated

intestinal fluid) was used as dissolution media up to drug release. Aliquots of dissolution fluid were removed at specified time intervals and analyzed for the amount of Montelukast sodium released by a spectrophotometer (UV 1700, Shimadzu, Japan) at a wavelength of 283.6 nm.

Results and Discussion

Effect of Ac-Di-Sol® and Crosspovidone level on drug release profile from core tablets[5,6]

The core compositions for one tablet are reported in Table 1. In order to perform different release patterns; depending upon different release mechanism involved, effect of Ac-Di-Sol® and Crosspovidone level on drug release profile from uncoated tablet (Formulations C_1, C_2, C_3 and C_4) were determined. The formulation containing highest amount of Ac-Di-Sol® (C_1) showed fast disintegration and fast release because of swellable disintegrant present in it. Ac-Di-Sol® is one of the best super disintegrant having excellent disintegrating ability. It swells to a large when it come in contact with water to disintegrate tablets and has a fibrous nature that allows intra particulate as well as extra particulate wicking of water even at low concentration. Formulation C_2 shows delayed in drug release as compared to formulation C_1 because of less amount of Ac-Di-Sol®. The formulation C_3 and C_4 containing Crosspovidone and these are also shows same release pattern as that of formulation C_1 and C_2. The Crosspovidone is water insoluble tablet disintegrant used at 2-5% concentration in tablet prepared by direct compression / wet and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency of crosspovidone strongly influence disintegration of tablets. Larger particles provide a faster disintegration than smaller particles. Crosspovidone can also be used as a solubility enhancer with the technique of co-evaporation. It can be also used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crosspovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate. Formulation C_1, C_2, C_3 and C_4 containing starlac® as a filler binder which is a co processed excipients consist of lactose and maize starch (85:15) produced by spray drying. As lactose is water soluble in nature and starch contains disintegrant property, upon contact with dissolution medium formulations containing Ac-Di-Sol® with Starlac® get easily erodes, rather than swelling of Ac-Di-Sol® in core tablet. The effect Ac-Di-Sol® level on drug release profile from uncoated tablet C_1 and C_2 and effect of crosspovidone level on drug release profile from uncoated tablet C_3 and C_4 are showed in Figure 1. All the formulation C_1, C_2, C_3 and C_4 showed similar release pattern so only formulation C_1 was selected for further study.

In vitro dissolution profile of drugs from timed-release press coated tablets

Effect of Erodible Material (Klucel EXF) Combined with Rupturable Material (EC) in the Outer Shell

The lag time and drug release profile of Montelukast Sodium from dry-coated tablets using different weight ratio of HPC-EXF/EC mixture are given in Table 2 and illustrated in Figure 1 and 2. By combining erodible polymer (HPC-EXF) with rupturable polymer (EC) lag time increases with increasing weight ration of HPC-EXF/EC in formulation F_{11} to F_{17}. But while using EC alone, lag time is lowest as compared to any weight ratio of HPC-EXF/EC. This is only because while combining hydrophilic HPC-EXF with EC; HPC-EXF acts as a binder too. As tablet comes in the contact of dissolution medium HPC-EXF starts hydrating but as EC is hydrophobic in nature it retards the hydration of HPC-EXF and as EC is semi permeable in nature[3] dissolution medium penetrates faster in EC coated tablet compared to along with HPC- EXF. As HPC-EXF forms a compact with EC water would not penetrate faster as compared to EC outer coating shell. Thus due to both concomitance effect lag time is increased with increasing weight ratio of EC/HPC-EXF. As HPC-EXF made a compact with EC; because of different weight ratio of EC/HPC-EXF, outer shell may get eroded first and then when sufficient internal pressure built because of AC-Di-Sol® present in formulation F_1 to F_7 outer shell broke into two halves and cause a stage of rapid drug release. Obviously, the period of lag time was different and dependent on the weight ratio of HPC-EXF/EC. In that also formulation F_1 having EC N7 grade and F_2 having EC N10 grade which are more rupturable than grade EC N22 which is used in formulation F_3 to F_7. The order of the time lag changed according to the weight ratio of HPC-EXF/EC mixture as follows: F_1 (50:50) 4 hrs, F_2 (50:50) 5 hrs, F_3 (50:50) 6 hrs, F_4 (87.5:12.5) 5 hrs, F_5 (75:25) 6 hrs, F_6 (25:75) 7 hrs and F_7 (12.5:87.5)

8 hrs. The finding indicates that the time lag of a press coated tablet can be modulated from 4 to 8 hrs by combining EC with HPC-EXF in different weight ratio. By increasing viscosity of EC grade combined with HPC-EXF lag time also increase. Figure 3 shows the possible scheme of drug released from the compression-coated tablets prepared by EC[7], HPC-EXF/EC mixture.

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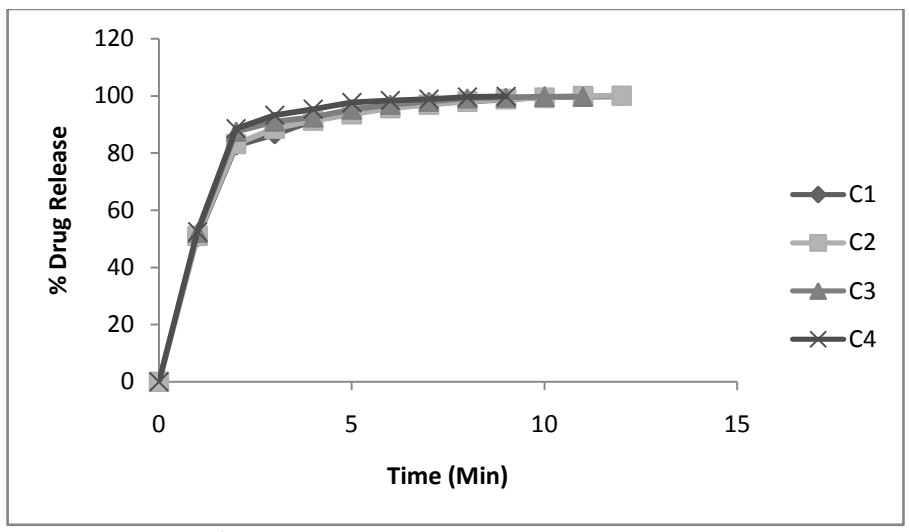

Figure 1: Effect of Ac-Di-Sol® level on Drug Release Profile from Uncoated Tablet (C_1-C_4).

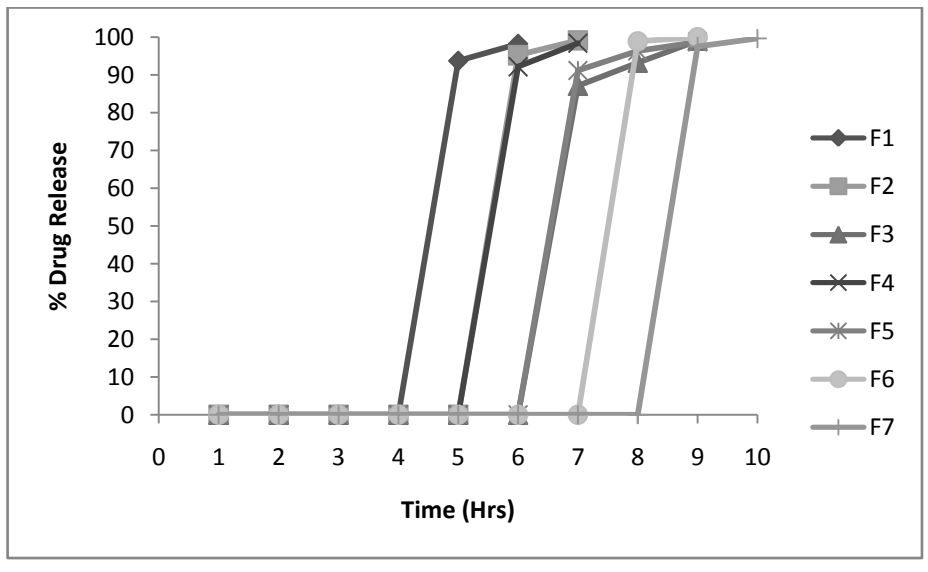

Figure 2: Effect of rupturable material (EC) combined with erodible material (klucel EXF) in the outer shell. (F_1-F_5).

Table 1: Composition of Core Tablets. (All values were given in mg/tablet).

Formulation	**C_1 (mg)**	**C_2 (mg)**	**C_3 (mg)**	**C_4 (mg)**
Montelukast Sodium	30	30	30	30
Starlac®	40	42	40	42
Ac-Di-Sol®	4	2	-	-
Crosspovidone	-	-	4	2
Magnesium Stearate	0.5	0.5	0.5	0.5
Aerosil®	0.5	0.5	0.5	0.5
Quinolline Yellow	q s	q s	q s	q s
Total Weight	75	75	75	75

Table 2: Effect of erodible material (Klucel EXF) combined with rupturable material (EC) in the outer shell.

Formulation		**Coating Material (200 mg)**	**Ratio (%)**
Formulation No.	**Core Tablet**		
F_1	**C_1**	Klucel EXF: EC N 7	50 : 50
F_2	**C_1**	Klucel EXF: EC N 10	50 : 50
F_3	**C_1**	Klucel EXF: EC N 22	50 : 50
F_4	**C_1**	Klucel EXF: EC N 22	75:25
F_5	**C_1**	Klucel EXF: EC N 22	87.5:12.5
F_6	**C_1**	Klucel EXF: EC N 22	87.5:12.5
F_7	**C_1**	Klucel EXF: EC N 22	87.5:12.5

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