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(Research Article)

Design and Evaluation of Chronopharmaceutical Drug Delivery System for Asthma Using Natural Polymers

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ABSTRACT

A new oral chronopharmaceutical drug delivery system for asthma was developed by using press-coating technology. Tablets composed of an outer shell made up of different natural gums and their combination and core tablet containing Montelukast sodium as a model drug. Press coated tablets with different weight ratio of Xanthan Gum (XG) and Locust Bean Gum (LBG); as an outer coating shell and Starlac 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 with 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 natural polymers, showed acid resistance and time-released functions on in vitro dissolution study.

Key Words: Chronopharmaceutical drug delivery system; Xanthan Gum (XG); Locust Bean Gum (LBG); Press-coated tablet, TIMERxR technology.

INTRODUCTION

Chronobiology is the study of biological rhythms and their mechanisms. Biological rhythms are defined by a number of characteristics[1]. The term ‘‘circadian’’ was coined by Franz Halberg from the Latin circa, meaning about, and dies, meaning day[2]. Oscillations of shorter duration are termed ‘‘ultradian’’ (more than one cycle per 24 h). 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[1]. Pharmaceutics is an area of biomedical and pharmaceutical sciences that deals with the design and evaluation of pharmaceutical dosage forms (or drug delivery systems) to assure their safety, effectiveness, quality and reliability (Figure-1). Traditionally, drug delivery has meant getting a simple chemical absorbed predictably from the gut or from the 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[3]. 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. Ideally, chronopharmaceutical drug delivery systems (ChrDDS) should embody time-controlled and site-specific drug delivery systems[4]. Advantages are safer, more effective and reliable therapeutic effect taking into account advances in chronobiology and chronopharmacology, system biology and nanomedicine[5,6]. For example, it has recently been demonstrated that it is possible to perform a continuous label-free detection of two cardiac biomarker proteins (creatin kinase and myoglobin) using an array of microfabricated cantilevers functionalized with covalently anchored anti-creatin kinase and anti-myoglobin antibodies by antigen–antibody molecular recognition[7]. Clinical applications of such nanotechnological approach lie in the field of early and rapid diagnosis and even design of ChrDDS against acute myocardial infarction. Evidence suggests that an ideal ChrDDS should: (i) be non-toxic within approved limits of use, (ii) have a real-time and specific triggering biomarker for a given disease state, (iii) 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), (iv) be biocompatible and biodegradable, especially for parenteral administration, (v) be easy to manufacture at economic cost, and (vi) be easy to administer in to patients in order to enhance compliance to dosage regimen. To our knowledge such ideal ChrDDS is not yet available on the market. The majority of these features may be found at the interface of

chronobiology, chronopharmacology, system biology and nanomedicine.

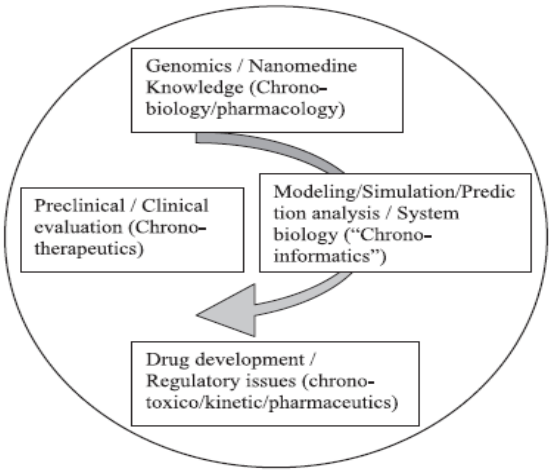

Figure-1: Key steps to be well-integrated for successful ChrDDS design and evaluation.

TIMERxR TECHNOLOGY

The TIMERxR technology (hydrophilic system)[8] combines primarily xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERxR gum matrix, which expands to form a gel and subsequently releases the active drug substance. This system can precisely control the release of the active drug substance in a tablet by varying the proportion of the gums, together with the third component, the tablet coating and the tablet manufacturing process. A chronotherapeutic version of this technology platform is being tested in clinical trial with a bioactive agent known as AD 121 against rheumatoid arthritis. Potential application of this technology is the development of an oral, CR opioid analgesic oxymorphone[9].

MATERIALS AND METHODS

Materials

Montelukast sodium were gifted from Lupin Pharmaceuticals Ltd, Pune and used as a model drug. Starlac, Ac-Di-Sol®, Crosspovidone, Xanthan Gum (XG) and Locust Bean Gum (LBG) were supplied from Lucid Colloids; aerosil, magnesium stearate was 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.

Methodology

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[10]. 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[11,12]

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-2. 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 gellable material Xanthan Gum (XG) combined with gellable material Locust Bean Gum (LBG) in the outer shell

Formulation F_1 to F_5 shows increase in lag time and decrease in Montelukast Sodium release rate with increase in weight ratio of Xanthan Gum/Locust Bean Gum. Formulation F_1 to F_5 contains Xanthan Gum/Locust Bean Gum weight ratio of 00:100, 25:75, 50:50, 75:25 and 100:00 respectively.
The formulation F_1 having outer layer of xanthan gum, which showed the lag time upto 10 hrs, the initial increase in drug release rate on increasing the concentration of xanthan gum can be explained on the basis that a higher binder concentration led to an increase in hardness of the tablet, while the porosity and capillary pore sizes were reduced[13]. This in turn reduced the wicking of water into the tablet and consequently the swelling and drug release rates are slowed. Xanthan gum is a polysaccharide consisting of a cellulose backbone and Trisaccharide side chains containing glucuronic acids that give this polymer a negative charge. Although primarily used as a suspending agent, xanthan gum has been reported to function as a matrix retardant in solid dosage forms[14-18]. This in turn reduced the wicking of water into the tablet and consequently the swelling and drug release rates are slowed. These tablets showed a considerable swelling at a pH of 6.8 and the drug was dispersed in the swollen matrix formed by the polysaccharide.
The formulation F_5 having outer layer of locust bean gum, which showed the lag time upto 4 hrs, Locust bean galactomannan were found to be soluble in water. Cross-linked galactomannan however led to water-insoluble film forming product showing degradation in colonic microflora[19]. However, dissolution study performed on theophylline tablets coated with cross-linked galactomannan showed the mechanical instability of these coatings in the dissolution media[20] thereby suggesting the non suitability of such films as colon carriers.
The lag time and drug release profile of Montelukast Sodium from dry-coated tablets using different weight ratio of Xanthan Gum: Locust Bean Gum mixture are given in Table-2 and illustrated in Figure-3.

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 gellable material (Xanthan Gum) combined with gellable material (Locust Bean Gum) in different ratio.

Formulation		Coating Material (200 mg)	Ratio (%)
Formulation No.	Core Tablet		
F_1	C_1	Xanthan Gum	100
F_2	C_1	Xanthan Gum: Locust Bean Gum	25 : 75
F_3	C_1	Xanthan Gum: Locust Bean Gum	50 : 50
F_4	C_1	Xanthan Gum: Locust Bean Gum	75 : 25
F_5	C_1	Locust Bean Gum	100

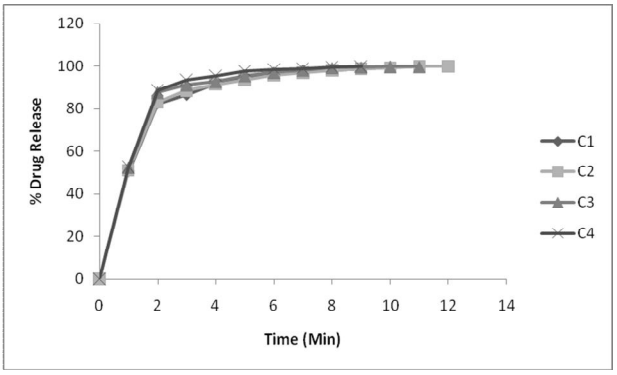

Figure-2: Effect of Ac-Di-Sol® level on Drug Release Profile from Uncoated Tablet (C_1-C_4).

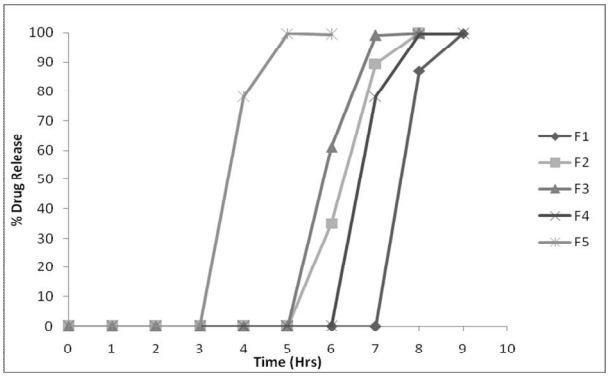

Figure-3: Effect of gellable material (Xanthan Gum) combined with gellable material (Locust Bean Gum) in the outer shell.

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