Original Research Article

Development and characterization of chronomodulated drug delivery system of captopril

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Abstract

Background: Hypertension shows circadian rhythm that there is a rise in pressure from the time of waking or before (about 4 to 8 a.m.), in most people. Conventional drug delivery system of captopril is inappropriate for the delivery of drug, as they cannot be administered just before the symptoms are worsened, because during this time the patients are asleep, bedtime dosing of captopril will not provide a therapeutic plasma drug concentration at the early hours of morning because of poor pharmacokinetic profile and shorter half-life of 1.9 hours. Thus, this study attempts to design and evaluate a chronomodulated pulsatile drug delivery system of captopril which was aimed to release the drug after a lag time of 6 hours. **Materials and Methods:** Present delivery system was prepared by rupturable coating method. The core containing captopril as a bioactive compound were prepared by direct compression method and then coated sequentially with an inner swelling layer containing hydrocolloid HPMC E5 and an outer rupturable layer consisted of Eudragit RL/RS (1 : 1). Total 12 formulations with different levels of inner swelling layer and outer polymeric layer were prepared and subjected to various processing and formulative parameters like the effect of core composition, level of swelling layer, and rupturable coating on lag time was investigated. *In vitro* drug release and rupture tests were performed using United States Pharmacopoeia paddle method at 50 rpm in 0.1N HCl and phosphate buffer of pH 6.8. **Results:** The results showed that as the amount of inner swelling layer increases, the lag time decreases and as the Eudragit coating level increases, the lag time increases and percent water uptake of time-dependent pulsatile release system decreases. The presence of an osmotic agent and effervescent agent helped in shortening of lag time. **Conclusion:** The system was found to be satisfactory in terms of release of the drug after the lag time of 6 hours.

Key words: Captopril, circadian rhythm, rupturable layer, swelling layer, time-dependent pulsed release system

INTRODUCTION

Various diseases like asthma, hypertension, ischemic heart disease, and arthritis show circadian variation that demand time-scheduled drug release for effective drug action, for example, inflammations associated with morning stiffness, asthma, and heart attack in early hours of the day.[1] Treating these diseases with immediate release dosage forms may be impractical if the symptoms of the disease are pronounced during the night or early morning. Therapy with modified release dosage forms with zero order drug release theoretically leads to controlled and constant levels of drug in plasma throughout the day. In order to optimize therapy in terms of safety, patient compliance, and efficacy, chronopharmaceutical formulations based upon time-controlled drug delivery systems are considered to be potential therapeutic options.[2]

Epidemiological studies document that the frequency of many cardiovascular diseases, including myocardial infarction and stroke, varies predictably in time over 24 hours (the circadian period).[3] Congestive heart failure and myocardial infarction are manifested more frequently during the night or early in the morning.[4] Blood pressure which arises notably just waking up is usually responsible for these attacks.[5] However, for such diseases, conventional drug delivery systems are inappropriate for the delivery of drug, as they cannot be administered just before the symptoms are worsened, because during this time, the patients are asleep.

To overcome these problems of conventional dosage forms, the present study attempts to design and evaluate a chronomodulated pulsatile drug delivery system of captopril by rupturable coating method. The tablet has to be taken (once a day) at bed time which was aimed to have a lag time of 6 hours and will release the

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drug in the early hours of morning. Such novel time-controlled pulsatile delivery system consists of three laminar layers: from the center to outside, the core table containing pharmacological active compound, osmotically active agent, and effervescent agent; an inner swelling agent layer; and outer water-insoluble polymer membrane. The core serves as a reservoir, and the release controlling layers protect the core from the environment, e.g., water, acidic pH, and enzymes until the drug is released after a predetermined lag phase. The coatings can erode[6,7] / dissolve,[8] rupture, or alter their permeability[9] at the required time. Pulsatile drug delivery systems are classified into single-unit systems (capsule-based systems, systems based on osmosis, systems with eroding or soluble barrier coating, and systems with rupturable coating) and multiple unit systems (system based on change in membrane permeability and system with rupturable coating).[10] Single-unit rupturable pulsatile drug delivery system was chosen as the model system over erodible pulsatile drug delivery system or Pulsincap® and PORT® system because of ease of manufacturing, better reproducibility of the lag time, and rapid drug release after a lag time.[11]

The press-coating techniques have been applied for many drugs that require modification of drug release, masking of bitter test, and protection of volatile substances. This technique has many advantages because no special coating solvents or coating equipment are needed for coating of tablets and manufacturing speed is faster. Recently, the application of this technology has also been investigated for timed-release dosage forms, as timing-release tablets,[12] time clock systems,[13] and delayed-release tablets.[14]

Table 1: Composition of core tablet formulations

Ingredients	Quantity (in mg)
Captopril	25
Potassium chloride	47
MCC	60
Sod bicarbonate	30
Lactose	60
Starch	60
Aerosil	12
Magnesium stearate	3
Talk	3
Weight/tablet	300

MATERIALS AND METHODS

Materials

Captopril (Wockhardt, Aurangabad, India) was chosen as model drug. Potassium chloride and sodium bicarbonate (Ranbaxy, Fine chemicals limited New Delhi, India) were used as osmotic agent and effervescent agents, respectively. Microcrystalline cellulose PH 102 (Reliance cellulose Pvt., Ltd. Hyderabad, India) was incorporated for its unique compressibility and super disintegrating property, lactose monohydrate (Ranbaxy, Fine chemicals limited New Delhi, India), Starch I.P (Spectrochem Pvt limited Mumbai, India), talk and magnesium stearate (S.D. Fine chemicals limited Mumbai, India), and colloidal silicon dioxide (MCC laboratories limited, Mumbai, India) were used as other components of core tablets. HPMC E5 was used as an inner swelling layer (Medley Pharmaceuticals limited, Gujarat, India). The rupturable coating was Eudragit RL and Eudragit RS (Degussa India Pvt limited, Mumbai, India).

Preparation of core tablets

Formula for the preparation of the core tablets is shown in Table 1. All excipients were mixed for 20 minutes and passed through a 120-mesh size sieve and directly compressed into 300 mg tablets using 8 mm flat punches on a rotary tablet machine. Core tablets without potassium chloride (D-F1) and without sodium bicarbonate (D-F2) were also prepared and these ingredients were replaced with lactose as inert filler.

Development of pulsatile release tablets

Pulsatile release tablets were prepared by coating core tablets with different levels of an inner swelling layer comprising of HPMC E5 and an outer polymeric layer consisting of Eudragit RL/RS (1 : 1) dispersed in acetone/isopropyl alcohol (60/40 v/v) using PEG 4000 (5% w/w of polymer content) as a plasticizer. Different levels of coatings of both inner swelling layer and outer polymeric layer for different formulations are shown in Table 2. Inner swelling layer was applied by direct compression (press coating), i.e., half of the

Table 2: Different core content, inner layer, and outer coating concentrations for all tablet formulations

Formulation	Pot chloride (mg/tab)	Sod bicarbonate (mg/tab)	Inner swelling layer HPMC E5 %	Outer polymeric layer Eudragit RS/RL (1 : 1) %
A-F1	47	30	20	2
A-F2	47	30	20	4
A-F3	47	30	20	6
B-F1	47	30	30	4
B-F2	47	30	30	6
B-F3	47	30	30	8
B-F4	47	30	30	10
C-F1	47	30	40	6
C-F2	47	30	40	8
C-F3	47	30	40	10
D-F1	-	30	30	6
D-F2	47	-	30	6

coating material was placed in the die cavity, the core tablet was carefully positioned in the center of the die, and cavity was filled with the other half of the coating material. Coating materials were compressed around the core tablet using 10-mm punch. However, outer polymeric layer was incorporated by dip-coating method, i.e., by dipping the press-coated tablets in coating solution and drying repeatedly until a desired thickness was achieved. After finishing the coating process, the tablets were then placed in an oven at 50°C for 2 hours to remove the solvent.

Evaluation of pulsatile release tablets

In vitro drug release studies

The *in vitro* drug release from coated tablets was carried out using United States Pharmacopoeia (USP) paddle apparatus at 50 rpm and 37 ± 0.5°C. HCl (0.1N) and phosphate buffer (pH 6.8) were used as the dissolution medium. Initially, tablets were subjected to dissolution in 0.1N HCl for 2 hours and after that media were changed to phosphate buffer (pH 6.8). The samples were withdrawn at regular intervals and analyzed by UV spectrophotometer at 217 nm for the presence of the drug (n = 3).

Rupture test

The time at which the outer coating layer starts to rupture is defined as the lag time. It was determined visually by using the USP dissolution apparatus II (900 ml of 0.1N HCl for initial 2 hours and then media was changed to phosphate buffer of pH 6.8, 37 ± 0.5°C, 50 rpm, n = 3). In addition, the rupture behavior of pulsatile release tablets was photographed by a digital camera.[15]

Effect of inner swelling layer concentration on the lag time

Core tablets were coated with 20% w/w, 30% w/w, and 40w/w of HPMC E5 as inner swelling layer and subjected to *in vitro* dissolution study. Outer polymer layer is not varying it is same in the formulations A-F3, B-F2 and C-F1. Effect of swelling layer concentration over lag time and release behavior was observed using a spectrophotometer, as described in method under *in vitro* drug release studies.

Effect of outer polymer concentration on lag time

To study the effect of outer polymeric layer concentration on lag time, press-coated tablets were coated with different levels of Eudragit RL/RS (1 : 1), i.e., 4, 6, 8, and 10% w/w (inner swelling layer remained the same). Effect of outer polymer concentration on lag time and release behavior was observed using a spectrophotometer, as described in method under *in vitro* drug release studies.

Effect of outer polymer concentration on water uptake performance of pulsed release tablets

The % water uptake of pulsatile release tablets was determined in medium-filled containers placed in a horizontal shaker (100 ml of 0.1N HCl, 37°C, 74 rpm, n = 3). At predetermined time points, the tablets were removed from the dissolution medium, carefully blotted with tissue paper to remove surface water, weighed, and then placed back in the medium up to the time when the coating of the tablet started to rupture.[16]

% water uptake was calculated as follows:

$$\text{Water uptake (\%)} = \frac{Wt - Wo}{WO} \times 100$$

Where, Wt is weight of wet tablet at time t and W_0 is weight of dry tablet.

Effect of sodium bicarbonate and osmotic agent on drug release characteristics

Core tablets with and without sodium bicarbonate and potassium chloride were prepared individually and coated with same polymeric inner (HPMC E5, 30%) and outer layers (Eudragit RL/RS 1 : 1, 6 mg/cm^2). To observe the effect of osmotic agent and sodium bicarbonate on lag time, the tablets were subjected to *in vitro* dissolution study (n = 3) and release profiles were compared.

Effect of paddle speed on the lag time and drug release characteristics

Coated tablets were subjected to *in vitro* dissolution study at different paddle speeds (50 and 100 rpm). Other conditions remained the same as described in *in vitro* dissolution study. Effect of paddle speed on the lag time and drug release behavior was observed and analyzed by using a spectrophotometer (n = 3).

Effect of pH of dissolution medium on the lag time

Developed pulsatile release tablets (optimized formulation B-F2) were subjected to *in vitro* dissolution study in different dissolution mediums with varying pH values, i.e., pH 1.2, pH 5.5, pH 6.8, and pH 7.2. Effect of pH of dissolution medium on the lag time was observed and analyzed by using a spectrophotometer (n = 3).

Stability studies

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines. Optimized ChrDDS (Chronopharmaceutical drug delivery system), sealed in aluminum packaging coated inside with polyethylene and various replicates were kept in the humidity chamber maintained at 40 ± 0.5°C, 50 ± 0.5°C, and 60 ± 0.5°C at 75% RH for three months (Yorco Scientific Industries, India). At the end of studies, samples were analyzed for physical appearance, drug content, and *in vitro* dissolution studies. The log percentage drug remaining was plotted against time and slope was determined. The effect of temperature on the degradation was studied by plotting log K *vs* 1/T. The value of K at 25° was extrapolated from the plot and shelf life was calculated by substituting K_{25} in equation, $T_{0.9} = 0.1040/ K_{25}$.[17]

RESULTS AND DISCUSSION

Design of the pulsatile release tablets

The time-dependent pulsatile release tablet system developed in the present study was a reservoir device where the tablet cores were surrounded by two consecutive layers, a swelling layer, and a rupturable layer, respectively. The swelling layer consisted of HPMC E5 as the swelling agent because of its swelling nature

and its eroding behavior and can be applied by direct compression method. Eudragit RL and RS are water-insoluble, swellable, and pH-independent film formers. Because the number of quaternary ammonium groups of Eudragit RL was two times higher than that of Eudragit RS, resulting in faster drug release from Eudragit RL than Eudragit RS, dosage forms can be coated with different ratios of Eudragit RL and RS to provide ideal drug release model.[18] Therefore, to achieve the pulsed release system or time-dependent system, Eudragit RL and Eudragit RS are used in combination in this study.

Water influx was through the semipermeable rupturable outer coating which leads to expansion and erosion of an intermediate layer, which ultimately resulted in rupture of the outer coating [Figure 1], the drug was then released rapidly within a short period after certain lag time due to the strong rupturing of the coating. The rupturing sequence of a pulsatile release tablet is shown in Figure 1.

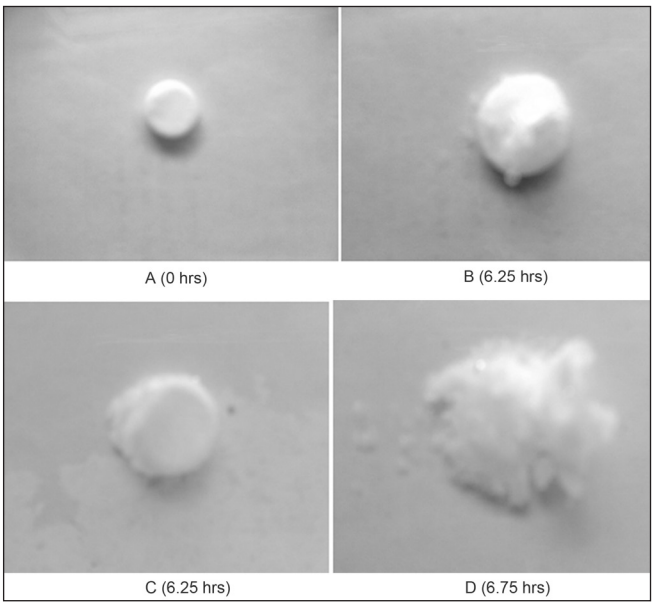

Figure 1: Rupture sequence of pulsed release tablets

In vitro drug release studies

Release studies were carried out to examine the pulsatile release characteristics of the developed systems. Captopril, a freely water-soluble drug, was used as a model drug. The drug was not released prior rupturing of the coating. The *in vitro* drug release of 10 formulations is shown in Figure 2. *In vitro* dissolution results showed that the fast and complete drug release after lag time was observed in formulations A-F1, B-F1, B-F2, and C-F2 and expected lag time (6 hours) was observed in formulations B-F2 and C-F2. But, because of economic reasons, B-F2 was considered as the optimum formulation. Based on highest regression value (r^2 = 0.4230 to 0.7377) obtained while Kinetic treatment indicated that for all the twelve formulations, Peppa's was the best fit model and 'n' values (n = 0.2040 to 0.4135) which is less than 0.5. This indicates that anomalous non-Fickian release would be implicated.

Effect of inner swelling layer concentration on the lag time

Thickness of swelling was the critical parameter which influenced the rupture of outer polymer coating. Figure 3 shows that after the lag time, the drug release from the time-dependent pulsed release tablet with 20% w/w HPMC E5 layer was lower compared with that from the tablet with 30% w/w HPMC E5 layer. Further increase in the inner swelling layer concentration to 40% w/w resulted in early burst of the tablet. It indicates that the lag time of pulsed release tablet decreased with increase in the inner swelling concentration. As the amount of swelling agent increased, it exerted more pressure over the outer layer, resulting in rapid rupturing of the tablet. The expanded swelling layer facilitated the entry of dissolution medium to the core containing effervescent agent, which further synergized the rupturing of the outer layer. Therefore, a 20% HPMC E5 layer might not be enough for the complete rupture of the outer layer, whereas a 30% w/w concentration of inner swelling layer was found to be optimum to rupture the outer polymeric layer.

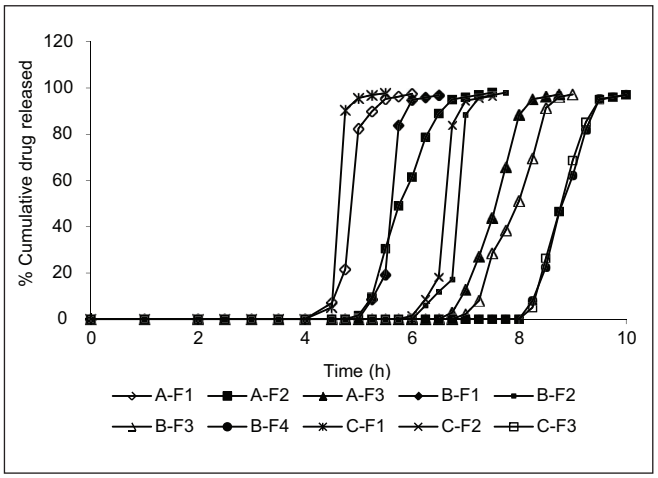

Figure 2: *In vitro* drug release profile of all the 10 formulations with different Levels of inner swelling layer and outer polymeric layer concentrations

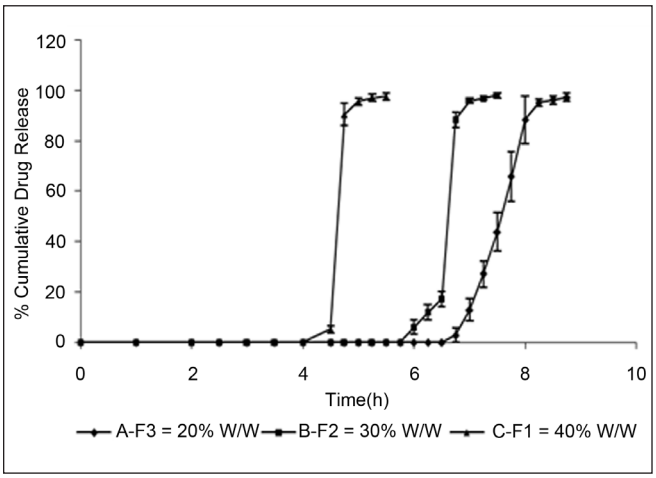

Figure 3: Effect of inner swelling layer concentration on lag time of the pulsed release system. Inner swelling layer concentrations were C-F1 = 40% w/w, B-F2 = 30% w/w, A-F3 = 20% w/w

Effect of outer polymer concentration on lag time and water uptake performance of pulsed release tablets

The drug release and the water uptake prior to rupture were investigated as function of the amount of rupturable outer polymeric layer. The results [Figure 4] show that lag time increased with increasing the outer coating level, the drug was released rapidly and completely at Eudragit coating levels of 4 mg/cm^2 and 6 mg/cm^2. At the higher Eudragit coating levels of 8 mg/cm^2 and 10 mg/cm^2, the drug release was slower after the lag time; this was again caused by the lower degree of rupturing of the thicker coating. Higher outer polymeric coating levels retarded the water uptake interestingly [Figure 5], all curves showed an almost linear water uptake with time until a critical water level, where the outer Eudragit coating ruptured. The critical water uptake level was slightly higher at higher level of Eudragit coating. This could be explained by the higher mechanical strength of the thicker coating requiring a higher degree of swelling (water uptake) for rupturing.[19]

Outer polymer concentions were B-F1 = 4 mg/cm^2, B-F2 = 6 mg/cm^2, B-F3 = 8 mg/cm^2, B-F4 = 10 mg/cm^2.

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Effect of sodium bicarbonate and osmotic agent on drug release characteristics

To generate osmotic pressure inside the core, potassium chloride was added as an osmotic agent. Formulations D-F1 (without osmotic agent) and D-F2 (without effervescent agent) increases the lag time as compared with optimized formulation B-F2 [Figure 6]. This is because the presence of an osmotic agent helped in drawing water toward the tablet which resulted in shortening of lag time. Similarly, the presence of sodium bicarbonate in their core showed slightly lower lag time due to generation of carbon dioxide, which resulted in building up of pressure inside the core and helped in early rupturing of the outer polymeric layer.

From all the above parameter studies and observations, it can be assumed that the first step in drug release is penetration of water in the core tablet by diffusion through Eudragit outer polymeric film and the rate and amount of water entered is dependent on outer film thickness. The HPMC E5 layer was swelled when it comes in contact with water. No significant increase in volume was observed before water reached the HPMC layer. Initially, a short period of no expansion was observed, after that fast volume expansion was observed. The penetration rate of water accelerated due to polymer chain relaxation. When water reached the core, potassium chloride and drug dissolved and an osmotic gradient across the membrane was produced. Further osmotic pressure played a key role to imbibe water from environment continuously. Meanwhile, the film stretched faster as soon as the osmotic pressure gradient developed. MCC had a significant effect on the release rate. This can be accounted for by the fact that after extramembranous water was imbibed into the intramembrane, the swelling of MCC would lead to increasing

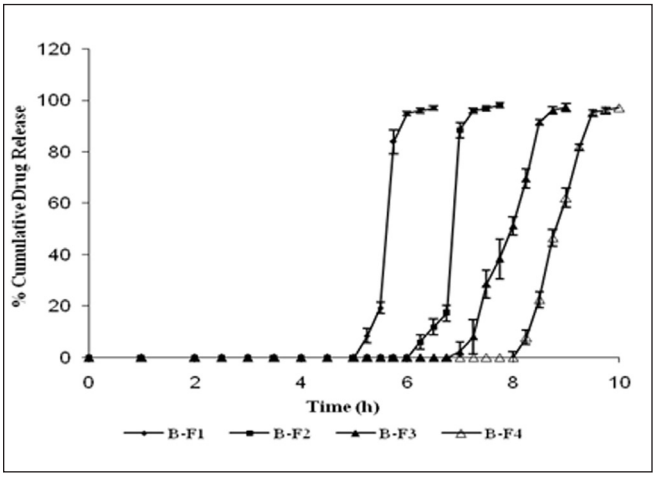

Figure 4: Effect of outer polymer concentration on lag time of pulsed release tablets. Outer polymer concentrations were B-F1 = 4 mg/cm^2, B-F2 = 6 mg/cm^2, B-F3 = 8 mg/cm^2, B-F4 = 10 mg/cm^2

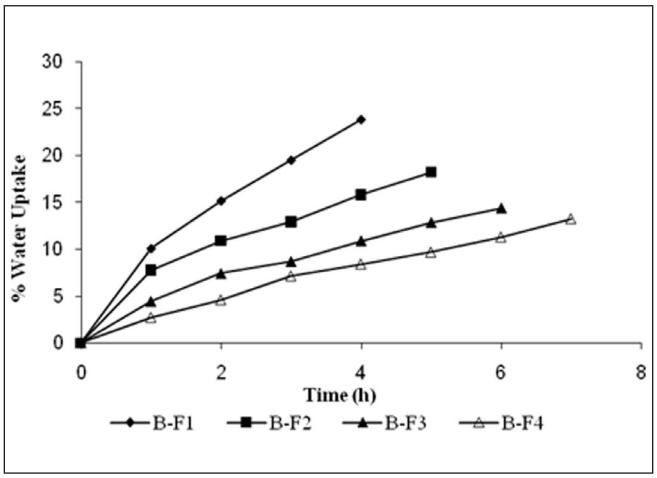

Figure 5: Effect of outer polymer concentration on water uptake of pulsed release tablets. Outer polymer concentrations were B-F1 = 4 mg/cm^2, B-F2 = 6 mg/cm^2, B-F3 = 8 mg/cm^2, B-F4 = 10 mg/cm^2

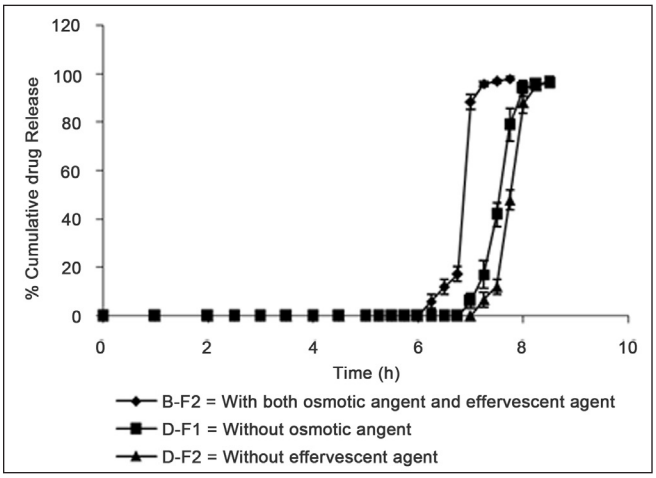

Figure 6: Effect of sodium bicarbonate and osmotic agent on drug release characteristics of pulsed release tablets

static pressure inside the membrane, which would accelerate drug release from the core. After an optimum pressure development,

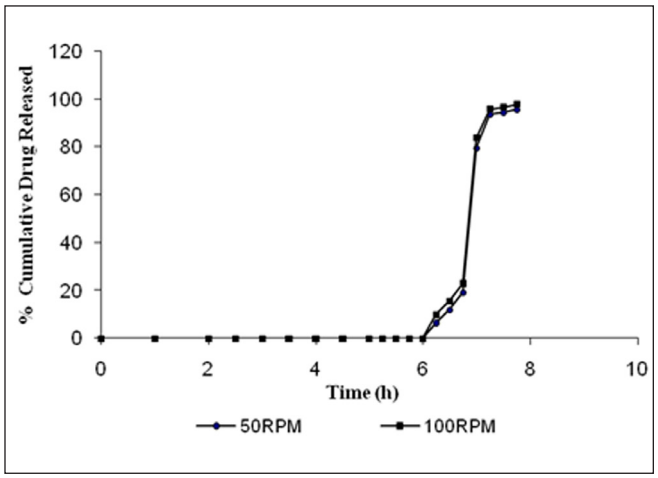

Figure 7: Effect of paddle speed on drug release profile of pulsed release tablets

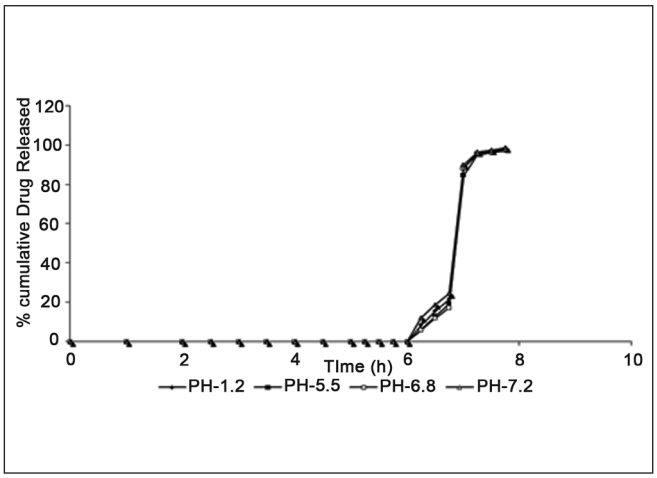

Figure 8: Effect of pH of dissolution medium on drug release profile of pulsed release tablets

fractures were stretched into the film leading to faster release of the drug. At this moment, the membrane is converted from a semipermeable membrane into porous membrane. With increasing film thickness, a stronger expansion is necessary to perforate the membrane.

Effect of paddle speed and pH of dissolution medium on the lag time and drug release characteristics

When such timed release tablets are orally administered, they are transferred from stomach to small intestine or colon while retaining the intact tablet shape. During this transit process, the pH of gastrointestinal juice around the tablet changed markedly from pH 1.2 to pH 8. Therefore, determination of dissolution behavior in various dissolution media was necessary. No significant difference in drug release was observed for release study in different pH or under different rotational speeds [Figures 7 and 8]. This shows an advantage for the system, as it predicts no change in the performance of the system at increased gastric motility.

Stability studies

Accelerated stability studies indicated a shelf life of approximately two years. The formulation was fairly stable as revealed by stability study conducted as per WHO and ICH guidelines.

CONCLUSION

The ChrDDS was successfully developed. The system was found to be satisfactory in terms of release of the drug after the lag time of 6 hours in colonic region. The dosage form can be taken at bed time (10 pm) and will release the content in the early hours of morning when the symptoms of cardiovascular diseases are more prevalent. This dose is to control and ensure protection against the early morning surge in BP and the associated increased risk of cardiovascular events. The release of the drug was sharp and complete after the lag time, which is necessary for any pulsatile drug delivery system.

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