DUAL RELEASE CHRONOTHERAPEUTIC SYSTEM OF POORLY WATER SOLUBLE ANTIHYPERTENSIVE DRUG CARVEDILOL: DESIGN, DEVELOPMENT AND *IN VITRO* CHARACTERIZATION

Vipra R. Vaidya[a], Dilesh J. Singhavi[a]*, Mayuri N. Yengade[a] and Shagufta Khan[a]

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ABSTRACT

The current research investigation's goal was to design a core-in-cup type pulsatile system of an antihypertensive drug (carvedilol phosphate) to reduce the evening and early-morning symptoms of hypertension. An inclusion complex of this drug was prepared with hydroxyl propyl beta cyclodextrin to increase carvedilol solubility. Using direct compression method, various batches of core tablets were formulated using Croscarmellose sodium as a superdisintegrant. Core tablets of the optimized formulation were press coated with backing layer and release-retarding plug layer. An *in vitro* release research was performed after evaluating the physicochemical characteristics of the core in cup design tablets. Based on the lag time of 8 h between the first and second pulse releases, a batch containing sodium alginate (100 mg) and hydroxypropyl methylcellulose K4M (100 mg) was chosen as the optimum batch. Thus, the dual-release core-in-cup pulsatile tablets may be utilized for managing the hypertension symptoms appearing in chronological order.

Keywords: Pulsatile, solubility, inclusion complex, lag time, dissolution, dual release

INTRODUCTION

The oral route is the utmost preferred and appropriate option for drug administration. It offers the maximum active surface area among all the routes. The conventional dosage form is associated with great fluctuations in the drug level in the plasma and body tissues, with resulting uninvited toxicity and reduced effectiveness. Maintaining the drug level in the plasma within the effective range is vital for better action when using the conventional dosage form. Sustained-release oral medication delivery methods were developed in response to this problem as well as others including frequent dosing and unpredictable drug absorption. Any of the numerous methods available may be used by a sustained-release formulation to maintain a drug's delivery rate[1]. However, under some circumstances, a pulse release of the drug is necessary to coincide with the onset of the symptoms of an illness that has a circadian rhythm. Pulsatile drug-delivery systems (PDDS) will be ideal for dealing with such diseases. A PDDS that can be administered at night, before the patient goes to bed, but releases the therapeutic agent early in the morning could be a desirable chronopharmaceutics system[2]. Battu et al. developed multi-unit chronotherapeutic system for treating angina pectoris. Firstly, they prepared solid dispersions containing nifedipine (NF) using a kneading technique. They used guar gum (GG) and sodium starch glycolate (SSG) in the ratios 1:1 and 2:1. They prepared Eudragit L100 and RS100 coated pellets using these solid dispersions for pulsatile delivery of drug and concluded that their drug release profiles had been optimized for chronotherapy of angina[3].

Core-in-cup tablets are innovative oral pulsatile release formulations in which the bottom and the wall of the core tablets are surrounded by an inactive material and there is a top layer of a hydrophilic material that swells. This system offers drug release after a definite lag period during which the topmost layer is generally eroded[4]. Rewar Suresh et al. developed a novel oral PDDS centered on a press coated core-in-cup tablet. The core, which contained eprosartan mesylate, was formulated using technique of direct compression. The cup (impervious coating) was made up of a lipophilic cellulose acetate propionate polymer, and the upper layer was made of hydrophilic swelling polymers (sodium alginate, hydroxypropyl methylcellulose (HPMC K4M), sodium carboxy methylcellulose) of varying concentrations.

[a] Department of Pharmaceutics, Institute of Pharmaceutical Education and Research, Borgaon (Meghe), Wardha- 442 001, Maharashtra, India
*For Correspondence: E-mail: dileshsinghavi@rediffmail.com

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The lag time was enhanced by increasing the level of the hydrophilic uppermost coat, and release of the drug was decreased. Therefore, it was concluded that the composition of the erodible polymeric material used in the top layer can be used to control the system action[5].

Antihypertensive drugs are used to prevent complications arising from high blood pressure. The symptoms of hypertension are at 7 pm and between 4 am and 8 am[6]. To treat the problem, a dual pulse drug release device might be appropriate. Carvedilol phosphate (CV) (nonselective β-adrenergic blocking agent)[7] was selected as a model drug in hypertension in this study.

The current study's focus was to get the initial pulse of drug release right away (to deal the initial peak of symptoms) and a second pulse after a lag time (to manage the second peak of symptoms). The formulation used in the study consisted of two rapid-release components separated by a plug layer. Immediate-release tablets were prepared to get a pulse of drug release. The plug between the rapid-release components was used to provide the lag period between the two pulses.

MATERIALS AND METHODS

Materials

Cadila Pharma Limited (Gujarat, India) provided CV, Roquette Private Limited (Lestrem, France) provided hydroxy propyl beta-cyclodextrin (HP-β-CD). Loba Chemie Private Limited provided hydroxypropyl methyl cellulose (HPMC K4M), sodium alginate (SA), ethyl cellulose (EC), and xanthum gum (XG) (Mumbai, India). The remaining components were all of high analytical purity.

Inclusion complex of CV

Phase solubility testing

By employing the approach outlined by Higuchi and Conners, a phase solubility study was done[8]. A surplus of CV (10 mg) was added to screw-capped bottles (10 mL capacity) full of distilled water with a range of concentrations of HP-β-CD (0-14 mM). The above dispersions were shaken upto 72 h at 37 ± 0.5 °C on a rotary flash shaker. When equilibrium was reached, the mixture was filtered by Whatman filter paper No. 42, and the absorbance was measured at 242.0 nm using a double-beam UV spectrophotometer (model UV2401 PC).

Plotting the drug's millimolar solubility vs. the concentration of HP-β-CD resulted in the phase solubility figure. Applying the equation for the straight line to the phase solubility graph, the apparent complexation constant (K1:1) of the inclusion complex was found:

$$K1{:}1 = \text{slope}/\text{intercept}\ (1\text{-slope}), \quad (1)$$

Where, K1:1 = apparent complexation constant and

S_0 (intercept) = intrinsic solubility of the CV without use of the complexing agent HP-β-CD

HP-β-CD-CV complex formation via the solvent evaporation method

HP-β-CD and CV were dissolved in a 1:1 ratio in 100 cc of pure (analytical grade) ethanol. The ethanol was evaporated using hot-air oven at the temperature of 60 °C. The resultant powder was collected and screened through a 60 # sieve. The complex obtained was stored in a glass vial and used for further studies[9].

Characterization of HP-β-CD-CV complex

X-ray diffraction testing

To evaluate the change in the drug's solid state that occurred during the formation of the CV- HP-β-CD complex, X-ray diffraction analysis was carried out using an XRD diffractometer (Rigaku-XSmartlab, Germany) with CuKα radiation. CV, HP-β-CD, physical mixes of CV and HP-β-CD, and the CV- HP-β-CD complex were examined. Scanning of samples was done from 0° to 80°.

Drug content

The inclusion complex's drug content was evaluated by dissolving a portion of the inclusion complex (≈ 10 mg CV) in 25 mL of pH 7.4 phosphate over a period of 20 minutes. The volume was raised by the addition of same buffer to 50 mL. Using Whatman filter paper no. 42, the resulting solution was filtered and diluted as required, and determination of the absorbance was done at 242.0 nm.

Solubility study

Approximately 12.5 mg CV of the drug's inclusion complex was taken. A stoppered volumetric flask with a capacity of 100 mL was used to add 10 mL of three different media [acid buffer pH 1.2, phosphate buffer pH 6.8 and pH 7.4) to this. By keeping on a mechanical shaker at ambient temperature, the flask was shaken for 24 h. Then, Whatman filter paper No. 42 was used to filter the solution, and aliquots were suitably diluted with respective medium for estimation of drug amount.

Formulation of core tablet

Inner tablets were created via the direct compression method using the inclusion complex (CV:HP-β-CD, 1:1M), microcrystalline cellulose (MCC), Croscarmellose

Table I: Composition of core tablets

Sr. No.	Ingredients	Different batches			
		C I	C II	C III	C IV
1	Complex (carvedilol phosphate + HP-β-CD)	50.21	50.21	50.21	50.21
2	Microcrystalline cellulose	46.79	44.79	42.79	40.79
3	Croscarmellose sodium	2	4	6	8
4	Magnesium stearate	1	1	1	1
	Total	100 mg	100 mg	100 mg	100 mg

sodium (CCS) and magnesium stearate (Table I). After mixing the inclusion complex, MCC, and CCS for 20 minutes, magnesium stearate was added. The blend was mixed for a further 10 minutes. The core tablet was obtained by compressing the resultant blend (powder) using a tablet press that uses a single, flat 6-mm punch. A flat punch was used to make tablets of weight 100 mg[10].

Evaluation parameters of core tablets

In vitro drug release studies[11]

A paddle apparatus (USP Apparatus 2) (Model DA-3, Veego Scientific Devices, Mumbai) was employed to assess the *in vitro* release of the inner tablets. The dissolution medium was taken to be 500 mL each of acidic buffer pH 1.2 and phosphate buffer pH 7.4. The paddle was rotated at 100 rpm with the temperature set at around 37.5 °C. A 5 mL sample was taken every 30 minutes up to 120 minutes. At 244.2 nm, the samples' absorbance was measured spectrophotometrically.

Preparation of core-in-cup dual pulsatile tablets[12,13]

The dual pulse tablets were prepared using flat-faced punches. A die was filled by EC powder. To make an EC bed on a level surface, it was softly compressed. The core tablet was put in the middle of the bed, and the area between it and the die wall was manually filled with EC (100 mg), enclosing the core tablet's rounded surface completely. Polymers (alone or in combination) were added as plug layer on top of the core tablet. Table II displays the makeup of each tablet. The tablet was compressed slightly, and the immediate release powder blend was added on top of the plug layer. To develop the desired dual release pulsative core-in-cup tablet, the tablet and the layers were compressed.

Evaluation parameters

In vitro drug release behavior of dual release pulsatile tablets[14]

Using a paddle apparatus (USP Apparatus 2) (Model DA-3, Veego Scientific Devices, Mumbai), the behaviour of the pulsatile system's *in vitro* release rate was assessed. To simulate the pH changes along the length of the gastrointestinal tract, three distinct dissolving mediums: phosphate buffer (pH 6.8), acidic buffer (pH 1.2) and phosphate buffer (pH 7.4) were utilised successively. The acid buffer with a volume of 500 mL was used for 2 h for the first pulse of drug release (i.e., immediate release). Since the usual gastric emptying period is 2 h, the dissolution

Table II: Composition of backing layer and plug layer

Formulation	Backing layer (mg)	Composition of plug layer			Lag time (h)
		Sodium alginate (mg)	HPMC K4M (mg)	Xanthan gum (mg)	
CC1	200	200			6
CC2	200		200		5
CC3	200			200	7
CC4	200	100		100	6
CC5	200	100	100		8
CC6	200		100	100	9

medium was switched to pH 6.8 phosphate buffer for the next 3 h, and then the medium was changed to pH 7.4 fresh phosphate buffer. The evaluation continued until the second pulse of drug release. The paddle's rotational speed was held constant at 100 rpm, while the vessel's internal temperature was held constant at 37 ± 0.5°C. At certain intervals, 10 mL of the samples were collected, and the volume was filled with brand-new dissolving media. The withdrawn samples were examined spectrophotometrically at 243.2 nm, 244.2 nm, and 242 nm in acidic buffer pH 1.2 for the first 2 h, phosphate buffer pH 6.8 for the following 3 h, and phosphate buffer pH 7.4 for the next 7 h, respectively, and the percent cumulative release over the sampling time was calculated.

Surface morphology during *in vitro* release study

At certain intervals (initial "0 h," after 2 h, and after 8 h), dual release tablets (CIV) were pulled from the dissolution machine and dried to make moisture-free. The samples were then divided up using an intact slice of the swollen area on the tablet's flat face. After that, the sample was placed on a sample holder so that a scanning electron microscope (Model Supra 5, Carl Zeiss, Germany) could inspect it.

RESULTS AND DISCUSSION

Study of phase solubility

To examine the drug's solubility characteristics, the phase solubility approach was used (Fig. 1). It was noticed that as the HP-β-CD concentration raised, CV solubility enhanced, recommending an AL-type curve due to a 1:1 molar complex formation in distilled water[15]. In distilled water, it was discovered that the HP-β-CD -CV complex's stability constant (KS) was 735.4 M-1. This indicates a strong affinity between the CV and HP-β-CD[16].

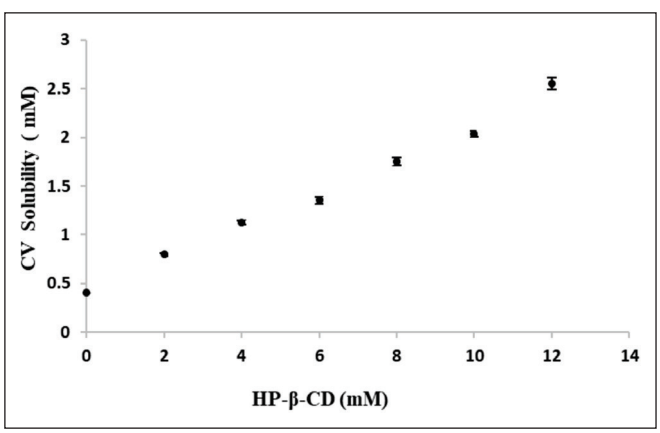

Fig. 1: Phase solubility of CV with increasing concentration of HP-β-CD

Preparation, characterization and evaluation of inclusion complex

The solvent evaporation approach was utilized to produce the CV HP-β-CD complex at a 1:1 molar concentration. X-ray diffractogram of the CV had a well resolved peak at θ = 17.78°, showing that the maximum content was >1700, with an interplanar distance (d value) of 4.98 θ. This indicates CV is highly crystalline.

The absence of crystallinity in the HP-β-CD diffractogram suggests that the material is amorphous. The physical mixing of HP-CD with CV had all of the CV peaks on the X-ray diffractogram. The bands in the 2θ values of crystallinity of CV were found to be intact in the physical mixture. Inclusion complex of CV did not reveal its peaks and showed diffused peaks which indicate conversion of its crystalline to amorphous nature (Fig. 2)[17].

Drug content

The CV: HP-β-CD complex's drug content was found to be 9.21 ± 0.32 mg/37.5 mg of complex. This indicates

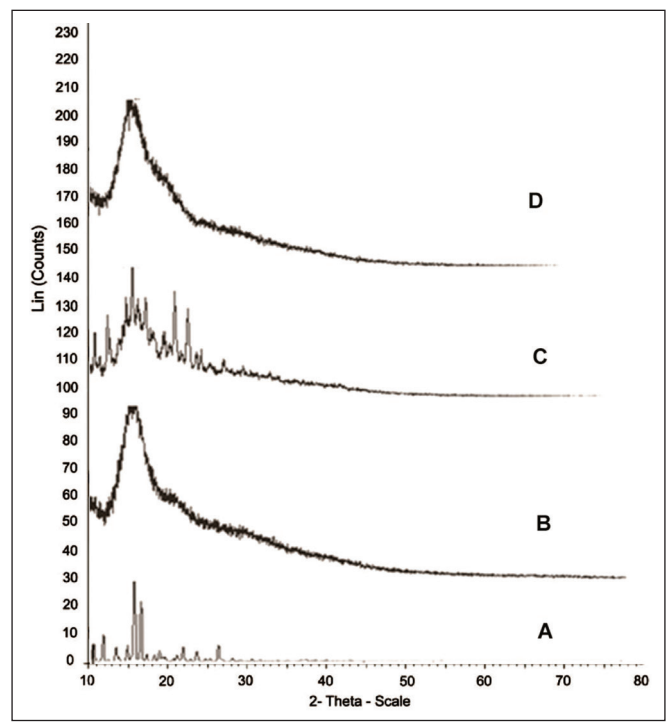

Fig. 2: X-ray diffractograms of A. CV B. HP-β-CD C. Physical mixture of CV and HP-β-CD D. CV-HP-β-CD inclusion complex

that the drug had been loaded as desired in complex and that the solvent evaporation method is effective[18]. Due to the generation of the CV- HP-β-CD complex, the solubility of the CV had increased by a factor of more than 71, 45, and 34 in acidic buffer pH 1.2, phosphate buffer pH 6.8, and phosphate buffer pH 7.4, respectively.

Core tablet release characteristics *in vitro*

When a core tablet of CV interacts with a dissolution medium, it disintegrates speedily due to the higher concentration of CCS. Formulation CIV, with a highest concentration of CCS, disintegrated in the least time (8% w/w CCS, 113 ± 0.57 sec) compared with the formulations CI (2% w/w, 120 ± 0.577 sec), CII (4% w/w, 119 ± 1.15 sec) and CIII (6% w/w, 117 ± 1.15 sec) (Fig. 3), which suggests that when the concentration of CCS is increased, the disintegration time of the tablet was decreased and dissolution rate was increased (Fig. 3).

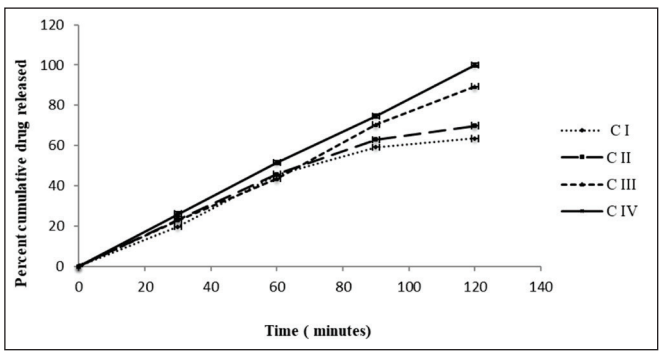

Fig. 3: Comparative cumulative amount of CV release from core tablets CI, CII, CIII and CIV in acid buffer pH 1.2

Dual release pulsatile tablets' *in vitro* drug release characteristics

All the formulated pulsatile tablets showed dual-pulse release behavior, having a different lag period between the pulses (Fig. 4). The EC was used as a backing layer, and the sodium alginate, HPMC K4M and xanthan gum (in combination or alone) were used as the plug layer. When the acid buffer came in contact with the designed formulation, the top layer of the tablet disintegrated immediately. This causes the CV to release quickly and

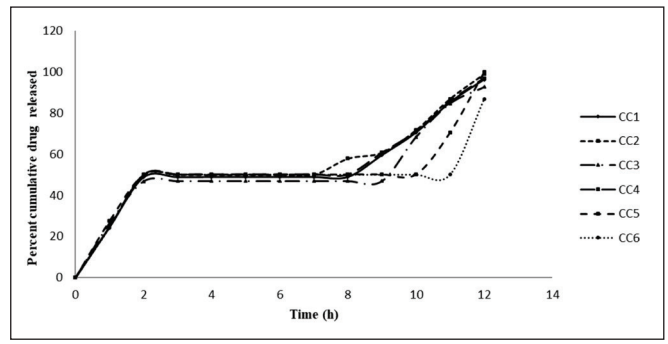

Fig. 4: Comparative cumulative amount of CV release from pulsatile tablets CCI, CC2, CC3, CC4, CC5 and CC6

gives out the initial pulse of release. For 3 h, instead of the acidic buffer, a phosphate buffer with a pH of 6.8 was used, and subsequently one with a pH of 7.4. The polymer plug was responsible for the lag time after the first pulse release of CV from the tablets. After the plug layer was eroded or ruptured, a rapid CV release from the core tablet was observed.

All the batches showed a lag time in the range of 5–9 h. When sodium alginate was used as the plug layer in formulation CCI, the lag time was 6 h. Similarly, when sodium alginate with xanthan gum was used as the plug layer in formulation CC4, a lag phase of 6 h was found.

As shown in Table II, the lag time (6 h) was observed in formulation CC1 due to formulation of thick gel layer of sodium alginate. When HPMC K4M alone was used as the plug layer in formulation CC2, a lag phase of 5 h was found. When xanthan gum alone was used in formulation CC3, a lag phase of 7 h was obtained. Using xanthan gum as the plug layer increased the lag time. This was due to the ability of the polymer to form a gel structure and promote the viscous environment and retard the imbibition of the dissolution fluid[19]. Incorporation of xanthan

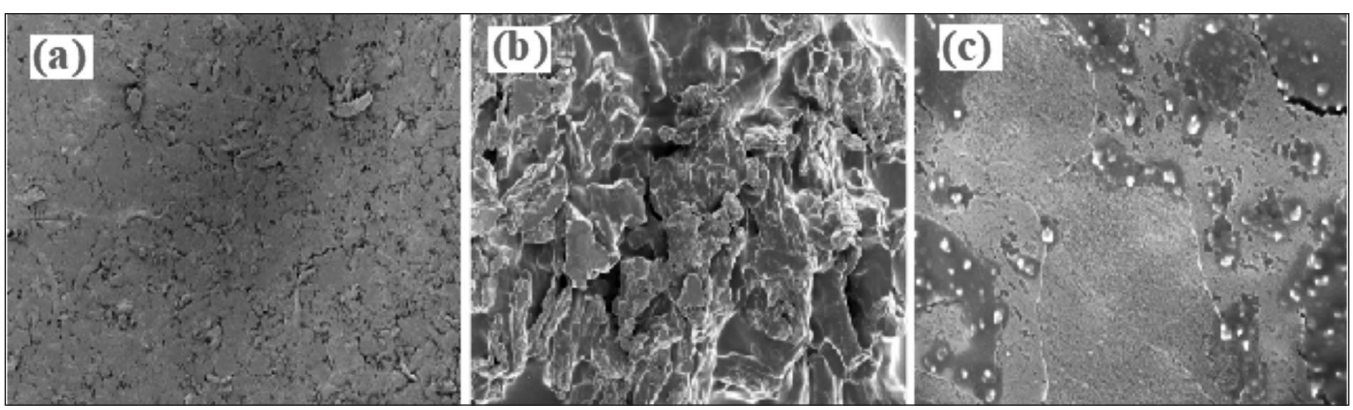

Fig. 5: SEM photomicrographs of optimized formulation CC5 showing surface morphology at (a) '0 h' (b) ' 2h' and (c) '8 h' during dissolution study

gum in the sodium alginate of the plug layer showed the lag time (6 h) in formulation. Batch CC5 demonstrated the necessary lag period of 8 h, which was followed by a second pulse of drug release. The plug layer for this batch was made up of a mixture of sodium alginate and HPMC K4M. The lag time may have been higher because of two reasons: (1) Partly spiral HPMC K4M chains interpenetrate the network of sodium alginate chains, or (2) the swelling of HPMC K4M initiated the creation of a gluey gelatinous layer which modified the diffusion of the medium. A lag phase of 9 h was observed when HPMC K4M and xanthan gum were put together to make the plug layer in formulation CC6. The longer diffusional channel that must be travelled by the dissolution media in order to reach the core tablet and a higher density of the polymer matrix could both be contributing factors to the increased lag phase[20].

Scanning electron microscopy (SEM)

The photomicrographs proved that the time controlled pulsatile press coated tablets showed a uniform surface morphology (Fig. 5 a) in SEM photomicrographs taken at initial 0 h, SEM photomicrographs taken after 2 h of dissolution confirmed the removal of top layer (Fig. 5 b) and SEM photomicrographs after 8 h showed breaking of plug layer (Fig. 5 c). SEM study further confirmed that drug release occurs by breaking of tablets into three halves

CONCLUSION

Dual release pulsatile tablets were developed. The effect of polymers on lag time and drug releases from the formulation was compared. Batches CC5 showed first pulse of CV release within 2 h. The plug layer, which contained sodium alginate and HPMC K4M, produced an 8 h lag phase before a second pulse of CV release, which resulted in a release that was time-controlled and requirement-focused. Hence, this developed formulation can be valuable for the time regulated delivery of an antihypertensive drug and could offer effective control for treatment of hypertension.

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