

Research article

Preparation and Bio Pharmaceutical Evaluation of Chrono Pharmaceutical Drug Delivery System of Atenolol

Apollo james^{*1}, Jasmina khanam¹, Mohanraj Palanisamy², Arun Radhakrishnan³

¹Department of Pharmaceutical Technology, Jadavpur University, Kolkata, West Bengal, India.

²Department of Pharmaceutics, Nandha College of Pharmacy, Erode, Tamilnadu, India.

³Department of Pharmaceutics, JSS College of Pharmacy, (JSS Academy of Higher Education and Research, Mysuru) Nilgiris, Tamilnadu, India

ABSTRACT

A time-adjustable pulsatile release system containing atenolol as an active pharmaceutical agent was developed for bedtime dosage administration and release of medicine in the early morning to manage elevated blood pressure. The system contained an immediate release (IR) core, a sustained-release (SR) plug, and a mucoadhesive cup layer and it was designed by the cup and core technique. The immediate-release layer was composed of atenolol, croscarmellose sodium, microcrystalline cellulose (MCC), sorbitol, talc, and magnesium stearate. The SR plug was composed of hydroxyl propyl methylcellulose (HPMC), polyvinyl pyrrolidone (PVP), MCC, Lactose, talc, and magnesium stearate. The mucoadhesive cup contains polycaprolactone and mucoadhesive polymer chitosan. Bilayer tablets were punched by applying different compressive forces. Based on the Release data of the drug from each layer F5 and S5 were selected for the preparation of the bilayer tablet. Cup composition containing 3% of chitosan provided the highest mucoadhesion time up to 10h. Pulsatile delivery of the drug from the formulation was observed at 300 min after the administration of the drug. The constructed pulsatile delivery systems were compared to that of commercially available atenolol IR tablet. The comparison demonstrated that the formulation is suitable for the intended chronopharmaceutical delivery of antihypertensive drugs.

Keywords: Chronopharmaceuticals, Pulsatile Drug Delivery, Hypertension, Mucoadhesive Polymer, Atenolol.

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***Correspondence:** Apollo James ✉ ajamespharma@gmail.com

Department of Pharmaceutical Technology, Jadavpur University, Kolkata, West Bengal, India.

INTRODUCTION

The goal of chronopharmaceutical medication delivery is to synchronize the illness's inherent chronological time and therapeutic administration [1]. When a disease exhibits chronological behavior, it is not required to maintain a constant drug concentration throughout the day, but it is necessary to deliver the optimum dose at a specific moment. Heart rate and blood pressure have a distinct diurnal pattern in both normotensive and hypertensive patients. The heart rate and blood pressure are higher in the early morning and lower at night while sleeping [2, 3, and 4]. According to previous studies, during the hours of 6:00 a.m. and 12:00 p.m., patients had a 29 %, 40 %, and 49 % greater risk of cardiac mortality, heart attack, and stroke respectively in the time span of 6.00 am and 12pm^[5]. Conventional drug delivery systems release the medicine instantly and it has to be administered during the peak hours to maintain the drug concentration throughout the day. In such situations, chrono pharmaceutical drug delivery methods are user-oriented [6]. In the present study, a time adjustable pulsatile release system containing atenolol as an active pharmaceutical agent for bedtime dosage administration and early morning release of the medicine to

manage blood pressure. Atenolol is a cardioselective beta-blocker used in normalizing the heart rate, reducing the strain on heart and blood pressure. Atenolol is a BCS class III drug with an elimination half-life of 6-7h, pKa Value of 9.6, and bioavailability of 45-50% [7]. This drug delivery system is aptly designed to release the drug adequately when required, to avoid the presence of a high dose of atenolol throughout the day in blood circulation, and to reduce the adverse reactions [8, 9]. The study involves designing of 'core in cup' drug delivery system in which the core tablet is an immediate-release tablet, the plug is a sustained atenolol release polymeric layer and the cup is a mucoadhesive polymeric layer. The mucoadhesive cup adheres to the mucosal membrane of the gastrointestinal tract lengthening the time of drug retention in the stomach. The direct compression method was used to make the core and the cup tablet. Objectives of the present study are preparation and evaluation of pulsatile drug delivery system of atenolol and comparison of the drug release profile with the marketed atenolol tablet.

MATERIALS AND METHODS

The drug atenolol was procured from Carbanio.com.

Microcrystalline cellulose [MCC], chitosan and sodium starch glycolate [SSG] were procured from Lobachemie. Talc, cross carmellose sodium [CCN] magnesium stearate, polycaprolactone, sorbitol, lactose and hydroxy propyl methyl cellulose (HPMC) were sourced from SD fine chemicals.

Pre-formulation studies

Pre-formulation is the primary step of product development in which the physicochemical properties of the active pharmaceutical ingredient and other excipients are studied before product development to check their physiochemical effects on the quality of product formulation and performance [10]. The pre-formulation studies conducted are as follows.

Analytical method development

Preparation of Calibration Curve

Spectrophotometer method is used to assay the drug. A standard calibration curve of pure drug atenolol was plotted with the concentration Vs. absorbance values measuring at $\lambda_{\max}$ of 224 nm. A series of diluted solutions were made with solvent methanol and diluent 0.2M phosphate buffer [11]. The linear regression curve is used to measure an unknown concentration of the drug.

Solubility studies

A saturation solubility study of atenolol was carried out according to BCS guidelines. In 500ml conical flasks, 25mg of atenolol was added to 250ml of each medium [0.1N HCl pH 1.2, distilled water pH 7.0, acetate buffer pH 4.5 and phosphate buffer pH 6.8]. Flasks were shaken in an orbital shaker at 37°C for 48 hours. The samples were then filtered and diluted before being analysed with a UV spectrophotometer [12].

Melting point determination

The determination of the melting point aids in the identification of the material and its purity. The melting point device can be used to determine the melting point [13].

Drug – excipient compatibility studies using differential scanning calorimeter (DSC)

Using a differential scanning calorimeter, the thermograms of the drug and excipients were recorded. As a baseline, an empty pan was used. About 1 g of drug/excipients/drug and excipient mixture was weighed and sealed in a small aluminium pan and was heated to 20-400°C at a rate of 10°C/min with constant purging of dry nitrogen 50ml/min. A blank pan was sealed and used as a reference. DSC thermogram was obtained using automatic thermal analyzer equipment. DSC thermogram was analyzed to check the compatibility of the drug and the excipients [14].

Study of flow property Study of flow property (angle of repose, bulk and tap densities, Carr index, Hausner's ratio) of powder material

Angle of repose: The angle of repose was used to determine the frictional force in a loose powder, and the angle of repose was measured using the fixed funnel method. As a function of the powder flow property, the maximum angle (θ) permitted between the surface

of the powder pile and the horizontal plane was determined [15] using the formula $\theta = \tan^{-1}(h/r)$, here, h is the height of the cone and r is the radius of the cone base.

Bulk density, ρ_b

It is the ratio of the mass of the powder (M) to the volume, V (including the inter-particle void volume) of an untapped powder sample, ($\rho_b = M/V_o$).

Tapped density (ρ_t) is higher than bulk density; it is obtained after mechanically tapping a cylinder containing the sample. It is calculated by the ratio of the mass of the powder (M) and tapped volume, V_t attained after tapping 100 times using mechanical tapped density tester ($\rho_t = M/V_t$).

Measure of powder compressibility

The Compressibility index (Carr's Index) is a measure of a powder's propensity to be compressed, based on bulk and tapped densities. In free-flowing powders, inter particle interactions are less, and bulk and tapped densities will be closer in value. Poor flowing materials are cohesive in nature, resulting in a wider gap between bulk and tapped densities [15]. The Compressibility Index, which is determined using the following formula,

$$\text{Carr's index} = \left[\frac{(\rho_t - \rho_b)}{\rho_t} \right] \times 100$$

Where, ρ_t is the tapped density ρ_b is the bulk density

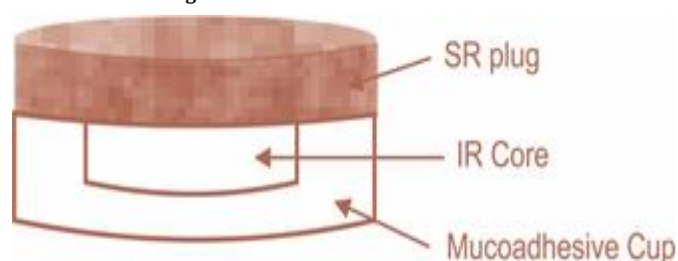
Hausner's Ratio: The flow ability of powders or granules is expressed by Hausner's ratio ($=V_o/V_t$), where V_o is the untapped apparent volume (cm^3) and V_t is the final tapped volume (cm^3) [15].

PREPARATION OF PULSATILE TABLETS

Formulation of core in cup tablet

A 'core in cup' tablet with a sustained-release (SR) plug layer, an immediate release (IR) core, and a mucoadhesive cup (figure 1) was prepared by direct compression method. The pulsatile core in the cup bilayer tablet was made with a 12 mm punch. With a low compression force (1 ton), the IR layer was compressed in a 6 mm punch. The cup material, a mixture of polycaprolactone and chitosan was filled into a 12 mm punch die and slightly pressed. The core tablet was placed in the slightly pressed bed and subsequently filled the gap between the die wall and tablet with polycaprolactone and chitosan mixture (110 mg). The top of the core tablet was then filled with the SR mixture and compressed to form a tablet (3 tone) [16, 17].

Figure: 1. Fabricated tablet for illustration



To achieve the desired drug release profile, a number of IR tablet trials with various concentrations of super disintegrants (cross carmellose sodium and sodium starch glycolate) were made (table 1). Various trials were also carried out to optimize the release profile of the SR layer and the mucoadhesive cup (Table 2 and 3).

Table 1: Different batches of immediate-release (IR) tablet

Ingredients	Composition of formulations (mg)					
	F1	F2	F3	F4	F5	F6
Atenolol	13	13	13	13	13	13
Cross carmellose sodium (CCS)	-	-	-	3	6	9
Sodium starch glycolate (SSG)	3	6	9	-	-	-
MCC	10	10	10	10	10	10
Sorbitol	37.1	34.1	31.1	37.1	34.1	31.1
Talc	0.325	0.325	0.325	0.325	0.325	0.325
Magnesium stearate	0.325	0.325	0.325	0.325	0.325	0.325
Total weight	63.75	63.75	63.75	63.75	63.75	63.75
Punch size	6mm					
Compression force	1 ton					

Table 2: Different batches of sustained release (SR) tablet

Ingredients	Composition of formulations (mg)					
	S1	S2	S3	S4	S5	S6
Atenolol	12	12	12	12	12	12
HPMC	10	15	20	10	15	20
PVP in alcoholic solution	2.8	2.8	2.8	-	-	-
MCC	60	55	50	62.8	57.8	52.8
Lactose	22	22	22	22	22	22
Talc	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Total weight	107.8	107.8	107.8	107.8	107.8	107.8
Punch size	12 mm					
Compression force	3 tons					

Table 3: Mucoadhesive cup layer

Formulation	Chitosan (mg)	Polycaprolactone (mg)
M1	1.1 (1%)	108.9
M2	2.2 (2%)	107.8
M3	3.3 (3%)	106.7

EVALUATION OF CORE IN CUP TABLET

Hardness test

The Monsanto hardness tester was used to determine the hardness of the tablets (force necessary to break the tablet). Hardness was measured by placing the tablet between the moving and fixed jaws of the apparatus and applying pressure. Six tablets were used in the experiment [18].

Friability test

Friability refers to a tablet's ability to endure mechanical stress during handling. It aids in determining the tablet's vulnerability to fragmentation, chipping, and other forms of damage. The tablets were placed in a friabilator and spun at 25 rpm for four minutes.

Weight variation test

The average weight of 20 tablets was obtained after each tablet's weight was measured individually. The tablet passes the weight variation tests if not more than two tablets are beyond the prescribed limits, according to the USP specification [19].

$$\text{Average weight} = \frac{W_{\text{total}}}{n_{\text{tab}}}$$

Where W_{total} is the total weight of tablets and n_{tab} is the number of tablets

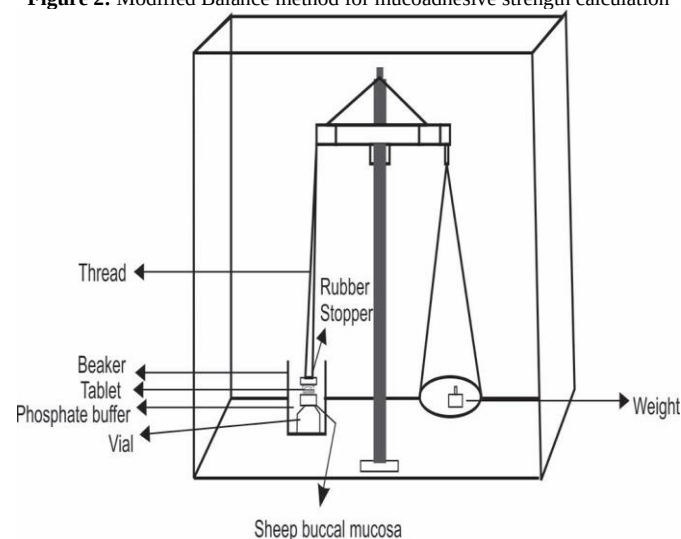
Disintegration test

The disintegration test apparatus was used to test the tablets' disintegration time. Water, 0.1 N HCl, were two distinct mediums used. The tablets were inserted in the apparatus's basket's six tubes. At a rate of 29 to 32 cycles per minute, the basket was pushed up and down in the media [20].

Mucoadhesive strength

The mucoadhesive strength of the 3 combinations of polycaprolactone and chitosan were measured. The force required to detach the drug from the attached membrane (porcine GI mucosa) was determined using the modified balance method. Porcine gastric mucosa with a thick layer of mucus was affixed to a rubber cork that had previously been attached to the vial in the bottom of a beaker with the relevant medium at a level slightly above the mucosa. The weight was attached to the tablet through a rubber beaker and brought into touch with the porcine mucosa and kept undisturbed for 5 minutes. The mucoadhesive strength was measured by adding weights to the right-side pan in incremental increments and recording the weight at which the tablet disengaged from the mucosa [21].

Figure 2: Modified Balance method for mucoadhesive strength calculation



Mucoadhesion residence time

The tablets must remain adherent to the gastro intestinal mucosa to retain the drug in GIT for certain period. Hence an *ex vivo* mucoadhesion test was used to determine the tablet's residence time in the gastro intestinal mucosa. Cyanoacrylate glue was used to adhere the sample of bovine GI mucosa on a stainless-steel plate measuring 8.5 cm x 5 cm. Further, each tablet was stuck to the mucosa with a specific pressure (500 g for 30 s). The prepared plate assembly was placed in a beaker containing 0.1N HCl at a 60° angle, then in a shaking water bath at 37°C and 15 rpm [22].

In vitro drug release studies

Each drug layer (IR core, the SR plug, and the core in a cup tablet), was evaluated separately to study the drug release profile. The primary factor for selecting the optimal formulation among trials in each layer preparation was *in vitro* drug release. Each data is the average of three repetitions.

In vitro drug release from IR core tablet and SR plug

In vitro drug release experiments for the atenolol core tablets and the SR plug layer were conducted individually using the USP dissolution apparatus II. The temperature was kept at 37°C. 0.1 N HCl was chosen as the dissolution medium for IR tablets. The dissolution media was agitated at 50 rpm [23, 24]. At predetermined time intervals, a predetermined number of aliquots were removed for analysis and subsequently, replaced with an equal amount of fresh dissolution medium. A spectrophotometer set to 224nm wavelength was used to examine the aliquots.

In vitro drug release from bilayer tablet (core in cup tablet)

In USP dissolution apparatus II, a dissolution test for the bilayer tablet was performed. The medium used for the first 300 min was 730 mL of 0.1M HCl solution. The tablet was then subjected to a 6.8 pH phosphate buffer solution by the addition of 0.2 M Na₃PO₄.12H₂O into the existing media (25). A spectrophotometer set to 224nm wavelength was used to examine the withdrawn samples. Similarly, the drug release profile of the marketed atenolol IR tablet was investigated and compared with the core in cup formulation.

Modeling of drug release

To examine the drug release kinetics, the data were fitted into zero order, first order, Korsmeyer-Peppas, Higuchi, and Hixson-Crowell models (26).

Water uptake and erosion studies

Water absorption and erosion were studied using the USP dissolution apparatus type I. The weight of the empty basket and the tablets were recorded before starting the experiment. The tests were carried out in the same prescribed conditions as the dissolution test. At predetermined times, individual tablets were taken out of the medium. The basket and tablets were weighed following the completion of the test. The tablets were dried at 80°C until they attain a constant weight. After they had cooled to room temperature, the tablets were weighed again. To compute the % erosion, the below formula was used (27,28).

$$\% \text{ erosion} = \frac{W_i - W_f}{W_i} \times 100$$

Where W_i represents the initial weight of the tablet and W_f represents the final weight of the dried tablet.

The excess weight gain of the tablet at each time interval was used to calculate water uptake by the tablet.

$$\text{Weight increased} = \frac{W_{\text{wet}} - W_f}{W_f} \times 100$$

Where W_{wet} represents the weight of the wet tablet

Stability study

The stability tests on the tablets were carried out in compliance with ICH guidelines. The tablets were maintained in two different study conditions. One batch of tablets was kept in a desiccator for three months at 25°C and 60% RH in the presence of anhydrous calcium chloride in polypropylene containers. Another pair was kept in a stability chamber at 40°C and 75 RH for three months. Three months later, dissolution tests and the physical appearance of the tablets were evaluated [29].

In-vivo Studies: Preparation and biopharmaceutical evaluation of Chrono pharmaceutical drug delivery system of atenolol

Number of days each rabbit was housed for 3 weeks under standard conditions with a 12 h light/dark cycle with free access to water and a basal diet for 1 week. Animals weighing about 1 to 5 Kilograms was selected and divided into the above-mentioned groups. Further, they were subjected to fasting for 12 hours with access to drinking water. After 12 hours, the prepared formulations were administered (16mg/kg) through the oral route by keeping them in an upright position. Blood samples of 1 ml has been collected from the tail vein using a needle at 15, 30, 60, 120, 180, 240, 300, 360, 420, 480 and 540 minutes after administration. All blood samples were immediately put into heparin then it will be subjected to centrifugation at 4000 rpm for 10 min to separate the plasma. Then the plasma was frozen and stored at -20°C until the analysis. The kinetic parameters including C_{max}, T_{max}, AUC was analysed. [35,36]

RESULTS AND DISCUSSION**Pre-formulation Studies**

The graphical plot of absorbance (y) vs concentration (x) yielded the linear calibration curve equation ($y = 0.0394x + 0.0204$, $R^2 = 0.9971$), which was used to calculate the amount of drug released in dissolution studies of different batches of products.

Solubility studies

Saturation solubility of atenolol was observed as 13.3 ± 0.48 , 12 ± 0.51 , 10.12 ± 0.28 mg/mL at 25°C in double-distilled water (DDW), 0.1 N HCl, and pH 6.8 phosphate buffer. The drug was found to be sparingly soluble in water, practically insoluble in HCl and acetate buffer, and soluble in a pH 6.8 phosphate buffer.

Melting point determination

The melting point of atenolol was found to be 123-125°C. It was comparable to the melting point reference provided by the USP.

Drug – excipient compatibility study using differential scanning calorimeter

DSC was used to determine the compatibility between drug and excipients used in the formulations. Individual components, such as atenolol, cross carmellose, sorbitol, MCC, HPMC, magnesium stearate, chitosan, and the physical mixture of drug and excipients,

were investigated using DSC. The thermograms of the physical mixture revealed no interactions, implying that there were no incompatibilities between drugs and excipients.

Study of flow property

(angle of repose, bulk and tap densities, Carr's index, Hausner's ratio) of powder material

Angle of repose

The flow characteristics and compressibility of powder mixes are critical in defining the quality and reproducibility of direct compression tablets. According to the USP, a powder sample with an angle of repose of 25-30° has a good flow property. All the powder mixes had angle of repose ranging from 28-30°. The angle of repose of all the formulations is given in table 4.

Bulk density

The bulk density of the powder mix affects the flowability of the powder. Low bulk density associated with agglomerated particles negatively influences the flowability and of the powder. The observed bulk density of the formulations is given in table 4.

Tapped density

Tapped density is more in the case of regularly shaped particles than irregularly shaped particles. Determined tapped density was mentioned in table 4. These values were used for the calculation of the Hausner's ratio and Carr's index.

Carr's index: Carr's compressibility index values have been used to define the flow properties of the powders. Carr's index for the studies was in the range of 10-14. These values indicate the excellent flowability of the powders.

Hausner's ratio

Hausner's ratio is related to the interparticle friction between the particles. For a satisfactory flow property, Hausner's ratio should be less than 1.25. Table 4 lists the IR tablet's Hausner's ratio [30].

Table 4: Flow properties of immediate release formulations

Evaluation parameters	Formulations					
	F1	F2	F3	F4	F5	F6
Angle of repose	29.36	28.01	28.69	29.05	28.25	29
Bulk density	0.25	0.27	0.28	0.25	0.30	0.21
Tapped density	0.29	0.28	0.29	0.31	0.34	0.29
Carr's index	13.8	10.69	12.88	13.31	12.89	10.70
Hausner's ratio	1.15	1.13	1.13	1.15	1.12	1.13

Evaluation of core in cup tablet

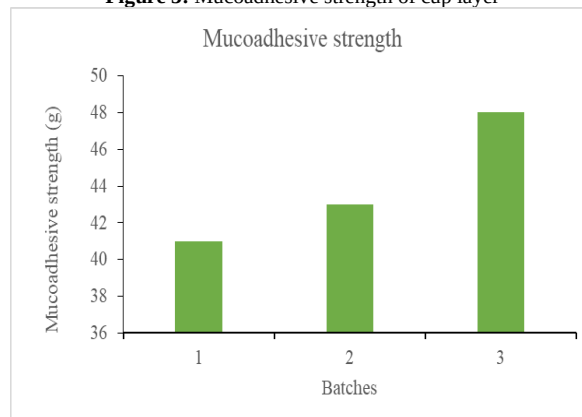
All of the quality control tests on the core tablet were successful. The tablet's thickness was 3.51±0.04mm, while its diameter was 6.08±0.01mm. The hardness (5.51±0.3 kg/cm²) was within acceptable limits. The tested tablets had a friability of 0.25%. The average weight of 20 tablets was 284±0.9 mg. The core tablet disintegrated instantly in both alkaline and acidic environments. F5 disintegrated the fastest (1 minute) [31].

Mucoadhesive strength

Figure 1 depicts the findings of the mucoadhesive strength study. It was established how much strength (g) was required to

separate the tablet from the membrane. The mucoadhesive strength of the cup layer is determined by the chitosan content. The formulation with the lowest chitosan concentration (M1) detached faster than the formulation with the highest chitosan concentration (M2). Among the other formulations, M3 had the strongest mucoadhesive strength.

Figure 3: Mucoadhesive strength of cup layer



Mucoadhesion residence time

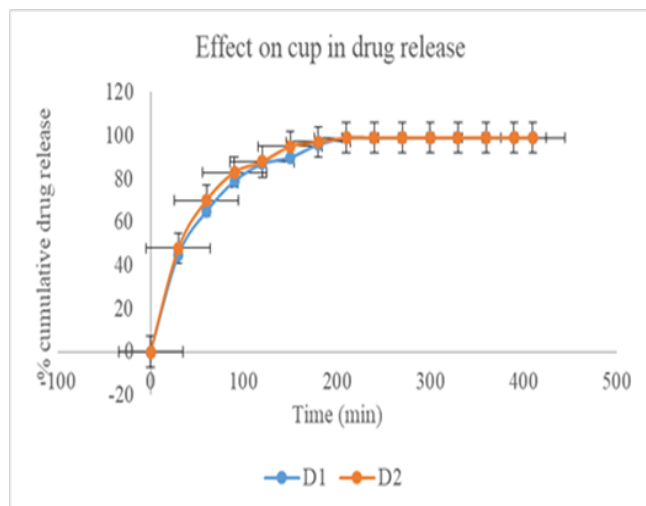
All the three formulations stayed adhered to the mucosal membrane at least for 10 h. The layer containing 3% of chitosan stayed unchanged in its adhesion properties till the end of the study compared to the formulations containing 1 and 2% chitosan.

In vitro drug release studies

The drug release from various formulations was measured using the USP dissolution apparatus II. The drug release from bilayer tablet components such as the IR core, the SR plug, and the influence of the cup on drug release were studied separately to identify the best formula. This study was successful in assessing the effects of polymers and identifying the best formulation for pulsatile drug release with desirable properties. The core tablet was initially studied to find the qualities of immediate drug release.

Effect of disintegrants on drug release from IR core

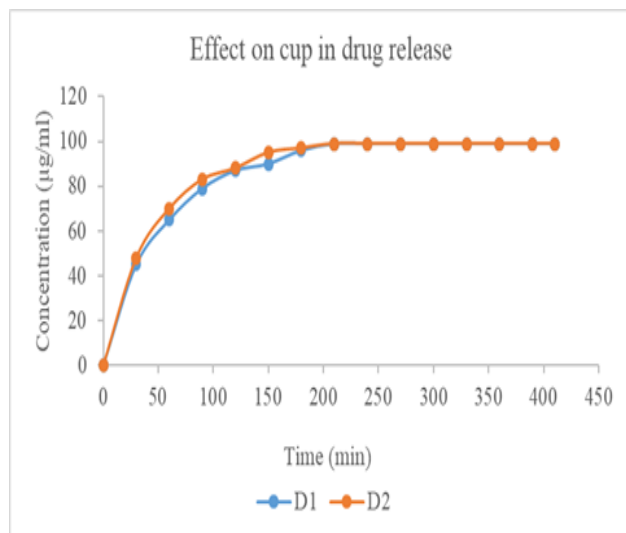
Figure 2 shows the *in vitro* cumulative release of atenolol from the IR core tablet in 1000 mL 0.1N HCl at 37°C and 50 rpm. To get an immediate release following the lag time, CCS/SSG was incorporated as a super disintegrant in the core tablet. Super disintegrants speed up the disintegration of direct compressible tablets and improve the solubility of medications that are difficult to dissolve. Formation of pore and swelling are two distinct mechanisms involved in the dissolution of CCS and SSG. The drug release mechanism is dependent on the concentration of super disintegrant. Disintegration will be minimal when swelling predominates (in case of 9 mg, Table 1). The formulation F5 with CCS (in case of 6 mg) delivered the medication in 30 min (94.62%). Whereas, formulation with SSG (F2) released 89.9% of atenolol after 30 min. The drug release from six trials of IR core tablets is depicted in the graph. From the release profiles, F5 was selected for further 'core in cup' tablet preparation [33].

Figure 4: Cumulative drug release (%) from IR core tablets

F1: 3mg SSG, F2:6% SSG, F3:9% SSG, F4: 3% CCS, F5: 6% CCS, F6: 9% CCS

Effect of the mucoadhesive cup in drug release

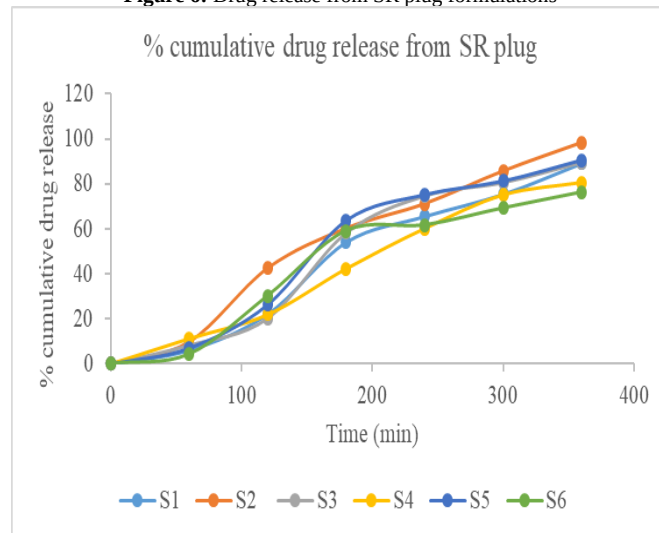
To identify the effect of the cup in drug release from the core in cup tablet drug release was studied with the 'core in cup' tablet without the plug layer (D1) and the IR core tablet (D2) alone. In both cases, the immediate release core was exposed to the dissolution media which facilitates the leaching of water into the core and immediate disintegration of the IR tablets. Because the drug release profiles of both D1 and D2 were similar, the influence of the polycaprolactone and chitosan layer on drug release was minimal, and the effect of the plug layer had to be investigated (Figure 5).

Figure 5: Effect of cup in drug release profile

Study of drug release from SR plug

The sustained release polymeric plug contributes to the lag period prior to the onset of drug release from the IR core. To maintain a low concentration drug in the blood during the lag period and to reach the therapeutic concentration faster, the tablet plug was made with a sustained-release polymer HPMC and atenolol. With different concentrations of HPMC and MCC, six distinct

formulations were prepared. When HPMC comes into contact with water, it produces a viscous gel layer that aids in the sustained release of atenolol from the plug. The swelling expansion of the polymer prevents water from accessing the IR core, so HPMC produces a sustained drug release from the plug. As the swelling progresses, the plug's rigidity deteriorates, causing the plug layer to erode. All six plug formulations were able to release the drug for up to 360 minutes. Figure 4 depicts the influence of HPMC concentration on medication release. Formulation S2 released 98% of the drug at 360 min. Hence S2 was selected for the plug layer preparation.

Figure 6: Drug release from SR plug formulations

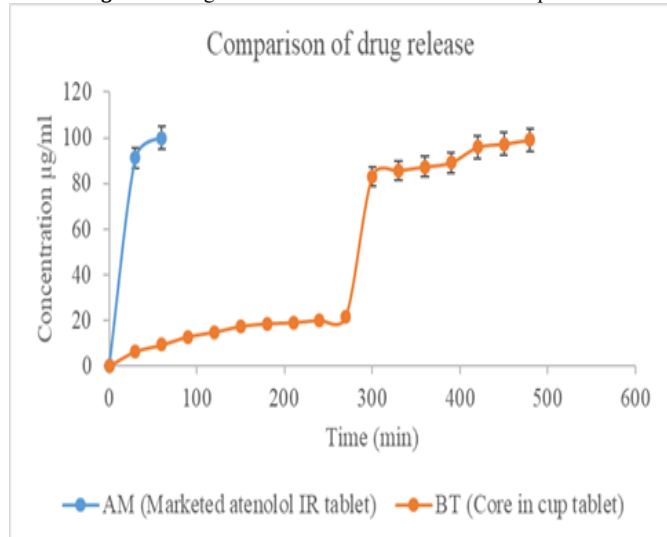
S1 (10mg HPMC and 2.8mg PVP), S2 (15 mg HPMC and 2.8mg PVP), S3 (20 mg HPMC and 2.8mg PVP), S4 (10% HPMC), S5 (15% HPMC), S6 (20% HPMC)

Drug release from core in cup tablet and comparison with marketed atenolol IR tablet

To make the final 'core in cup' tablet, compositions of F5 core tablet, S2 plug, and polycaprolactone and chitosan (M3) cup were used. Accordingly, a 'core in cup' tablet (BT) was prepared. It was observed that 22.89 % of the drug was released from the 'core in cup' tablets till 270 min when the plug was actively diffusing the drug. At 300 min, burst release of medication was observed, and there was a sudden drastic increase of drug release from 22.89-85.68%, and, cumulative % release had reached 99.1% till 420 min, as drug release happened from the core formulation (IR) too. The cumulative drug release (%) data as obtained from the 'core in cup' tablet (BT) was compared to that of marketed product (Devolol 50mg) atenolol IR (AM) tablets. The IR tablet AM showed drug release of 90.19 % of atenolol in 30 min in medium 0.1N HCl, whereas, 22.89% of the drug was released from the 'core in cup' formulation till 270 min in 0.1N HCl. The AM had no lag time, whereas the BT had a lag period of up to 270 min (**Figure 7**). The calculated f2 value for AM and BT was 7. Since the f2 value was lesser than 50 the drug release profiles are confirmed different for

both the formulations. The drug release profile indicates that the created 'core in cup' tablet can be used as a pulsatile drug delivery device.

Figure 7: Drug release from IR tablet and 'core in cup' tablet

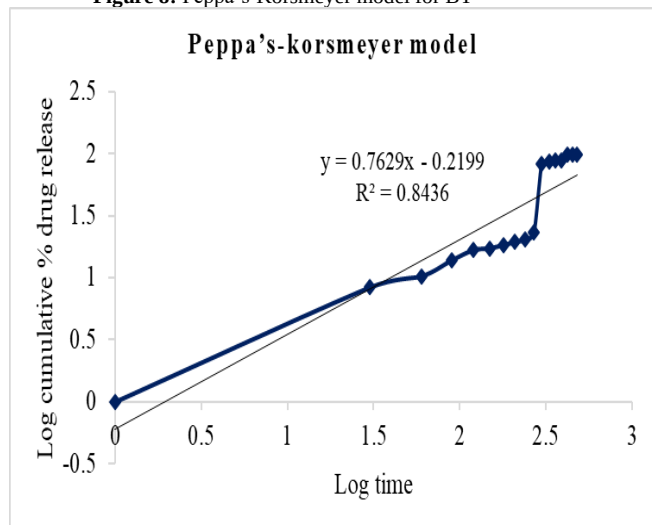


Drug release kinetics

Table 5: The correlation coefficient values for dissolution kinetics data (formulation BT)

Zero order R ²	Higuchi R ²	Peppas's-Korsmeyer		First order R ²	Hixon Crowell model R ²
		R ²	N		
0.6319	0.4867	0.9895	0.592	0.5248	0.5563

Figure 8: Peppas's-Korsmeyer model for BT



The release of atenolol from BT fits well into Korsmeyer-Peppas model as indicated by the value R^2 value (0.9895) and the profile is linear (Table 5 and Figure 8). It can be concluded that the mechanism of drug release from BT follow diffusion and swelling mechanism. The exponential coefficient (n) value was found to be in >0.5 indicating that non Fickian diffusion mechanism.

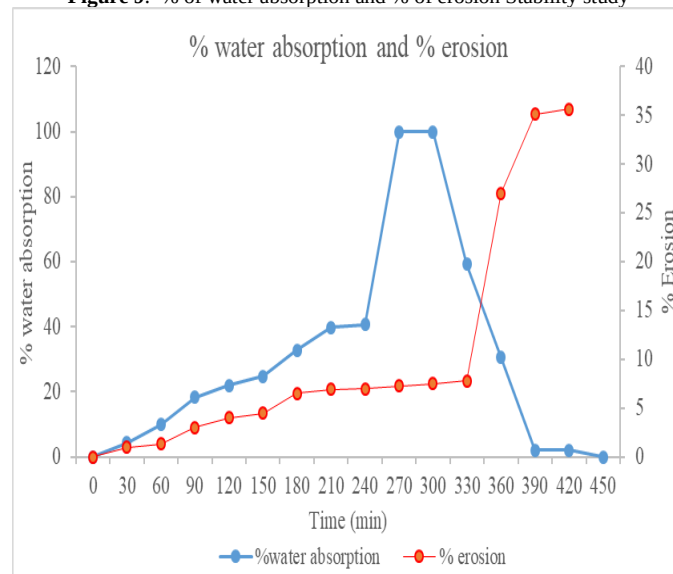
The release profiles exhibit biphasic stages as it involves release of drug from SR system initially at 0.1M HCl medium up to

270 min which is followed by burst release of drug and finally drug was released steadily in the last stage. In other models, linear profiles were not obtained.

Water uptake and drug erosion studies

The atenolol cup and core tablet were tested for water uptake and erosion in both phosphate buffer pH 6.8 and 0.1 N HCl. When the tablet was placed in 0.1 N HCl, HPMC plug layer absorbed the most water. The rate of water absorption increased gradually, reaching a maximum at time 300 min. The amount of water absorbed remained constant until the pH was raised in the phosphate buffer solution. There was a rapid drop in water absorption after 300 min, followed by the layer's quick disintegration. Figure 9 depicts the relationship between polymer water uptake and polymer breakdown in various pH solutions [34].

Figure 9: % of water absorption and % of erosion Stability study



Formulation F3 was kept for three months in both standard long-term storage (20°C, 60% RH) and accelerated stability (40°C, 75% RH). After the trial period, the tablets were examined for drug release, friability, hardness, and product look. The findings of the tablets' early tests showed no significant differences.

Table: 6 *In-vivo* concentration of Atenolol

Time	Concentration (ng/ml)
0	0
15	23.2
30	27.8
60	30.3
120	31.9
180	35.6
240	40.7
300	47.8
360	97.03
420	53.7
480	30.3
540	12.5

In-vivo Studies

Preparation and biopharmaceutical evaluation of Chrono pharmaceutical drug delivery system of atenolol

The kinetic parameters including Cmax, Tmax, AUC was analysed. [35,36] *In-vivo* concentration of atenolol with respective to the time was shown in the table 6 and their relative plasma drug concentration was illustrated in figure 10.

Figure 10: Plasma Drug Profile of Chrono pharmaceutical drug delivery system of atenolol

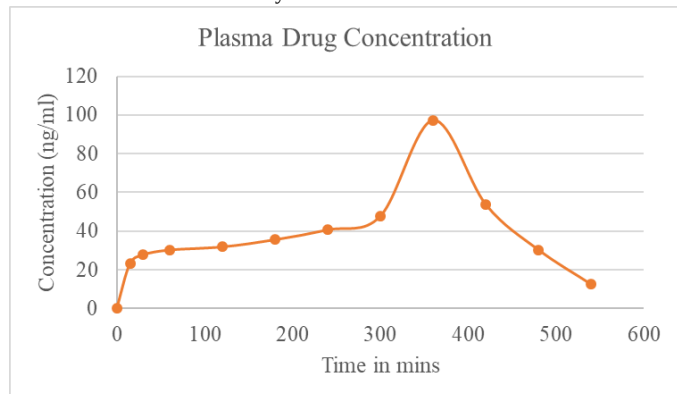


Table 7: Pharmacokinetic parameters

Tmax	360 mins
Cmax	97.3 ng/ml
AUC	22,759.8 mins. ng/ml

CONCLUSION:

A promising pulsatile core in cup drug delivery system was successfully produced with the desired lag time. The mucoadhesive chitosan polymeric cup proved effective in extending the drug's GI retention period up to 10 h. Throughout the lag period, the formulation was continually releasing atenolol at a low concentration (22.89%) from the sustained release plug (270 min). At 300 min, the drug was released quickly and instantly from the IR core, with the release of atenolol reaching 85.64 % in 30 min. Core in cup drug release profile was compared with the commercial atenolol immediate release tablet. The marketed atenolol tablet released 90.19 % of atenolol in 30 min without any lag time. The drug release profile from the core in cup tablet demonstrated that it is suitable for the chronological delivery of atenolol.

REFERENCES

- Bonthagarala B, Vadrevu S, Nama S, et al, 2014. American Journal of Biological and Pharmaceutical Research.1(1):28-33.
- Bowles NP, Thosar SS, Herzig MX, et al, 2018. Chronotherapy for hypertension. Current hypertension reports. 20(11):1-24.
- Sah ML, Juyal V, 2012. Programmed delivery of verapamil hydrochloride from tablet in a capsule device. Brazilian Journal of Pharmaceutical Sciences.48:237-42.
- Latha K, Uhumwangho MU, Sunil SA, et al, 2013. Chronobiology and Chronotherapy of Hypertension-A review. International Journal of Health Research. 3(3):121-31.
- Krishnaswamy R. Development of Bioresponsive Chronopharmaceutical Drug Delivery System in Treatment of Asthma & COPD Using Colon Targeted Mucoadhesive Tablets in Capsule System (Doctoral dissertation, JKK Nattraja College

- of Pharmacy, Kumarapalayam).
- Chaudhary SS, Patel HK, Parejiya PB, et al, 2015. Chronomodulated drug delivery system of urapidil for the treatment of hypertension. International journal of pharmaceutical investigation. 5(2):107.
- Pizzuto M, Portelli J, Serracino-Inglott A, et al. Chronopharmacology of antihypertensives.
- Saleem U, Iman S, Akhtar MF, et al, 2019. Chronopharmacology: appraising the influence of biorhythms on the efficacy and safety of antihypertensive drugs. Critical Reviews™ in Eukaryotic Gene Expression.29(6).
- Trevor M Jones, 2018 CHAPTER 1: Preformulation Studies, in Pharmaceutical Formulation: The Science and Technology of Dosage Forms, pp. 1-41.
- About MK, Mohammad A, Isbera M, et al, 2017. Development and Validation Uv Spectrophotometric Method for Determination Of Atenolol In Pure Materials And Pharmaceutical Dosage. Indo American J Pharm Res. 7(4):8179-4.
- Hamidi S, Jouyban A, 2015. Solubility of atenolol in ethanol+ water mixtures at various temperatures. Journal of the Serbian Chemical Society.80(5):695-704.
- Silva AC, Gállico DA, Guerra RB, et al, 2014. Study of some volatile compounds evolved from the thermal decomposition of atenolol. Journal of Thermal Analysis and Calorimetry.115(3):2517-20.
- Dourado D, 2019. Thermal Analysis as a Useful Tool in Drug-Excipient Compatibility Studies: The Impact in Pharmaceuticals Products. Biomed. J. Sci. Tech. Res. 2019 Oct 31;22:16634-6.
- Lau E, 2001. Preformulation studies. Handbook of modern pharmaceutical analysis.3:173-224.
- Wang H, Cheng L, Wen H, et al, 2017. A time-adjustable pulsatile release system for ketoprofen: in vitro and in vivo investigation in a pharmacokinetic study and an IVIVC evaluation. European Journal of Pharmaceutics and Biopharmaceutics.119:192-200.
- Sokar MS, Hanafy AS, El-Kamel AH, et al, 2013. Pulsatile core-in-cup valsartan tablet formulations: in vitro evaluation. asian journal of pharmaceutical sciences. 8(4):234-43.
- Jain D, Raturi R, Jain V, et al, 2011. Recent technologies in pulsatile drug delivery systems. Biomater. 1(1):57-65.
- Chaudhary SS, Patel HK, Parejiya PB, et al, 2015. Chronomodulated drug delivery system of urapidil for the treatment of hypertension. International journal of pharmaceutical investigation. 5(2):107.
- Patil S, Talele GS, 2015. Gastroretentive mucoadhesive tablet of lafutidine for controlled release and enhanced bioavailability. Drug delivery.22(3):312-9.
- Shao Y, Li L, Gu X, et al, 2015. Evaluation of chitosan-anionic polymers based tablets for extended-release of highly water-soluble drugs. Asian journal of pharmaceutical sciences. 10(1):24-30.
- Cazorla-Luna R, Notario-Pérez F, Martín-Illana A, et al, 2019. Ruiz-Caro R, Tamayo A, Rubio J, Veiga MD. Chitosan-based mucoadhesive vaginal tablets for controlled release of the anti-HIV drug tenofovir. Pharmaceutics. 11(1):20.
- Chisty SJ, Tosha SM, Ashima AZ, et al, 2016. Formulation and in vitro evaluation of modified pulsincap of amlodipine besylate: an improved approach for the treatment of hypertension. Turk J Pharm Sci. 2016;1;13(1):81-90.

23. Ashwini MS, Ahmed MG, 2013. Design and evaluation of Pulsatile drug delivery of Losartan Potassium. Dhaka University Journal of Pharmaceutical Sciences. 12(2):119-23.
24. Patel VD, Yegnoor AK, 2017. Development and evaluation of Celecoxib core in cup tablets for pulsatile drug delivery. Research Journal of Pharmacy and Technology.10(3):755-64.
25. Craciun AM, Barhalescu ML, Agop M, et al, 2019. Theoretical modeling of long-time drug release from nitrosalicyl-imine-chitosan hydrogels through multifractal logistic type laws. Computational and mathematical methods in medicine.
26. Patil AS, Dandagi PM, Masthiholimath VS, et al, 2011. Development and characterization of chronomodulated drug delivery system of captopril. International journal of pharmaceutical investigation. 1(4):227.
27. Chauhan BS, Jaimini M, Sharma S, et al, 2014. Effect of formulation variables on the swelling index of acyclovir sustained release tablets using xanthan gum and sodium alginate. Research Journal of Pharmaceutical Sciences ISSN. 2319:555X.
28. Lachman L, 1965. Physical and chemical stability testing of tablet dosage forms. Journal of pharmaceutical sciences. 54(10):1519-26.
29. Chaurasia G, 2016. A review on pharmaceutical preformulation studies in formulation and development of new drug molecules. International Journal of Pharmaceutical Sciences and Research. 7(6):2313.
30. Sokar MS, Hanafy AS, El-Kamel AH, et al, 2013. Pulsatile core-in-cup valsartan tablet formulations: in vitro evaluation. asian journal of pharmaceutical sciences. 8(4):234-43.
31. Nagaraju R, Meera DS, Kaza R, et al, 2009. Core-in-cup tablet design of metoprolol succinate and its evaluation for controlled release. Current drug discovery technologies.6(4):299-305.
32. Sonani NG, Hiremath SP, Dasankoppa FS, et al, 2010. Design and evaluation of gastroretentive mucoadhesive cephalexin tablets. Pharmaceutical development and technology. 15(2):178-83.
33. Jain D, Raturi R, Jain V, et al, 2011. Recent technologies in pulsatile drug delivery systems. Biomatter. 1(1):57-65.
34. Mohanty C, Subrahmanyam KV, 2021. In-Vivo Pharmacokinetic Study of Matrix Tablets of Atenolol Prepared by Sintering Technique. Sch Acad J Pharm. 4:71-6.
35. Sultana A, Varun D. In Vivo Studies & Sem of Controlled Porosity Osmotic Pump (Cpop) Tablet of Atenolol.

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