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Formulation and Evaluation of Pulsatile Drug Delivery System of Ramipril for Controlling Morning Spate of B.P.

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Research Article

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Abstract

The aim of the study was to design pulsatile release capsule of Ramipril. Plasma norepinephrine level and plasma renin activity are elevated in the morning; both hormones have potential to induce coronary vasoconstriction, therefore, we can achieve peak plasma concentration of drug at morning and can control morning spate of B.P. compliances. The rapid release of the drug after a lag time consistent with the requirement for chronotherapeutics was achieved with developed formulation M-6 (swellable polymer; xanthan gum, core tablet; C-2, erodible tablet; E-2 and 10 % w/w coated capsule body) which show lag time of 4 hr. During the lag time, only 25 % drug released following rapid release (99.13 ± 83 % in 7 hr.) of the drug was observed. The ex-vivo absorption study conducted using everted chicken intestinal segment indicated a delay in absorption of the drug. Thus this approach can provide a useful means for timed release of Ramipril and may be helpful for patients with morning spate of BP.

Keywords: Chronotherapeutics, Ramipril, pulsatile delivery, swelling control

1. INTRODUCTION

Traditionally, drugs are released in an immediate or extended fashion. It has recently been reported that the time of drug administration can play a key role in determining the efficacy and tolerability of a pharmacological therapeutics. Indeed, the temporal rhythms of bodily functions have been shown to affect not only the incidence or severity of a number of disease conditions but also the pharmacokinetics as well as pharmacodynamics of most bioactive compounds in use[1-4]. However, in recent years, pulsatile drug release systems are gaining growing interest. A pulsatile drug release, where the drug is released rapidly after a well-defined lag-time, could be

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advantageous for many drugs or therapies[5–7]. Pulsatile drug delivery system is defined as the rapid and transient release of a certain amount of drug within a short time period immediately after a predetermined off-release period, i.e." lag time[8]. Pulsatile release systems can be classified into multiple-pulse and single-pulse systems [9]. A popular class of single-pulse systems is that of rupturable dosage forms.

For pulsatile release purposes, a variety of design strategies have been attempted. Baker proposed a core with osmotically active agents, e.g. drugs, covered with a semipermeable membrane [10]. Other systems consist of a drug-containing core, covered by a swelling layer and an outer insoluble, but semipermeable polymer coating or membrane [11–13]. Several coated, capsular and osmotic formulations have indeed been described [14, 15]. As close attention is paid to chronopharmacology [16], though it is in its infancy, great progress has been made in pulsatile tablets [17, 18] pulsatile microspheres [19], and pulsatile capsules [20-22], pulsatile implants [23] as an example, in this field have been successfully studied.

In the present article, the main oral pulsatile delivery systems proposed are surveyed with regard to the relevant formulation characteristics and release performance. By developing the pulsatile device, plasma peak is obtained at an optimal time, a number of doses per day can be reduced; saturable first-pass metabolism and tolerance development can also be avoided. Pulsatile drug release system, which allows the release of active pharmaceutical material in single or successive pulses at precise and well-controlled time periods, is a recently developed drug delivery system[24]. Drugs are usually encapsulated in one way or another within a barrier material, which is composed of an erodible or biodegradable polymer. Depending on the barrier material structure and thickness, different release lag times can be achieved. After the barrier material is dissolved, eroded or degraded, drugs are rapidly released from the inner reservoir core.

The objective of the present study was to develop and evaluate an alternative pulsatile drug delivery system consisting of a drug-containing hard gelatin capsule, a swelling layer and an insoluble polymeric coating, which used only approved excipients and was prepared by standard pharmaceutical procedures. The lag time was controlled by the erosion of the matrix tablet and subsequent complete rupturing of the polymer coating, allowing a fast drug release [25]. This novel system is a so-called "tablets in capsule device" [26, 27]. The designed capsule device consists of an impermeable capsule body and a soluble cap. Hence we made an attempt to formulate a pulsatile capsule-based drug delivery system for delayed delivery of Ramipril.

2. Materials and methods:

2.1 Material:

Ramipril was obtained by Zim laboratories Ltd. Nagpur, India. Cross polyvinyl pyrrolidone and Ethyl cellulose were procured from Ipca Laboratories Ltd. Ratlam, India. Microcrystalline cellulose (avicel PH 112) and spray dried lactose (directly compressible lactose) were procured from Aristo Pharmaceutical Ltd, Baddhi, India. Dibasic calcium phosphate dihydrate, Lactose anhydrous, Magnesium stearate, Talc, Guar gum, Xanthan gum, Dibutyl phthalate, Isopropyl Alcohol and Acetone. All other reagents were used of analytical grade. Empty Hard gelatin capsules of size 3 were purchased from local market of Raipur, India.

2.2 Preformulation studies:

2.2.1 Characterization of Ramipril:

IR Spectra of Ramipril was obtained using Shimadzu FT-IR Spectrophotometer, wavelength maxima (λmax) was determined by using Systronic 2201 double beam spectrophotometer, the Melting point of Ramipril was determined by the capillary method by using Melting Point Apparatus (Biocraft Scientific Pvt. Ltd). Partition coefficient was determined by with n-octanol. Standard curve was constructed in 0.1N HCl, 6.8 pH, and 7.4 pH phosphate buffer solutions.

2.2.2 Drug-excipient compatibility studies:

IR Spectra of Ramipril, excipient and drug + excipient was obtained using Shimadzu FT-IR Spectrophotometer and obtained peaks were interpreted. The procedure consisted of dispersing a sample (drug and excipient alone or mixture of drug and excipient) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min. the pellet was placed in the light path and the spectrum was obtained.

2.2.3 Micrometric properties:

The angle of repose of different formulation mixtures was determined by the fixed funnel method [28]. The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using a density apparatus (Electrolab Pvt. Ltd). The Carr's index (%) and the Hausner ratio were calculated [29].

2.3 Preparation of core tablets:

Core tablet of Ramipril was prepared by the direct compression technique. Lactose monohydrate, Avicel, and dibasic calcium phosphate was used as diluent in L-1 & L-2, C-1 & C-2 and B-1 & B-2 respectively, cross polyvinyl pyrrolidone (PVP) use as super disintegrant (4% and 6%), mixture of talc (1%) & magnesium stearate (1%) at 1:1 ratio was used as lubricant and 10 mg of Ramipril as active pharmaceutical ingredient. The composition of different core tablets formulation (given in Table 1) were tableted to 100 mg using 5.5 mm flat-faced punches using a multi-station tablet compression machine at modern laboratories Indore, India.

Table 1. Composition of different formulation codes.

Sr. no.	Ingredient	Formulations code					
		L-1	L-2	C-1	C-2	B-1	B-2
1	Ramipril (Drug)	10.0 mg	10.0 mg	10.0 mg	10.0 mg	10.0 mg	10.0 mg
2	Diluent (q.s.)	Lactose monohydrate		Avicel		Dibasic calcium phosphate	
		84.0 mg	86.0 mg	84.0 mg	86.0 mg	84.0 mg	86.0 mg
3	Cross PVP	4.0 mg (4%)	6.0 mg (6%)	4.0 mg (4%)	6.0 mg (6%)	4.0 mg (4%)	6.0 mg (6%)
4	Mg stearate (1%)	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg
5	Talc (1%)	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg

2.4 Preparation of erodible tablets:

The erodible tablet was prepared by direct compression. Different formulation of erodible tablet contains different amount of hydrophilic polymer guar gum (50% and 75%), the mixture of talc (2%) & magnesium stearate (2%) at 1:1 ratio was used as a lubricant and directly compressible lactose as a diluent to a quantity sufficient. The compositions of different formulations are given in Table 2. The resultant blends were tableted to 150 mg using 5.5 mm flat-faced punches using a multi-station tablet compression machine at Modern laboratories Indore, India.

Table 2. Composition of different formulation codes.

Sr. no.	Ingredient	E-1	E-2
1	Directly compressible lactose (qs)	69.0 mg	31.5 mg
2	Guar gum	75.0 mg (50%)	112.5 mg (75%)
3	Mg-stearate (2%)	3.0 mg	3.0 mg
4	Talc (2%)	3.0 mg	3.0 mg

2.5 Capsule coating:

Hard gelatin capsule bodies (separated from the caps) of size 3 were coated by using rotatory pan coater at SGSITS-Indore, India (Harison engineering Pvt. Ltd.). The three coating variable were selected e.g. 5%, 10% and 15% coating for observing the effect of different percent coating on drug release rate.

2.5.1 Coating solution:

Coating solution contains ethyl cellulose (95%) a water-insoluble polymer and plasticizer dibutyl phthalate (5%) as a 6% solution in a 50:50 v/v mixture of acetone and propane-2-ol.

2.5.2 Coating condition:

The capsule bodies were coated under Inlet air temperature: 30–35 °C, Bed temperature: 30 °C, Pan speed: 25 rpm, Atomizing air pressure: 1 bar, Spray rate: 2–2.5 g/min, Spray nozzle diameter: 1.0 mm.

2.6 Assembling of pulsatile drug delivery system

The pulsatile device was assembled as shown in fig no. 1. Swellable polymer, xanthan gum, and guar gum weighed 129 mg and 136 mg respectively into the pre-coated capsule body and lightly compacted. A core tablet was placed onto the compacted swellable polymer bad. An erodible tablet was inserted into the mouth of the capsule and positioned flush with the end of the coated body.

The capsule body is closed with a water-soluble cap of hard gelatin. The different pulsatile system was prepared by using different component of the system are presented in table 3.

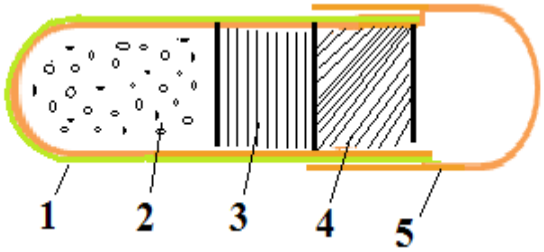

Figure 1. Capsule assembly containing- 1. The polymer coating, 2. Swelling polymer, 3. Core tablet, 4. Erodible tablet, 5. Soluble cap.

2.7 Evaluation of pulsatile drug delivery system:

2.7.1 In – vitro dissolution studies:

The dissolution testing of pulsatile drug delivery system was carried out using a USP Type I paddle apparatus (Electrolab TDT-60) in 900 ml of 0.1 N HCl for the first 2 h, followed by 900 ml of phosphate buffer (pH 6.8). The dissolution medium was maintained at 37±0.5 °C and the basket was rotated at 75 rpm. At different time intervals, 5 ml of sample was withdrawn and analyzed by UV-Visible spectrophotometer at 210 nm. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution vessel.

2.7.2 ex – vivo studies:

Ex - vivo studies were carried out to determine drug absorption through the intestine. The chicken intestine has to be confirmed as a suitable model for the human intestinal epithelium.

The intestine was isolated from a chicken. A median incision was made into the abdomen, the small intestine was freed, and the lumen was carefully cleared with a Krebs-Ringer solution. The intestinal segment was everted and the distal 10 cm part was used. The everted intestine is mounted between two cannulae which are fixed at a constant distance. One end of the isolated everted intestinal segment was fixed to a straight cannula and another end was fixed to bend cannula than tied using a thread (as shown in figure no. 2).

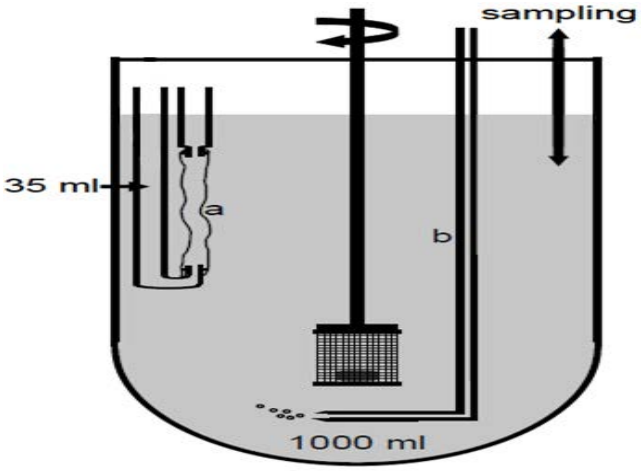

Figure 2. Dissolution/everted intestine system

Table 3. Assembly of different pulsatile system

Formulation code	% w/w capsule coating	Swellable polymer	Core tablet	Erodible tablet
M-1	5	XG*	C-2	E-1
M-2	5	XG	C-2	E-2
M-3	5	GG**	C-2	E-1
M-4	5	GG	C-2	E-2
M-5	10	XG	C-2	E-1
M-6	10	XG	C-2	E-2
M-7	10	GG	C-2	E-1
M-8	10	GG	C-2	E-2
M-9	15	XG	C-2	E-1
M-10	15	XG	C-2	E-2
M-11	15	GG	C-2	E-1
M-12	15	GG	C-2	E-2

*xanthan gum

**guar gum

The system was filled with Krebs-Ringer solution and was completely immersed into the dissolution vessel of the USP Type I dissolution apparatus [30-32]. Initially, dissolution study of pulsatile drug delivery system was carried out in 0.1 N HCl for 2 h. Then the dosage form was removed and transferred to phosphate buffer pH 6.8. During the study, assemblies were maintained at 37 ± 0.5°C, and aeration was ensured with a continuous supply of bubbled oxygen. The drug diffused from the dissolution medium (mucosal side) into the serosal side (absorption compartment) and was analyzed by a validated U.V. Spectrophotometer (Electrolab TDT-60) at regular time intervals of 30 min after filtration with Whatman filter paper.

2.7.3. Stability studies:

After ex – vivo study data evaluation formulation **M-6** was selected as a final formulation that subjected to accelerated stability study according to ICH guidelines (40±2

Table 4. Micromeritic properties core tablet formulations.

Sr. No.	Formulations code	Angle of repose	Hausner Ratio	Carr's index
1	L-1	42.0±0.350	1.29±0.02	22.71±0.64
2	L-2	42.83±0.610	1.32±0.02	24.9±0.49
3	C-1	32.16±0.360	1.12±0.01	11.0±0.38
4	C-2	32.65±0.420	1.5±0.01	13.46±0.36
5	B-1	38.2±0.610	1.21±0.03	17.8±0.52
6	B-2	39.5±0.460	1.26±0.03	19.2±0.56

No. of samples (n) = 3

Table 5. Evaluation of different formulations of core tablet.

Formulations code	Thickness in mm	Hardness (Kg/cm2)	% friability	Average weight of one tablet	% drug content	Disintegration time (min)
L-1	3.61±0.86	2.64±0.76	0.97±0.02	102.2±0.63	95.59±0.44	3.0±0.14
L-2	3.63±0.66	2.5±0.69	1.02±0.023	101.6±0.99	97.96±1.60	2.4±0.16
C-1	3.34±0.28	3.8± 0.49	0.314±0.01	100.8±0.71	98.15±0.67	6.2±0.24
C-2	3.36±0.19	3.62±0.43	0.52±0.014	100.7±0.71	99.98±2.14	5.1±0.29
B-1	3.78±0.52	3.01±0.51	0.764±0.01	102.4±0.83	96.26±0.96	4.0±0.41
B-2	3.79±0.36	2.9±0.42	0.842±0.02	103.3±0.56	98.13±1.06	3.2±0.39

No. of samples (n) = 3

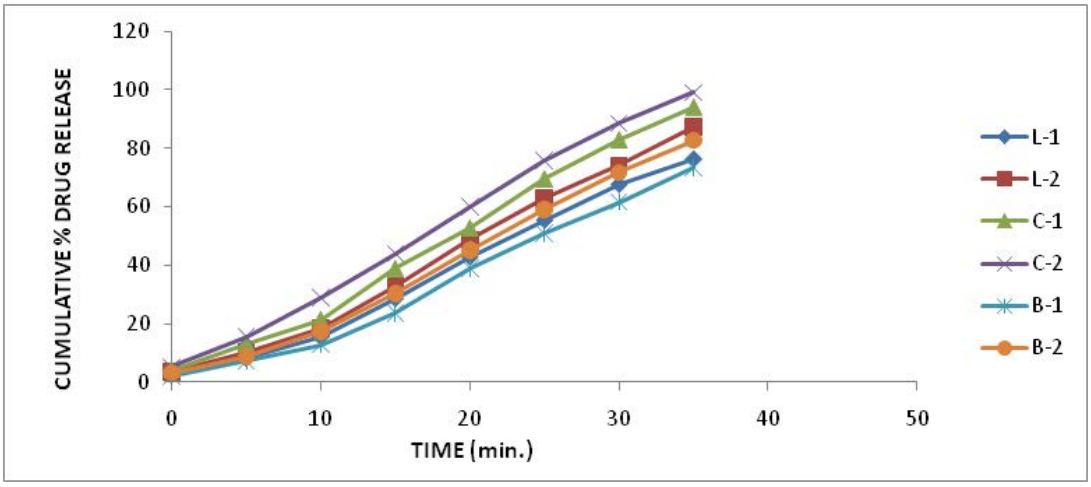

Figure 3. Cumulative percent of Ramipril released from core tablet.

°C/75±5% RH) for a period of 45 days in stability chambers (Remi – CHM-65). The samples (n=3) were taken out at 15, 30 and 45 days and evaluated for the drug content by U. V. Spectrophotometry estimation.

3. Results and discussion:

3.1. Characterization of Ramipril:

IR Spectra of Ramipril was shown peaks at 1743 cm-1, 1652 cm-1, 1187 cm-1, 756 cm-1 that represent Carboxylic acid C=O stretch, Amide C=O stretch, Amine C-N stretch, Aromatic C-H out of plane respectively. The wavelength maxima (λmax) of Ramipril was observed at 210 nm in methanol. The melting point of Ramipril was found at 109^{0}C by triplet study. The partition coefficient of Ramipril determined was 3.32. It indicates that studies comply with USP standards of Ramipril.

3.2. Drug-excipient compatibility studies:

The comparison of IR spectra of pure drug and drug with excipient shown that there was no change in the peak of Ramipril hence it is concluded that no interaction exists between Ramipril – Microcrystalline cellulose and Ramipril – Cross PVP.

3.3. Core tablet:

3.3.1. Micromeritic properties:

Micromeritic properties of core tablet formulations presented in table no. 4. The angle of repose range 31-35, 36-40 and 41-45 indicate good, fair and passable flow respectively. Hausner ratio range 1.12-1.18, 1.19-1.25, and 1.26-1.34 indicate good, fair and passable flow respectively. Carr`s index range 11-15, 16-20 and 21-25 indicate good, fair and passable flow respectively. Formulation C-1 and C-2 shown good flow properties, L-1 and L-2 had shown passable flow properties; B-1 and B-2 shown fair flow properties. Diluent Avicel showed good flow properties as compare to lactose monohydrates and dibasic calcium phosphate as per USP.

3.3.2. Evaluation of core tablets:

Evaluation results of different formulations of core tablet represented in table no. 5. All formulations were subjected to evaluation parameter according to pharmacopeia. The thickness of all tablets was found in the range of 3.34 – 3.79 mm. The Hardness of all tablets was found in the range of 2.5 – 3.8 kg/cm2. The % friability of all core tablets was found less than 1 % except L-2. The average weight of tablet was found in the range of 100.7 – 103.3 mg. No tablet has more than 7.5% weight variation, all tablets were passed as per USP. The Drug content of tablet was found between 95.59 – 99.98 %. The Disintegration time for different core tablet formulations was found in the range of 2.4 – 6.2 as per USP.

3.3.3. In-vitro dissolution study:

The dissolution rate of Ramipril from different core tablets formulations presented in Figure no. 3. Formulation C – 2 shown greatest release rate of Ramipril than other formulations. The sequences of drug release rate were -

C-2 > C-1 > L-2 > B-2 > L-1 > B-1

Table 6. Micromeritic properties erodible tablet formulations.

Sr. No.	Formulations code	Angle of repose	Hausner Ratio	Carr's index
1	E-1	32.57±0.260	1.13±0.02	11.42±0.34
2	E-2	34.25±0.310	1.15±0.03	13.012±0.42

No. of samples (n) = 3

Table 7. Evaluation of erodible tablets.

Sr. no.	Formulation code	Thickness (mm)	Hardness (Kg/cm2)	% friability	Average weight of one tablet (mg)
1	E-1	4.26±0.35	3.8±1.31	0.63±0.03	150.23±0.49
2	E-2	±0.16	2.9±1.42	0.98±0.03	148.62±0.16

Formulation C-2 containing Avicel as a diluent and 6% cross polyvinyl pyrrolidone (PVP) as superdisintegrant showed great release rate of drug hence formulation C-2 used for the preparation of pulsatile system.

3.4. Erodible tablet:

3.4.1. Micromeritic properties:

Micromeritic properties of erodible tablets formulations presented in table no. 6. Formulation E-1 and E-2 both showed good flow properties as per USP.

3.4.2. Evaluations of erodible tablets:

The results of evaluation of erodible tablets presented in table no. 7. Formulation E-1 containing low amount (50%) of the polymer showed better flow properties and greater thickness, hardness % friability than E-2, While E-1 has low average weight than E-2.

3.5. Capsule coating:

The capsule bodies were coated with water-insoluble ethyl cellulose which forms a semipermeable film having low puncture strength and low elongation capacity. Weights of 50 uncoated hard gelatin capsule bodies were 1.9 mg while weights of 50 hard gelatin capsule bodies coated with 5% w/w, 10% w/w and15% w/w were 2.1 mg, 2.2 mg, and 2.3 mg respectively.

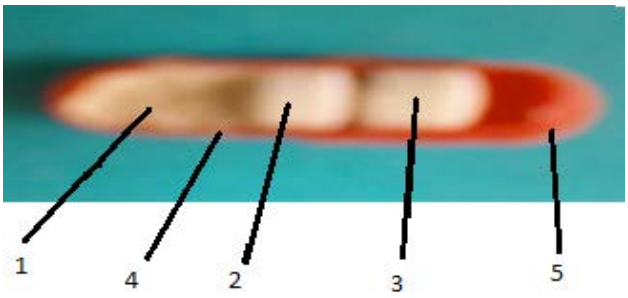

Figure 4. Photograph of assembled pulsatile drug delivery system; (1) Swellable polymer, (2) Core tablet, (3) Erodible tablet, (4) Ethylcellulose coated capsule body, (5) Soluble cap.

3.6. Assembling of pulsatile drug delivery system:

The pulsatile system developed in this study consisted of swellable polymer weighed into the pre-coated capsule body, a core tablet containing drug placed onto the compacted swellable polymer layer and an erodible tablet made up of hydrophilic polymers inserted into the mouth of the capsule. The capsule body is closed with a water-soluble cap.

3.7. Evaluation of pulsatile drug delivery system:

3.7.1. In – vitro dissolution studies:

In-vitro dissolution studies have been performed for all formulation of pulsatile drug delivery system (M-1 to M-12) by using USP Type I paddle apparatus (Electrolab TDT-60) in 900 ml of 0.1 N HCl for the first 2 h, followed by 900 ml of phosphate buffer (pH 6.8). Release pattern of Ramipril from various formulations of pulsatile drug delivery system after each 30 min are shown in figure no. 5.

Formulation M-1 to M-4 coated with **5% w/w** ethyl cellulose shown **no lag time**, all formulation (M-1 to M-4) were released drug completely after 2 hr. Formulation M-5 to M-8 coated with **10% w/w** ethyl cellulose shown **lag time** of **3 – 4 hr.** M-5 and M-6 shown lag time of 4 hr. M-5 release 37 % drug in lag time whereas M-6 release 25 % drug in lag time. M-5 and M-6 release drug 97.94 % and 99.13 % respectively in 7 hr. M-7 and M-8 shown lag time of 3 hr. M-7 release 28 % drug in lag time whereas M-8 release 20 % drug in lag time. M-7 and M-8 release drug 99.94 % and 99.82 % in 6 hr. Formulation M-9 to M-12 coated with **15% w/w** ethyl cellulose shown **lag time** of **5 – 5.5 hr.** M-9 and M-10 shown lag time of 5.5 hr. M-9 release 23 % drug in lag time whereas M-10 release 17 % drug in lag time. M-9 and M-10 release drug 69.13 % and 62.0 % respectively in 7 hr. M-11 and M-12 shown lag time of 5 hr. M-11 release 21 % drug in lag time whereas M-12 release 15 % drug in lag time. M-11 and M-12 release drug 73.34 % and 76.05 % respectively in 7 hr.

Formulation (M-1 to M-4) dissolve rapidly and shown no lag time because coating membrane is thin and it allows passes of dissolution media. M-5 and M-6 (lag time 4 hr.) shown greater lag time than M-7 and M-8 (lag time 3 hr.), similar M-9 and M-10 (lag time 5.5 hr.) shown greater lag time than M-11 and M-12 (lag time 5 hr.), because guar gum has greater swelling capacity than xanthan gum. Formulation M-5, M-7, M-9, M-11 shown greater drug release than formulation M-6, M-8, M-10, M-12 respectively, because E-1 (guar gum 50 %) shown release rate faster than E-2 (guar gum 75 %).

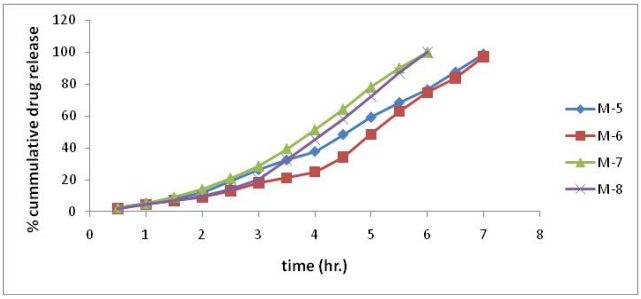

Figure 5. Drug release profile from the pulsatile system (M-5 to M-8).

The objective of this study was to develop a pulsatile dosage form which the drug releases with a lag time of 4–4.5 hr. and a fast drug release thereafter (single pulse). After in–vitro studies of different formulations it has been observed that formulation **M-5** and **M-6** are suitable for fulfill the object, therefore, these formulations proceeded for further studies (ex-vivo studies, kinetic assessment).

3.7.2. ex – vivo studies:

Ex – vivo studies were performed to determine the rate of absorption of the drug from intestinal epithelium. After evaluation of in – vitro dissolution release data formulation M-5 and M-6 were proceeded for ex–vivo studies. Absorption patterns of Ramipril from the intestinal epithelium of formulations code M-5 and M-6 shown in figure no 6.

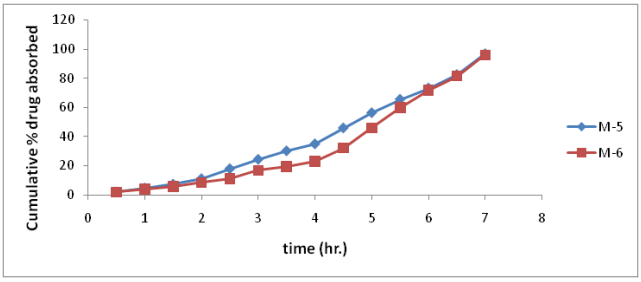

Figure 6. Absorption profile of drug from intestinal epithelium.

Ramipril is a highly lipophilic drug, therefore, it absorbs rapidly from intestine as soon as drug release from pulsatile drug delivery system. Formulation M-6 shown lag time of 4 hr. during the lag time 34 % drug was absorbed from the intestine and after lag time pulsatile system ruptured followed by the fast release of drug and after 7 hr. 96.93 % drug has been absorbed. Formulation M-5 show clear lag time of 4 hr. during the lag time 23 % drug was absorbed from the intestine and after lag time pulsatile system ruptured followed by the fast release of drug and after 7 hr. 98.93 % drug has been absorbed. Formulation M-6 shown greater delay release than M-5, therefore, **M-6** is one of the best suitable formulations to fulfilling the object of this study.

3.7.3. Kinetic analysis of release mechanism:

The drug release data of optimized formulation (M-6) were fitted to models representing Higuchi's, zero order, first order, Banker - Lonsdale and Korsmeyer's- Peppas equation kinetics to know the release mechanisms with the help of software Sigma plot (v12) generated graph presented in figure no. 7 and obtained regression coefficient value for different model presented in table no. 8. It was observed that the correlation coefficient values are higher (r^2 = 0.97) with the Korsmeyer–Peppas equation. Therefore mechanism of drug release mechanism from pulsatile system best explains by Korsmeyer–Peppas equation.

Table 8. Equations and obtained regression coefficients value for different model.

Sr. no.	Model	Equation	R2
1	Zero order	Qt = Q0 + K0 t	0.913
2	First order	ln Qt = ln Q0 – K1 t	0.701
3	Hixson–Crowell	W01/3 – Wt 1/3 = Ks t	0.739
4	Higuchi	Qt = KH t1/2	0.549
5	Korsmeyer–Peppas	Qt /Q∞ = Kk tn	0.991 (n = 2.11)
6	Baker–Lonsdale	(3/2) [1- (-1(Qt /Q∞))2/3] - (Qt /Q∞) = K t	0.50

Where,
Qt: the amount of drug released in time t
Q0: initial amount of drug in the tablet
k0, K1, KH, Ks: release rate constants
n: release exponent (indicative of drug release mechanism)
W: initial amount of drug in dosage form,
Wt: remaining amount of drug in dosage form at time t
Ks: a constant incorporating the surface–volume relation.

It was observed that the correlation coefficient values are higher (r2 = 0.97) with the Korsmeyer–Peppas equation. Therefore mechanism of drug release mechanism

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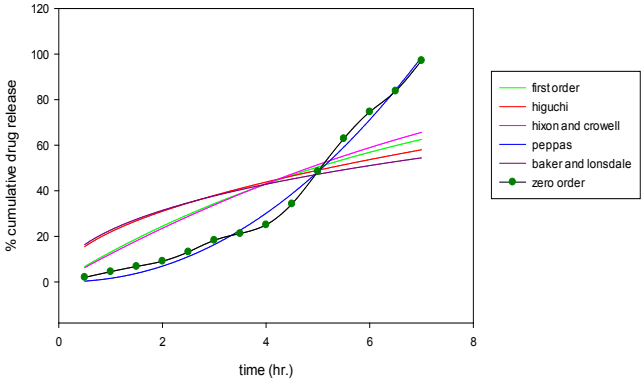

Figure 7. Release profile of formulation M-6 with model fitting by using Sigma plot software.

A more comprehensive, but still very simple, semi-empirical equation to describe drug release from polymeric systems is the so-called power law:

$$\frac{M_t}{M_\infty} = kt^n$$

Here, Mt and M∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively; k is a constant incorporating structural and geometric characteristic of the device, and n is the release exponent, indicative of the mechanism of drug release [33].

Korsmeyer et al. (1983) developed a simple, semi-empirical model, relating exponentially the drug release to the elapsed time (t):

Ft = atn

where a is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism, and the function of t is Mt/M∞ (fractional release of drug).

Peppas (1985) used this n value in order to characterize different release mechanism. For polymeric cylindrical controlled delivery systems, n = 0.45 indicates diffusion controlled drug release, n > 0.89 indicates swelling-controlled drug release and values in between 0.45 and 0.89 indicate anomalous transport i.e. drug release due to diffusion and erosion mechanism [34-36]. In this case, exponents were obtained by using software sigma plot (v 12); r2 = 0.9918 and n = 2.11, indicating that **swelling-controlled** drug release mechanism is involved in the drug release.

In the swelling-controlled release mechanism, the relaxation process of the macromolecules occurring upon water imbibition into the system is the rate controlling step. Water acts as a plasticizer and decreases the glass transition temperature of the polymer. Once the Tg equals the temperature of the system, the polymer chains undergo the transfer from the glassy to the rubbery state, with increasing mobility of the macromolecules and volume expansion.

3.7.4. Stability studies:

The results of accelerated stability studies presented in table no 9, indicated that E-2 did not show any physical changes (appearance) during the study period and the drug content (n=3; mean ± SD) was found above 98% at the end of 45 days.

This indicates that E-2 capsules exhibited good physical stability and acceptable potency at accelerated storage condition for 45 days also there was negligible change in % drug control of the pulsatile system under accelerated storage conditions.

4. Conclusion

The objective of this study was to develop a pulsatile dosage form which the drug releases with a lag time of 4–4.5 hr. and a fast drug release thereafter (single pulse). The

Table 9. Stability studies of the pulsatile system (M-6).

Sr. no.	Time interval (days)	% drug content				Standard deviation (±)
		N1	N2	N3	Mean	
1	0	99.96	99.98	99.95	99.96	0.013
2	15	99.68	99.72	99.68	99.69	0.023
3	30	99.45	99.52	99.41	99.46	0.055
4	45	99.26	99.29	99.24	98.26	0.025

rapid release of the drug after a lag time consistent with the requirement for chronotherapeutics was achieved with the developed formulation. The capsule bodies were coated with water-insoluble ethyl cellulose which forms a semipermeable film having low puncture strength and low elongation capacity. The polymers such as guar gum and xanthum are found to be responsible for delaying the release. Thus this approach can provide a useful means for pulsatile/programmable release (with a single pulse) of Ramipril and may help for patients with morning spate of BP.

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