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Review Article

FORMULATION AND INVITRO EVALUATION OF RAMIPRIL PULSATILE DRUG DELIVERY

[1]K. Sandeep, [2]Aerpula Manisha, [2]Kankali Swetha, [2]Kavali Hemanth, [2]Nalla Likitha.

[1]M.pharmacy, Department of Pharmaceutics, Faculty of Pharmaceutics, Joginpally BR pharmacy college, Hyderabad, Telangana, India
[2]B. Pharmacy, Department of Pharmaceutics, JOGINPALLY BR PHARMACY COLLEGE, Hyderabad, Telangana, India

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ABSTRACT
Ramipril as just a model drug, an ACE inhibitor used to treat hypertension and lower cardiovascular mortality after myocardial injury in cardiac stable patients with congestive heart failure, the current study set out to design and evaluate an oral, site-specific, pulsatile drug delivery system. A insoluble hard gelatin capsules body, a powder mixture, and a hydrogel plug serve as the foundation of the fundamental design. Ramipril, Ludiflash, Lycoat, MCC, and Talc powder was made and tested for flow characteristics and FTIR investigations. Based on the results, the F4 powder mix formulation was chosen for use in the subsequent production of pulsatile capsules. Hydrogel plug was created using both hydrophobic polymer alone and in combination. In order to maintain a proper lag period, hydrophilic polymer like HPMC K15M were combined with hydrophobic polymers such ethyl cellulose in ratios of 1:1, 1:2, and 2:1. It was discovered that drug release was regulated by the ratio of polymers utilised. The produced formulations' drug content, weight fluctuation, and in vitro release tests were all assessed. Ramipril was released from pulsincap after a preset lag time of 9 hours, according to research on the in vitro release of the pulsatile device. FTIR investigations verified that there was not an interaction between the medication and polymers. Based on in vitro research, P5F4 was determined to be the best formulation.

Key words: Time-dependent delivery; pulsatile system; Chronopharmaceutics; in vitro release experiments; Ramipril.

INTRODUCTION

Usually, medications either release immediately or over time. According to current research, the timing of medication administration can be a significant factor in influencing the effectiveness and tolerance of pharmacological therapies. In fact, it has been demonstrated that the time rhythms of body activities influence both the pharmacokinetics and pharmacodynamics of the majority of bioactive substances in use in addition to the occurrence or intensity of a number of illness disorders. [1,2,3,4.] Nonetheless, interest in pulsatile drug release devices has grown recently. For many medications or treatments, pulsatile drug release in which the drug is delivered quickly after a clearly defined lag could be useful.[5,6,7]. When a specified off-release interval, or "lag time," is followed by a quick and temporary drug release, it is said to be using a pulsatile drug delivery system.[8] Multiple-pulse & single-pulse systems are two different types of pulsatile release systems. [9] A frequent subgroup of single-pulse systems is those that use rupturable dosage forms. For pulsatile releasing purposes, a variety of design strategies have been tested. Baker proposed a core that is enclosed in a semipermeable and contains osmotically active materials, such as medications.[10]. Other systems consist of a drug-containing core, covered by a swelling layer and an outer insoluble, but semipermeable polymer coating or membrane[11,12,13.] 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.

Ramipril, A prodrug from the ACE inhibitor class of drugs, ramipril is used to treat hypertension. In the liver as well as, to a smaller extent, the kidneys, it is converted to ramiprilat. Angiotensin I (ATI) is converted to

Address for Correspondence: K. Sandeep**,** Department of Pharmaceutics, Faculty of Pharmaceutics, Joginpally BR pharmacy college, Hyderabad, Telangana, India, India; **E-Mail:** kothapallisandeep8@gmail.com

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angiotensin II by the enzyme ACE, which is competitively inhibited by the drug ramiprilat (ATII). An essential part of the renin-angiotensin-aldosterone system, ATII controls blood pressure (RAAS). Ramipril can be used to treat conditions including hypertensive, congestive heart failure, and nephropathy as well as to lower the mortality, myocardial infarction, and stroke rates in those who are at high risk for cardiovascular events.[24]

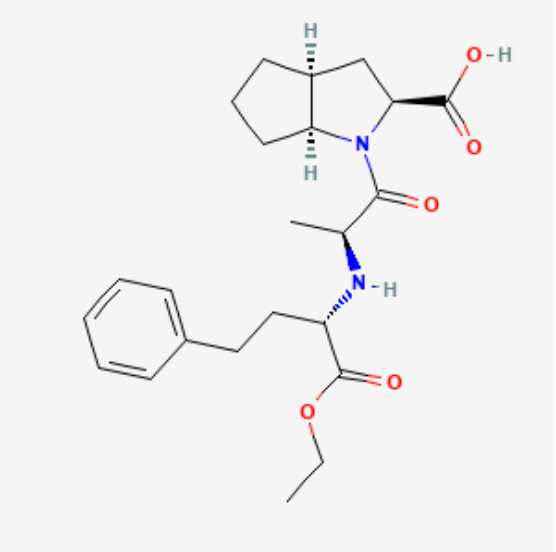


Figure No.1.Structure of Ramipril

Ramipril is an ACE inhibitor similar to benazepril, fosinopril and quinapril. It is an inactive prodrug that is converted to ramiprilat in the liver, the main site of activation, and kidneys. Ramipril at confers blood pressure lowing effects by antagonizing the effect of the RAAS. The RAAS is a homeostatic mechanism for regulating hemodynamics, water and electrolyte balance. During sympathetic stimulation or when renal blood pressure or blood flow is reduced, renin is released from the granular cells of the juxtaglomerular apparatus in the kidneys. In the blood stream, renin cleaves circulating angiotensinogen to ATI, which is subsequently cleaved to ATII by ACE. ATII increases blood pressure using a number of mechanisms. First, it stimulates the secretion of aldosterone from the adrenal cortex. Aldosterone travels to the distal convoluted tubule (DCT) and collecting tubule of nephrons where it increases sodium and water reabsorption by increasing the number of sodium channels and sodium-potassium ATPases on cell membranes. Second, ATII stimulates the secretion of vasopressin (also known as antidiuretic hormone or ADH) from the posterior pituitary gland. ADH stimulates further water reabsorption from the kidneys via insertion of aquaporin-2 channels on the apical surface of cells of the DCT and collecting tubules. Third, ATII increases blood pressure through direct arterial vasoconstriction. Stimulation of the Type 1 ATII receptor on vascular smooth muscle cells leads to a cascade of events resulting in myocyte contraction and vasoconstriction. In addition to these major effects, ATII induces the thirst response via stimulation of hypothalamic neurons. ACE inhibitors inhibit the rapid conversion of ATI to ATII and antagonize RAAS-induced increases in blood pressure. ACE (also known as kininase II) is also involved in the enzymatic deactivation of bradykinin, a vasodilator. Inhibiting the deactivation of bradykinin increases bradykinin levels and may sustain the effects of ramiprilat by causing increased vasodilation and decreased blood pressure.

MATERIALS & METHODS USED: Ramipril API was procured from Kreysun Pharmaceutical Private Limited, Hyderabad and Ludiflash, Lycoat, Hydrochloric acid & Methanol were procured from S.D Fine Chemicals, Microcrystalline cellulose, Talc were procured from Loba chemie pvt.ltd, Ethyl cellulose. HPMC K15M were procured from Otto Chemicals, Mumbai, Formaldehyde, Sodium hydroxide pellets,Potassium permanganate were procured from Qualigens fine chemicals, Mumbai.

Pulsin cap Desingning:

Designing or preparation of pulsincap capsules involves 3 steps:

- Making the gelatin capsule with cross-linked gelatin.
- Preparation of powder mixes for filling into cases.
- Ramipril's pulse capsule formulation

Preparation of Cross-Linked Gelatin Capsule:

Formaldehyde treatment:

One hundred hard gelatin capsules of size "0" were consumed. A wire mesh was used to place their bodies on top of the caps. The bodies which were put on a wire network were spread as a solitary layer. A desiccator containing 25 milliliters of 15% v/v formaldehyde solution was prepared. This was supplemented with 5 g of potassium permanganate. Desiccators containing formaldehyde liquid at the bottom were kept in equilibrium with their vapor by keeping the wire mesh containing the capsules' bodies on top. The desiccators were then tightly sealed right away. By exposing the capsules for varying amounts of time, the bodies were made to react with formaldehyde vapors, 2, 4, 6, 8, 10 hrs. After that, they were taken out, dried for 24 hours on filter paper to ensure that the reaction between the gelatin and the formaldehyde vapors was finished, and the capsules were kept in an open environment to make it easier to get rid of any remaining formaldehyde. The bodies of these capsules were sealed off with an untreated cap and kept in a polythene bag.

Use of Formaldehyde treatment:

Modifying the solubility of hard gelatin capsules was the primary objective of formaldehyde treatment. Cross-connecting of gelatin particles was accomplished by presenting to formalin fumes. A "Schiff's base condensation" occurs when the amino groups in the gelatin molecular chain react with the aldehyde groups in formaldehyde to make the gelatin insoluble in water during cross-linking. Gelatin and formaldehyde react to form an irreversible complex. The essential amine bunch present in gelatin responds with formaldehyde making it irreversibly bound. To produce formalin vapors, potassium permanganate was added to the formaldehyde solution. In a closed dessicator, bodies of hard gelatin capsules were exposed to formaldehyde vapors for varying amounts of time. The vapor equilibrates with the formaldehyde liquid, rendering the gelatin water insoluble.

Preparation of Ramipril Tablet For Filling Into Capsules:

Separately, each ingredient was passed through a #60 mesh sieve. The drug and MCC were mixed by adding a small amount of each to a mixing bowl at a time, blending it into a uniform mixture, and setting it aside.

The remaining ingredients were then incorporated geometrically, passed through a coarse sieve (#44 mesh), and a hydraulic press was used to compress the tablets. The machine's compression force was adjusted so that each batch had a hardness of 3 to 4 kg/cm2. For all formulations F1 through F8, the weight of the tablets (100 mg) remained constant.)

Table. N o . 1 Formulation table for filling the Ramipril Pulsincap with the blend

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Ramipril	10	10	10	10	10	10	10	10
Ludiflash	2	4	6	8	--	--	--	--
Lycoat	--	--	--	--	2	4	6	8
MCC	82	80	78	76	82	80	78	76
Mg. sterate	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2
Total	100	100	100	100	100	100	100	100

Formulation of Pulsincap of Ramipril :

Utilizing a variety of excipients and polymers in varying proportions, the modified release pulsincaps containing 4 mg of Ramipril were made. Based on disintegration time, the optimal capsule bodies that had been treated with formaldehyde for six hours were selected for the pulsincap formulation. The body of the capsule contained an enhanced formulation of the Ramipril tablet. Ethyl cellulose and water were combined to make the plug for

the formulation of hydrogel plugs. in various ratios of HPMC K15M. At first, the plug's total weight was determined to be 100 mg, and the hydrophobic-to-hydrophilic polymer ratios were determined to be 1:1, 1:2, and 2:1, respectively.

In vitro Dissolution Study:

In vitro dissolution of Ramipril tablets was studied in USP XXIV dissolution test apparatus. 900 ml Phosphate buffer 6.8 (simulated fluid) was used as dissolution medium. The stirrer was adjusted to rotate at 100RPM. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 209 nm. The volume withdrawn at each time interval was replaced fresh quantity of dissolution medium. Cumulative percent Ramipril released was calculated and plotted against time.

Evaluation Of Pulsincap Dosage Form:

In-vitro release studies:

Dissolution study was carried out to measure the release rate of the drug from the pulsincap formulation. In-vitro dissolution profile of each formulation was determined by employing USP I apparatus by rotating basket method. In order to stimulate the pH changes along GI tract 2 different dissolution media with pH 1.2, 6.8, 2 buffers were sequentially used, and therefore referred to as “Sequential pH change method”. The dissolution media were maintained at a temperature of 37 ± 0.5ºC throughout the experiment and the speed of rotation of basket maintained at 100 rpm. 900ml of dissolution medium was used at each time. Ramipril Pulsincaps was placed in basket in each dissolution vessel to prevent floating. While performing experiments, stimulated gastric fluid (SGF) pH 1.2 buffer was first used for 2 hrs (since the average gastric emptying time is 2hrs) and then removed and the fresh stimulated intestinal fluid (SIF) pH 6.8 buffer was added and used for remaining hours. 5 ml samples of dissolution fluid were withdrawn at predetermined time intervals with the help of a syringe. The volume withdrawn at each time interval was replaced with 5ml of fresh dissolution medium maintained at same temperature. The filtered samples were suitably diluted whenever necessary and assayed for Ramipril by measuring absorbance at 209 nm, by UV absorption spectroscopy. % CDR was calculated over the sampling times.

RESULTS&DISCUSSION.

PRFORMULATION STUDIES

Solubility: It was determined as per standard procedure.

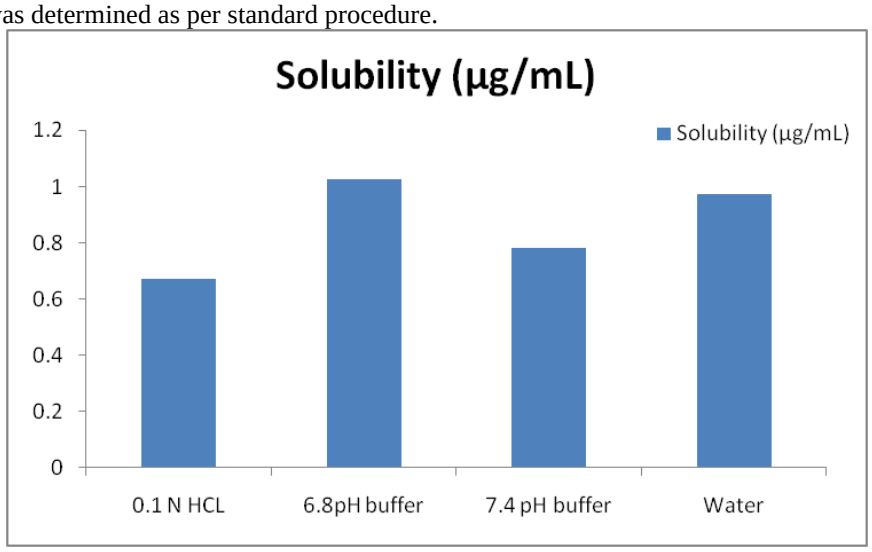
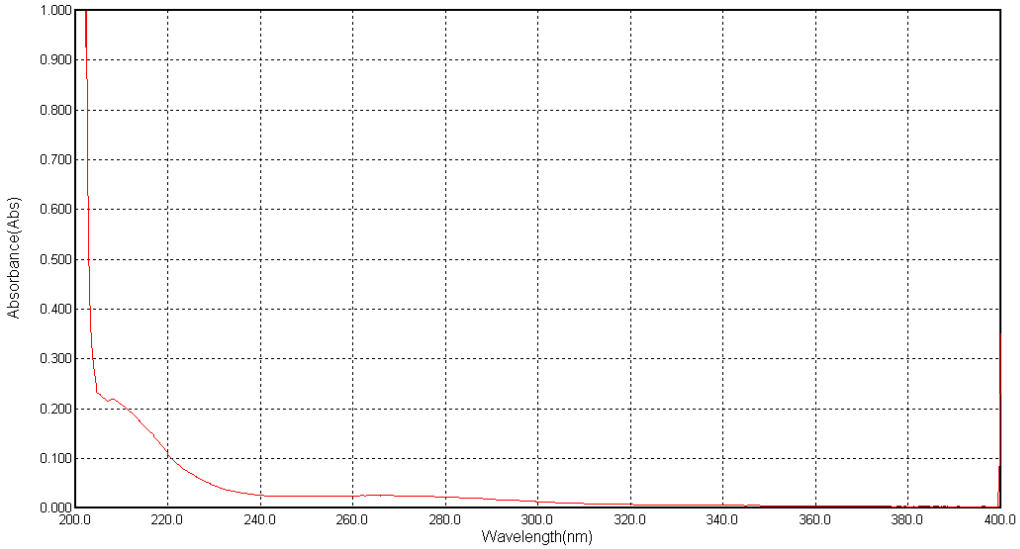


Fig: Solubility graph of Ramipril in various solvents

Discussion: The solubility of Ramipril was occurs more on 6.8 pH phosphate buffer with compare of 7.4 pH phosphate buffer and 0.1 N HCl solution.

Melting point: The melting point of Ramipril was found to be 105 -112ºC

Determination of λ max of Ramipril: The λ max of Ramipril was estimated by carrying out UV scan between the wavelength 200 to 400 nm which gave a highest peak at 209 nm and the same was selected for Ramipril.



Discussion: The maximum absorbance was found to be at 209 nm.

Calibration curve of Ramipril

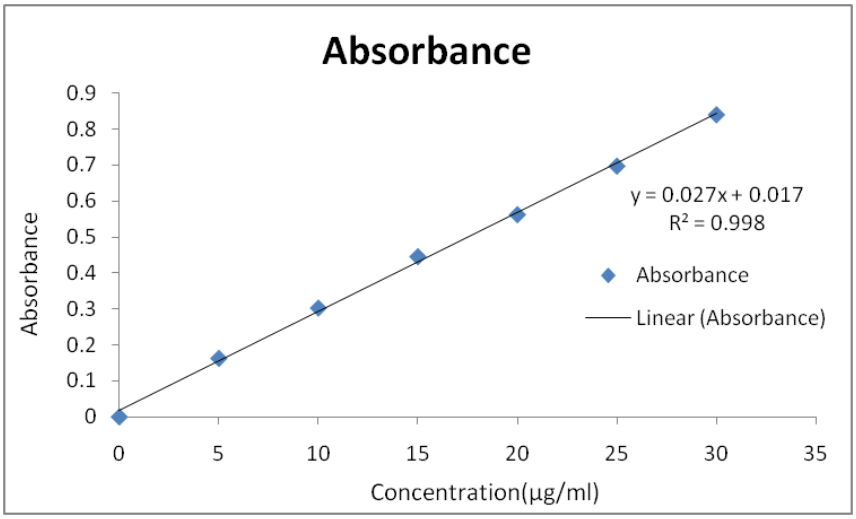


Fig calibration curve of Ramipril with 0.1N HCl

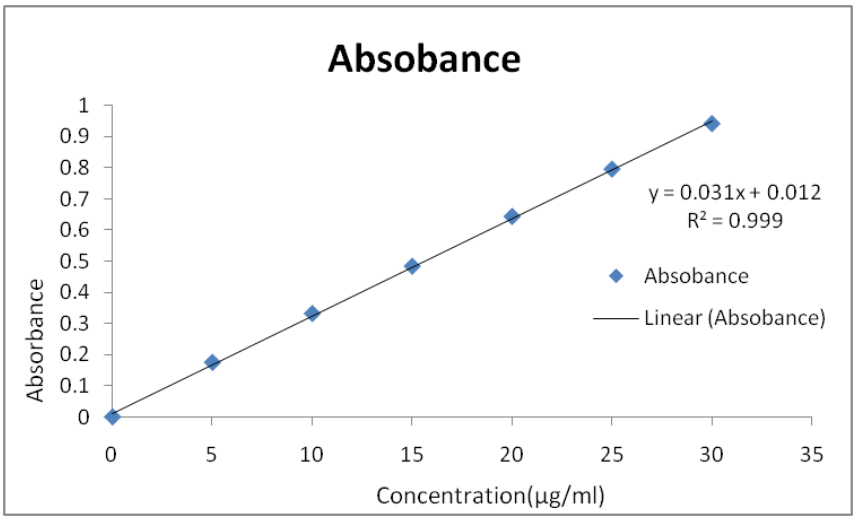


Fig: calibration curve of Ramipril with 6.8 pH Buffer

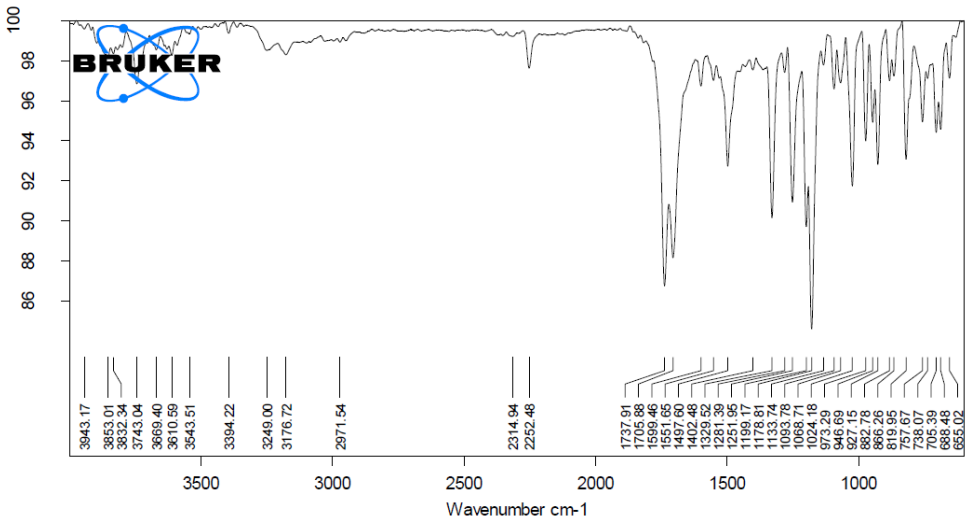
Discussion: The linearity was found to be in the range of 5-30µg/ml in pH 6.8 buffer and 0.1N HCl. The regression value was closer to 1 indicating the method obeyed Beer-lambert's law.

FTIR

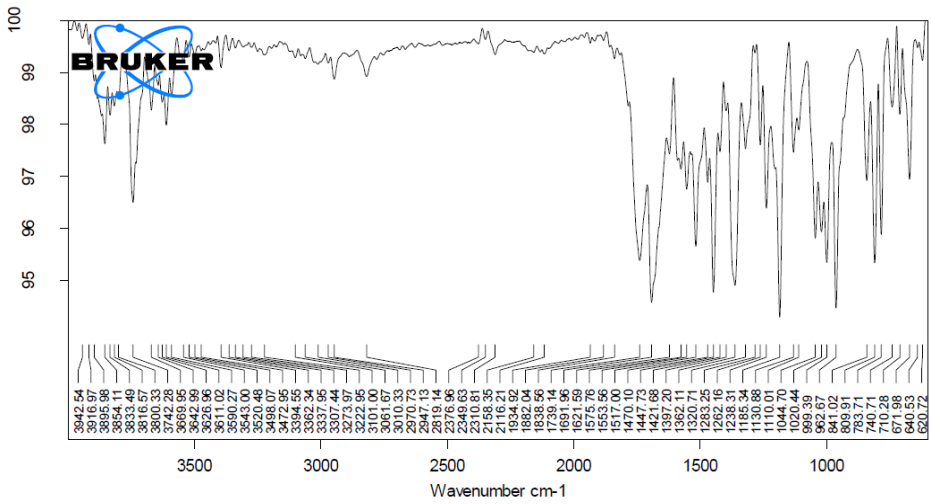
Drug-Excipient compatibility studies:

The IR spectrum of pure drug was found to be similar to the standard spectrum of Ramipril. From the spectra of Ramipril, combination of Ramipril with polymers, it was observed that all characteristic peaks of Ramipril were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and polymers. FTIR spectra of Ramipril, and Optimized formulation are shown in Figure respectively.

FTIR Spectra of Pure drug:



FTIR Spectra of Drug and Excipients:



Discussion: Form the drug excipients compatibility studies we observe that there are no interactions between the pure drug and (drug+ excipients) which indicates there are no physical changes.

Flow properties of powder blend:

Table 7.4 Flow properties of powder blend

Formulation Code	Angle of Repose±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio±SD
F1	26.29±0.24	0.358±0.41	0.421±0.41	16.21±0.02	1.11±0.24
F2	24.78±0.17	0.369±0.28	0.446±0.28	17.74±0.52	1.28±0.39
F3	26.24±0.38	0.342±0.974	0.472±0.32	15.56±0.36	1.36±0.15
F4	27.28±0.74	0.338±0.65	0.465±0.47	18.78±0.98	1.27±0.25
F5	26.21±0.32	0.387±0.81	0.432±0.12	14.92±0.42	1.32±0.36
F6	29.78±0.48	0.337±0.25	0.489±0.96	17.17±0.15	1.26±0.48
F7	24.28±0.67	0.357±0.48	0.421±0.32	16.32±0.15	1.18±0.26
F8	27.39±0.28	0.362±0.26	0.436±0.28	14.75±0.15	1.20±0.45

Discussion: The angle of repose of different formulations was ≤ 29.78 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.337g/cm3 to 0.387g/cm3. Tapped density was found between 0.421g/cm3 to 0.489g/cm3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 14.75-18.78 and Hausner's ratio from 1.11-1.36 which reveals that the blends have good flow character.

Characterization of Tablets

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table.

Table: Characterization Ramipril Tablets

Formulation code	%Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness	Friability (%)	Disintegrating time(sec)	Drug content (%)
F1	2.21	2.89	8.34	3.8	0.72	14	95.28
F2	1.08	2.64	8.48	3.9	0.43	15	97.14
F3	1.48	2.91	8.25	3.4	0.61	20	96.39
F4	2.36	2.48	8.62	4.0	0.79	13	99.42
F5	2.17	2.63	8.47	3.9	0.99	21	98.34
F6	2.58	2.75	8.38	3.5	0.82	16	96.81
F7	1.18	2.68	8.42	3.2	0.75	19	97.32
F8	2.84	2.82	8.19	3.5	0.71	17	99.45

Discussion:

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3-4 kg/cm2.All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 –F8 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The drug content values for all the formulations (F1-F8) was found to be in the range of 95-100%.

Dissolution studies of the tablets:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release.

Table 7.6: % Cumulative drug release of formulations F1-F8

Time(mins)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	15.28	29.36	42.18	46.28	24.48	37.08	45.89	46.89
10	27.41	42.42	56.83	58.34	35.82	43.48	56.24	57.24
15	36.36	59.35	67.49	67.25	49.45	49.05	70.42	68.42
20	43.74	79.63	71.65	85.66	58.21	65.78	78.19	77.19
30	55.25	86.49	83.48	93.25	63.48	78.36	82.46	85.46
40	72.17	89.31	91.41	99.85	69.82	86.09	93.78	96.53
50	88.75	98.53	99.84		78.49	89.31	97.53	
60	97.41				85.46	96.75		

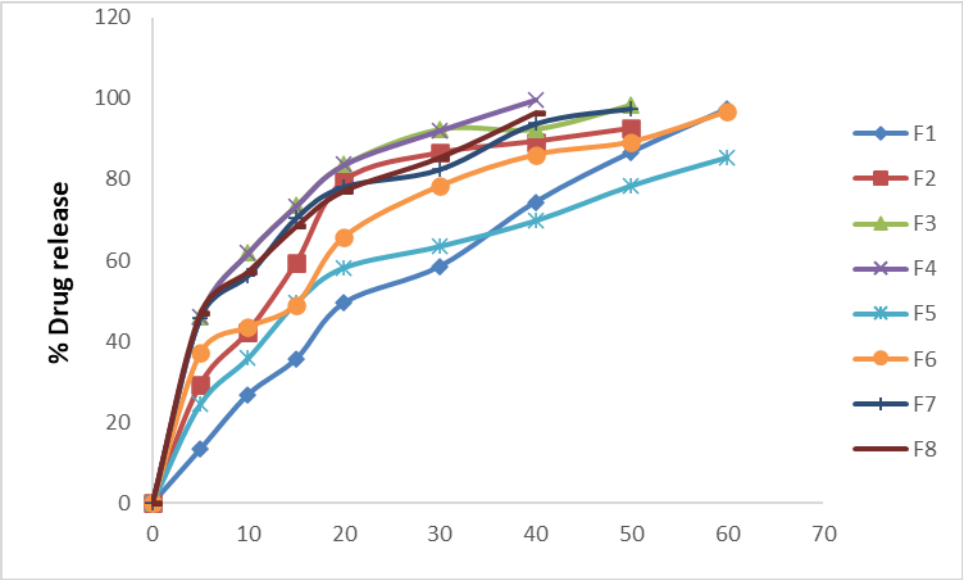


Fig: In vitro drug release of formulations F1-F8

Discussion: From the in vitro drug release in studies it was observed that the formulations containing ludiflash as a super disintegrant in different concentrations like 2, 4, 6 and 8%, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F4 formulation containing ludiflash 8% concentration shows maximum amount of drug release (98.51%) at the end of 40 mins.

Whereas formulations containing lycoat as a super disintegrant in different concentrations like 2,4, 6 and

8%, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F8 formulation containing lycoat with 8% concentartion shows maximum amount of drug release (98.51%) at the end of 40 mins.

So, F4 formulation containing 8% concentration of ludiflash shows max. release within 40 mins so that it is choosen as optimized formulation.

Evaluation of Formaldehyde Treated Capsules:

Physical test

Identification attributes: The size '0' capsules chosen were opaque, with white colored body and red cap. The normal capsule bodies were soft and sticky when touched with wet hand. After treating with formaldehyde, there were no significant changes in the physical appearance of the capsules except for the stickiness. The body of capsule was hard and non-sticking even when touched with wet hand due to treatment with the formaldehyde.

Visual defects: Among 100 capsules body which were treated with formaldehyde, about 15 to 20 capsule bodies showed visual defects. They were found to be shrunk and distortion into different shapes due to the complete loss of moisture.

Dimensions: Dimensional examination was done by using vernier calipers.

Average capsule length:

- Before formaldehyde treatment (untreated cap and body) : 20.7 mm
- After formaldehyde treatment(treated body and untreated cap) : 19.8 mm

Average diameter of capsule body:

- Before formaldehyde treatment : 7.3 mm
- After formaldehyde treatment : 6.9 mm

Average length of capsule body:

- Before formaldehyde treatment : 17.9 mm
- After formaldehyde treatment : 17.2 mm

Discussion: On formaldehyde treatment, the "0" size capsules bodies showed a significant decreases in length and diameter and attained hardness.

Chemical test:

Qualitative test for free formaldehyde: The formaldehyde treated capsules were tested for the presence of free formaldehyde by comparing color of sample solution with standard solution. It was found that the sample solution was not more intensity colored than the standard solution inferring that less than 20µg/ml of free formaldehyde was present in 25 capsule bodies.

Discussion: Limit test for the presence of residual formaldehyde, indicated that the amount of formaldehyde present in treated capsules was well within limits.

Optimization of formaldehyde treated capsule bodies exposed at various time intervals viz., 2, 4, 6, 8, 10hrs:

Table 7.7 Disintegration test for Treated Capsules

Code	Disintegration Time (hrs)	
	1.2 pH (2hrs)	6.8 pH (upto 24hrs)
F7 (2rd hr)	2	_
F8 (4th hr)	2	1
F9 (6th hr)	2	7
F10 (8th hr)	2	9
F11 (10th hr)	2	12

Discussion: Based on the disintegration studies, it was observed that the 6th hr treated capsule (F9) remained intact for 7 hrs so lag time was maintained. F10, F11 remain intact for 9, 12 hrs respectively and therefore they were not selected for the formulation because the required lag time was 6hrs. As the required lag time is 6hrs, F9 (6th hr treated capsule) was selected as optimized time for formaldehyde treatment for further studies.

Invitro release studies:

Dissolution study was carried out to measure the release rate of drug from prepared pulsincap formulation using USP I dissolution apparatus at 370C using 2 different dissolution media of pH 1.2, pH 6.8 phosphate buffers in order to mimic in vivo GIT conditions. Initially first 2hrs of dissolution was conducted in pH 1.2 buffer, followed by 10hrs of dissolution study in pH 6.8 phosphate buffer.

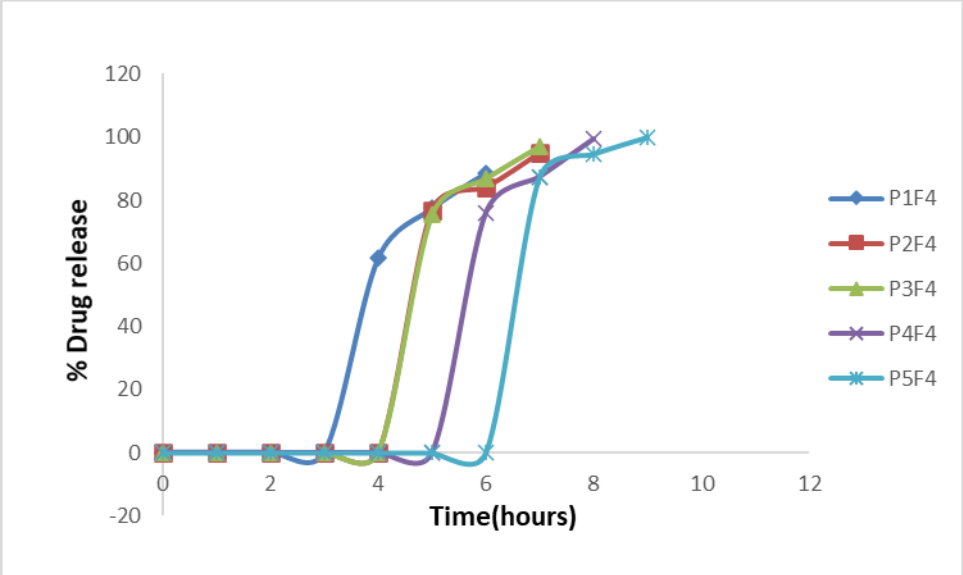


Figure 7.10 Dissolution plots for formulations P1F4 to P5F4

Discussion:

All the 5 formulations of Ramipril pulsincaps were subjected to dissolution studies. Formulations P1F4, P2F4, P3F4, P4F4, P5F4, contain the hydrogel plug with alone and combination of hydrophobic polymer and Hydrophilic polymer i.e., Ethyl cellulose: HPMC in the ratio of 1:1, 1:2 and 2:1 of total 100 mg weight of the plug. It was observed that a proper lag time of 6 hours was maintained with minimal upper GIT drug release for the combination of Ethyl cellulose and HPMC K15M hydrogel plug in the 2:1. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the formulation occurred after lag time. So basing on these observations, of all the 5 pulsincap formulations, P5F4 formulation containing hydrogel plug of ethyl cellulose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation.

RELEASE KINETICS:

Dissolution data was fitted in Zero order, First order, Higuchi's and koresmayer peppas equations. The regression coefficient "R" values for zero order, first order, higuchi's and peppas for formulation P5F4 was found to be 0.966, 0.835, 0.982, and 0.606 respectively.

The 'n' value is 1.302 for the optimised formulation P5F4 i.e., n value was >0.89 this indicates Super case II transport.

ZERO ORDER:

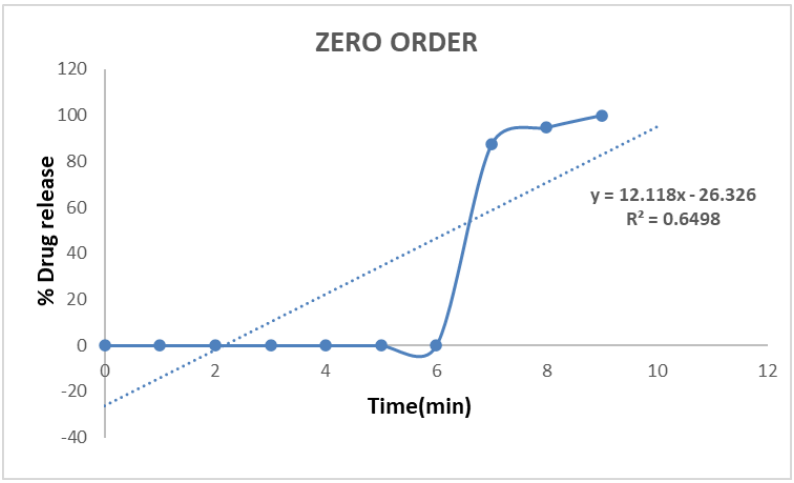


Figure 7.11 Zero order plot for optimized formulation P5F4

FIRST ORDER:

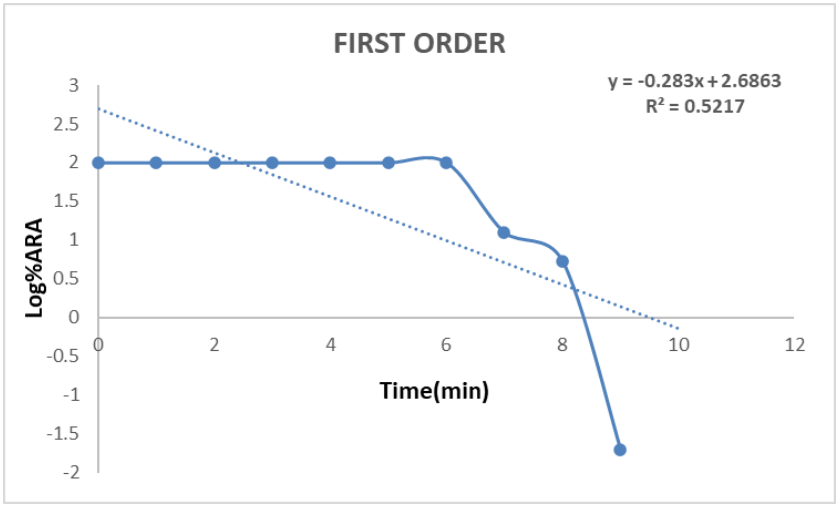


Figure 7.12 First order plot for optimized formulation P5F4

HIGUCHI PLOT:

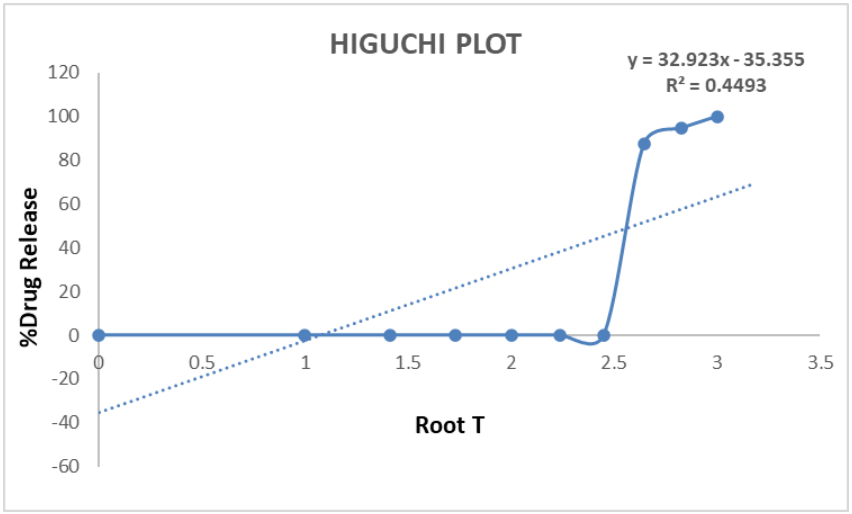


Figure 7.13 Higuchi's order plot for optimized formulation P5F4

PEPPAS PLOT:

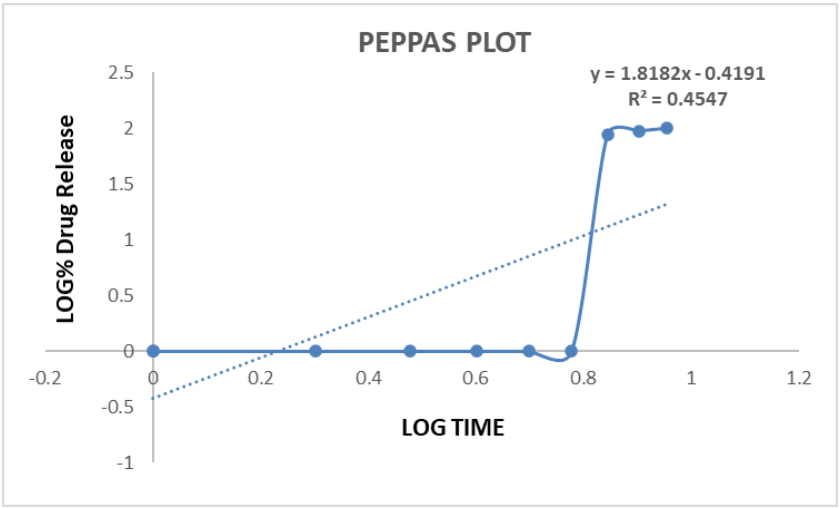


Figure 7.14 Koresmayer peppas order plot for optimized formulation P5F4

Table 7.9 Correlation coefficient "R" values of P5F4 optimized formulation

Models	R values
Zero order	0.649
First order	0.521
Higuchi	0.449
Koresmayer peppas	0.454
Peppas "n"	1.818

Discussion:

To analyze the mechanism of drug release from optimized P5F4 pulsincap formulation, data obtained from the drug release studies was subjected to different kinetic treatments. The correlation coefficient (R^2) was used as indicator of the best fitting for each of the models considered. The drug release kinetics for the optimized formulation P5F4 followed the zero order kinetics and follows super case II transport mechanism

SUMMARY:

The ability of a pharmaceutical treatment intended for oral administration to treat a condition depends on how well it is absorbed by the digestive system. It is generally known that the rate-limiting stage in the gastro intestinal absorption of a medicine from a solid dose form is frequently disintegration. Pharmaceuticals that are poorly soluble have been shown to be unpredictable and slow to be absorbed when compared to drugs that are more soluble. As a result, these medications pose significant obstacles to the creation of bioavailable dosage forms. Therefore, it is necessary to enhance the water solubility, rate of dissolution, and bioavailability of these drugs from their oral solid dosage forms. To improve the dissolving properties and bioavailability of medications that are only weakly water-soluble, mannitol and cross-povidone have been used as a solid dispersion method. This work has demonstrated how a solid dispersion method can considerably improve the Ivacaftor 's capacity to dissolve. Ivacaftor is cystic fibrosis transmembrane conductance regulator (CFTR). Following an EU-wide review of Ivacaftor, its use has been restricted in order to minimise the risks of cystic fibrosis. Therefore, an effective formulation that can increase the solubility and dissolution rate of this model medicine may be useful. In order to increase the solubility and, consequently, the dissolving rate, efficiency, and bioavailability of the weakly soluble medication Ivacaftor , investigations were conducted using the solid-dispersion technique using mannitol, Crospovidone, and SSG. The introduction section provided a succinct explanation of solid dispersions. In addition, in the chapter's introduction, numerous methods for improving solubility, particularly solid dispersion technology, were covered. The aim and objective was also discussed. Ivacaftor 's entire pharmacological profile and excipient profiles included information on their use, contraindications, and side effects. literature review of prior preparation and research on solid dispersions using a variety of medications and techniques. In-depth explanations of the methodology, materials used, and experimental techniques used in this study were provided. It was further taught how to make physical mixes and solid Ivacaftor dispersions via solvent evaporation and how all of the assessment parameters work. Ivacaftor solid dispersions were created using several carriers in varying drug and carrier ratios (1:1, 1:2 and1:3). Results of Ivacaftor solid dispersions made using the solvent evaporation method, including solubility, melting point estimation, drug content homogeneity, entrapment efficiency, and in vitro dissolution experiments, were discussed. Numerous analytical methods, including FT-IR studies, were used for solid-state characterization. The formulation **(F6)** combining Ivacaftor + Crospovidone (1:3) showed better results by solvent evaporation

method at the end of 60 min with drug release of 99.48%, hence it was chosen as the best formulation after comparing all the formulations (F1-F9).

CONCLUSION:

Over the past two decades there has been a growing appreciation on the importance of circadian rhythms on GIT physiology and on disease states, together with the realization of the significance of the drug administration on resultant pharmacodynamic and pharmacokinetics parameters. The significance of these day-night variations has not been over looked from the drug delivery perspective and pharmaceutical scientists have displayed considerable ingenuity in development of time delayed drug delivery systems to address emerging Chronotherapeutic formulations. Pulsincap technique helps us to deliver the drug at colon which helps to treat chronotherapeutic. The colon is a site where both the local and systemic delivery of drugs can take place; treatment could be more effective if it were possible for drugs to be targeted directly on the colon. In the present study, attempt was made to target the drug to the colon and intentionally delaying the drug absorption from the therapeutic point of view in the treatment of mild to moderate pain. Prior to formulation, Preformulation studies were carried out in order to establish compatibility between Ramipril and excipients by FTIR spectroscopy. The results revealed that the drug and polymers were satisfactorily compatible, without any significant changes in the chemical nature of Ramipril. The capsule bodies were made insoluble by formaldehyde treatment by exposing at various time intervals viz., 2, 4, 6, 8, 10hrs and then optimized by using disintegration studies and finally the optimized treated capsule bodies were then subjected to various physical and chemical tests such as identification attributes, visual defects, dimensional studies and qualitative test for free formaldehyde. Total 8 formulation was formulated using super disintegrant in different ratios by direct compression method. The formulations were subjected to flow properties and FTIR study. Based on the results obtained F4 containing 8% Ludiflash was considered as the optimum powder blend for fabrication of pulsincap capsule. Different concentration of the polymers like HPMC K4M, ethyl cellulose alone and in combination were used for the preparation of hydrogel plug to maintain the suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. The powder blend F4 was filled into the 6th hr formaldehyde treated capsule bodies and plugged with hydrogel polymers, 100mg hydrogel plug. The ratios of hydrophobic polymer like ethyl cellulose and HPMC K4M were taken in alone and 1:1, 1:2 and 2:1. Finally after arranging the plug, the joint of the capsule body and cap was sealed with a small amount of 1% ethyl cellulose ethanolic solution. The prepared pulsincaps were evaluated for Invitro studies. All the 5 formulations of Ramipril pulsincaps were subjected to dissolution studies. Formulations P1F4, P2F4, P3F4, P4F4, P5F4,contain the hydrogel plug with alone and in combination of hydrophobic polymer and Hydrophilic polymer i.e., Ethyl cellulose: HPMC in the ratio of 1:1, 1:2 & 2:1 of total 100 mg weight of the plug. It was observed that a proper lag time of 6 hours was maintained with minimal upper GIT drug release for the combination of Ethyl cellulose and HPMC K15M hydrogel plug in the 2:1. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the formulation occurred after lag time. So basing on these observations, of all the 5 pulsincap formulations, P5F4 formulation containing hydrogel plug of ethyl cellulose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation.

CONCLUSION:

The aim of this study was to explore the feasibility of time specific pulsatile drug delivery system of Ramipril to treat blood clot, and to lower the risk of stroke, heart attack. From the results obtained from executed experiments it can be concluded that: The Preformulation studies like pH, solubility and UV-analysis of Ramipril were compiling with BP standards. The FTIR Spectra revealed that, there was no interaction between polymer and drug. The solubility studies of empty gelatin capsule bodies, which were cross linked with formaldehyde treatment, revealed that they are intact for 24 hrs, and hence suitable for colon targeting. The polymers like HPMC K15M, and Ethyl cellulose can be used as hydrogel plugs to delay the release of Ramipril. The result of micromeritic properties showed good flow property of the powder blend indicating uniform distribution of drug within the various batches of capsule with negligible loss during the formulation stage. In conclusion, this system can be considered as one of the promising formulation technique for preparing time specific drug delivery systems and in Chronotherapeutic management. From the preliminary trials it was

concluded that it is possible to formulate the pulsatile drug delivery system by the design of time modified chronopharmaceutical formulation.

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