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FORMULATION AND *IN VITRO* EVALUATION OF DRY COATED FLOATING PULSATILE DRUG DELIVERY SYSYTEM OF ENALAPRIL MALEATE

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ABSTRACT: This research work deals with the development and evaluation of a floating pulsatile drug delivery system used in the treatment of hypertension intended as chronopharmacotherapy. Serious cardiovascular complications have been seen in majority of individuals with early morning-surge in blood pressure. The floating- pulsatile concept can help to deliver the drug at definite place and time when symptoms of disease are more critical. The system consisted of three different parts, a core tablet, containing the active ingredient, an erodible outer shell and a top cover buoyant layer. The dry coated tablet consists in a drug-containing core, coated by a hydrophilic erodible polymer (HPMC E50 and lactose) which is responsible for a lag phase in the onset of pulsatile release. The buoyant layer, prepared with Methocel E50, Carbopol 934P and sodium bicarbonate, provides buoyancy to increase the retention of the oral dosage form in the stomach applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. The developed formulations were evaluated for their buoyancy, *in vitro* dissolution and various other formulation factors. Results reveal that coating composition affects the lag time. Formulation containing Lactose as filler with 6.67% Crospovidone and coating composition using 30% lactose provide lag time of 4 h with 93.03% drug release in 6 h that shown a sigmoidal release pattern. These values were close to desired objective of producing lag time 4-5 h followed by fast drug release. Quantity and composition of the buoyant layer controls Floating time.

INTRODUCTION: Chronopharmacotherapy, the drug regime based on circadian rhythm, is recently gaining more attention worldwide [1]. Pulsatile drug delivery system has great importance not just for the treatment of disease that are influenced by the circadian rhythm of the body, but also for the potential it holds to prevent the down regulation of drug receptors and to achieve efficient therapeutic effects. Many systems in the human body such as cardiovascular, pulmonary, hepatic and renal systems show variation in their function throughout a typical day.

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They are naturally synchronized by the internal body clocks and are controlled by the sleep wake cycle. Each bodily system exhibits a peak time of functionality that is in accordance with these rhythmical cycles. Similarly, disease states affect the function of some of these systems in the body and therefore, they too exhibit a peak time of activity within a circadian rhythm [3].

A pulsatile drug delivery system is one that delivers the drug in rapid and transient manner within a short period of time. The rationale for use of proposed system is to deliver drug at a time when disease condition is in the most morbid and mortal state during 24 hours. Particular rhythm in onset and extent of systems were observed in diseases such as, bronchial asthma, rheumatic disease, ulcer, cancer, diabetes, attention deficit syndrome,

hypercholesterolemia, neurological disorder, angina pectoris, myocardial infarction and hypertension [4]. Results of several epidemiological studies demonstrate the elevated risk of different pathologies during a 24-hour cycle. Specifically, symptoms of rheumatoid arthritis and osteoarthritis, dyspnoea and epilepsy appear to have a peak during the night or early in the morning. Ischemic heart diseases, such as angina pectoris and myocardial infarction, are manifested more frequently during these times [5]. Blood pressure which arises notably just before waking up is usually responsible for these attacks.

In cardiovascular diseases the focus is to optimally deliver the antihypertensive or antianginal drug in higher amounts in early morning and lower amount at night. Holter monitoring of the electrical properties of heart has revealed 24 hour variation in the occurrence of ventricular premature beats with the peak in events in diurnally active person, between 6 a.m. and noon. The main sources of such a time dependency in cardiovascular philology and pathophysiology are the external interfering stimuli primarily physical and mental activity or stress, sleep-wake cycle and the endogenous rhythmicity [5]. Drugs that are capable of reducing the morning increase in norepinephrine and angiotensin II, have more cardio protective effect and a better blood pressure lowering effect [6].

Day-night pattern have been documented for BP, Arrhythmias, angina, myocardial infarction and stroke among other cardiovascular maladies. Risk of ischemic events is highest during the first few hours of the daily activity span and lowest during sleep [7].

The rennin- angiotensin –aldosterone system is activated in morning. Hence blood pressure rises rapidly in morning, the so called 'morning-surge' and that rise is associated with increased risk of cardiovascular events such as stroke and myocardial infarction [8].

Enalapril Maleate is an angiotensin- converting-enzyme (ACE) inhibitor has been reported one of the first choice of drug in all grades of essential as well as endovascular hypertension [9]. It has been effective for preventing the time-related occurrence of ischemia. However, for such cases, conventional drug delivery systems are inappropriate for the delivery of Enalapril maleate, as they cannot be administered just before the symptoms are worsened, because during this time the patients are asleep [1].

To follow this principle one must have to design the dosage form so that it can be given at the convenient time for example bed time for the above mentioned diseases with the drug release in the morning. Using current release technology, it is possible for many drugs by oral delivery through pulsed or pulsatile release, which is defined as the rapid and transient release of a certain amount of drugs within a short time-period immediately after a predetermined off-release period [10-11].

Chronotherapeutical devices based on osmotic pumps have been developed by Ma Gruder *et* al.[12] and Cutler et al.[13] A Pulsincap system[14] corresponds to a more sophisticated approach while it is composed by a capsule with an insoluble body and a hydrogel plug. Multiphasic drug release was achieved by using a three layer 18 tablet while similar devices were also developed and evaluated in a later stage [15, 16]. Time controlled coating systems were also developed by Ueda *et* al.[18] and Narisawa *et* al.[19] including single and multiple-unit dosage forms.

The disadvantage of these pulsatile release formulations is that they require a long residence time in the gastrointestinal track. With conventional pulsatile release dosage forms, the highly variable nature of gastric emptying process can result in in-vivo variability and bioavailability problems. The advantages for gastro-retentive pulsatile dosage forms are also pH dependent drug solubility or better drug bioavailability in stomach (e.g. Enalapril Maleate), when compared with lower parts of GIT. [1] Overall, these considerations led to the development of oral pulsatile release dosage forms possessing gastric retention capabilities.

Low density multiparticulate systems for floating–pulsatile release were developed by Sharma *et* al.[20] and Badve *et* al.[21] A pulsatile release formulation with the mucoadhesive properties was developed

by Karavas *et* al.[22] However, at the present time little is known about the *In- vivo* performances of the floating–pulsatile release system. Anuradha KS *et al;* prepared and evaluated a floating pulsatile drug delivery system of Metoprolol Tartrate. [23] Gazzaniga A *et al;* studied different grades of HPMC, results pointed out the robustness of Methocel E50-based systems with regard to values encompassed in the physiological range for gastrointestinal fluids [24].

Objective of this work was to develop and evaluate a pulsatile–floating drug delivery system.
The system consists of three different parts, a core tablet, containing the active ingredient, an
Erodible outer shell and a top cover buoyant layer (**Fig. 1**).

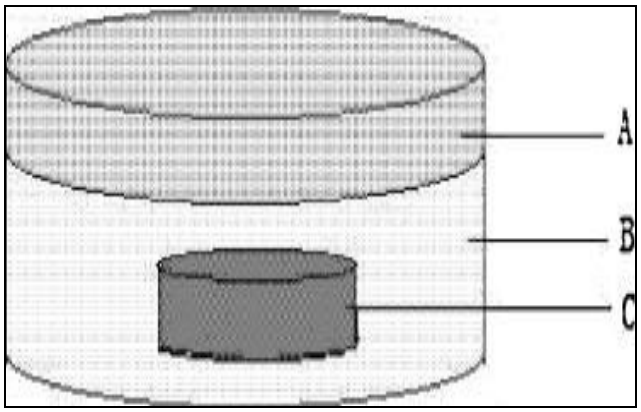

FIG.1: SCHEMATIC DIAGRAM OF FLOATING–PULSATILE RELEASE (FPRT) DRUG DELIVERY SYSTEM.

A: THE LAYER FOR BUOYANCY; B: THE LAYER FOR DRUG PULSATILE RELEASE; C: THE RAPID-RELEASE CORE TABLET.

One layer is for buoyancy and the other for drug pulsatile release. The pulsatile release system with various lag times was prepared by compression with different compostion ratio of erodible coating (press-coated systems) as described previously. [25–27]

Combined usage of Hydroxypropyl methylcellulose (HPMC) and carbomer in a gastric floating or mucoadhesive drug delivery system has been reported to improve the floating properties or mucoadhesiveness of the combined system [28, 29]. Ideally, the novel system could result in a floating dosage form with a prolonged gastric residence time and in a pulsatile dosage form, in which the drug is released rapidly in a time controlled fashion after rupturing of the coating [2].

MATERIAL AND METHODS:

Enalapril Maleate was obtained as a gift sample from Khandelwal Pharmaceutical Ltd., Rudrapur, India. Microcrystalline cellulose PH 101 (MCC) and Crospovidone was obtained as a gift sample from USV Ltd., Baddi, India. Hydroxypropyl methylcellulose E50 L.V. Premium (HPMC E50) and Carbopol 934 was obtained from Loba Chemie Pvt. Ltd., India. Talc was obtained from Central Drug House, India, while rests of the materials were obtained from Loba Chemie Pvt. Ltd., India. Methanol (Ranbaxy Fine chemical Ltd., India) and hydrochloric acid Pure (Loba Chemie Pvt. Ltd., India) were used of analytical grade.

Preparation of rapid release core tablet (RRCT):

Two types of core tablets of Enalapril Maleate (10 mg) were prepared one containing MCC as core filler while other having lactose, for determining the burst effect of filler after coating. These core tablets were prepared with different concentration of Crospovidone (3.33% – 6.67%) to get optimized formulation designated as RR1-RR6. These formulations were containing 1.67% talc as a glidant.

RRCTs were prepared by direct compression method. All the ingredients were passed through 60# mesh sieve separately and collected. The ingredients were weighed and mixed in a geometrical order. A thorough mixing was done by using pestle-mortar and then again passed it through 60# sieve. The powder was compressed by using 6.8 mm size punch to get a tablet of 60 mg weight using single punch tablet machine (Cadmach, Ahmedabad).

Preparation of Pulsatile Release Tablet (PRT):

The optimized RRCT was taken as core for the preparation of PRTs. For dry coating of optimized RRCT 260mg coatings of Methocel E50 and Lactose were used with two steps: In the first 130mg coatings were filled into the die (11.8mm in diameter), followed by RRCT placed in the center of die, and slightly pressed to fix the coatings around and under the core, and then the rest of the coatings were filled and compressed. In second RRCTs were selected, one of Lactose as filler and other one of MCC as filler for comparative release

study of respective PRTs. Different ratio of Methocel E50 and Lactose were taken to optimize the rationale lag time and release pattern. The tablet hardness was about 6 kg/cm^2. [25, 26.]

TABLE 1: COMPOSITION OF DIFFERENT FORMULATION WITH THEIR CORE COMPOSITION

For.Code	HPMC E50 (mg)	Lactose(mg)	Mg.Stearate(mg)	Core Composition
PT1	258.7	-	1.3	RR3
PT2	232.7	26	1.3	RR3
PT3	206.7	52	1.3	RR3
PT4	180.7	78	1.3	RR3
PT5	154.7	104	1.3	RR3
PT6	128.7	130	1.3	RR3
PT7	258.7	-	1.3	RR6
PT8	232.7	26	1.3	RR6
PT9	206.7	52	1.3	RR6
PT10	180.7	78	1.3	RR6
PT11	154.7	104	1.3	RR6
PT12	128.7	130	1.3	RR6

Effect of Different Concentration of Crospovidone on Release Pattern:

The release profile of systems (PRTs) containing different concentration of crospovidone like 6.67%, 15% and 25% were compared. These systems were containing in core microcrystalline cellulose as core filler and the outer coating containing 30% lactose.

Preparation of Floating Pulsatile Release Tablet (FPRT):

Floating bi-layer tablets were prepared by using modified direct compression technique. The effervescent agent and excipients were mixed thoroughly with a mortar and pestle for 5 minutes and to form a homogeneous directly compressible powder for buoyant layer.

Dry coated tablet (optimized PRT) was prepared by placing 50% of pulsatile release layer in 11.8 mm die and optimized RRCT was placed on it. Further remaining quantity of pulsatile release layer was added in cavity so as to cover the RRCT and finally pre-compressed it with lower compression pressure (hardness, 3-4 kg/cm^2) by using single punch tablet machine. The weighed amount (100 mg) of floating layer powder composition was kept on pre-compressed tablet (PRT) in die, and then finally compressed it to give certain hardness (about 6±1 kg/cm^2).

TABLE 2: COMPOSITION OF BUOYANT LAYERS

S.No.	Excipients	F1	F2	F3	F4
1.	HPMC E50	60	50	40	30
2.	Carbopol 934 (mg)	30	40	50	60
3.	$NaHCO_3$ (mg)	10	10	10	10

Physicochemical Characterization of tablets:

The thickness (n=10) and hardness (n=5) of tablets were determined using Vernier Calipers and Monsato tablet hardness tester respectively. The weight variation of test tablets (n=20) was carried out as per I.P., Disintegration test (n=5) performed on Disintegration test apparatus in purified water. For content uniformity, 10 tablets crushed individually and dissolved in methanol. The drug solution was filtered. Aliquots were diluted suitably with methanol and analyzed spectrophotometrically at 210.0 nm.

Dissolution Study (Lag time optimization):

The rotating basket method (USP apparatus-I) was employed for dissolution test study. The medium was 900 ml of 0.1N HCl (pH 1.2) at 37±0.5^{0}C and the rotating speed was 100 rpm. At appropriate time intervals, 5 ml of the solution was withdrawn, filtered, and assayed by a UV Spectrophotometer at 202.1 nm, while an equal volume of fresh dissolution medium was added into the apparatus. Dissolution tests were performed in triplicate. The lag time was determined by extrapolation of the upward part of release profile to the time axis. The lag time was determined by extrapolation of the upward part of release profile to time axis [33]

Floating lag time and floating time study:

Three randomly selected tablets were put into the

individual flask containing 400 ml of 0.1N HCl solutions. Then the time in minutes for each tablets to go from bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) were measured. The sample mean and standard deviation were calculated. [26]

Stability Studies:

The accelerated stability study was carried out. The optimized formulation was subjected to stability studies for 3 months according to ICH guidelines. The samples were packed in an aluminum foil placed in a tightly closed high density polyethylene bottle and kept it at 40 ± 2^0C/75% ± 5% RH [28] After the interval of 3 months, the tablets were withdrawn and evaluated for thickness, hardness, diameter, colour, drug content, *in vitro* drug release (lag time), floating lag time and floating duration. [23, 27,28,33]

RESULTS AND DISCUSSION: In the present study, 6 formulations (RR1-RR6) of Rapid Release Core Tablet were prepared containing different amount of crospovidone (3.33-6.67%) as disintegrant along with other additives. Tablets were studied for hardness, thickness, weight variation, disintegration and dissolution. The formulation RR3 and RR6 were shown almost same disintegration time and release profile containing MCC and Lactose as filler respectively. RR3 and RR6, both formulations used 6.67% Crospovidone as a disintegrant. The thickness and hardness were observed 1.33±0.03mm, 1.43±0.04 mm and 3.1±0.2 kg/cm^2, 3.2±0.1 kg/cm^2 respectively.

The lag time was optimized by coating different coating compositions using press coating technique (PT1-PT12). *In-vitro* release pattern of final formulations were carried out to determine whether the drug release profile after lag time followed sigmoidal release pattern.

It was found that all PRT formulations showed satisfactory features in terms of thickness, diameter and hardness. In vitro drug release (lag time) study of 12 formulations showed differences in drug release pattern (lag time) as shown in (**Table 1**). Formulation PT1, PT2, PT7 and PT8 showed higher lag time because these PRT formulations formed thicker gel in gastric fluid so that burst release was not possible and drug diffused out slowly; while formulations PT6, PT11, PT12 showed lower lag time due to high amount of lactose (**Table 1).**

Formulation PT3, PT4, PT5, PT9 and PT10 showed lag time of 4 hours (~10% drug release). Formulation PT3, PT4, PT5 released 31.05%, 45.12%, 93.03% drug respectively after 4 hours. Formulation PT9 and PT10 released 41.44% and 92.07% drug after 4 hours respectively. Hence PT5 and PT10 showed higher cumulative % drug release. The study revealed that the formulations containing more than 30% lactose in coating layer composition were shown more friability (not acceptable); and shorter lag time because with increasing the amount of Lactose in HPMC, the release was being erosion controlled.

TABLE 3: EVALUATION PARAMETERS AND LAG TIME ANALYSIS OF PRTs

Form. Code	Thickness (mm) Mean± S.D.	Diameter (mm) Mean± S.D.	Hardness (Kg/cm^2) Mean± S.D.	%Friability Mean± S.D.	Lag time ($t_{10\%}$)	%Drug Release (6 hours)
PT1	2.27±0.12	11.8±0.01	6.0±0.32	0.29±0.043	7 hours	4.88
PT2	2.29±0.09	11.81±0.07	5.98±0.14	0.43±0.057	5 hours	19.46
PT3	2.31±0.011	11.8±0.0.10	5.96±0.17	0.52±0.12	4 hours	31.05
PT4	2.33±0.08	11.82±0.12	6.1±0.32	0.81±0.24	4 hours	45.12
PT5	2.35±0.13	11.8±0.05	6.04±0.12	1.21±0.28	4 hours	93.03
PT6	2.36±0.10	11.8±0.14	6.18±0.23	1.46±0.16	3 hours	101
PT7	2.28±0.14	11.83±0.15	5.94±0.50	0.24±0.010	6 hours	11.44
PT8	2.31±0.10	11.84±0.07	6.2±0.34	0.39±0.08	5 hours	21.78
PT9	2.33±0.12	11.8±0.14	6.0±0.21	0.57±0.15	4 hours	41.44
PT10	2.34±±0.09	11.83±0.09	6.08±0.53	0.86±0.23	4 hours	92.07
PT11	2.36±0.9	11.8±0.04	6.15±0.15	1.13±0.32	3 hours	100
PT12	2.37±0.18	11.82±0.13	6.2±0.46	1.54±0.29	2.5 hours	100

After 5 hours PT4 was not showed satisfactory burst release, while formulation PT5 and PT10 shown sigmoidal release pattern which almost superimposed to each other. Hence PT5 and PT10 showed the satisfactory release pattern.

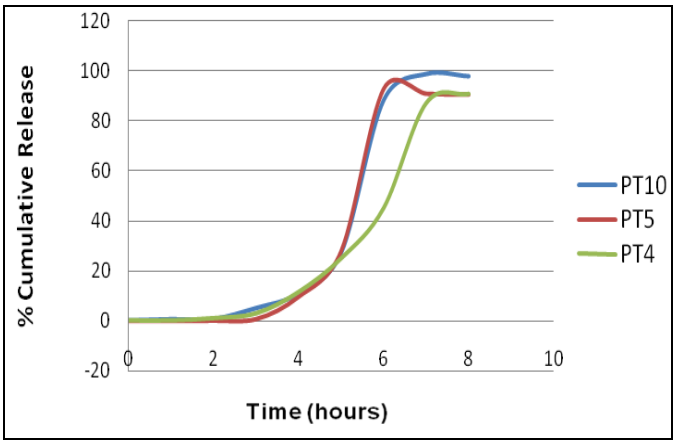

FIG. 2: COMPARATIVE RELEASE PROFILE OF PT4, PT5 AND PT10

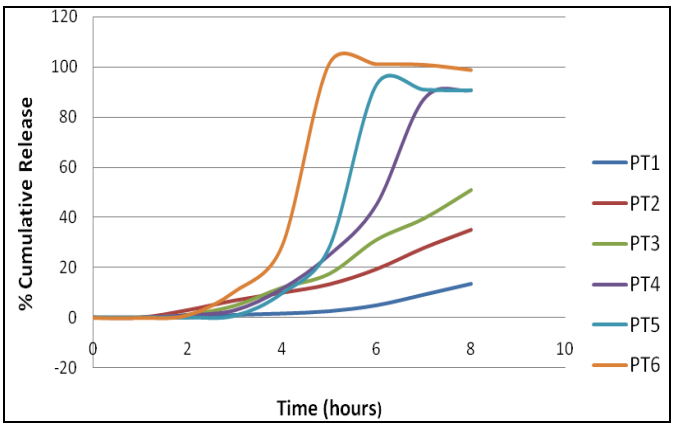

FIG. 3: RELEASE PATTERN OF PRT FORMULATIONS CONTAINING "RR3 TABLET" AS CORE

Formulation **PT5** and **PT10** were found to have same drug release pattern, containing 40% and 30% lactose in coating layer composition respectively. PT5 had core with MCC (RR3), while PT10 had core with lactose (RR6).This release pattern indicated that Lactose has more burst effect (power) as compare to MCC**,** so gave better pulsatile release.

The formulation PT5 and PT10 were shown required lag time ($t_{10\%}$) of 4 hours. During 4-5 hours almost 30% drug was released which compensate the early morning surge in blood pressure and after 5 hours rest of the Enalapril Maleate was released rapidly which after 3-4 hours got peak plasma concentration of Enalaprilat to control the working time hypertension (6 a.m.-2 p.m.).

The comparative study among formulations containing 6.67%, 15% and 25% Crospovidone (PT5, PT13 and PT14) along with MCC as core filler revealed that as well as the amount of Crospovidone increased more than 6.67%, the release being more diffusion controlled not showing burst release (**Fig.5**). So it was concluded that MCC in high amount responsible for burst release from the system, only 6.67% crospovidone was sufficient for rapid penetration of water due to its significant wicking action.

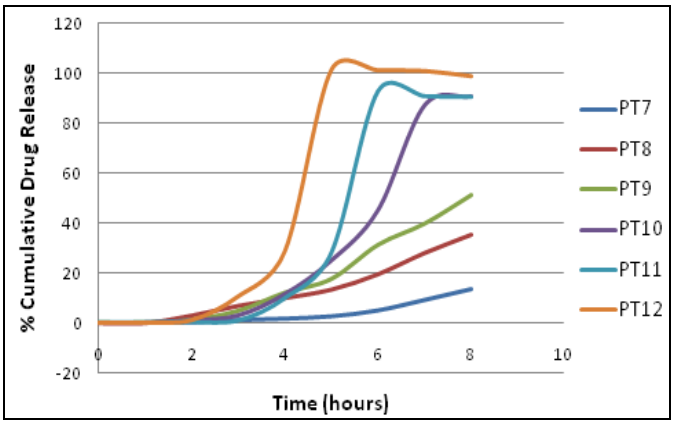

FIG. 4: RELEASE PATTERN OF PRT FORMULATIONS CONTAINING "RR6 TABLET" AS CORE

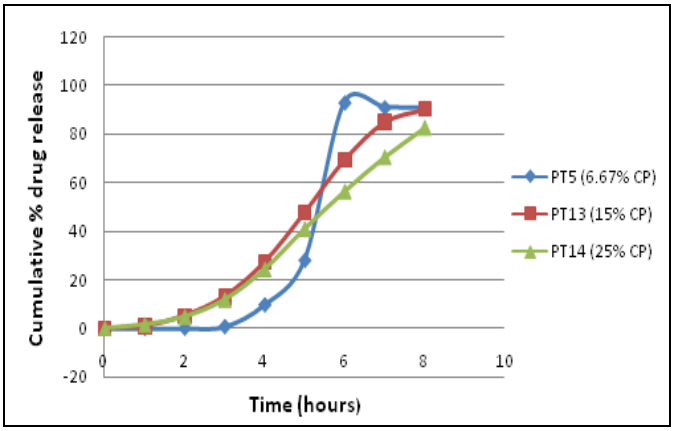

FIG. 5: COMPARATIVE DRUG RELEASE PROFILE OF PRTS CONTAINING 6.67%, 15% AND 25% CP AS CORE DISINTEGRANT.

PT10 formulation was selected as optimized formulation because it shown satisfactory features in terms of dimensions, hardness, friability, lag time and release pattern.

FPRT formulations were prepared and evaluated for thickness, hardness, friability, floating lag time

and total floating time. It was found that all formulations showed total floating time more than 8 hours. Formulations FF1 and FF2 showed % friability within the limit as specified in IP, while FF3 and FF4 was failed in % friability test because 20% and 40% tablets respectively showed detachment upper floating layers during friabilator stress. Carbopol is fluffy in nature having less adhesiveness, so in high amount may detach the layers.

All formulations showed floating lag time less than 12 minutes, while formulation **FF1** showed least floating lag time (~6 minutes). This study revealed that with increasing the concentration of Carbopol 934 in floating layer composition, floating lag time is increased because Carbopol is highly crosslinked microgel forming thicker gel in acidic medium and hydration rate is slow.

Results of Accelerated stability studies revealed that tablets did not show any change in physical appearance and dimensions during the study period. The drug content (n=5) was 99.03±0.56%. The dissolution profile, floating lag time and floating time of these tablets also did not show any significant change. This signifies that optimized formulation has stability and potency at accelerated conditions.

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