Design and Characterization of Chronotherapeutic Drug Delivery of Enalapril Tablets

K.Haritha*, Mrs.A.Lavanya, Dr.K.Umashankar , Dr.M.Kishorebabu
Department of Pharmaceutics,
Krishna Teja Pharmacy College,
Renigunta Road,Tirupati, chittoor (D.t),
Andhar Pradesh, India.

Corresponding Author:
Mrs.A.Lavanya
Asst.Proffessor
Department of Pharmaceutics,
Krishna Teja Pharmacy College,
Renigunta Road,Tirupati, chittoor (D.t),
Andhar Pradesh, India.

Abstract

Enalapril is an angiotensin-converting enzyme (ACE) inhibitor, primarily used for the treatment of hypertension, congestive heart failure, and heart attack. It belongs to BCS class III having a half-life of 12 hrs and 25% bioavailability. The purpose of the present work was to develop a press-coated, floating-pulsatile drug delivery system. The core tablet was formulated using the super-disintegrants crosprovidone and croscarmellose sodium. A press-coated tablet (barrier layer) contained the polymer carrageenan, xanthan gum, HPMC K4M, and HPMC E15LV. The buoyant layer was optimized with HPMC K100M, sodium bicarbonate, and citric acid. The tablets were evaluated for physical characteristics, floating lag time, swelling index, FTIR, DSC, and in vitro and in vivo behavior. The 5% superdisintgrant showed good results. The FTIR and DSC study predicted no chemical interactions between the drug and excipients. The formulation containing xanthan gum showed drug retaining abilities, but failed to float. The tablet containing HPMC K15M showed a high swelling index. The in vitro release profiles of Enalapril from PRT prepared using HPMC E15LV as retarding polymer are characterized by a predetermined lag time (4.1±0.2 h for K6+F4), the duration of which depends on the kind and amount of the polymeric layer applied on the cores as well as type of superdisintegrant in core tablet. The developed system offers a simple and novel technique for pulse release of drugs. From the results it is concluded that the PRT we prepared could achieve a rapid release after lag time of 4±0.2h with the relatively low variability. The release mechanism of the tablet followed the Korsmeyer-Peppas equation and a first-order release pattern.

Keywords: Floating, Press-coated, HPMC K100M, HPMC E15LV, Pulsatile, Delivery

INTRODUCTION

Oral drug delivery systems are most popular, safe and convenient for the obvious merits of oral route of drug administration. In all the oral controlled dosage forms drug concentration is maintained in the therapeutic window so that it releases the drug for a prolonged period of time. But certain conditions that requires drug release after a lag time i.e., chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology [1]. several diseases show variation in circadian rhythm. Circadian i.e., 24 hrs time structure is the most common oscillation met in a number of diseases suchas asthma and osteo arthritis where the severity of diseases and symptoms are mostly happening at night, in case of rheumatoid arthritis pain is very severe at the morning, in duodenal ulcer gastric acid secretion is high at night times [2]. Capillary resistance and vascular reactivity are higher in the morning and decrease in the evening times [3,4]. For such chrono pathological conditions chronotherapeutic systems plays significant role, because these formulations release the drug whenever the symptoms are high. Such systems are designed to enable a pulsatile release of drug after a predetermined off release period i.e., lag time which controls the chronopathological conditions [5]. The present investigation is focused on development and evaluation of pulsatile tablets of enalpril an anti hypertensive agent. Pulsatile tablets releases certain amount of drug molecules with in a shorter duration spontaneously after

predetermined lag period [5]. Enalapril is an anti hypertensive agent which is used to treat hypertension and it's an ACE (angiotensin converting enzyme) inhibitor. Enalapril lowers the hypertension/ blood pressure by reducing peripheral vascular resistance without increasing heart rate, contractility and cardiac output. Many types of hypertension in patients suffering from diabetes and severe kidney failures can be easily treated with enalapril. It is best suitable drug for the treatment of heart failure. The bioavailability is 55% and its half life is 11 hrs; the absorption of enalapril will not be affected by taking food [6]. The concept of present investigation is aimed to develop and evaluate enalapril core in cup tablets by direct compression method which delivers the drug by chronotherapeutic approach.

Materials

Enalapril active pharmaceutical ingredient was a gift sample from Cipla pharmaceutical company, Mumbai. PVP K90, talc, HPMC K4M, cross povidone, cross carmellose sodium, sodium starch glycolate, ethyl cellulose, MCC were procured from S.D. Fine chemicals. Mumbai. Magnesium stearate was obtained from Sigma Aldrich Company. Galen IQ 720 was used as directly compressible vehicle and it was obtained from Beneo palatinit industry, Germany. All other reagents used were of analytical grade throughout the study.

Preparation of the Rapid Release Tablet (RRT) [11]

The inner core tablets were prepared by using direct compression method. Different preliminary batches of core tablets were taken in to fix concentration of superdisintegrant in tablet. Concentration of super disintegrants varies from 1 to 4 mg/tablet. Powder mixtures of Enalapril, crosscarmellose sodium (Ac-Di-Sol), KYRON T314, lactose and ingredients were dry blended for 20 min. followed by addition of magnesium stearate. The mixtures were then further blended for 10 min, 60 mg of resultant powder blend (theoretically equivalent to 20 mg of Enalapril) was compressed using rotary tabletting machine (Cadmach Machinery, Ahmedabad, India)with a 6mm punch and die to obtain the core tablet.

Table1 : Formulations of core tablet

Ingredients(mg)	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**
Enalapril (mg)	20	20	20	20	20	20	20	20
CCS(mg)	1	2	3	4	-	-	-	-
KYRON T 314(mg)	-	-	-	-	1	2	3	4
Mg-Stearate(mg)	8	8	8	8	8	8	8	8
Lactose(mg)	31	30	29	28	31	30	29	28
TOTAL (mg)	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**

Evaluation of the Rapid Release Tablet (RRT)Determination of Drug Content

Total 10 tablet were weighed and powder equivalent to 25 mg of Enalapril wasweighed and dissolved in methanol then filtered through Whatman filter paper. Solution was analysed for content by UV-Spectrophotometer at 236 nm using methanol as blank.

Disintegration test

The tablet was put into 100 ml distilled water at 37 ± 2oC. Time required forcomplete dispersion of a tablet was measured with the help of a digital tabletdisintegration test apparatus.

Hardness test

Pfizer hardness tester was used for the determination of hardness of tablets. The tablet was placed in contact between the plungers and handle was pressed. The forceof fractured was recorded.

Friability test

The friability of all the tablets studied was determined using a Roche friabilator. In the disinteration time study,
From above study two batches II and VI were selected as optimized batches.

Preparation of the Floating and Pulsatile Release Tablet (FPRT) [11]

FPRT was designed to comprise PRT and top cover buoyant layer. PRT was taken as the layer for pulsatile release.

Preparation of the Pulsatile Release Tablet (PRT)

Each powder used as erodible outer shell i.e. HPMC K4, HPMC E15 LV, carboxy methylcellulose sodium (NaCMC) was passed through a 500µm. RRT was taken as core. Studies were carried out on different combination of polymers, which were considered as preliminary batches. Dissolution study was carried out for above batches and by observing result it was necessary to carry out experiment on individualpolymers.

Table 2 : Addition of polymer for pulsatile release tablet containing crosscarmellose sodium

Sr No.	**Ingredients**	**Formulation Codes**								
		C1	C2	C3	C4	C5	C6	C7	C8	C9
1	HPMC K4 M	140	160	180	-	-	-	-	-	-
2	NaCMC	-	-	-	140	160	180	-	-	-
3	HPMCE15 LV	-	-	-	-	-	-	230	260	290

Table 3 : Addition of polymer for pulsatile release tabletcontaining KYRON T314

	Ingredients	**Formulation Codes**					
		K1	K2	K3	K4	K5	K6
1	HPMC K4 M	140	160	180	-	-	-

For HPMC K4, 60 mg of powder was filled in a die followed by RRT in the center of die. Slightly pressed the tablet to fix the coatings around and under the core, then the rest of the coatings was filled and compressed. Same procedure was appliedto rest of the powders i.e. for HPMC E15LV and NaCMC. For the above batches dissolution study was conducted from which optimized batches were selected and only that batches were conducted for further study.

Compositions of the Buoyant Layers

The compositions of the buoyant layer of the FPRT for floating testing were shown in Table 6.8. All powdered excipients were mixed for 5 min using a mortar andpestle to form a homogenous directly compressible powder mix. Different fillers were used to adjust the tablet weight and effect of fillers on floating time was observed.
For the preparation of FPRT tablet, batch K3 and K6 were used in compression with buoyant layer.

Table 4: Compositions of the Buoyant Layers

Sr No.	Ingredients	Formulation codes				
		F1	**F2**	**F3**	**F4**	**F5**
1	HPMC K 100M	150	150	150	150	150
2	Sodium bicarbonate	20	40	80	40	20
3	Citric acid	20	40	80	40	20
4	Dicalcium phosphate	20	-	-	-	-
5	Microcrystalline cellulose	-	20	-	-	-
6	Lactose	-	-	20	20	20

EVALUATION OF FLOATING AND PULSATILE RELEASE TABLET [47-48]

Physical evaluationFriability test

The friability of all the tablets studied was determined using a Roche friabilator.

Hardness test:

Pfizer hardness tester was used for the determination of hardness of tablets.The tablet was placed in contact between the plungers and handle was pressed.The forceof fractured was recorded.

Determination of Drug Content:

Total 10 tablet were weighed and powder equivalent to 20 mg of Enalapril was weighed and dissolved in methanol then filtered through Whatman filter paper. Solution was analysed for Enalapril content by UV Spectrophotometer at 236 nm using methanol as blank

In Vitro Buoyancy Determination [11]

Floating behavior of the tablet is determined by using USP dissolution apparatus II in 500 ml of 0.1 N HCl which is maintained at 37±0.5°C, rotated at 50 rpm. The floating lag time as well as total floating time is observed.

Swelling Index determination

Tablets were weighed individually (designated as W1) and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C±1°C. At regular 1-h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then re-weighed (W2) and swelling index (SI) was calculated using the following formula:

$$SI = \frac{W2-W1}{W1} \times 100 \quad (6.1)$$

DISSOLUTION STUDIES [11]

Parameters

A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 15 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µ membrane filter and diluted to a suitable
concentration with 0.1N HCl. Absorbance of these solutions was measured at 236 nm using Varian cary-100 double beam UV spectroscopy. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

CHARACTERIZATION AND PREPARATION OF CALIBRATION

CURVE OF Enalapril

Determination of λ max and preparation of standard curve

The UV spectrum obtained is shown in Fig.7.1**.** The wavelength of maximum absorbance (λ max.) was found to be at 236 nm for 0.1 N HCl (Simulated gastric Fluid) solutions. Using absorbance-concentration data; calibration curve was plotted and is shown in Fig. 7.2. The plot of Absorbance v/s Concentration (µg/ml) was foundto be linear in the concentration range of 0 to 50 µg/ml and obeys the Beer-Lambert's law in the same ranges.

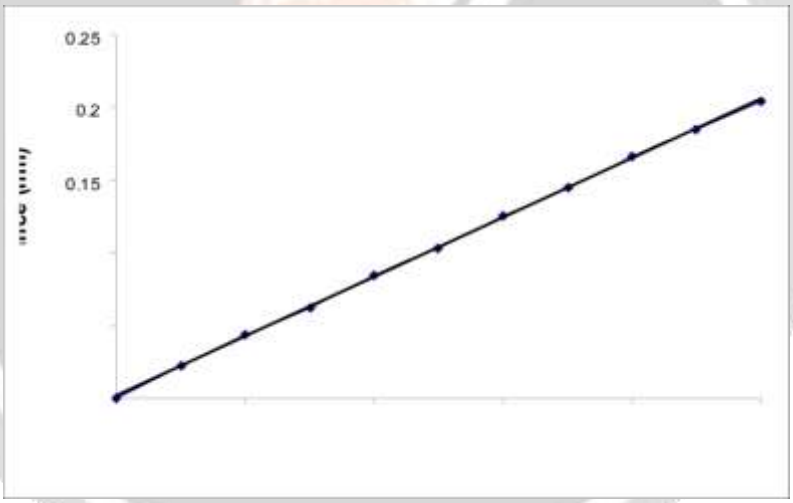

Fig. 1 : Calibration Curve of Enalapril

Physicochemical parameters of the A.P.I.

Physical characterization of candidate drug

Table No.5: Physical properties of candidate drug

Bulk density (g/ml)	0.235
Tapped density (g/ml)	0.423
Carr's index (%)	44.44

Compatibility Study by DSC DSC analysis of pure Enalapril

The drug showed sharp endotherm at 172.41^{o}C with starting at 172.14^{o}C. The reported value is 172.5^{o}C. The DSC thermo gram is presented in Figure No.7.4

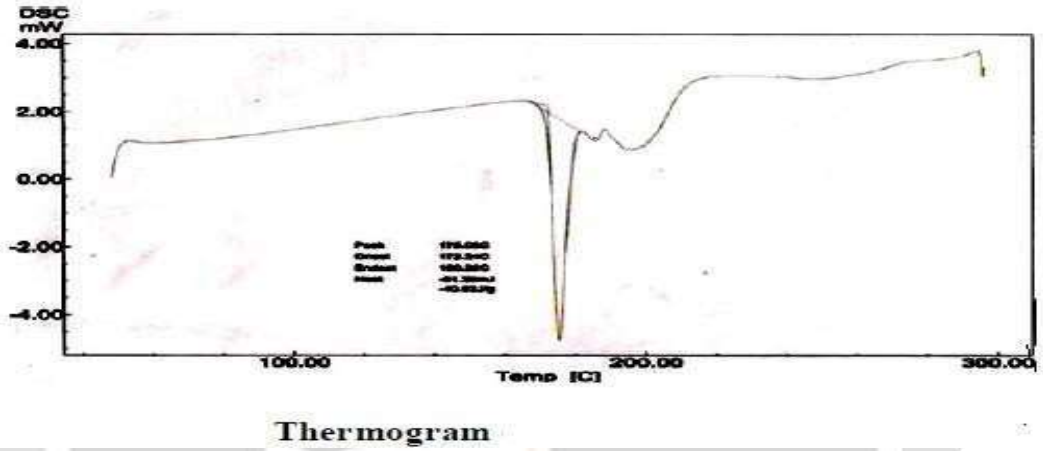

Figure 2 No.: DSC analysis of Enalapril

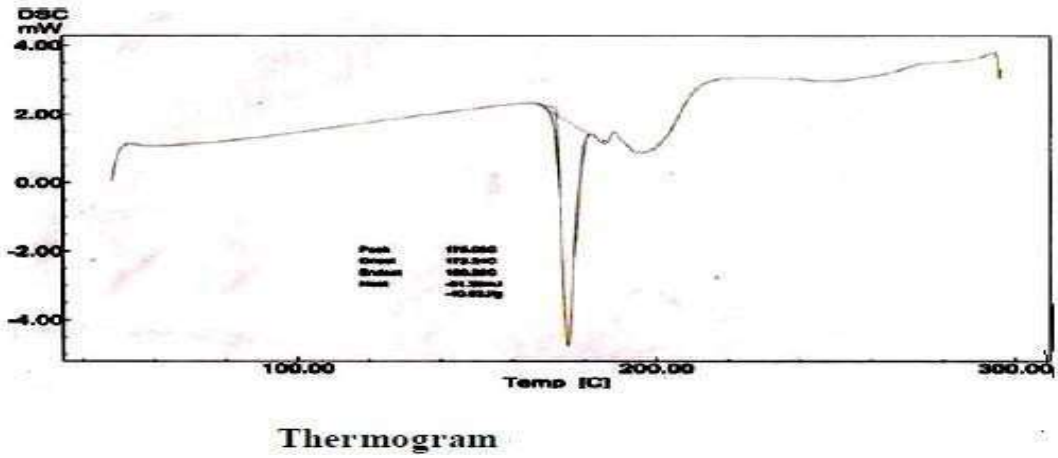

Figure 3.The thermo gram obtained By The D.S.C technology withEnalapril and Microcrystaline cellulose

No significant change is observed in melting point

EVALUATION OF RAPID RELEASE TABLET (RRT)

Table 6 : Evaluation of RRT

Formulation	Hardness Kg/cm^2	Friability (%)	Drug Content (mg%)	Disintegration Time(S)
I	3.8	0.62±0.12	99.22	45
II	3.4	0.69±0.14	98.92	11
III	3.7	0.65±0.11	99.85	30
IV	3.8	0.62±0.11	99.72	28
V	3.6	0.60±0.14	99.35	24
VI	3.2	0.67±0.13	99.97	11
VII	3.9	0.63±0.16	99.65	49
VIII	3.6	0.60±0.11	99.78	10.4

In all formulation, the hardness test indicated good mechanical strength, whereas friability is less than 1% which indicated that tablet had good mechanical resistance.Drug content was found to be high (>99.20) and uniform in all tabletformulations. It was ranged from 98.92 to 99.85 and uniform in all tablet formulations. Absorption maxima was determined by scanning different concentration of solution of drug Enalapril. Absorption maxima was 236 nm and method obeys Beer's law in concentration range 0 to 50 µg/ml, with good correlation coefficient (0.9997).When a standard drug solution was assayed repeatedly (n=6),relative error (accuracy) and relative standard deviation (precision) were foundto be 0.72 and 0.93 % respectively.

The tablets were subjected for evaluation of the in-vitro disintegration time and it was observed that the time for formulation varied from 10 to 52 second. It was observed that the time for formulation varied from 10 to 52 second. It was observed that when KYRON T314 was used as disintegrant, tablet was disintegrate within short time due to easy and high swelling ability of KYRON T314as compared to CCS. It is observed that disintegration time of tablet decreased with increased in concentration of CCS and KYRON T-314. But by disintegration study it was observed that hardness plays important role. For development of pulsatile release study disintegration time must be short to obtain burst effect therefore having less hardness. Hence by observing results it was concluded that batches II and VI were optimized batches which was confirmed by dissolution study.

Dissolution Study Of Rapid Release Tablet (RRT)

Table 7: Dissolution testing of Batch I-IV

Time(min)	% Drug Release			
	I	**II**	**III**	**IV**
0	0	0	0	0
1	48.84	49.23	53.43	54.78
2	55.67	57.87	62.49	65.98
3	63.87	66.9	69.45	70.1
4	68.93	70.92	74.82	76.9
5	77.68	79.99	82.56	83.76
6	83.56	86.79	88.93	89.92
7	88.94	90.56	92.39	93.44
8	94.69	97.84	98.7	99.45
9	98.95	98.9	99.28	
10	99.87	99.99	100.09	

Table 8 : Dissolution Testing of batch V-VIII

Time(min)	% Drug Release			
	V	VI	VII	VIII
0	0	0	0	0
1	50.26	55.9	54.87	54.37
2	54.98	69.78	62.93	60.23
3	61.03	75.98	67.4	63.45
4	68.9	83.56	76.79	78.98
5	79.97	89.91	83.59	86.73
6	84.78	93.45	89.99	90.17
7	90.83	97.99	94.98	95.68
8	95.98	100.2		99.9
9	99.58			100.09

From above two graphs it was cleared that Rapid increase in dissolution of Enalapril with increasein KYRON 314 may be attributed to rapid swelling and disintegration of tablet into primary particles. CCS exhibit capillary activity and pronounced hydration, with little tendency of gel formation and disintegrate the tablet rapidly but into larger masses of aggregated particle and laterresulting in slow release of drug.

EVALUATION OF THE FLOATING AND PULSATILE RELEASE TABLET(FPRT):

It was observed that the disintegration time for formulation varied from 10 to 52 second. It was observed that when KYRON T314 was used as disintegrant, tablet was disintegrate within short time due to easy and high swelling ability of KYRON T314 as compared to CCS. It is observed that disintegration time of tablet decreased with increased in concentration of CCS and KYRON T-314. But by disintegration study it was observed that hardness plays important role. For development of pulsatilerelease study disintegration time must be short to obtain burst effect therefore having less hardness. Hence by observing results it was concluded that batches II and VI were optimized batches which were confirmed by dissolution study.

Pulsatile Release Tablet (PRT)

For this study, the core tablets containing Enalapril (RRT) were compression coated with different powder such as HPMC K4, HPMC E15LV, sodium carboxymethylcellulose, used as outer erodible shell. Dissolution studies were carried

out on combination of polymers as well as on individual polymers. Dissolution studies resulted that batches prepared with combined polymers formed too sticky mass to release the drug when polymers came into contact with dissolution medium. From this it was resulted that combined polymers are not suitable for pulsatile drug delivery system Core tablet containing crosscarmellose sodium was compression-coated with HPMC K4, HPMC E15LV, sodium carboxymethylcellulose and these batches were taken as preliminary batches for the study of individual polymers. The in vitro release profiles of Enalapril from different-coated systems in 0.1 M HCl solution was provided in Figure 7.18,7.19, 7.20.

Fig 7.18 shows that HPMC K4M gives the lag time of 4 hours then follow thesigmoidal release pattern with 100% drug release at 10^{th} hour. As the concentration ofthe HPMC K4 coating increases from 140 to 180 mg the lag time extended to 5 hoursand then follow the delayed release profile with the 100 % drug release at the 17^{th} to 18^{th} hour From Fig 7.19, it was observed that carboxymethylcellulose sodium (NaCMC) shows the lag time of 2 hours, resulting in rapid and complete drug releaseat 10^{th} hour. But these tablet did not maintain its shape throughout dissolution processwhich might be concluded that such tablet cannot be floated for longer period of the time. Due to this reason tablet (PRT) of Carboxymethylcellulose sodium (NaCMC) was not studied further.From fig 7.20 it was observed that HPMC E15LV shows the lag time of 3 hours then follow the sigmoidal release pattern with 100% drug release at 9^{th} hour. As the concentration of the HPMC E15LV coating increases from 240 to 290 mg the lag time extended to 4.5 hours and then follow the delayed release profilewith the 100 % drug release at the 12^{th} to 14^{th} hour.From above discussion it was cleared that carboxymethylcellulose

sodium (NaCMC) cannot be used to develop a successful pulsatile drug delivery system as it cannot give sufficient lag time and is unable to maintain its shape.

Table 9 : Dissolution Testing of batch C1-C9

Time (hrs.)	**% Drug Released**								
	C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**
0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0
2	5	3	0	27.91	0	0	20	0	0
3	10.95	5.67	0	52.39	30.87	24.97	27.98	5.98	0
4	25.4	7.45	0	64.98	51.9	41.74	51.54	15.9	5.98
5	38.81	24.87	8.01	78.49	68.76	65.89	65.89	29.87	30.98
6	49.86	39.66	25.03	90.72	80.95	79.8	77.97	45.76	50.39
7	66.54	50.32	43.56	95.69	91.69	90.98	83.78	53.21	67.29
8	78.24	67.53	65.75	98.19	96.98	96.5	90.98	68.98	80.96
9	96.9	88.27	80.55	99.85	99.81	99.78	99.55	77.98	86.19
10	99.61	94.93	89.6			99.95		85.82	93.98
11		98.88	95.38			99.96		90.89	98.42
12		99.97	98.3					95.97	99.88

Other two polymers can be used to develop effective pulsatile drug delivery system. But these two polymers were giving delayed release pattern after sufficient lag time instead of giving pulsatile release pattern(complete and rapid drug release at once).This may be due to the effect of superdisintegrants (crosscarmellose sodium). Due to the insufficient swelling of crosscarmellose sodium, it could not give burst release required for complete drug release. Hence these two polymers were further studied by using KYRON T 314 as superdisintegrant in core tablet. Different batches of pulsatile release tablet of HPMC K4M and HPMC E15LV were prepared using KYRON T 314 in core tablet. Fig 7.21, 7.22 shows drug release pattern of batches K1-K6. By studying dissolution profile it was observed that batch K6(290mg) was optimized batch. As the coated tablet was placed in the aqueous medium, it was observed that the hydrophilic polymeric layer started erosion, which underwent progressive modification in terms of thickness and consistency. In the second phase of the dissolution procedure, the coating layer gradually starts to erodeup to a limiting thickness. After this stage, a rupture of the shell was observed underthe pressure applied by the swelling of the core tablet and Enalapril released. This pressure was high due to high swelling property of KYRON T314 and which resultedin burst effect along with complete and rapid drug release. In case of other batches i.e K1, K2, K4 and K5 amount of coating polymer was too less to achieve desired lagtime. Due to high swelling of inner core tablet coating of K1, K2, K4 and K5 formulations could not maintain too long and result in complete drug release within short time. All of this process corresponded to a lag time capable of exhibiting a pulsatile release of the drug. The profiles relevant to the coated tablet showed that alag phase was followed by the quickly delivery of the active principle. The delay duration clearly depended on the kind and amount of hydrophilic polymer as which was applied on the core. Invitro the lag time of the tablet coated with 290-mg HPMC E15LV was 4.1±0.2 h and given burst with 96.88% and after this the % drug release remains constant due to non maintenance of sink condition.

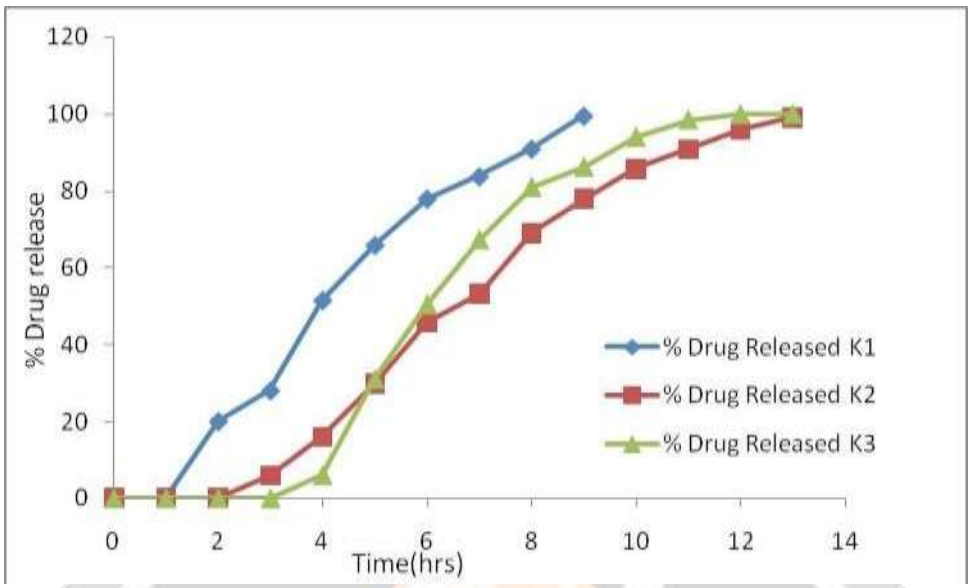

Fig 4 : In vitro release profiles of Enalapril from the pulsatile release tablet (PRT) coated with different amount of HPMC K4M+Core tablet containingKYRON T 314.

Table 10: Dissolution Testing of batch K1-K6

Time (hrs.)		**% Drug Released**				
	K1	**K2**	**K3**	**K4**	**K 5**	**K6**
0	0	0	0	0	0	0
1	0	0	0	0	0	0
2	20	0	0	15.98	3.98	0
3	27.98	5.98	0	43.78	39.98	0
4	51.54	15.9	5.98	54.89	59.79	0
5	65.89	29.87	30.98	63.79	71.98	54.98
6	77.97	45.76	50.39	76.89	80.98	74.89
7	83.78	53.21	67.29	87.99	88.93	87.89
8	90.98	68.98	80.96	95.92	94.99	94.98
9	99.55	77.98	86.19	99.89	99.99	98.99
10		85.82	93.98		100.0 9	99.98
11		90.89	98.42		99.89	100.04
12		95.97	99.88		100.0 5	99.97
13		99.2	99.96		100.03	100.06
14					99.99	100.09

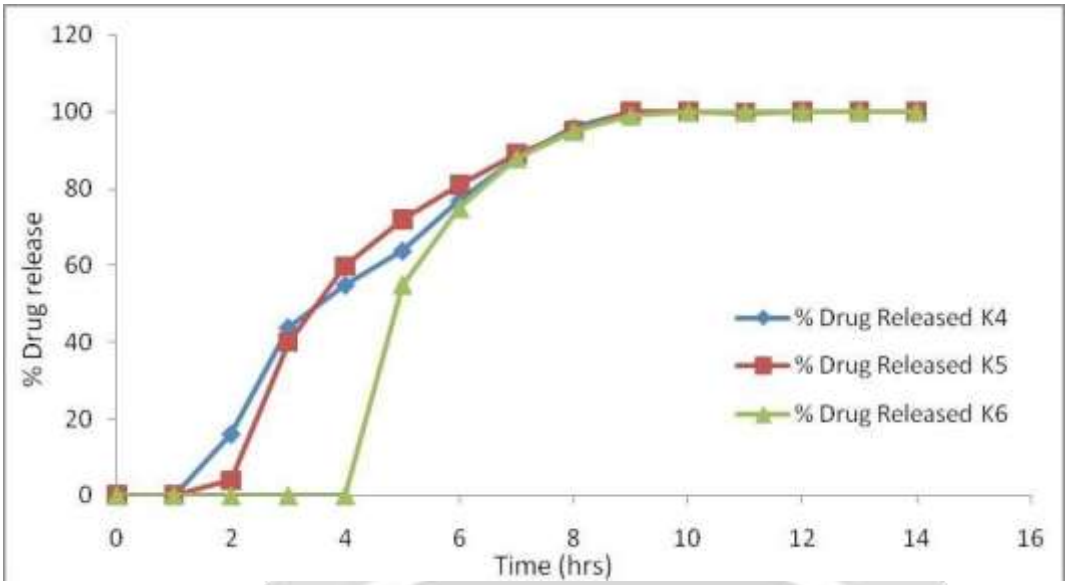

Fig 5 : In vitro release profiles of Enalapril from the pulsatile release tablet (PRT) coated with different amount of HPMC E15LV+Core tablet containing KYRON T 314

In Vitro Buoyancy Determination

Table no Onset of time for floating of various formulations

Formulation	Onset of time for floating
F1	Greater than 1 hr
F2	Formulation showed no floating
F3	Remaining floating was no more than 3 h
F4	float completely within 1 min and remained floating over a period of 12 h
F5	Greater than 15 min

Floating behavior of tablet depends on added fillers in buoyant layer. Tablets containing lactose floated earlier than tablets prepared with the inorganic filler dibasic calcium phosphate. This could be explained by the different densities, lactose containing tablet had the lowest density (1.0 g/cm^3 at a hardness of 4.3 Kg/cm^2), whereas the dibasic calcium phosphate tablet had a much higher density (1.9 g/cm^3 at a hardness of 5.2 Kg/cm^2). In addition, lactose has a higher water solubility, resulting in faster water uptake of medium into tablet. Microcrystalline cellulose, an insoluble filler with high water uptake and disintegration capability, resulted in disintegration of tablet. CO_2 did not accumulate in buoyant layer of tablet and escaped through the disintegrated tablet, floating was therefore not achieved. Based on these results, lactose was identified as the filler of choice and used for further investigation.

F4 formulation was used for further investigation.

SWELLING INDEX DETERMINATION

Tablet containing HPMC K4M showed high swelling index as compared to HPMC E15LV and NaCMC which might be due to hydration property of HPMC K4M. NaCMC showed swelling property but after some time tablet could not maintain its shape and integrity (Eq 6.1) HPMC K4M and HPMC E15LV showed constant increase in swelling index up to 10 h. (Fig 7.23)

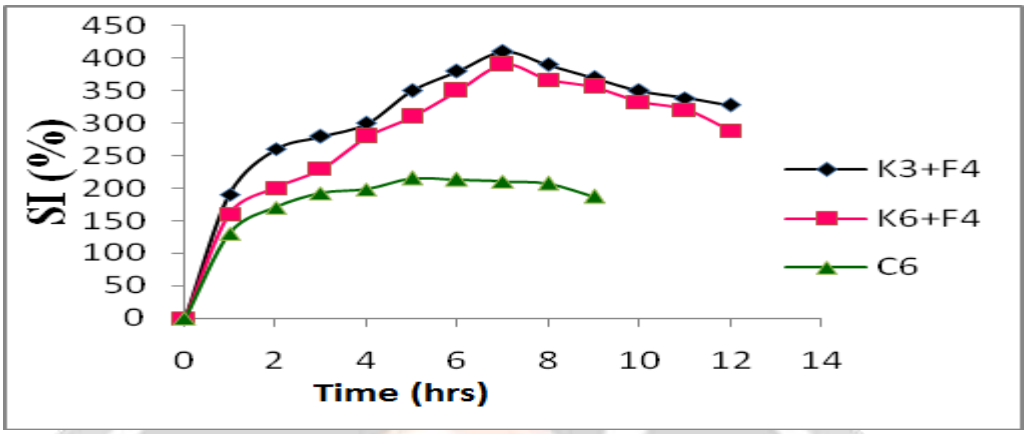

Fig 6: Swelling index of tablets of K3+F4, K6+F4 and C6

FLOATING AND PULSATILE RELEASE TABLET (FPRT)

The FPRT was manufactured as described above and consisted of the buoyant layer F4 (Table 6.8) combined with a PRT containing 20 mg Enalapril core tablet compression- coated with 290 mg of HPMC E15LV (Formulation K6).

Table 11 : Dissolution testing of batch K6+F4

Time (hrs.)	% Drug Released
0	0
1	0
2	0
3	0
4	11.09
5	54.98
6	74.89
7	87.89
8	94.98
9	98.99
10	99.98
11	100.04
12	99.97
13	100.06
14	100.09

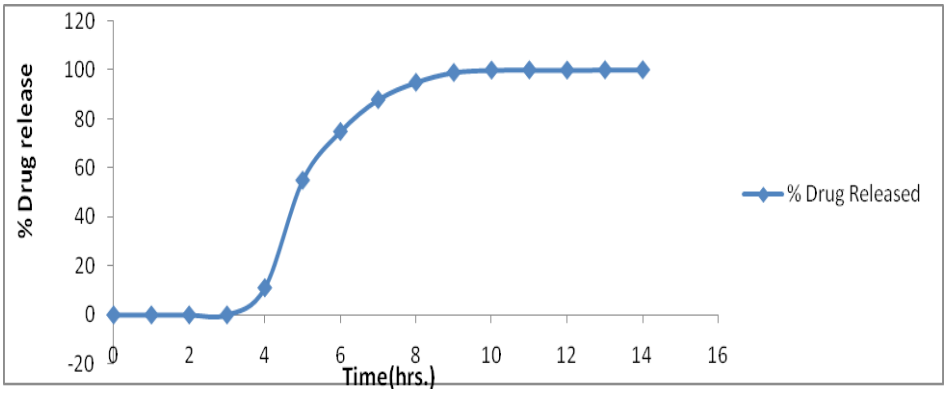

Fig.7 : In vitro release profiles of Enalapril from the floating–pulsatile release tablet (FPRT) Of batch K6+F4

Evaluation Of Floating and Pulsatile Release Tablet:

Only FPRT tablets of optimized batch (K6+F4) were evaluated for friability test, hardness test and drug content. In formulation, the hardness test indicated good mechanical strength. Hardness was ranged from 3.8 to 4.0 Kg/cm^2.Friability was ranged from 0.5 to 0.56. Friability is less than 1% which indicated that tablets had good mechanical resistance. Drug content was found to be high (>99.23). It was ranged from 99.32 to 99.45 and uniform in all tablet formulations. An ultraviolet (UV) spectrophotometric method was given at 236 nm and method obeys Beer's law in concentration range 5 to 50 µg/ml, with good correlation coefficient (0.9997).

Table 12 : Evaluation Of Floating and Pulsatile Release Tablet

Srno.	Formulations	Hardness (Kg/cm^2) Friability (%)	content(%)	
1	K6+ F4	3.8	0.43±0.11	99.45

CONCLUSION

The core containing KYRON T-314 disintegrate the tablet within short time due to easy and high swelling ability of KYRON T-314 as compared to CCS The PRT containing the buoyant material, such as HPMC K100M, $NaHCO_3$,and citric acid achieved a satisfactory buoyant force in vitro, whereas the floating onset time was less than 1 min. The pulsatile releasing mechanism of PRT is based on the exploitation of the peculiar interaction between hydrophilic polymeric coating and the aqueous gastrointestinal fluids.

The in vitro release profiles of Enalapril from PRT prepared using HPMC E15LV as retarding polymer are characterized bya predetermined lag time (4.1±0.2 h for K6+F4), the duration of which depends on the kind and amount of the polymeric layer applied on the cores as well as type of superdisintegrant in core tablet. The developed system offers a simple and novel technique for pulse release of drugs. From the results it is concluded that the PRT we prepared could achieve a rapid release after lag time of 4±0.2h with the relatively low variability. The drug release profile of optimized batch K6+F4 was found to be follow korsmeyer and peppas model. So it is concluded that formulation release the drug by diffusion and erosion method.

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