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FORMULATION AND EVALUATION OF FLOATING PULSATILE TABLET IN TABLET DRUG DELIVERY SYSTEM FOR HYPERTENSION

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ABSTRACT

The objective of this study was to prepare and characterize floating pulsatile tablet of Captopril giving pulsatile release for hypertension. Floating pulsatile drug delivery gives highest concentration at the early morning when it is needed the most. So it increases the patient compliance and decreases the side effects. Floating pulsatile tablets were prepared by direct compression method using HPMC K4M, avicel PH101, sodium starch glycolate and sodium bicarbonate polymers to achieve pulsatile drug release. Effects of all the polymers, with different concentrations, on physical properties of floating pulsatile tablets were investigated. To evaluate the effect of HPMC and sodium bicarbonate concentrations, 3^2 factorial designs was employed and for avicel PH101 and sodium starch glycolate, 2^2 factorial designs was employed. The optimization of core tablet was done on the basis of disintegration time. The optimization of floating pulsatile tablet was done based on the floating lag time & release rate. The core tablet formulation C3 and floating pulsatile tablet formulation F1 were selected as optimum production formulation. The Floating lag time, floating time, drug content, disintegration time and in-vitro drug release were found to be 43.4 sec, >8hrs, 99.06%, 45.6 sec, 95.3% respectively. Stability study at 40 ºC±2 ºC / 75 ± 5% RH revealed that there was no significant change in disintegration time, drug content and % CDR after 45 days. So, prepared formulation was stable during stability study. The developed floating pulsatile tablet

can be effectively used for oral administration in case of hypertension as it releases the drug in a pulsatile manner up to 7 hours thus improving patient compliance.

KEYWORDS: Floating pulsatile tablet, Captopril, Chronotherapy, Hypertension.

Hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. Normal blood pressure at rest is within the range of 100-140mmHg systolic (top reading) and 60-90mmHg diastolic (bottom reading). High blood pressure is said to be present if it is persistently at or above 140/90 mmHg. Heart rate and blood pressure both exhibit a strong circadian pattern with values for blood pressure, double product typically peaking in the Early morning period compare with till late afternoon, and then drops off during night.[1]

Captopril belongs to class of ACE inhibitors and because of its vasodilatation action it is used for cardiovascular diseases like hypertension, myocardial infarction, congestive heart failure, and prophylaxis in cardiovascular risk subject. It is used in diabetic nephropathy and scleroderma crises. It is a BCS class II drug having high solubility and low permeability. The drug shows high solubility in pH 1.2 and as pH increases chances of drug degradation may occur.[2]

The emerging chronotherapeutic requirements have led to much interest on systems able to release drugs in a 'pulse' at circadian timing correlated with specific pathological disorder. This acted as a push for the development of "Pulsatile Drug delivery Systems" referred to for the purpose of describing the liberation of a drug in a programmed fashion after a predetermined off-release period. At the end of the lag-phase, drug release takes place either in a prompt or sustained fashion, and thereafter it can also be repeated in one or more further pulses. However, patterns envisaging singles or multiple rapid and transient drug outputs are generally considered as the most challenging and even appealing mode of liberation.[3,4]

Chronopharmacotherapy, the drug regime based on circadian rhythm, regulates many body functions in human beings, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc. Human beings greatly vary in their biochemical and physiologic status over a 24-hour period due to the existence of a number of circadian rhythms.[5]

Heart rate and blood pressure both exhibit a strong circadian pattern with values for blood pressure, double product typically peaking in the Early morning period compare with till late afternoon, and then drops off during night (hypertension).[6-8]

MATERIALS AND METHODS

Captopril API was kindly supplied as gift samples by Torrent Pharmaceuticals Pvt. Ltd. Avicel 101pH, Sodium starch glycolate, HPMC K4M, Sodium bicarbonate were purchased from Chemco, Rajkot. In addition, 10 station rotary tablet punch machine (Rimek mini press I), a UV-Spectrophotometer, UV 1800 Double beam (Shimadzu UV 1800), a Monsato hardness tester (Sheetal scientific industries, Ahmadabad), a Roche friabilator (Popular traders), Dissolution tester (Electrolab TDT-08L), Disintegration (Electrolab ED-2L) were used in this study.

Drug Excipient compatibility study

Drug excipient compatibility was studied by Infrared spectroscopy. The drug powder was mixed homogeneously with other formulation excipient. This homogeneous mixture was pressed to form pellets using KBr press. The prepared pellet was placed in the sample holder and kept in the instrument to record the IR peaks.

Analytical method for estimation of Captopril

Preparation of 0.1 N HCl - 0.1N HCl was prepared by diluting 8.5 mL of concentrated hydrochloric acid to 1000 mL with distilled water.

Analytical method[48]

100mg of captopril was accurately weighed and transferred into 100mL volumetric flask. It was dissolved and diluted to volume with 0.1N HCl to give stock solution containing 1000µg/mL. The standard stock solution was then serially diluted with 0.1N HCl to get 1 to 10µg/mL of captopril. The absorbances of the solution were measured against 0.1N HCl as blank at 204 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/mL) to obtain the standard calibration curve.

Preparation of tablet

Preparation of Rapid Release Core Tablet (RRCT)

Captopril RRCT was prepared by direct compression method. All the ingredients were weighed and mixed properly. Magnesium stearate and talc were added in required quantity

and mixed with powder mixture. The powder was added to feed and compressed by 5mm punch by single punch tablet machine.

Preparation of Floating Pulsatile Release Tablet (FPRT)

The composition of buoyant layer was optimized by using 3^2 full factorial designs. Dry coating of optimized RRCT was done by using HPMC K4M. Dry coated tablet was prepared by placing 50% of pulsatile release layer in 10.5 mm die and RRCT was place on it. Further remaining quantity of pulsatile release layer was added in cavity so as to cover the RRCT and finally compressed by using single punch tablet machine.

Preliminary trials

Various trial batches of floating beads were formulated by varying polymer Concentration. Preliminary trials of captopril floating pulsatile tablet were shown in the (Table 1).

Pre-compression evaluations

Bulk density[10]

The powder sample under test was screened through sieve no. 18 and the sample equivalent to 10 g was accurately weighed and filled in a 50 mL graduated cylinder and the powder is levelled and the unsettled volume, V_0 was noted.

The bulk density was calculated in g/cm^3 by the formula,

Bulk density (ρ_0) = M/V_o

Where, M = mass of powder taken

V_o = apparent unstirred volume

Tapped density[10]

The powder sample under test was screened through sieve no. 18 and the weight of sample equivalent to 10 g was filled in 50 mL graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a constant rate for 100 times. Volume was considered as a tapped volume V_f. The tapped density was calculated in g/ cm^3 by the formula,

Tapped density (ρ_t) = M/V_f

Where, M = weight of sample powder taken

V_f = tapped volume

% Compressibility or Carr's index[10]

Based on the poured density and tapped density, the % compressibility of the granules was computed using the Carr's compressibility index:

$$\text{Carr's Index (\%)} = \frac{[(TBD - LBD)]}{TBD} \times 100$$

Hausner ratio [10]

Hausner ratio was calculated using the formula:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Poured density}}$$

Angle of repose[10]

Angle of repose of the granules was determined by height cone method. A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula:

$\tan \theta = 2h / D$

Where h = height,

D = diameter of the pile

Post compression parameters

General Appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Tablet's shape, colour, presence or absence of an odour and surface texture were observed visually.

Thickness and diameter[11]

The thickness and diameter of the tablet can be dimensionally measured by vernier caliper scale.

Weight variation[11]

20 tablets was selected randomly from the lot and weighed individually to check for weight variation. Weight variation specification as per I.P.

Hardness[11]

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into halves by compression .It was measured using a tablet hardness tester (Pfizer Hardness Tester).

Friability[11]

The pharmacopoeia limit of friability test for a tablet is not more than 1% using tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations). However, it becomes a great challenge for a formulator to achieve friability within this limit for FDT product keeping hardness at its lowest possible level in order to achieve a minimum possible disintegration time. This test is recommended for tablets prepared by direct compression and molding techniques to ensure that they have enough mechanical strength to withstand the abrasion during shipping and shelf life.

%Water uptake[12]

The % water uptake of optimized Pulsatile Release Tablet (PRT) was compared with other Pulsatile release tablet with same concentration as that of optimized Pulsatile release tablet by using USP dissolution apparatus type I.

In this study six tablets were placed in the basket of dissolution apparatus by using 0.1N HCl as dissolution medium at 37± 0.5^{0}C. Tablets were withdrawn at a time interval of 30 min, blotted with tissue paper to remove the excess water and weighed on the analytical balance. % water uptake was calculated by using the following formula :

$$\text{Water uptake (\%)} = \frac{Wt - Wo}{Wo} \text{ X } 100$$

Drug content[13]

Tablet was finely powdered and powder was taken in a volumetric flask. It was dissolved and diluted to 100mL with 0.1N HCl. Further dilutions were made according to the need. The absorbance of the solution was measured at 204 nm using UV spectrophotometer.

Disintegration time[11]

In vitro disintegration time of six tablets from each formulation was determined using tablet disintegration apparatus. In vitro disintegration test was carried out at 37 ± 2˚C in 900 mL 0.1N HCl.

In vitro drug release[11],[16-17]

The dissolution test was performed using USP dissolution apparatus I. A sample (5mL) of the solution was withdrawn from the dissolution apparatus at different time intervals and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to solvent. Absorbances of these solutions were measured using a UV/Visible double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Factorial design[12]

In factorial designs, levels of factor are independently varied, each factor at two or more levels. A factor is an assigned variable such as concentration, temperature, lubricating agent, drug treatment or diet. Factor may be qualitative or quantitative. The levels of a factor are the values or designations assigned to the factors. The runs or trials that comprise full factorial experiments consist of all combinations of all levels of all factors. The effect of a factor is the change in response caused by varying the levels of the factor. The important objective of a factorial experiment is to characterize the effect of changing the levels of factor or combination of factors on the response variable. The predictions based on results of an undersigned experiment will be less variable. The optimization procedure is facilitated by construction of an equation that describes the experimental results as a function of the factors. A polynomial equation can be constructed, where the coefficients in the equation are related to the effects and interactions of the factors. The general equations constructed for 2^2 and 3^2 factorial experiment are of the following form.

$$Y = \beta 0 + \beta 1\, X1 + \beta 2\, X2 + \beta 12\, X1\, X2 \text{- - - - - - - - - - - - - - - - - -} (1)$$

$$Y = \beta_o + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1 X_1 + \beta_{22} X_2 X_2 + \beta_{12} X_1 X_2 \text{- - - - - -} (2)$$

Where,

Y is the measured response,

$\mathbf{b_o}$ is the intercept,

$\mathbf{X_1}$ and $\mathbf{X_2}$ are factors,

$\mathbf{b_1}$, $\mathbf{b_2}$.... represents the coefficients computed from the response of formulation in the design. The magnitude of the coefficients represents the relative importance of each factor. Once the polynomial equation has been established, an optimum formulation can be found by grid analysis. Factorial designs for optimization are shown in (Table 2, 3).

Stability studies[11],[18]

Stability of a drug is defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity an light and enables recommended storage conditions, re-test periods and shelf lives to be established.

ICH specifies the length of study and storage conditions:

- Accelerated testing 40°C ± 2°C / 75 % RH ± 5 % for 6 months

In this investigation Preparation will be store for 45 days at 40°C ± 2°C / 75 % RH ± 5 %, every 15 days drug content of the preparation was checked.

RESULTS AND DISCUSSION

Solubility study of Captopril showed that Captopril is freely soluble in water and 0.1N HCl. The IR peaks showed the presence of the functional groups in the drug molecule. Individual sample of drug was evaluated for the identification study using FTIR spectroscopy. FTIR spectrum of pure drug Captopril showed the characteristic peaks appeared (Fig.1) at 2986 cm^{-1} (COOH stretch), 1742 cm^{-1} (C=O Stretch), 1198 cm^{-1} (SH stretch) and 1378 cm^{-1} (C-N Stretching) shown in (Fig. 1). The possible interaction between Captopril and the polymers were studied by Infrared spectroscopy. Individual samples of drug as well as physical mixture of drug and polymer were evaluated for the compatibility study using FTIR spectroscopy and are depicted in (Fig. 2) and the values of peak are indicated in (Table 4). FTIR spectrum of formulation of Captopril floating pulsatile tablet showed the characteristic peaks appeared (Fig. 2) at 2875.7 cm^{-1}(COOH stretch), 1748.13 cm^{-1} (C=O Stretch), 1197.41 cm^{-1} (SH stretch) and 1367.96 cm^{-1} (C-N Stretching). The frequencies of functional groups of drug Captopril remained intact in mixture containing different polymers so it was concluded that there was no major interaction occurred between the drug and excipients used in the study.

A UV-visible spectrophotometer (Shimadzu UV-1800) with 1 cm matched quartz cells was used for spectrophotometry identification of drug. 12 mcg/mL solution of Captopril was prepared in 0.1 N HCl. Further this solution was estimated by UV-Visible spectrophotometer at 204 nm. The active and overlay spectra's are shown in (Fig. 3, 4). The absorbance of all the concentrations is shown in (Table 5). The graph of absorbance Vs concentration was

plotted and depicted in (Fig. 5). Captopril exhibited maximum absorption at 204 nm and obeys Beer's law in the range of 2-12 µg/mL in 0.1 N HCl dissolution media.

Linear regression of absorbance on concentration gave equation:
Y=0.0459x - 0.0273 with a correlation coefficient of 0.9957 for 0.1 N HCl.

Calibration curve of Captopril was plotted in water by various concentrations in the range of 2 µg/mL-12µg/mL. Regression coefficient was found to be 0.995 which showed linear relationship between absorbance and concentration.

Result of Preliminary trials for the selection of core ingredients

Different disintegrants were used to prepare core tablet. The screening of different disintegrants was done on the basis of disintegration time. The disintegration time of all the preliminary batches are depicted in (Table 6). As shown in (Table 6), P3 batch showed less disintegration time compared to other batches. Hence it was concluded that P3 batch was optimized batch amongst all others batches.

Result Preliminary trials for the selection of coating ingredients

Different coating polymers were used to prepare floating pulsatile tablet. The screening of different coating polymers was done on the basis of % drug release. The % drug releases of all the preliminary batches are depicted in (Table 7). The graph of %CDR Vs Time is shown in (fig .6). Drug release study was done for the selection of optimized batch. Different polymers showed different drug release. HPMC E 50, carbopol 934, sodium alginate showed drug release before the required time. HPMC K15, HPMC K100 showed very less release of drug up till 7 hrs. HPMC K4M gave satisfactory release of drug at specific period of time. Until 5 hrs, the drug release was found to be very low compared to other batches. The burst release was observed after 5 hrs and the drug was released up to 7 hrs.

Optimization through full factorial design

Core tablets were prepared by applying 2^2 factorial designs. Total 4 batches were prepared of the core tablet as given in (Table 2). A suitable polynomial equation involving the individual main effects and interaction factors was selected based on the estimation of several statistical parameters, such as the multiple correlation coefficient (r^2), adjusted multiple correlation coefficient (adjusted r^2) and the predicted residual sum of squares (PRESS), provided by the Design-Expert software.

For the response surface methodology involving Factorial design, a total of 9 experiments were performed for two factors at three levels each for coating tablet. A suitable polynomial equation involving the individual main effects and interaction factors was selected based on the estimation of several statistical parameters, such as the multiple correlation coefficient (r^2), adjusted multiple correlation coefficient (adjusted r^2) and the predicted residual sum of squares (PRESS), provided by the Design-Expert software.

Results of Precompression studies

Precompression studies like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose were performed of all batches. The results of these parameters are shown in (Table 8). Mixture showing good flow property should have Carr's index in the range of 12-16, Hausner's ratio less than 1.25 and angle of repose between 20 and 30. The results showed that the flow property of the mixture was good as it was in the range of the good flowability in all parameters.

Post compression evaluation of core and floating pulsatile tablet

As shown in (Table 9) weight variation, thickness, diameter, hardness, % friability, % drug content, disintegration time of core tablets were checked. All the tablets passed weight variation test as the % weight variation was within the pharmacopeial limits of 10%. The thickness and diameter of the tablet was dimensionally measured by vernier caliper scale. Core tablet mean thickness and diameter of 4 formulations were found to be in range 2.5±0.6 to 2.65±0.3 and 5±0.01 to 5.2±0.02 respectively. The standard deviation values indicate that all formulation were within the range. Hardness of core tablets was found to be in the range of 3.33±0.15 to 3.7±0.2. The prepared tablets of all the formulations possessed good mechanical strength with sufficient hardness. The % friability was less than 1% in all the formulations indicating that the friability was within the prescribe limits. The results of friability showed that the tablet exhibited good mechanical strength. In order to obtain burst release, disintegration time should be much lower. Disintegration time was in the range of 45.6±0.6 to 72.6±1.2. The disintegration time was dependent on the concentration of the avicel PH 101 and sodium starch glycolate. As the concentration of avicel PH 101 and sodium starch glycolate increases, there is decrease in the disintegration time. The % drug content of core tablets were in the range of 97.06±0.15 to 99.06±0.15. The result showed that the % drug content was found within the limit of USP (90%– 110%). C1 batch was optimized formula because its disintegration time was 45 sec and % drug content was found to be 99.06.

Evaluation of floating pulsatile tablet

The general appearance of a tablet includes shape, colour, presence or absence of an odour and surface texture were observed visually. The results are depicted in (Table 10). As shown in (Table 11) weight variation, thickness, diameter, hardness, % friability, floating lag time, floating time of floating pulsatile tablets were checked. All the tablets passed weight variation test as the % weight variation was within the pharmacopeial limits of 5% for floating pulsatile tablet. Floating pulsatile press coated tablet thickness and diameter of 9 formulations were found to in the range of 4.32±0.2 to 4.68±0.5 and 10.5±0.1 to 10.8±0.4 respectively. The standard deviation values indicate that all formulation were within the range. Hardness of floating pulsatile tablets was found to be in the range of 4.56±0.2 to 4.83±0.4. The prepared tablets of all the formulations possessed good mechanical strength with sufficient hardness. The % friability was less than 1% in all the formulations indicating that the friability was within the prescribe limits. The results of friability showed that the tablet exhibited good mechanical strength. Floating lag time mainly depends on the concentration of sodium bicarbonate. The results showed that as the concentration of the sodium bicarbonate was increased, the floating lag time was decreased. The presence of the osmotic agent helped in drawing water towards the tablet which resulted in shortening of lag time. The tablet with higher sodium bicarbonate concentration showed lower lag time due to generation of carbon dioxide, which resulted in building up of pressure and rupturing of the tablet. The floating time of all the formulations of floating pulsatile tablets is shown in (Table 11). The floating time of floating pulsatile tablet was dependent on the concentration of HPMC. The range of the HPMC concentration selected gave floating time of more than 8 hours which was the required factor. The tablets should be floating for more than 7 hours as the formulation gave release up to 7 hours which was fulfilled by all the formulations. F3 batch was optimized because it having lowest floating lag time that is 43.4.

% Water uptake

% Water uptake of all the formulations is depicted in (Table 12). The % water uptake is mainly depended on the concentration of HPMC. As the concentration of HPMC was increased, there was increase in the % water uptake. So the formulation containing highest amount of HPMC showed higher water uptake. The graph of % water uptake Vs Time is shown in (Fig. 7).

In-vitro drug release study

The dissolution test was performed using USP dissolution apparatus I. Absorbance of these solutions was measured using a UV/Visible double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve. %CDR was calculated and depicted in (Table 13). The graphs of %CDR Vs time were plotted and depicted in (Fig. 8). The results showed that the % drug release was depended on the coating layer of the floating pulsatile tablet. F3 formulation showed the best release profile as the burst release was obtained between 6 to 7 hours compared to other formulations. In vitro dissolution results showed that the fast and complete drug release after expected lag time was observed in formulations F3, F1and F2. But depending upon floating lag time F3 was considered as the optimum formulation.

Response surface analysis for Optimization of final batch

Selected independent variable: HPMC K4M (X1) and Sodium bicarbonate concentration(X2)
Selected dependent variable: Floating lag time (Y1), %CDR at 6 hr (Y2),% CDR at 7 hr (Y3) (Table 14).

Contour plot

2D and 3D surface plot showed that increase in concentration of Sodium bicarbonate decreased the floating lag time and from this surface plot the batch F3 HPMC K4M (90%) Sodium bicarbonate (10%) showed the lowest floating lag time and hence it was optimized from the surface plot. (Fig. 9, 10, 11).

Stability study

Stability study of optimized batch F3was done at Accelerated testing 40°C ± 2°C / 75 % RH ± 5 %, interval of 15, 30 and 45 days. (Fig. 12).

After 15,30 and 45 days of interval Drug content, disintegration, percentage drug release of floating pulsatile was measured and it was found that percentage drug release of the tablet was 94.7, 95.32 and 95.8% respectively, drug content was found to be 99.01,98.85 and 98.76 respectively and disintegration time was found to be 45.34,47.56 and 47.97 respectively. Result shows that the batch F3 was stable for 45 days at accelerated condition. (Table 15,16).

TABLE 1: PRELIMINARY TRIALS OF CAPTOPRIL FLOATING PULSATILE TABLET.

Ingredients	P1 (mg)	P2 (mg)	P3 (mg)	P4 (mg)	P5 (mg)	P6 (mg)
Core tablet						
Captopril	25	25	25	25	25	25
Sodium starch glycolate	8	-	8	6	4	2
Dicalcium phosphate	7.5	11.5	-	12	-	10.5
Microcrystalline cellulose	7.5	11.5	-	-	12	-
Avicel 101PH	-	-	12	-	-	10.5
Magnesium- stearate	Trace	Trace	Trace	Trace	Trace	Trace
Talc	Trace	Trace	Trace	Trace	Trace	Trace
Coating tablet						
HPMC E50	180	-	-	-	-	-
HPMC K4M	-	180	-	-	-	-
HPMC K15	-	-	180	-	-	-
Carbopol 934P	-	-	-	180	-	-
Sodium alginate	-	-	-	-	180	-
HPMC K100	-	-	-	-	-	180
Sodium bicarbonate	20	20	20	20	20	20
Magnesium- stearate	Trace	Trace	Trace	Trace	Trace	Trace
Talc	Trace	Trace	Trace	Trace	Trace	Trace

TABLE 2: 2^2 FACTORIAL DESIGN FOR OPTIMIZATION OF CAPTOPRIL CORE TABLET.

Run	Avicel 101PH (mg)	Sodium starch glycolate (mg)
C1	70	8
C2	60	6
C3	70	6
C4	60	8

TABLE 3: 3^2 FACTORIAL DESIGNS FOR OPTIMIZATION OF CAPTOPRIL FLOATING PULSATILE TABLET.

Batches	Coded value		Actual value	
	Factor 1 amount of HPMC K4M (X_1)	Factor 2 amount of Sodium bicarbonate (X_2)	Factor 1 amount of HPMC K4M (X_1) (%)	Factor 2 amount of Sodium bicarbonate (X_2) (%)
F1	+1	-1	90	5
F2	+1	0	90	7.5
F3	+1	+1	90	10
F4	0	-1	80	5
F5	0	0	80	7.5

TABLE 4: FREQUENCIES OF PRINCIPLE PEAKS IN IR SPECTRA OF CAPTOPRIL AND MIXTURE.

Sr. No	Group	Range IR peak(cm^{-1})	IR peak (cm^{-1}) of pure Captopril	IR peak (cm^{-1}) of mixture	Observation
1	COOH	2500-3000	2986	2875.7	No interaction
2	C=O	1742	1742	1748.13	
3	SH	1198	1198	1197.41	
4	C-N Stretching	1367	1378	1367.96	

TABLE 5: CALIBRATION CURVE OF CAPTOPRIL IN 0.1 N HCL.

Concentration (µg/ml)	Absorbance
0	0
2	0.07±0.01
4	0.158±.005
6	0.233±.0.013
8	0.337±.033
10	0.45±0.032
12	0.51±0.009

TABLE 6: DISINTEGRATION TIME OF SCREENING BATCH OF CORE TABLETS.

Batch	Disintegration time (sec)
P1	90.2±0.22
P2	82.4±0.5
P3	**60.6±0.71**
P4	70.8±0.7
P5	79.5±0.5
P6	66.7±0.8

TABLE 7: CUMULATIVE % DRUG RELEASE OF PRELIMINARY BATCHES OF FLOATING PULSATILE TABLET.

Time (hr)	P1	P2	P3	P4	P5	P6
0.5	0	**0**	0	0	0	0
1	0	**0**	0	0	0	0
1.5	6.77	**0**	0	0	8.63	0
2	12.1	**0**	0	6.28	17.7	0
2.5	20.1	**0.3**	0	13.25	23.12	0
3	29.9	**0.7**	0.14	13.08	24.36	0.24
3.5	38.8	**1.4**	1.22	26.08	39.9	1.3
4	44.29	**2.5**	1.68	28.08	45.3	2.3
4.5	53.68	**4.1**	3.7	31.33	59.7	4.18
5	59.5	**5.2**	4.6	39.8	61.28	5.38
5.5	69.17	**8.6**	8.5	49.4	72.15	10.4
6	79.66	**59**	17.9	57.05	79.6	18.8
6.5	87.2	**75**	45.4	77.55	93.07	40.3
7	93.8	**94.1**	74.06	92.2	96	62.28

TABLE 8: PRECOMPRESSION STUDIES.

Batch	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F1	0.44 ± 0.02	0.51 ± 0.04	12.94 ± 0.04	1.15 ±0.04	24.04 ± 0.146
F2	0.46 ± 0.03	0.53 ± 0.03	12.45 ± 0.02	1.14 ±0.03	25.23 ± 0.947
F3	**0.46 ± 0.003**	**0.53 ± 0.03**	**12.75 ± 0.02**	**1.14 ± 0.005**	**21.23 ± 0.041**
F4	0.47 ± 0.04	0.54 ± 0.03	12.85 ± 0.04	1.13 ± 0.002	24.01 ± 0.062
F5	0.51 ± 0.02	0.57 ± 0.03	12.57 ± 0.04	1.13 ±0.02	23.12 ± 0.567
F6	0.45 ± 0.04	0.52 ± 0.02	13.02 ± 0.03	1.14 ±0.07	21.21 ± 0.342
F7	0.48 ± 0.03	0.55 ± 0.04	12.86 ± 0.03	1.14 ± 0.03	22.43 ± 0.987
F8	0.46 ± 0.02	0.53 ± 0.05	13.64 ± 0.04	1.15 ±0.02	22.72 ± 0.98
F9	0.442 ±0.02	0.512 ±0.04	13.67 ±0.05	1.15 ±0.02	24.32 ±0.23

TABLE 9: EVALUATIONS OF CORE TABLETS.

Batch	Weight variation	Thickness (mm)	Diameter (mm)	Hardness	% Friability	% Drug content	Disintegration time(s)
C1	**105.35±0.35**	**2.56±0.2**	**5.2±0.02**	**3.7±0.2**	**0.31±0.1**	**99.06 ±0.15**	**45.6±0.6**
C2	105.4±0.25	2.65±0.3	5±0.01	3.4±0.2	0.49±0.03	97.83 ±0.25	71.6±1.2
C3	106.6±0.26	2.62±0.4	5.1±0.01	3.33±0.15	0.27±0.09	98.03 ±0.2	71.6±0.9
C4	106.16±0.2	2.5±0.6	5.1±0.01	3.3±0.26	0.36±0.06	98.13 ± 0.2	64.6±0.76

TABLE 10: GENERAL APPEARANCE OF TABLET.

Property	Inference
Shape	Round
Color	White
Odor	No odor
Surface texture	Smooth

TABLE 11: EVALUATION OF FLOATING PULSATILE TABLET.

Batches	Weight variation ± SD	Thickness (mm)	Diameter (mm)	Hardness	% Friability	Floating lag time(s)	Floating time(h)
F1	357.8±0.97	4.32±0.2	10.8±0.4	4.73±0.40	0.6±0.03	68.4±0.5	>8
F2	353.9±0.87	4.5±0.1	10.72±0.3	5.1±0.2	0.4±0.08	55.8±0.3	>8
F3	**356.5±0.5**	**4.68±0.5**	**10.5±0.3**	**4.83±0.4**	**0.48±0.1**	**43.4±0.5**	**>8**
F4	358.1±0.7	4.5±0.3	10.52±0.5	4.66±0.15	0.46±0.05	70.5±0.7	>8
F5	355±0.3	4.35±0.5	10.5±0.2	4.83±0.40	0.41±0.05	63.6±0.3	>8
F6	355.3±0.35	4.44±0.7	10.5±0.5	4.56±0.20	0.30±0.05	54.45±0.4	>8
F7	353.6±0.52	4.8±0.2	10.56±0.5	4.56±0.25	0.58±0.02	69.7±0.4	>8
F8	357.5±0.41	4.42±0.3	10.54±0.2	4.6±0.35	0.68±0.05	62.4±0.7	>8
F9	353.2±0.52	4.32±0.4	10.6±0.6	4.76±0.47	0.51±0.07	49.7±0.4	>8

TABLE 12: % WATER UPTAKE OF BATCHES F1 TO F9.

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	9.9±0.34	9.6±0.66	9.99±0.57	9.63±0.72	10.03±0.40	10.56±0.7	10.15±0.43	10±0.2	9.9±0.28
2	13.3±1.7	14.36±0.66	14.8±0.53	14.9±1.2	14.56±1.1	14.73±1.76	14.96±0.3	14.65±0.9	13.87±0.9
3	14.76±1.05	15.23±0.5	15.9±0.45	16.21±0.5	15.88±0.4	16.2±1.3	15.96±0.5	15.8±0.35	15.74±0.52
4	16.33±0.4	16.4±0.52	16.8±0.27	17.06±0.58	16.94±0.3	17±.0.62	17.2±0.5	16.32±0.33	16.48±0.42
5	16.93±0.55	16.8±0.3	17.05±0.25	17.32±0.45	17.38±0.16	17.52±0.28	17.35±0.46	16.73±0.30	16.8±0.46
6	17.47±0.36	17.07±0.24	17.56±0.32	17.55±0.42	17.54±0.51	17.7±0.26	17.64±0.35	17.03±0.24	17.02±0.41
7	18.27±0.23	18.21±0.17	18.74±0.35	17.8±0.17	17.72±0.15	17.97±0.33	17.73±0.31	17.17±0.17	17.50±0.184

TABLE 13: CUMULATIVE % DRUG RELEASE OF BATCHES F1 TO F9.

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	**0**	0	0	0	0	0	0
0.5	0	0	**0**	0	0	0	0	0	0
1	0	0	**0**	0	0	0	0	0	0
1.5	0	0	**0**	0	0	0	0	0	0
2	0	0	**0**	0	0	0	0	0	0
2.5	1.04±0.32	0.45±0.41	**0.76±0.3**	1.72±0.33	1.43±0.12	0.55±0.35	1.82±0.3	1.86±0.32	1.55±0.34
3	2.34±0.62	1.04±0.68	**1.34±0.4**	2.68±0.11	2.2±0.3	1.5±0.41	3.53±0.5	3.88±0.23	4.32±0.43
3.5	4.37±0.54	1.78±0.26	**1.65±0.5**	3.67±0.3	3.8±0.4	5.14±0.2	4.6±0.1	5.8±0.53	6.76±0.54
4	6.94±0.42	2.78±0.52	**2.3±0.6**	5.97±0.3	9.42±0.31	8.23±0.43	10.42±0.28	13.68±0.36	10.23±0.32
4.5	8.87±0.4	3.71±0.41	**2.6±0.4**	12.4±0.5	18.18±0.4	14.1±0.3	53.9±0.5	48.5±0.3	55.22±0.3
5	13.13±0.3	6.43±0.75	**3.3±0.34**	67.3±0.65	79.66±0.2	75.5±0.65	87.2±0.65	87.02±0.21	82±0.5
5.5	29.8±0.6	9.8±0.5	**25±0.5**	89.3±0.3	85.9±0.3	87.1±0.5	93.3±0.2	92.3±0.6	89±0.6
6	45.75±0.2	45.64±0.2	**36±0.4**	92.6±0.4	90.6±0.5	91.9±0.6	93.32±0.4	94.8±0.8	93.5±0.3
6.5	53.18±0.3	57.24±0.8	**57±0.2**	94.5±0.6	92.6±0.7	92.9±0.1	94.09±0.2	95.35±0.4	94.2±0.3
7	88.96±0.7	85.7±0.4	**95.3±0.5**	94.76±0.3	94.7±0.2	94.3±0.3	95.02±0.6	95.4±0.3	95.21±0.5

TABLE 14: DESIGN MATRIX OF 3^2 FULL FACTORIAL DESIGNS.

Batches	Coded value		Actual value	
	Factor 1 amount of HPMC K4M (X_1)	Factor 2 amount of Sodium bicarbonate (X_2)	Factor 1 amount of HPMC K4M (X_1) (%)	Factor 2 amount of Sodium bicarbonate (X_2) (%)
F1	+1	-1	90	5
F2	+1	0	90	7.5
F3	+1	+1	90	10
F4	0	-1	80	5
F5	0	0	80	7.5
F6	0	+1	80	10
F7	-1	-1	70	5
F8	-1	0	70	7.5
F9	-1	+1	70	10

TABLE 15: STABILITY DATA OF OPTIMIZED BATCH F3.

Batch F3	Disintegration time (sec)	Drug content (%)
D15	45.34±0.23	99.01±0.1
D30	47.56±0.43	98.85±0.3
D45	47.97±0.37	98.76±0.23

TABLE 16: STABILITY DATA OF CUMULATIVE% DRUG RELEASE OF BATCH F3.

Time	D0	D15	D30	D45
0	0	0	0	0
0.5	0	0	0	0
1	0	0	0	0
1.5	0	0	0	0
2	0	0	0	0
2.5	0.76±0.3	0.73±0.6	0.74±0.33	0.76±0.6
3	1.34±0.4	1.29±0.3	1.32±0.21	1.38±0.3
3.5	1.65±0.5	1.58±0.12	1.62±0.11	1.65±0.1
4	2.3±0.6	2.2±0.5	2.4±0.17	2.54±0.4
4.5	2.6±0.4	2.4±0.32	2.46±0.04	3.01±0.43
5	3.3±0.34	3.4±0.22	3.65±0.33	3.6±0.6
5.5	25±0.5	27±0.27	28.3±0.55	29.3±0.2
6	36±0.43	37.5±0.65	37.87±0.3	40±0.7
6.5	57±0.2	59±0.28	61±0.3	64±0.3
7	95.3±0.5	94.7±0.3	95.32±0.54	95.8±0.5

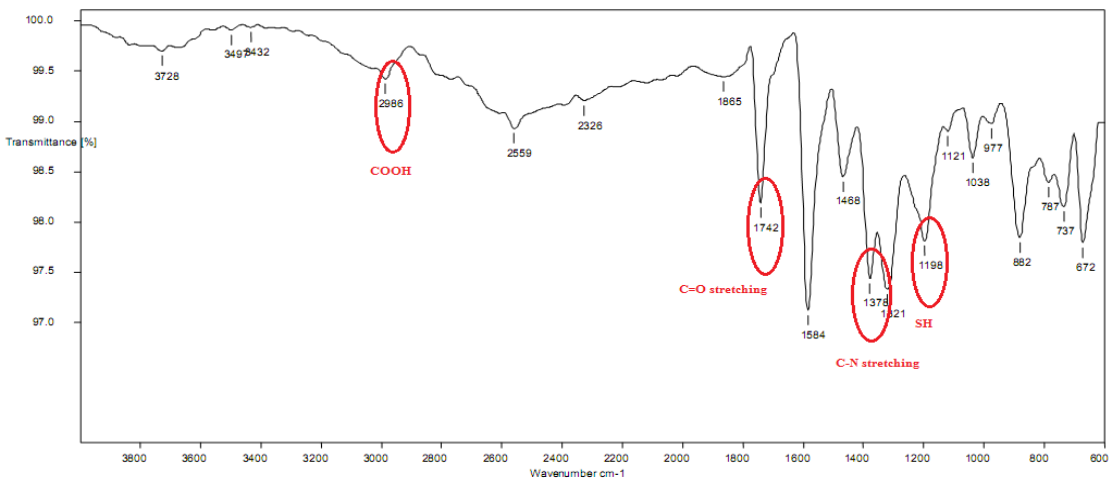

Fig. 1: FTIR spectra of Captopril.

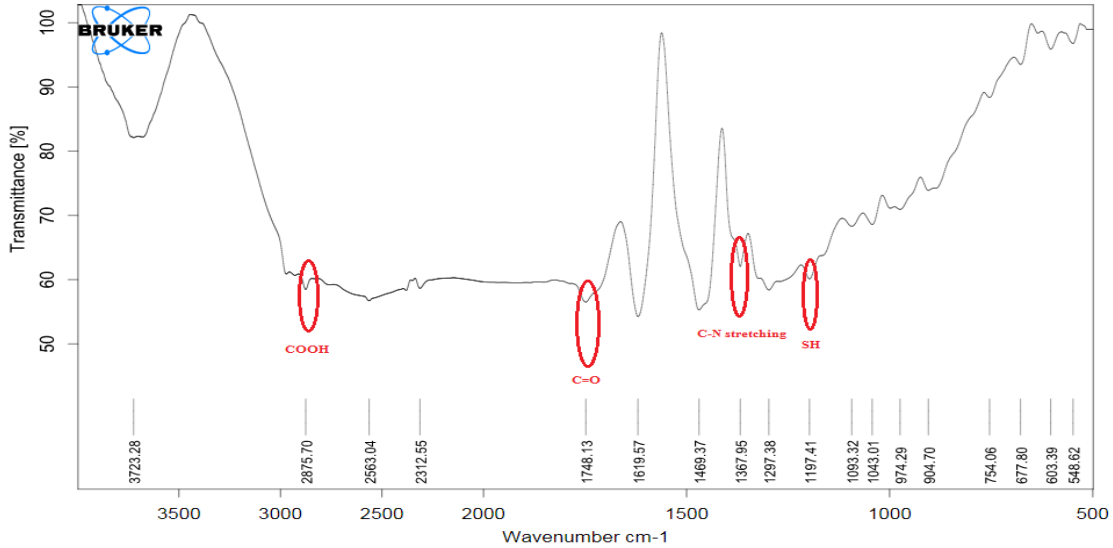

Fig. 2: FTIR spectra of formulation.

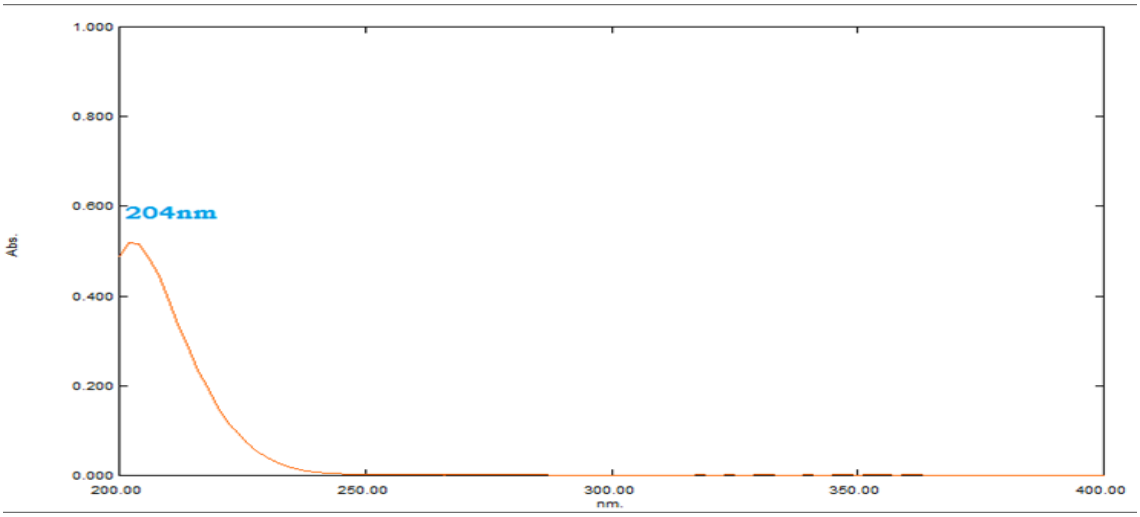

Fig. 3: Spectrophotometric images of Captopril at 204nm.

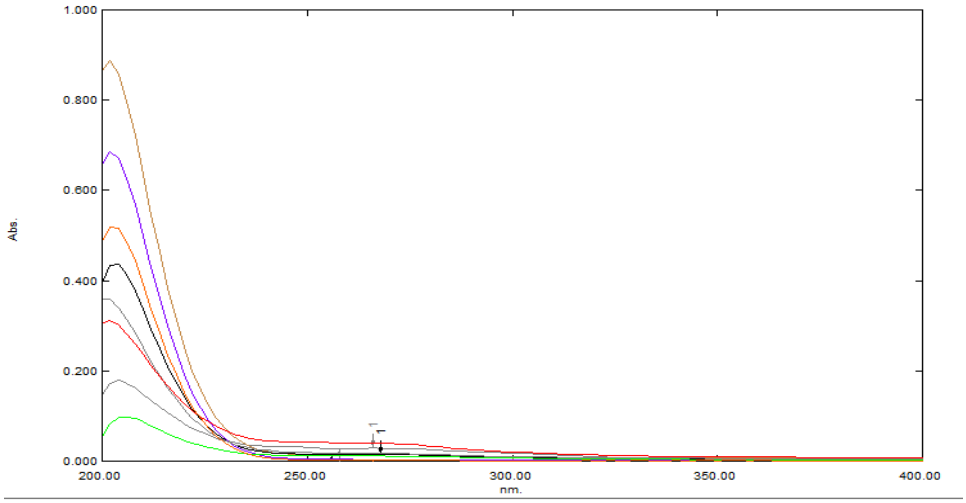

Fig. 4: Overlay spectrophotometric image of Captopril at 204 nm.

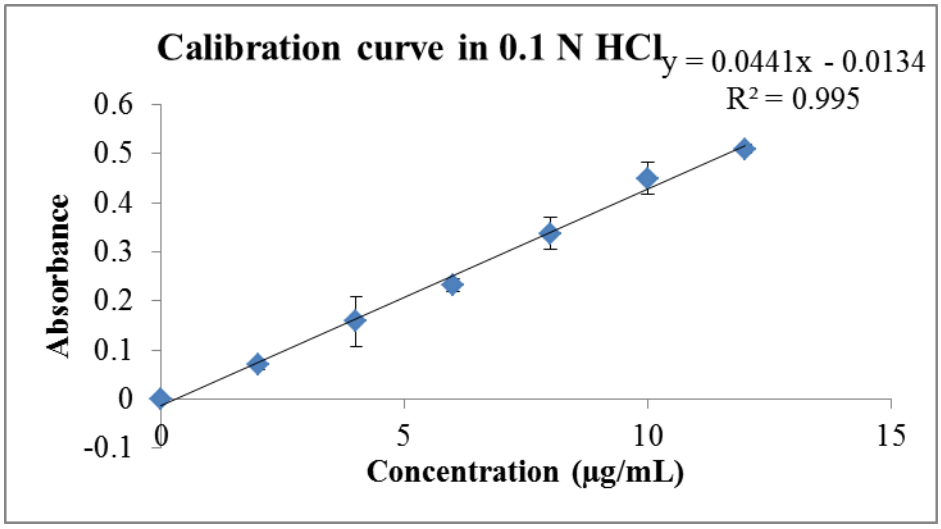

Fig. 5: Standard curves of Captopril in 0.1N HCl.

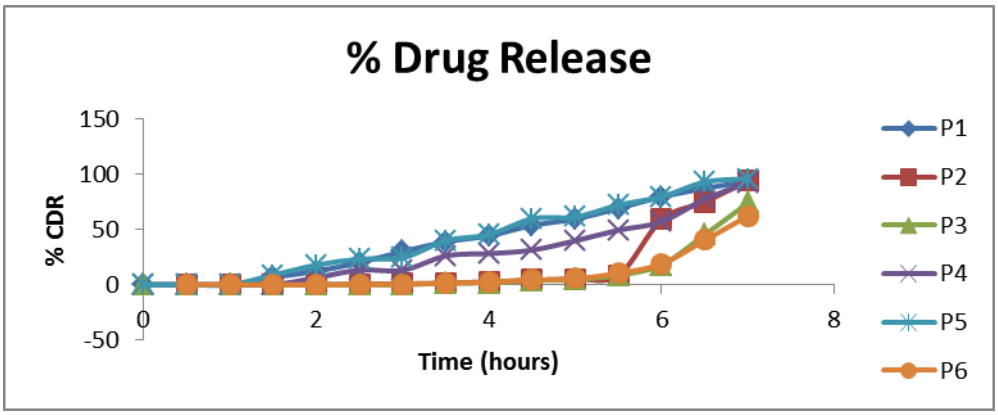

Fig. 6: Drug release profile of Preliminary batches.

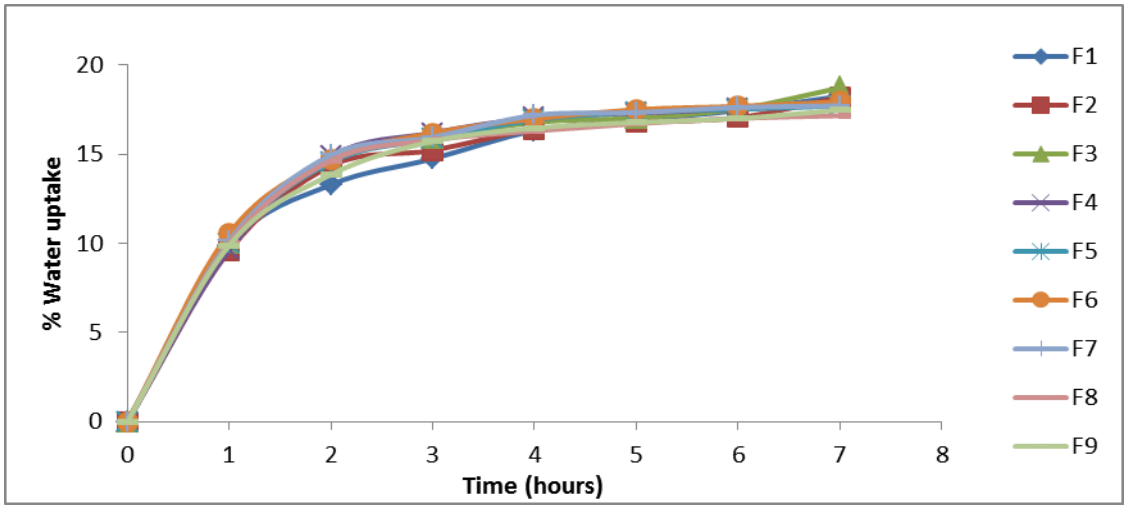

Fig. 7: % Water uptake of batches F1 to F9.

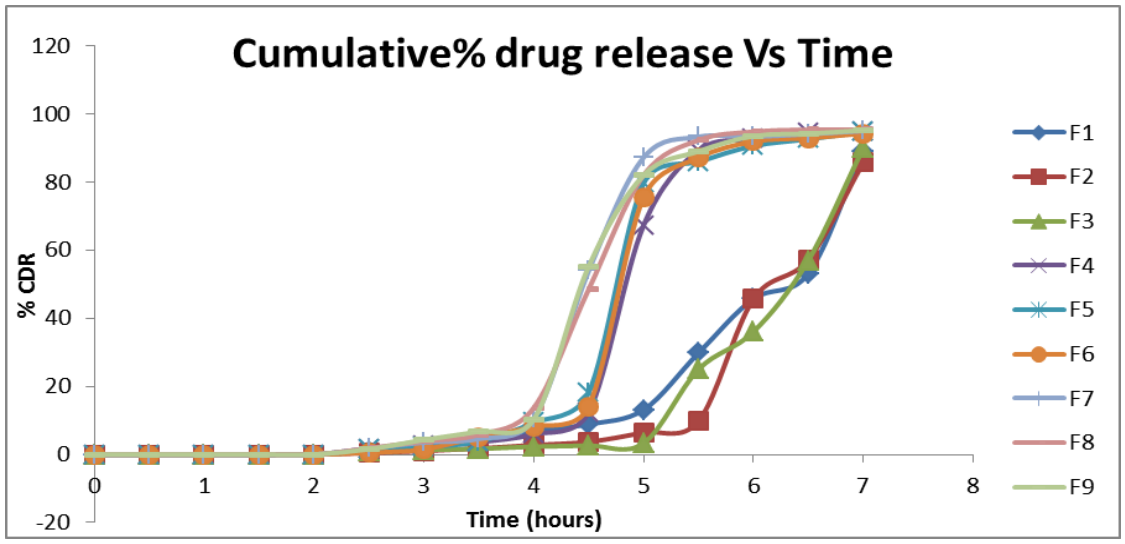

Fig. 8: Drug release profile of batches F1 to F9.

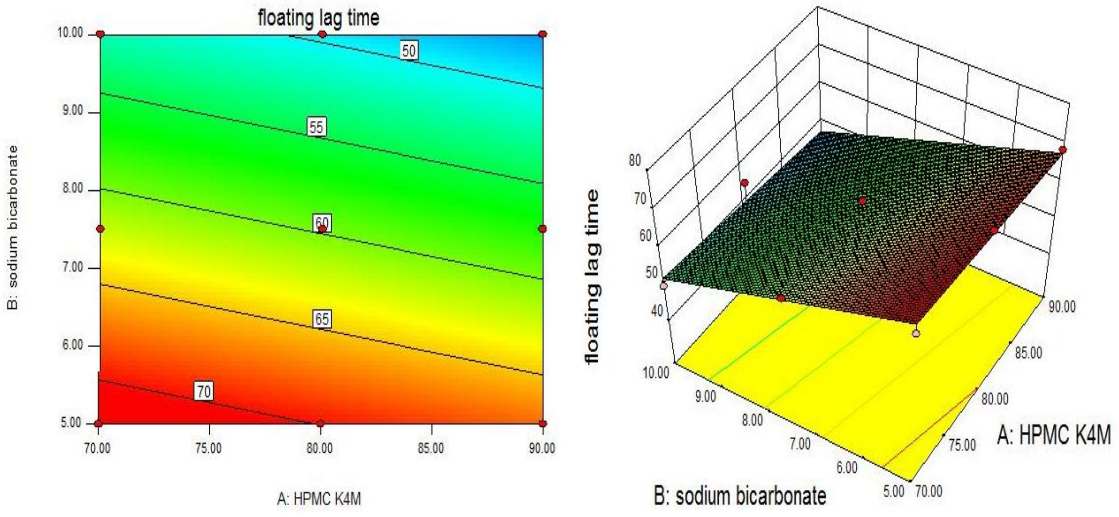

Fig. 9: 2D and 3D surface of response Y1 (Floating lag time).

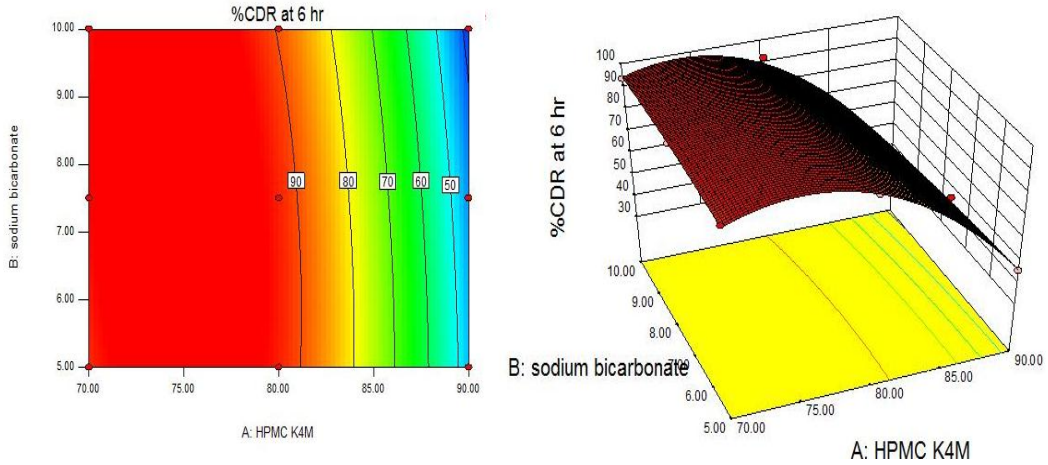

Fig. 10: 2D and 3D surface of response Y2 ((%CDR at 6 hr).

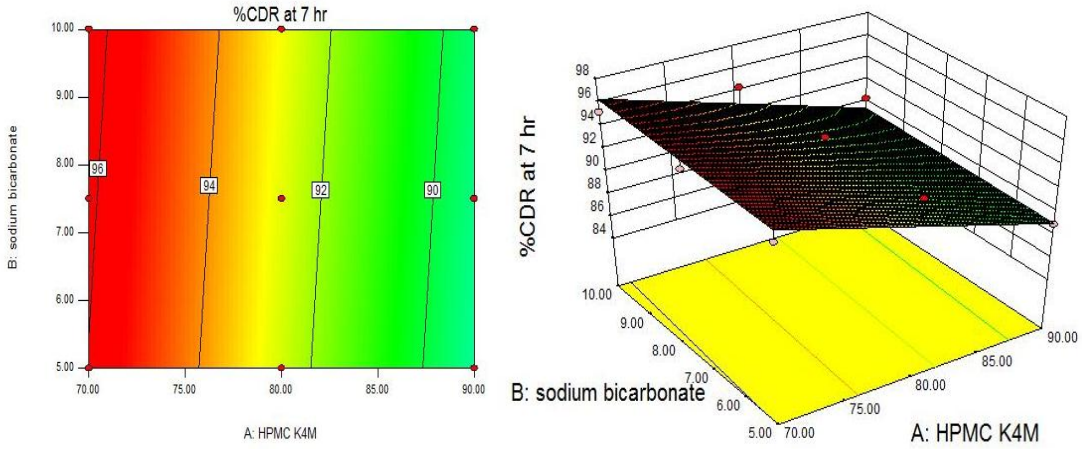

Fig. 11: 2D and 3D surface of response Y2 (%CDR at 7 hr).

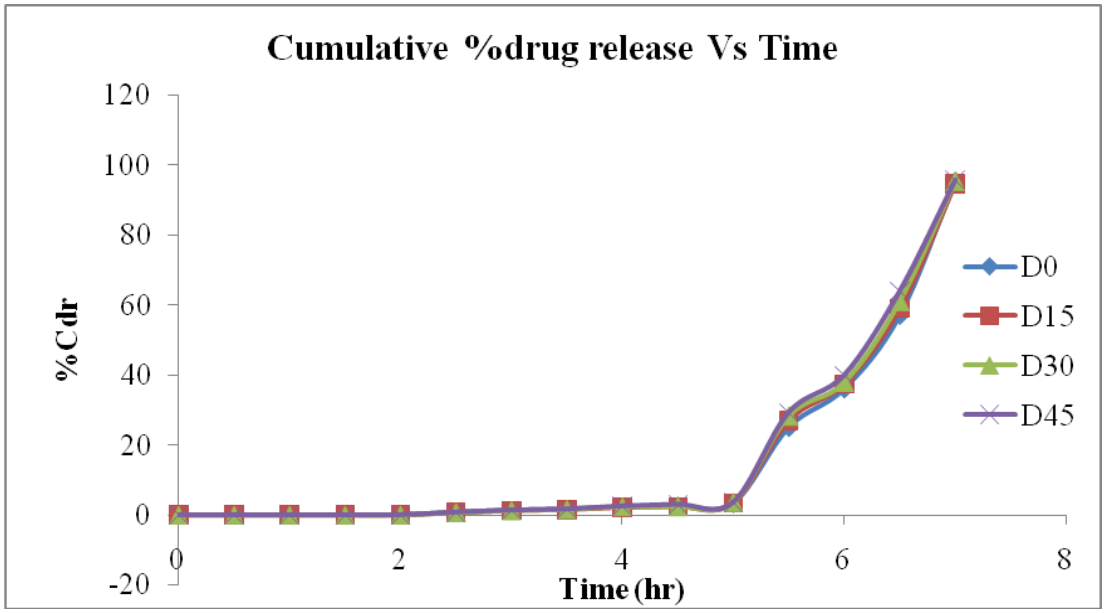

Fig. 12: Drug release profile of optimizes batch at zero day, after 15th, 30th and 45th day.

SUMMARY AND CONCLUSION

Captopril is Angiotensin Converting Enzyme Inhibitors, block either the production or action of angiotensin-II, thereby reduce vascular resistance and (potentially) blood volume. It is having shorter half life of 2 hours. Majority of individuals' blood pressure rises in the early morning hours, which lead to serious cardiovascular complications. Captopril as a floating pulsatile drug delivery gives highest concentration at the early morning when it is needed the most.

During Preformulation studies, solubility analysis revealed that Captopril was Freely soluble in 0.1 N HCl and water. Ultraviolet spectroscopic method was performed for estimation of Captopril. Captopril showed λmax 204 nm in 0.1 N HCl. Regression coefficient for calibration curve was found 0.995 in 0.1N HCl. Infrared spectra of pure drug and physical mixture of drug with other excipients confirmed the compatibility between drug and other excipients.

Floating pulsatile tablet were prepared by direct compression method using HPMC K4M, avicel PH101, sodium starch glycolate and sodium bicarbonate polymers to achieve pulsatile drug release. Effects of all the polymers, with different concentrations, on physical properties of floating pulsatile tablet were investigated. To evaluate the effect of HPMC and sodium bicarbonate concentrations, 3^2 factorial design was employed and for avicel PH101 and sodium starch glycolate, 2^2 factorial design was employed. The optimization of core tablet was done on the basis of disintegration time. The optimization of floating pulsatile tablet was done based on the floating lag time & release rate. The core tablet formulation C1 and floating pulsatile tablet formulation F3 was selected as optimum production formulation. The Floating lag time, floating time, drug content, disintegration time and *in-vitro* drug release were found to be 43.4 sec, >8hrs, 99.06%,45.6 sec, 95.3% respectively. The FTIR results reveal that drug & polymers were chemically compatible. From regression value it revealed that all formulations followed Hixon Crowell model, which indicates that the drug release follows swelling-erosion. Stability study at $40^0C \pm 2^0C$ / 75 ± 5% RH revealed that there was no significant change in disintegration time, drug content and % CDR after 45 days. So, prepared formulation was stable during stability study. The developed floating pulsatile tablet can be effectively used for oral administration in case of hypertension as it releases the drug in a pulsatile manner up to 7 hours thus improving patient compliance.

Thus, it can be concluded that the present work can be considered as one of the promising formulation for preparing floating pulsatile drug delivery system of Captopril and can be effectively used in chronotherapeutic management of hypertension by opening a new therapeutic dimension to an existing drug molecule.

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