

Formulation and Evaluation of Gastroretentive Floating Tablet of Captopril for the Treatment of Hypertention by Using Natural Polymers

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Abstract

Aim: The aim of the study was to formulate gastroretentive floating tablet of captopril using combination of polymers such as chitosan and xanthan gum.

Method: The tablet dosage form was formulated using Chitosan and xanthan gum with the varying concentrations from 0-60%. All the nine formulated tablet batches were characterized for its pre-compression and post compression parameters such as compressibility index, hausner's ratio, bulk and tapped densities and % swelling index, floating lag time and content uniformity. The in-vitro drug release from the tablet was determined using USP Type II dissolution apparatus and the samples were analyzed by UV-Vis Spectrophotometer at 211nm.

Results: The total floating time of 8 hrs was observed for all the formulated tablets. The % swelling index was found to be in the range of 145-195%. The drug content uniformity was found to be within the acceptable range of 95-105%. The results for in-vitro drug release were found to be 95% after 8 hrs, indicating the gastroretentive floating of the drug.

Conclusion: Hence, formulating a gastroretentive tablet formulation for captopril helps in overcoming the limitation of short half-life and pH sensitivity.

Keywords: Chitosan, Captopril, Xanthan gum, gastroretentive tablets.

INTRODUCTION

Despite considerable advancements in drug delivery, oral drug delivery system is by far the most preferred and convenient route because of low cost of therapy, ease in administration, patient compliances and flexibility in formulation^(1, 2). Controlled release drug delivery system is one which delivers the drug at a predetermined, predictable and controlled rate locally or systemically for a specified period of time^(3, 4). Some drugs exhibits poor bioavailability because of various reasons such as degradation of drug in stomach or incomplete absorption. Drugs which are easily absorbed from gastrointestinal tract and drugs having short half-lives are eliminated rapidly through systemic circulation^(5, 6). For that reason, a gastroretentive drug delivery system is developed to prolong gastric retention time of drug. GRDDS enhances bioavailability, therapeutic efficacy and may also decrease dose of the drug^(7, 8).

GRDDS can be achieved by different mechanisms of retention such as by floating, by sedimentation, by mucoadhesion or by swelling. The principle purpose of the floating drug delivery system or hydro-dynamically balanced system is to float over the gastric contents and remain buoyant in stomach for prolonged period of time without affecting gastric emptying time. The floating tablets are used to increase the gastric residence time and to improve drugs absorption window^(9, 10).

Captopril, (1-[(2S)-3-mercapto-2-methyl propionyl]-lproline), an ACE-Inhibitor (Angiotensin-Converting Enzyme Inhibitor), has been widely used for the treatment of hypertension and congestive heart failure. The development of oral controlled release dosage form is little

bit difficult.^(11, 12) The drug is freely soluble in water and has biological half-life after is 1.7 hr after oral administration. It is stable at pH 1.2, and as the pH increases, the drug becomes unstable and undergoes a degradation reaction. Captopril is unstable at high pH of intestinal fluid; therefore, it is difficult to obtain sustained release using conventional sustained release oral drug delivery system^(13, 14).

Natural polymers remain attractive primarily because they are inexpensive readily available, be capable of chemical modification, non-carcinogenicity, mucoadhesivity, biodegradable, biocompatible, high drug holding capacity and high thermal capacity and ease of compression⁽¹⁵⁾. Chitosan is a natural polymer and versatile polymer obtained by alkaline deacetylation of chitin. The deacetylated chitin derivative chitosan is more useful and bioactive polymer, it has many reactive amino side groups which offer possibilities of modification. These properties make chitosan good candidate stomach-specific drug delivery system. Xanthan gum is a linear, high molecular weight extracellular heteropolysaccharide, produced commercially by viscous fermentation of gram negative bacterium *Xanthomonas campestris*. It has been also used as effective excipients for sustained release formulation; it not only retards drug release, but also provides time independent release kinetics.

The present study mainly acclaims the formulation of gastroretentive floating tablets for captopril. Hence, an attempt has been initiated to formulate a sustained released dosage form using different polymers such as chitosan and xanthan gum⁽¹⁶⁾.

MATERIALS AND METHODS

Chemicals

The drug Captopril was procured from Astra life care Pvt. Ltd., Rajoda, Gujarat, India. All other chemicals and excipients of analytical grade were used for the study. Sodium carbonate, citric acid, xanthan gum and chitosan were procured from Hi-media chemicals, Mumbai. PVP K-30, magnesium stearate and talc were procured from Thermosil fine chem industries, Pune.

Preparation of captopril tablets

The nine trial batches were formulated using various concentrations of the sodium bicarbonate and polymers. In the preliminary batches sodium bicarbonate was utilized in concentration range of 15-20% as floating agent in combination with 10% of citric acid. During trial, tablets containing 0-60% of Chitosan alone as well as 0-60% of xanthan gum alone were formulated and evaluated for floating lag time and drug release pattern. The direct compression technique was adopted to formulate trial batches of tablets using the formulae shown in Table 1.

All the batches were evaluated for various parameters and the formulations showing optimized results were determined. The concentration of sodium bicarbonate (10%) and citric acid (5%) was optimized for the study. All the ingredients were accurately weighed, grinded and uniformly mixed together. The resultant powder mixtures were compressed using direct compression technique.

Fourier transform infrared (FTIR) analysis

FT-IR spectra of pure drug captopril, polymers and drug polymer mixture were recorded separately in order to investigate the drug-excipients compatibility. FT-IR spectra of pure Captopril, xanthan gum, chitosan and mixture of Captopril, Xanthan gum, Chitosan were recorded from 400cm⁻¹ to 4000 cm⁻¹ using Shimadzu 8100S .

Pre-compression parameters^(17, 18)

Bulk density (BD)

Bulk density defined as the total mass per bulk volume of powder. BD was determined by pouring the weighed amount of powder into a measuring cylinder. The initial volume was noted which represented as the bulk volume. Using this value, the bulk density was calculated according to the formula mentioned below. It was expressed in g/mL.

$$BD = m/V_b$$

Where,

m= mass of powder

V_b = bulk volume

Tapped density (TD)

Tapped density defined as the total mass per tapped volume of powder. The volume was measured by tapping the bulk powder for 100 times. It was expressed in g/mL.

$$TD = m/V_t$$

Where,

m= mass of the powder

V_t = tapped Volume of the powder

Hausner's ratio (H.R.)

H.R defines as the measurement of frictional resistance of the drug. The ideal range for H.R should be within 1.2-1.5, and was determined by dividing tapped density and bulk density.

$$H.R. = T.D. /B.D$$

Compressibility index (CI)

The flowability of the powdered material was evaluated by comparing the bulk density and tapped density of powder and the rate at which the powder gets compressed is known as compressibility index. Compressibility index was calculated using the following formula,

$$C.I. = (1-1/H.R.) \times 100$$

Angle of repose (Θ)

Angle of repose defined as the maximum angle possible between the surface of powder pile and the horizontal plane. The angle of repose was determined by using funnel method. The funnel was fixed at a particular height (2.5 cm) on a stand and the powder sample was passed through the funnel until it formed a pile. Further addition of powder was stopped as soon as the pile touches the tip of the funnel. A circle was drawn across it without disturbing the pile and the radius and height of the pile were noted. The angle of repose was calculated by following equation

$$\tan \Theta = h/r$$

Where,

Θ= angle of repose

h= height of pile

r= radius of the pile

Post compression parameters^(19, 20, 21)

Weight variation test

Formulated tablets were tested for weight uniformity. 20 tablets were weighed individually as well as in bulk. The average weight was calculated and then % weight variation was determined using following formula

$$\% \text{ weight variation} = \frac{\text{average weight} - \text{individual weight}}{\text{average weight}}$$

Tablet thickness

The thickness of tablet was determined by measuring the thickness and diameter using Vernier caliper.

Hardness

Hardness was measured by Monsanto hardness tester by randomly selecting three tablets. Hardness was expressed in kg/cm².

Friability

Ten tablets were weighed and then placed in friabilator, which was rotated for 4 minutes at a speed of 25 rpm; tablets were reweighed after removing from the friabilator.

$$\%F = \left[1 - \left(\frac{W_t}{W} \right) \right] \times 100$$

Where,

W – Initial weight

W_t – Final weight

In- vitro dissolution studies

In vitro dissolution study was performed using USP Type II: Paddle apparatus in a dissolution media (0.1N HCl). The temperature was maintained at 37±0.5°C and the

rotations of the paddle were maintained at 50 rpm. The tablets were placed in 900mL of 0.1N HCl and 10 mL of sample was withdrawn at specific time intervals and was replenished back with fresh 0.1N HCl. The absorbance of sample was measured using UV-Visible Spectrophotometer (Shimadzu UV-1700) at λ_{max} 211 nm.

Floating lag time

The tablets were placed in a 100 mL beaker containing 0.1N HCL. The time required by the dosage form to float onto the surface of the simulated gastric fluid after its introduction was measured. This time taken for the dosage form to emerge on the surface of medium was known as the floating lag time (FLT) and total duration of time during which the dosage form remains buoyant was known as total floating time (TFT) recorded.

Drug content uniformity

Ten tablets were weighed accurately and powdered using a motor pestle. The powder equivalent to 50 mg of captopril was transferred to a 100 mL volumetric flask and then dissolved using 0.1N HCl. Further suitable dilutions were prepared and the samples were analyzed for the drug content using UV- Vis spectrophotometer (Shimadzu UV-1700) at 211 nm.

Swelling index

The swelling behaviour of a dosage form was measured by studying its weight gain or water uptake (WU) after placing it into an aqueous solution. Formulated tablets were weighed individually (W_0) and placed separately into petri dish containing 50 mL 0.1 N HCl. The petri dishes were placed in incubator maintained at $37 \pm 0.5^\circ\text{C}$. The tablets were removed from petri dish, at predetermined intervals of time and reweighed (W_t) and the % swelling index was calculated using following formula,

$$\% WU = \frac{W_t - W_0}{W_0}$$

Where,

WU – Water uptake

W_0 – Weight of tablet before immersion

W_t – Weight of tablet after time interval t

RESULTS AND DISCUSSION

The aim of this study was to develop a floating gastro retentive tablet of captopril for the treatment of hypertension, based on combination of chitosan, xanthan gum and sodium bicarbonate. Sustained drug release was achieved by reducing the floating lag time and prolonging floating duration.

Fourier Transform Infrared (FTIR) analysis

The IR spectra of pure captopril showed characteristic bands at 2874-2972/cm indicating C-H stretching. A prominent peak was obtained at 2563.60/cm indicating SH stretch. A peak was observed at 1742.32/cm indicating C = O of -COOH group, 1582.67/cm indicating C = O of Amide. Peaks were shown at range 1305- 1375/cm indicating OH bending, 1227.5/cm indicating C-O stretching, 1192.05/cm indicating CN stretching. Thus it is evident that all the characteristic peaks that were present in the spectra of pure drug.

The characteristics peaks of captopril were observed at 2874.52, 1742.32, 2563.60, 1582.67, 1192.05, and 1305.78 as shown in Figure 1. In physical mixture of drug and polymers (Figure 2) the characteristics peak of drug were clearly appear at nearly same wavelength indicating no interaction between drug and polymers.

Pre-compression parameters of powder blend

The formulation blend of API and excipients was prepared and evaluated for various parameters as explained above. Bulk density was found to be in the range of 0.50-0.60 g/cm³. The results for tapped density were found to be in the range of 0.64-0.70 g/cm³. The Hausner's ratio (H.R) was found to be in the range of 1.10-1.25 while the compressibility index was found in between 10.50-20.50%. Angle of repose of all the formulation batches was obtained between 25-30°. The results for the pre-compression parameters show excellent flow ability of all powder blends, as depicted in Table 2.

Table 1: Composition of trial batches

Ingredients	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉
Captopril	50	50	50	50	50	50	50	50	50
Chitosan	200	175	150	125	100	75	50	25	0
Xanthan gum	0	25	50	75	100	125	150	175	200
PVP K30	30	30	30	30	30	30	30	30	30
Sodium bicarbonate	30	30	30	30	30	30	30	30	30
Citric acid	15	15	15	15	15	15	15	15	15
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Total	340	340	340	340	340	340	340	340	340

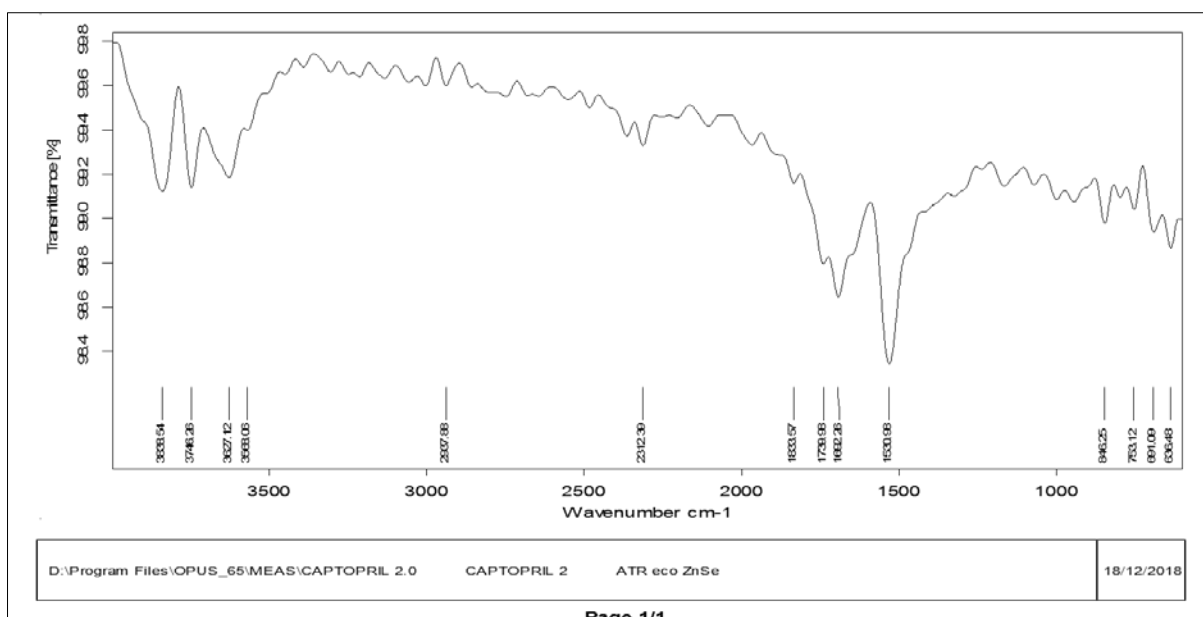


Figure 1: IR spectrum of captopril

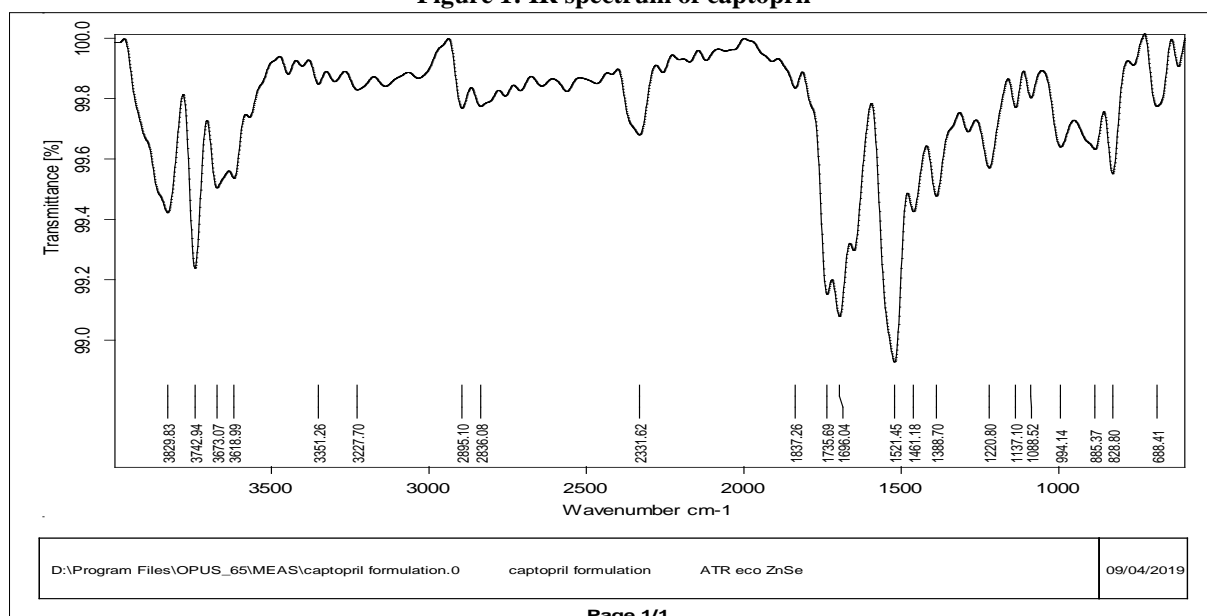


Figure 2: IR spectrum of drug-polymer mixture

Table 2: Results for pre-compression parameters

Batch	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Compressibility index (%)	Hausner's ratio	Angle of repose (°)
F ₁	0.59 ±0.02	0.69 ±0.01	14.49 ±0.01	1.16 ±0.05	25.2 ±0.02
F ₂	0.57 ±0.05	0.67 ±0.02	14.92 ±0.05	1.17 ±0.04	26.8 ±0.05
F ₃	0.51 ±0.07	0.64 ±0.05	20.31 ±0.04	1.25 ±0.02	25.6 ±0.04
F ₄	0.53 ±0.03	0.65 ±0.04	18.46 ±0.06	1.22 ±0.04	26.4 ±0.02
F ₅	0.52 ±0.04	0.64 ±0.08	18.75 ±0.01	1.23 ±0.03	27.6 ±0.05
F ₆	0.57 ±0.06	0.66 ±0.02	13.63 ±0.06	1.15 ±0.08	28.2 ±0.07
F ₇	0.56 ±0.01	0.68 ±0.04	17.64 ±0.05	1.21 ±0.02	27.3 ±0.05
F ₈	0.54 ±0.02	0.66 ±0.01	18.18 ±0.01	1.22 ±0.01	25.8 ±0.03
F ₉	0.58 ±0.05	0.65 ±0.05	10.76 ±0.02	1.12 ±0.03	29.9 ±0.04

Table 3: Results for post compression Studies

Batches	Hardness (Kg/cm ²)	Friability (%)	Thickness (mm)	Weight variation	% Drug content
F ₁	4.22 ±0.82	0.34 ±0.02	3.24 ±0.01	351 ±0.52	86.58
F ₂	4.48 ±0.65	0.40 ±0.01	3.25 ±0.04	353 ±0.85	97.34
F ₃	4.29 ±0.084	0.33 ±0.03	3.25 ± 0.02	343 ±1.08	102
F ₄	4.98 ±1.23	0.31 ±0.01	3.24 ± 0.02	358 ±0.95	98.63
F ₅	4.64 ± 0.95	0.49 ±0.05	3.23 ±0.03	348 ±0.74	100.56
F ₆	4.05 ±0.53	0.35 ±0.02	3.24 ± 0.01	346 ±0.88	97.43
F ₇	4.07 ±0.74	0.45 ±0.01	3.25 ±0.04	352 ±1.02	99.63
F ₈	3.94 ±0.59	0.51 ±0.05	3.23 ± 0.02	340 ±0.87	100.02
F ₉	4.26 ±1.02	0.32 ±0.04	3.24 ±0.01	338 ±0.69	93.71

Post compression parameters for formulation**Weight variation**

The weight of tablets from all formulation batches was found within range 350±15mg. Hence, the weight of all formulation batches was found to be within the limit (Table 3).

Thickness

The thickness of tablets from all formulation batches was found between the range 3±0.20 mm (Table 3).

Hardness

Hardness of formulation batches F₁- F₉ was observed within the range of 4-5 Kg/cm² (Table 3).

Friability

Friability of all the formulation batches was observed below 0.60% which was in acceptable limit (<1.0%) (Table 3).

Drug content

The % drug content of all the formulation batches F₁-F₉ was observed in between 95-105%, indicating content uniformity of the formulations (Table 3 and Figure 2)

Swelling index

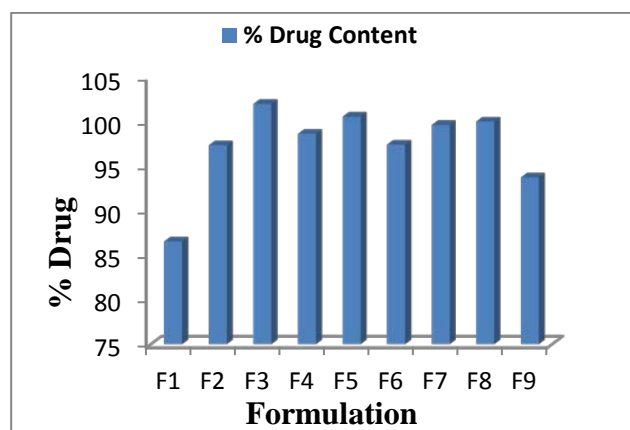
Based on the swelling index study of all the formulation batches it was observed that as the concentrations of polymers increases swelling property of tablets also increases. Formulation F₁ shows least swelling while formulation F₉ shows maximum swelling property (Table 4).

Floating lag time

Buoyancy lag time or floating lag time specifies the time needed for the tablets to float in the medium. Table 5 depicts that the formulation batches F₄-F₆ has more floating time as compared to other formulation batches. It was observed that formulation batch F₁ shows least floating time since it is composed of single polymer. Thus, as the concentration of polymers increases, drug release decreases. Hence, the 1:1 concentration of polymers provides sustained drug release upto 12 hrs (Figure 3).

In vitro dissolution studies

The results of the in-vitro drug release showed a sustained drug release over a time of 8 hrs as shown in Figure 4.

**Figure 2: % Drug Content****Table 4: Swelling index**

Formulation Code	Swelling Index (%) After 8 hrs
F1	145
F2	170
F3	185
F4	179
F5	182
F6	166
F7	160
F8	172
F9	191

Table 5: Floating Lag time

Formulation Code	Floating Lag Time [FLT] (Sec)	Total Floating Time [TFT] (Hrs.)
F1	82	>8hr
F2	85	>8hr
F3	81	>8hr
F4	90	>8hr
F5	80	>8hr
F6	81	>8hr
F7	91	>8hr
F8	83	>8hr
F9	86	>8hr

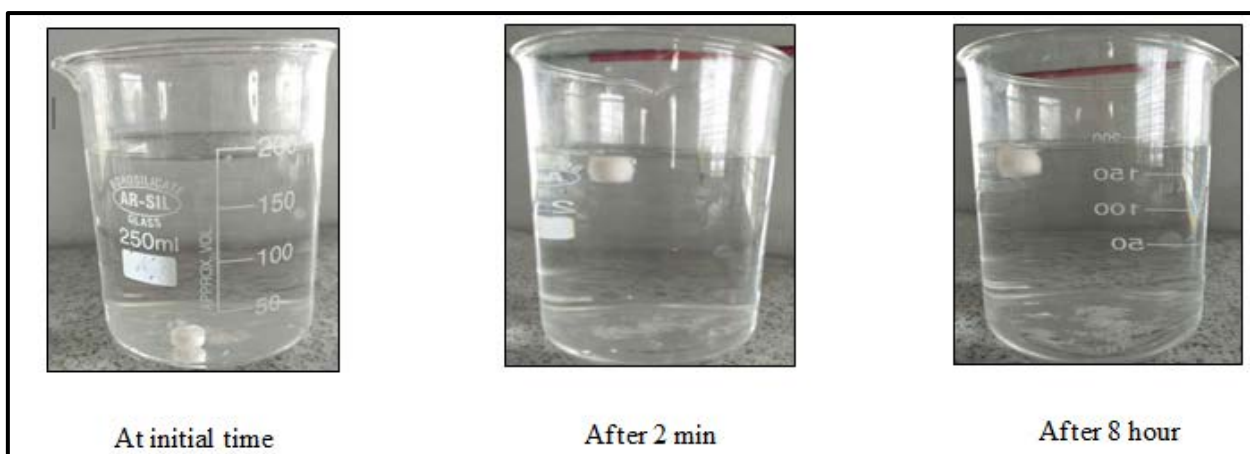


Figure 3: Photograph showing the floating lag time of formulated tablets

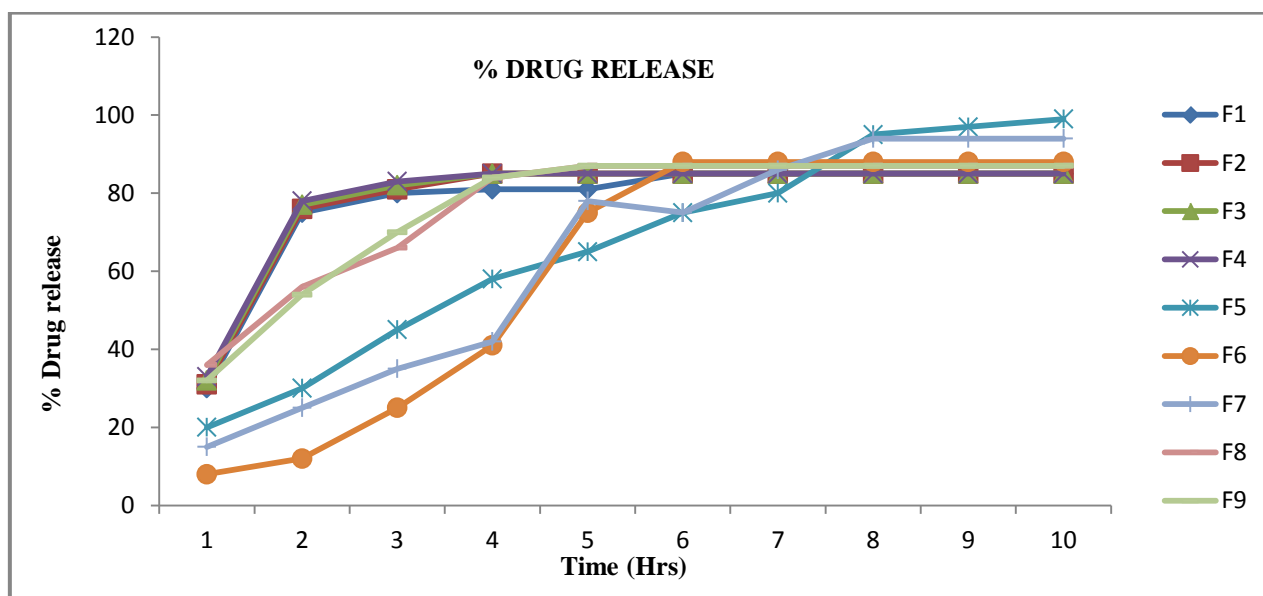


Figure 4: In-vitro drug release of captopril tablet formulations

CONCLUSION

The drug captopril indicated for hypertension and cognitive heart failure has been found to have short half-life and pH sensitivity. Thus, this study was mainly focussed on formulating a gastroretentive floating tablet. The formulated tablet dosage form composed of sodium bicarbonate and citric acid in the concentration of 10% and 5% respectively. As the concentration of polymers increased the drug release was minimized. Hence, the ratio of polymers chitosan and xanthan gum was optimized to 1:1 concentration to obtain sustained drug release upto 12 hrs. Thus, the limitations of captopril may be overcome by formulating a gastroretentive tablet dosage form.

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