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Formulation and Evaluation of Floating Tablet of Captopril

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Abstract: The present study was undertaken to prolong the release of orally administer. Captopril in the floating tablets by using different grade of hydroxypropylrmethylecellulose. Formulations were optimized using different viscosity grades of hydroxypropylmethylecellulose. Lactose and citric acid were used in different concentration as a channeling and chelating agent to obtain best optimized formulation and designed to prolong the gastric residence time (GRT). Formulations were evaluated by floating lag time and *in vitro* drug release method. Results revealed that the effect of channeling and chelating agent at different concentration had significant effect on the release of the drug from hydrophilic matrix tablet. Three different viscosity grades of hydroxypropylrmethylecellulose namely K100M, K 15M and K 4M were used as a floating polymer or intention of polymer. It was observed that different viscosities not only influence the drug release from hydrophilic matrix but they also affect the floating properties of tablets. Dissolution profiles were subjected for various kinetic treatments to analyze the release pattern of the drug and we found that drug release by diffusion mechanism and followed square root kinetics or Higuchi's kinetics. The *in vitro* release profiles of drug from all the plots shows high linearity (r^2= 0.9813 to 0.9954). Optimized formulations were again subjected for thickness, friability, hardness, uniformity of content, uniformity of weight, in *vitro* dissolution. Floating lag time, floating time and stability studies. Results revealed that the floating formulation of the Captopril is the best formulation to obtain better therapeutic effect and hydroxypropylrmethylecellulose at a concentration of 35% up to some extent it increases the Bioavailability of the drug to retain the dosage form on the desired site for effective period of the time.
Key words: Floating drug delivery system, gastric retention time, HPMC, Lactose, and captopril.

Introduction

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is be dilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility. Furthermore, the relatively short gastric emptying time in humans this normally averages 2-3 hrs. Through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. After oral administration, such a dosage forms would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. Gastroretentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH

environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients.[1, 2, 3, 4] Captopril is an angiotensin converting enzyme inhibitor; it inhibits the conversion angiotensin I to angiotensin II. As angiotensin II is a vasoconstrictor and a negative feedback mediator for renin activity, lower angiotensin II levels results in a decrease in blood pressure. It has been widely used for the treatment of hypertension and congestive heart failure. Captopril acts orally and the dosage used for the treatment of congestive heart failure ranges from 50 to 150 mg daily. After oral ingestion of a single dose the maximum hemodynamic effect is observed after 45–90 min. The drug is freely water-soluble and it has elimination half-life after an oral dose is 2-3 h. It is stable at pH 1.2, and as the pH increase, the drug becomes unstable and undergoes a degradation reaction. Captopril has been a drug of choice in hypertension management. However, after single oral dosing of the drug, the antihypertensive action is only effective for 6–8 h. Development of a controlled delivery system for captopril would bring many advantages for patients. The development of oral controlled release formulations for captopril is difficult because of in vivo and *in vitro* instability. The drug also undergoes from dose dumping and burst phenomenon (being freely water soluble) when formulated as controlled or sustained release formulation. So present investigation under taken to develop a controlled release oral solid dosage form[5, 6, 8, 9, 10].

Experimental Work

Material and Method

Captopril was obtained as a gift sample from Torrent Pharmaceuticals Ltd, Ahmadabad. Hydroxyproprylmethylcellulose, K4M, K15M, K100M. Microcrystalline cellulose, Lactose, sodium bicarbonate, magnesium sterate, and talc were obtained from CDH (P) Ltd, New Delhi.

Preparation of floating hydrophilic matrix tablet

Ingredients were weighed accurately and mixed thoroughly. All the composition mix together except magnesium sterate and punched the composition in tablet punching machine. Reduction of slugs is done in order to obtain granules for compression and passed granules through the 20 mm sieves. After that magnesium sterate was added in the granules and compressed to form tablet by using single punch tablet machine. The tablets were white round and flat, the details of composition are given in Table 1.

Floating behavior of the tablets

The *in vitro* buoyancy was determined by the floating lag time (time period between placing the tablet in the medium and the floating time) method described by Rosa *et al*, 1994. Tablets were placed in a 100 ml beaker containing 0.01 N HCL. The time required for the tablets to rise to the surface and float was taken as the floating lag time.[7, 23, 24]

Evaluation of Tablets[12,17]

Hardness

The tablet was placed between two anvils of hardness tester (Monsanto) and force (kg) was gradually increases in order to get exact reading. The reading at the marked scale was recorded for the pressure, which is required to break the tablet.

Friability

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and
weighed again .The observed value should not be more than 1 %.
The percentage friability was measured using the following formula.

$$\% F = \{1-(W_t/W)\} \times 100$$

Where, % F = friability in percentage, W = Initial weight of tablet, W_t = weight of tablets after revolution.

Drug content[11,16]

Five tablets for each batch were taken and triturated. Powder equivalent to 100mg of drug was weighed and transferred to beaker and then 0.01N HCL was added and it was then shaken for 5 minutes and finally 0.01N HCL was added to make the volume up to 100ml and solution was then sonicated for 15 minutes and filtered through whatman filter paper. Finally a solution was diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 203nm using UV/Visible spectrophotometer jasco V-530 against 0.01N HCL blank.

Weight variation[19]

Twenty tablets were randomly selected from each batch and individually weighed using an electronic balance. The average weight and standard deviation of 20 tablets was calculated. Mean and SD were calculated show in (Table No 4). Weight values were reported in milligrams.

Preparation of Standard Curve in 0.01N HCL.[18]

10 mg accurately weighed captopril was dissolved in the 10ml 0.01N HCL. From this stock solution different dilutions were prepared in the concentration range of 10, 20, 30, 40 and 50 µg/ml in 10 ml volumetric flask and absorbance was taken at 203 nm. Standard curve was prepared (Figure No 1) by the observations recorded in (Table No 2). Correlation coefficient = 0.9991

***In vitro* dissolution studies**

In vitro dissolution studies of all the formulations of floating tablets of captopril were carried out in 0.01 N HCl at 37 ± 0.5°C. The study was performed for 12 h and cumulative drug release was calculated at every one-hour time interval. *In vitro* dissolution studies of all the formulations are shown in figure 2, 3 and 4, 5. Using different viscosity grades of hydroxyl-propylmethylecellulose (Table No 1) to prepare the floating tablet. It was observed that the different viscosity grade HPMC polymer to effect the drug release pattern. The dissolution study was carried out under sink condition.

Mechanism of drug release [13-15]

To find out the mechanism of drug release from hydrophilic matrices, the dissolution data of floating tablet of each batch treated with different kinetic release equations.

The released data were plotted according to following equations,

- Zero order : $M = M_0 - K_0 t$
- First order : $\text{Log } C = \text{Log } C_0 - K_t/2.303$
- Higuchi square root law : $Q = kt^{1/2}$
- Korsemeyer's model : $M_t/M_\infty = kt^n$

Where, M, C and Q is the amount of drug released at time t, M_0 and C_0 is total amount of drug and K_0, K_t and k are corresponding rate constant.

In case of Korsemeyer's model M_t/M_∞ is the fractional drug release at time t, k is a constant incorporating the properties of the macromolecular polymeric systems and the drug, n is a kinetic constant, which is used to characterize the transport mechanism. The value of n for a cylinder is < 0.5 for fickian release, 0.5 < n < 1.0 for Anomalous transport (Non- Fickian diffusion), 1.0 for Case-II transport, >1.0 for Super Case-II transport type release.

Table 1: Composition of Floating Tablets of Captopril

Ingredients (mg)	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	50	50	50	50	50	50	50	50	50
HPMC K4M	70	-	-	-	-	-	-	-	-
HPMC K15M		70	-	-	-	-	-	-	-
HPMC K100M			70	80	60	50	70	70	70
NaCO3	12	12	12	12	12	12	12	12	12
Citric acid	5	5	5	5	5	5	7	3	5
Lactose	30	30	30	30	30	30	30	30	35
MCC	30	30	30	50	40	20	28	32	25
Mg state	3	3	3	3	3	3	3	3	3
FLT (sec)	42	48	45	30	40	55	30	65	40
TFT (h)	>12	>12	>12	>12	>12	>12	>12	>12	>12

MCC is microcrystalline cellulose, FLT is floating lag time and TFT is total floating time

Table No. 2 Calibration curve of captopril

S.No.	Concentration	Absorbance
1	0	0.0000
2	10	0.3201
3	20	0.5472
4	30	0.8169
5	40	1.0885
6	50	1.3413

Figure: 1 calibration curve of captopril

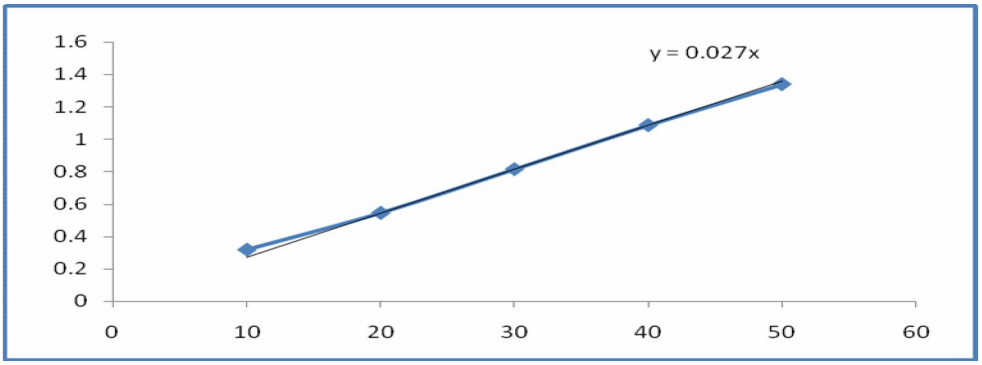


Table No:-3 Result of flow properties of granules of captopril.

Code	Angle of repose (θ)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's index (%)	Hausner ratio (Hg)
F1	27.02	0.48	0.57	18.75	1.08
F2	22.29	0.52	0.60	13.33	1.15
F3	30.11	0.42	0.52	19.23	1.23
F4	24.22	0.46	0.57	19.29	1.23
F5	31.38	0.57	0.63	9.52	1.10
F6	24.22	0.52	0.57	8.77	1.09
F7	27.02	0.44	0.54	18.05	1.22
F8	25.64	0.42	0.63	30.15	1.50
F9	28.36	0.46	0.54	14.81	1.19

Table No-4 Result of post compression properties of captopril floating tablet

Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	% Weight variation (mg)
F1	3.45±0.05	5.8	0.11	98.23	201±5
F2	2.97±0.02	5.4	0.13	98.75	198±4
F3	3.71±0.09	5.5	0.11	99.28	203±6
F4	3.51±0.10	5.9	0.12	98.13	197±5
F5	3.13±0.03	6.0	0.12	97.86	202±5
F6	3.15±0.07	5.7	0.14	99.12	199±6
F7	3.45±0.11	5.6	0.13	98.45	197±4
F8	3.35±0.08	5.9	0.11	98.11	204±5
F9	3.87±0.08	6.0	0.13	97.25	201±5

Table 5: Kinetic Treatment to Dissolution Profile of Tablets

Code	Zero order		First order		Higuchi		Koremeyer and peppas	
	K_0	r^2	K_1	r^2	K	r^2	N	r^2
F1	5.8362	0.9099	-0.1086	0.9834	7.5518	0.9936	0.505	0.997
F2	5.9988	0.9575	-0.0969	0.9746	27.344	0.9883	0.491	0.993
F3	5.9399	0.9688	-0.0801	0.9794	26.915	0.9881	0.493	0.982
F4	5.9764	0.9464	-0.0658	0.9913	27.305	0.9813	0.485	0.994
F5	5.8084	0.9516	-0.0687	0.9936	26.549	0.9876	0.483	0.994
F6	5.8312	0.9376	-0.0893	0.9819	26.714	0.9775	0.425	0.971
F7	6.0061	0.964	-0.0854	0.955	27.384	0.9954	0.53	0.994
F8	5.8534	0.9804	-0.0968	0.964	26.455	0.9949	0.494	0.975
F9	5.8046	0.9613	-0.0881	0.9794	26.443	0.991	0.649	0.992

Figure 2:- Cumulative percentage release of different formulation

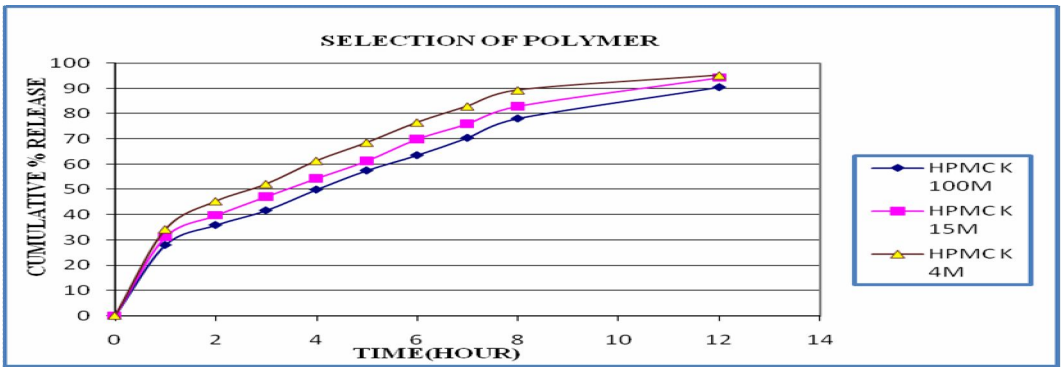


Figure 3:- Effect of HPMC Concentration

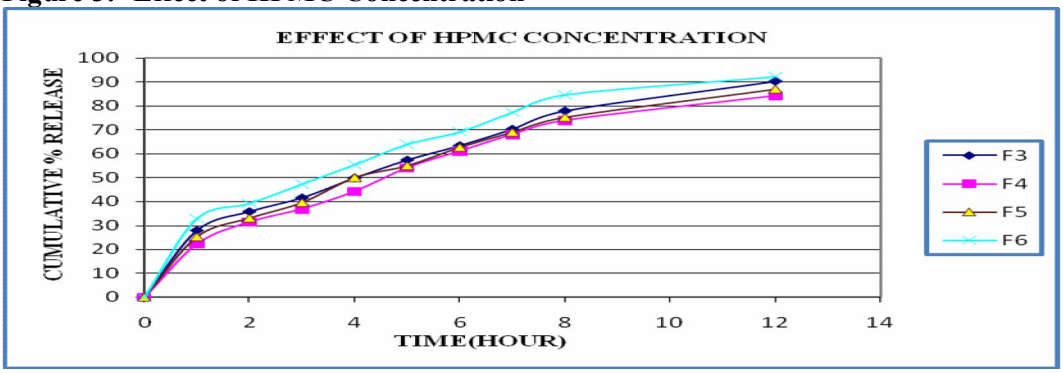


Figure 4:- Effect of Citric Acid

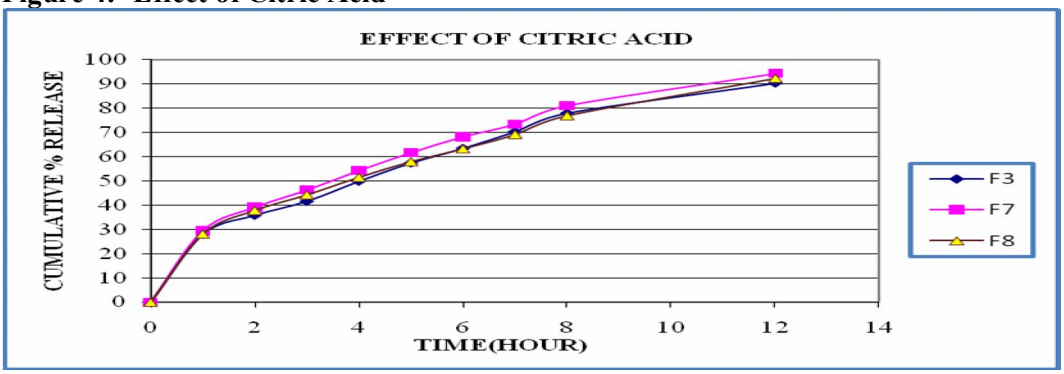


Figure 5:- Effect of Lactose

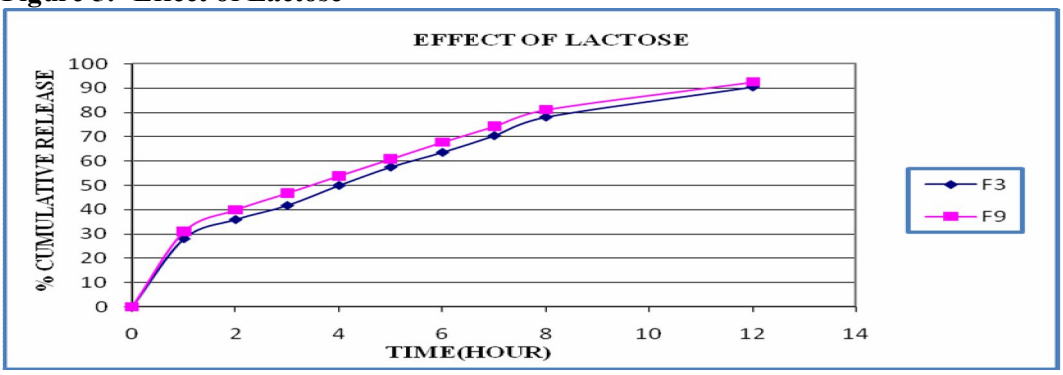


Figure 6: Zero order release kinetics of optimized formulation (F3)

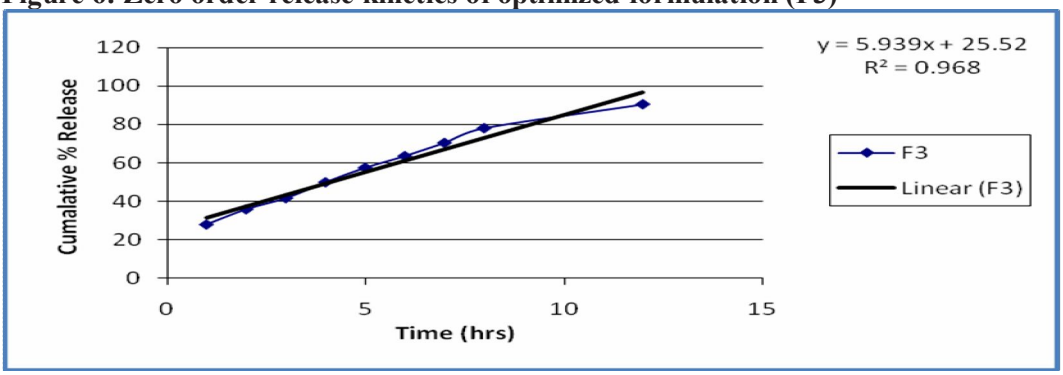


Figure 7: Korsmeyer and Peppas release kinetics of optimized formulation (F3)

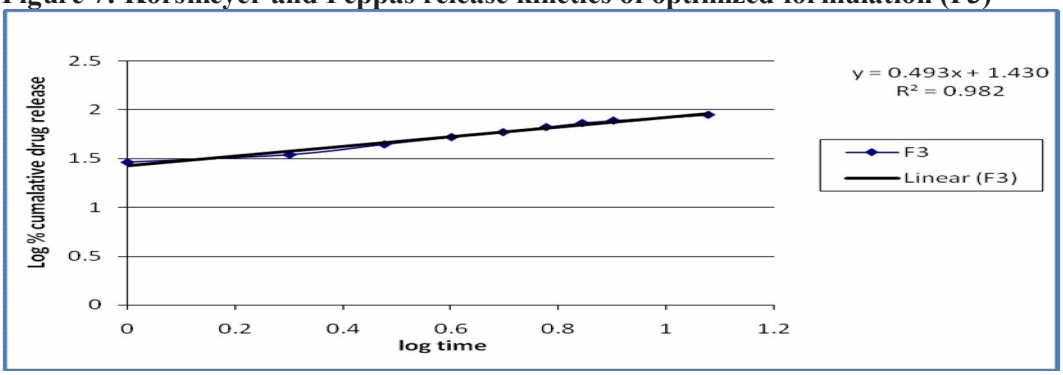
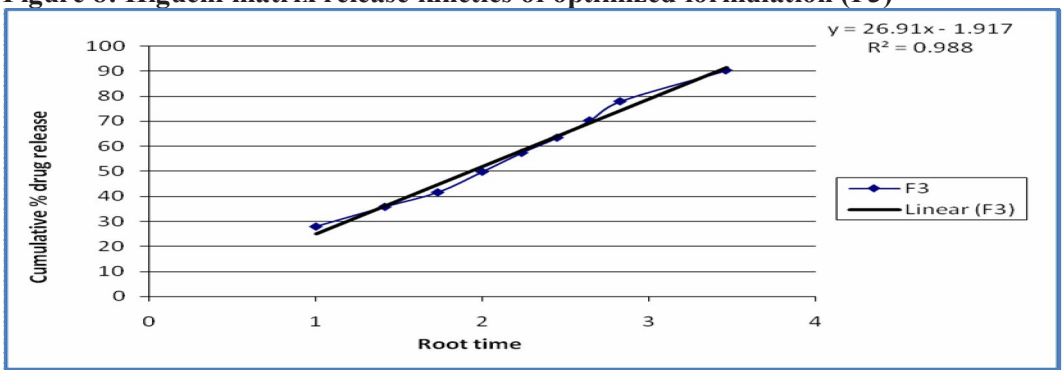


Figure 8: Higuchi matrix release kinetics of optimized formulation (F3)



Result and Discussion

Floating tablets of captopril were developed in order increase the gastric residence time of drug, so that they can be retained in stomach for longer time and help in controlled release of drug up to 24 h. The tablets were made using different gel forming polymers such as HPMC K4M, HPMC K15M and HPMC K100M along with effervescing agent sodium bicarbonate and citric acid to optimize the drug content, *in vitro* buoyancy and *in vitro* drug dissolution studies. The selection of viscosity grade of a polymer is an important consideration in the formulation of tablet. All the formulations were prepared by direct compression method.

Preformulation studies

Preformulation is the first step in development of new formulation. The Physical appearance and melting point of drug were found to be concordant with that mentioned in USP, 24-NF. Respectively this shows the purity of the sample. IR spectrum of the drug sample was obtained by FT/IR (Jasco – 470 plus). Its characteristic absorption bands showed and proved identity of drug. Solubility of captopril was determined in various aqueous and non-aqueous solvents. The drug was found to be soluble in, distill water, ethanol, 0.01N HCL and PBS (ph 7.4). The partition coefficient value (Log $P_{o/w}$) of captopril was found to be 0.95 in n-octanol: aqueous solution.

Determination of calibration curve

Absorption maxima of the drug were determined by UV spectrophotometric method using UV/Visible spectrophotometer (jasco V530 plus). The λ_{max} of drug in 0.01N HCL is 203 nm. The standard curves of drug were prepared in 0.01N HCL in the concentration range of 10 to 50µg/ml. A straight line with r^2=0.9991 was found indicating that the drug follows Beer's law within the specified concentration range.

Powder characterization of captopril granules

The value showed that the powder has compressibility index vary from 8 – 30 and hausner ratio varies from 1.1-1.23. This showed good compressibility except F4, F5 and F8 batch, Bulk density and tapped density vary from 0.42-0.57 and 0.52-0.63, whereas angle of repose varied from 22°-31° which ensured good flow properties of powder.

Evaluation of tablet

The general appearance of tablets, its visual identity and overall 'elegance' is essential for acceptability, the shape of all the formulation remained off white, smooth, flat faced circular and no visible cracks. The thickness of the tablet measured by vernier calipers, the hardnees of the tablet was measured by monsanto tester and was ranged between 5.4 to 6.0 kg/cm^2. The friability was measured by rose friabilator and was found 0.11 to 0.14 %, and this parameter given the satisfactory mechanical resistance of the tablet. The drug content estimations showed values in the range of 97.25 to 99.28%. These results showed the good drug content uniformity of the tablet. The entire tablet passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ± 7.5% of the weight. The result shown in table No 4. After the analysis of the above formulation and optimization study we can conclude that optimized formulation is the best and promising formulation for the delivery of the drug in order to provide the controlled release & increased gastro retentive drug delivery system.

***In vitro* dissolution studies**

The release profiles of formulations F1, F2 and F3, prepared by using HPMC K4 M, K15 M and K100 M, illustrated in (Table No 1) and (Figure No 2). Floating lag time was found to be 42, 48 and 45 second and cumulative percentage drug releases were 95.23, 94.15, and 90.35% for above batches. The release profiles showed tri-phasic with initial burst effect (less than 30 min) followed by a polymer-controlled slower release in the second phase. The difference in burst effect was the result of difference in the viscosity of the polymers. As it can be seen from (Figure No 2) Polymeric system with low viscosity polymer (HPMC K4 M, K15 M) yielded a faster initial burst effect except HPMC K100 M. There has been considerable interest in using different grades of HPMC in controlled release drug delivery system due to their hydrophilic nature and fast hydration.

The release profiles of formulations F3, F4, F5 and F6 prepared by using HPMC K100 M, are illustrated in (Table No 1) and (Figure No 3). Floating lag time was found to be 45, 30, 40, 55 seconds and cumulative % drug release was 90.94, 84.26, 87.13, and 92.16% respectively for F3, F4, F5, F6 batch. *In vitro* release profile showed on increasing the concentration of polymer released rate decreased but it also reduced the floating time.

Floating lag time for above batches that contain varying amount of sodium bicarbonate and citric acid was found to be 30 to 65 seconds. Sodium bicarbonate and citric acid of 6 % and 2.5 % respectively selected for formulation of floating tablet having floating lag time of less than 50 seconds. The concentration of gas-generating agent affected the floating lag time, as the amount of gas-generating agent was increased, the floating lag time decreased. The incorporation of gas-generating agent exhibited reduction in the floating lag time.

Floating lag time was found to be 45, 30 and 65 seconds and cumulative percentage drug release is 90.35, 94.32, and 92.30 % in batches F3, F7 and F8 respectively. The release profiles of formulations F3, F7 and F8 prepared by using HPMC K100 M, are illustrated in (Table No 1) and (Figure 4). It is reported that citric acid level greatly influenced the drug release, irrespective of hydroxypropylrmethyle - cellulose grade. The captopril release from the floating tablet was found to be 90.35, 94.32 and 92.30 % with hydroxypropylrmethylecellulose K100 M. *In vitro* release profile showed that on increasing the concentration of citric acid released rate increased but it also reduced the floating time.

Floating lag time was found to be 45 and 40 for batch F3 and F9 respectively. The release profiles of formulations F3 and F9 prepared by using HPMC K100 M are illustrated in (Table No 1) and (Figure 5). The cumulative percentage drug release from the floating tablet was found to be 90.35 and 92.54 %. Lactose was used as diluents as well as channeling agent in the floating delivery of the drug. *In vitro* release profile showed that on increasing the concentration of lactose release rate increased.

Data treatment

The different models of data treatment are shown in below. To find out the mechanism of drug released from all the formulations of captopril floating tablets, the data were treated according to zero order, first order, Higuchi square root law and Korsemeyer's

equation pattern. As clearly indicated in (Table No 3), the correlation coefficient value of all the formulations showed that the formulations did not follow zero order release pattern but batch F3, F7 and F8 showed fair zero order. When the data were plotted according to the first order equation, the formulations showed a fair linearity, with correlation coefficient values between 0.9550 to 0.9936.

Release of the drug from a floating matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix in to the *in vitro* study, which depends on the concentration. As gradient varies, the drug is released and the distance for diffusion increased. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square root kinetics or Higuchi's kinetics. In this experiment, the *in vitro* release profiles of drug from all the plots showed high linearity (r^2= 0.9813 to 0.9954). This represents the release process under the drug diffusion through polymer matrix.

To confirm the diffusion mechanism, the data were fitted to Korsemeyer's equation, F3 formulation showed linearity with exponent value (n) ranging 0.49. However, indicates the coupling of swelling and diffusion mechanism so called as Fickian diffusion. The relative complexity of this formulation and its components may indicate that the drug release is controlled by more than one process.[13-15]

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