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Formulation and *in vitro* evaluation of captopril floating tablets by using natural polymers

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Abstract
The objective of this research is to formulate and develop gastroretentive floating matrix tablets of Captopril using natural polymers by effervescent system which will retain the drug upto 12 hours, to prepare and evaluate floating tablets of Captopril using natural polymers karaya gum, badam gum alone and in combination. Sodium bicarbonate is used as effervescent component, tablets were compressed using direct compression and wet granulation methods. The prepared tablets showed acceptable physico-chemical characteristics, floating characteristics (floating lag time, floating time), swelling index, drug content and evaluated for *in vitro* release characteristics for 12hours in 0.1N HCl. Drug compatibility with excipients was checked by FTIR studies. Formulations with low concentration of polymers were unable to produce the desired action. The formulations prepared with combination of polymers (Karya gum+ Badam Gum) was retarding the drug release up to 12 hours (F_{11}=96.68). From the release kinetics data it was evident that the formulation followed Higuchi release mechanism.

Keywords: Captopril, floating tablets, karaya gum, badam gum

1. Introduction
Oral delivery of drugs is the most preferable route of drug delivery. Oral route is considered as a natural, uncomplicated, convenient and safe due to its ease of administration, patient compliance and flexibility in formulation and cost effective manufacturing process [1]. These immediate release dosage forms have some limitations such as: Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{ss} values fall or rise beyond the therapeutic range. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever overmedication occurs.

To overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide number of therapeutic benefits.Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue [2].

Majority of the drugs are well absorbed from all the regions of the G.I tract while some are absorbed only from specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, as well as to the degradation of the drug by the microorganisms present in the colon. Controlled release or Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for drugs [3] which are

1. Acting locally in the stomach
2. Absorbed incompletely due to relatively narrow window of absorption in the GIT.
3. Unstable in the intestinal or colonic environment such as captopril.
4. Exhibit low solubility at high pH values such as verapamil HCl, diazepam and chlordiazepoxide.

Gastroretentive Drug Delivery Systems can be defined as retention of oral dosage forms in the upper GIT, causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. Drug Candidates for

Gastric Retention are Captopril, Furosemide, Riboflavin, Ranitidine, Diazepam, Chlordiazepoxide, Verapamil HCl, and diazepam. Advantages includes Enhanced Bioavailability, Minimized adverse effects at the colon, Reduced frequency of dosing, Reduced fluctuations of drug conc., Sustained drug delivery, Targeted therapy for local ailments in the upper GIT, Less irritation and low cost.

Captopril is widely used as anti- hypertensive agent, to treat congestive heart failure, kidney problems caused by diabetes, and to improve survival after a heart attack. It belongs to BCS class III (high solublility and low permeablility). Bioavailability was found to be 70–75%, half-life is nearly 2 hours.

The objective of this present investigation is to formulate floating matrix tablets of Captopril by direct compression and wet granulation methods using natural polymers i.e., karaya gum and badam gum alone and in combination to prolong the gastric residence time and increase the drug bioavailability. When comparing the two methods, direct compression method shows fast drug release from the tablet. Wet granulation method shows controlled/delayed release of the drug from the tablet. All the formulations were evaluated for their pre and post compression parameters and *in vitro* dissolution studies.

2. Materials and Methods

2.1. Material Collection

Captopril Procured From Ranbaxy Laboratories Ltd., New Delhi. Provided by SURA LABS, Dilsukhnagar, Hyderabad. Karaya Gum, Badam Gum, Sodium Stearyl Fumarate, Aerosil, $NaHCO_3$, MCC, PVP K30 was received from Merck Specialities Pvt Ltd, Mumbai, India.

2.2. Methods

Method of Preparation of Captopril Floating Tablets

Direct Compression Method [4, 5]

Drug and all other ingredients were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15min. Tablets were prepared by mixing the drug Captopril 50mg with gas generating agent sodium bicarbonate and other ingredients in motar and pestle for 10min, and then fabricated with sodium stearyl fumarate & aerosil for 5min. The lubricated blend was compressed using 8mm round faced punch using rimek mini press tablet compression machine. (Table: 1) The compression force used was kept constant for the process, to obtain tablet of hardness 4-6kg/cm^2.

Table 1: Formulation for Captopril Floating Tablets by Direct Compression Method

Ingredients mg/tablet	F_1	F_2	F_3	F_4	F_5	F_6
Captopril	50	50	50	50	50	50
Karaya Gum	25	50	-	-	-	-
Badam Gum	-	-	25	50	-	-
Karaya Gum+ Badam Gum	-	-	-	-	25(10,15)	50(25,25)
Sodium Stearyl Fumarate	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5
$NaHCO_3$	20	20	20	20	20	20
MCC	150	125	150	125	150	125
Total Weight	250	250	250	250	250	250

Wet Granulation Method [6]

Properly weighed drug and excipients are blended for 10 minutes. 5% w/v PVP K 30 in isopropyl alcohol was added to form a uniform wet mass. The granules of desired size are obtained by passing the wet mass through sieve no. 18. The granules are dried in hot air oven. The dried granules are then mixed with aerosil for 10 minutes and compressed to tablets at predetermined weight in tablet punching machine using 8mm die.

Table 2: Formulation for Captopril Floating Tablets by Wet Granulation Method.

Ingredients mg/tablet	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Captopril	50	50	50	50	50	50
Karya Gum	25	50	-	-	-	-
Badham Gum	-	-	25	50	-	-
Karyagum+ Badham Gum	-	-	-	-	25(15,10)	50(25,25)
Sodium Stearyl Fumarate	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5
$NaHCO_3$	20	20	20	20	20	20
PVP K30 in Iso propyl Alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
MCC	150	125	150	125	150	125
Total Weight	250	250	250	250	250	250

3. Evaluation of Tablets

Pre-Compression Parameters

Powder characteristics of powder blend of Captopril with other excipients. [7] Physical mixtures of drug with excipients were evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner ratio. (Table 3)

3.1 Angle of repose

The angle of repose for powder of each formulation was determined by the fixed funnel method. The powder was allowed to flow out of the funnel orifice on a plane paper kept on horizontal surface. This forms a pile of angle of powder on the paper. The angle of repose was calculated by substituting the values of the base radius"r" and pile height "h" in the following equation.

$$\text{Tan } \theta = h / r$$
$$\theta = \tan (h / r)$$

3.2 Bulk density

The powder weighing 20 gm flow in a fine stream into a graduated cylinder and final volume was noted. The bulk density was obtained by dividing the weight of the sample in grams by final volume in cm^3 and it was determined by equation given below,

$$\text{Bulk density} = \text{Bulk mass} / \text{Bulk volume}$$

3.3 Tapped density

The powder weighing 20 gm was allowed to flow in a fine stream into a graduated cylinder of a mechanical tapping device. The measuring cylinder was tapped for 100 times and final tapped volume was noted. The tapped density was calculated by using equation given below,

$$\text{Tapped density} = \text{Bulk mass} / \text{Tapped volume}$$

3.4 Carr's index

The percentage compressibility of a powder was a direct assessment of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below,

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

3.5 Hausner's ratio

It is essential to determine the compressibility strength of powders. It was determined by using following equation,

$$\text{Hausner's ratio} = \text{Tapped density} / \text{Bulk density}$$

Post-Compression Parameters

The designed compression tablets were studied for weight variation, hardness, thickness, friability, drug content, floating lag time, total floating time and swelling index. (Table 4)

3.6 Weight variation test: [8]

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

%Deviation = (Individual weight- Average weight/Average weight) × 100

3.7 Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Lab hosp hardness tester and the average is calculated and presented with deviation.

3.8 Thickness

Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

3.9 Friability

It is a measure of mechanical strength of tablets. Lab hosp friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25rpm for 4minutes (100 rotations). At the end of test, the tablets were re-weighed, and loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W_1 - W_2)/W_1] \times 100$$

W_1=Initial weight of tablets
W_2=Weight of the tablets after testing

3.10 Determination of drug content: [9]

All tablets were tested for their drug content. Ten tablets were finely powdered, quantities of the powder equivalent to one tablet weight of captopril were accurately weighed, transferred to a 100ml volumetric flask and the volume adjusted to 100ml with 0.1N HCl and were allowed to stand to ensure complete solubility of the drug. Further 1ml of the above solution was diluted to 100 ml with 0.1N HCl and the absorbance of the resulting solution was observed at 270nm in UV-Visible spectrophotometer.

3.11 Swelling index: [10]

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium as 0.1N HCl at 37±0.5 °C. After 12h, each dissolution basket containing tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance (Wensar). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formulae

Swelling index = (Wet weight of tablet – Dry weight of tablet)/ Dry weight of tablet.

3.12 *In vitro* buoyancy studies: [11]

The *in vitro* buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa *et al*) the tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as total floating time respectively (TFT).

3.13 *In vitro* drug release studies [12]

Dissolution parameters:

Apparatus	:	USP-II, Paddle type
Dissolution medium	:	0.1N HCl
RPM	:	50
Sampling intervals (hrs)	:	0.5,1,2,3,4,5,6,7,8,9,10,11,12
Temperature (bowl)	:	37 ˚C ±0.5 ˚C

Procedure

900ml of 0.1N HCl was placed in vessel and the USP apparatus-II (Paddle type) was assembled. The medium was allowed to equilibrate to temperature of 37 ˚C ±0.5 ˚C. Tablet was placed in the vessel the apparatus was operated for 12 hrs at 50rpm. At definite time intervals, 5ml of the sample solution was withdrawn filtered and then 5ml of fresh dissolution medium was replaced. Suitable dilutions were done and analysed spectrophotometrically at 270nm using UV-visible Spectrophotometer. (Table 5)

3.14 Application of release rate kinetics to dissolution data: [13-15]

The Kinetics of the drug release of floating tablet were described by using mathematical models such as, Zero order, First order, Higuchi, Korsmeyer-peppas which are shown in figures 5 to 8.

3.15 Stability studies

Stability studies as per ICH guidelines were carried out for optimized formulation in stability chamber (drug content and *in vitro* drug release). The stability studies were carried out at 40 ± 2 ^{0}C / 75 ± 5% RH for 3 months. (Table no: 6 &7.)

4. Results and Discussion

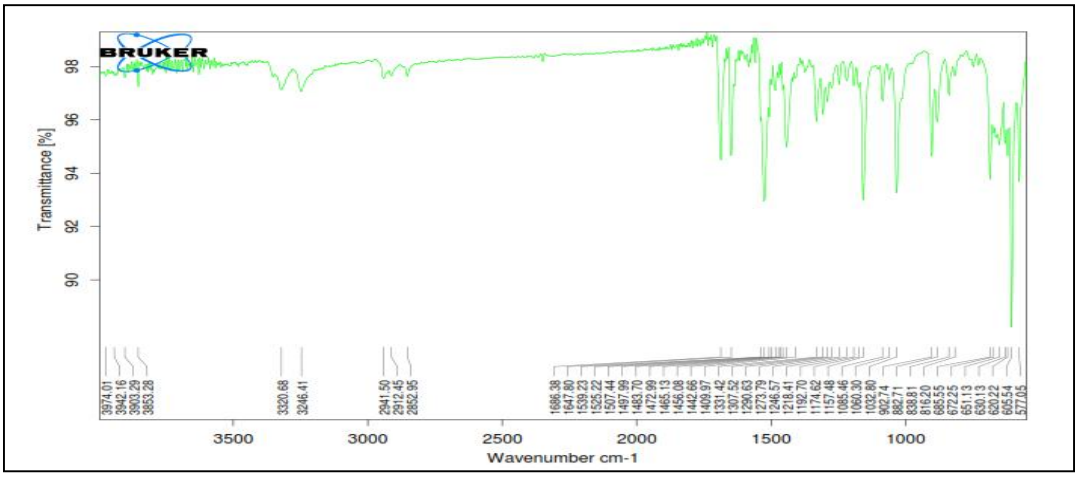

Fig 1: FTIR Spectrum of Pure Captopril

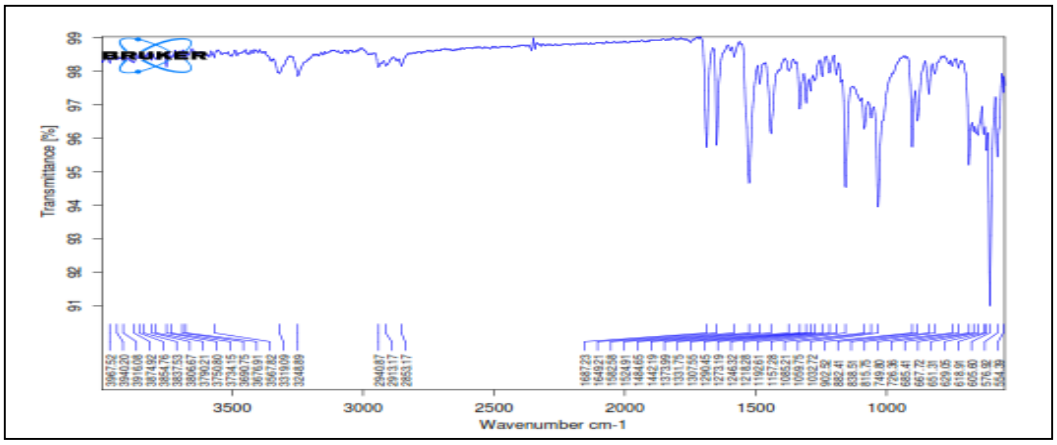

Fig 2: FTIR Spectrum of Drug and Excipients

- **Pre-Compression Studies**

Table 3: Pre-Compression parameters

Formulation Code	Angle of Repose	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's Ratio
F_1	24.20±1.0	0.33±0.02	0.416±0.00	20.10±1.52	1.25±0.019
F_2	26.62±0.98	0.316±0.03	0.365±0.01	16.32±0.11	1.19±0.00
F_3	21.36±0.82	0.317±0.01	0.372±0.00	13.58±0.92	1.170±0.013
F_4	27.89±0.80	0.348±0.01	0.416±0.01	16.27±0.039	1.19±0.022
F_5	19.08±0.72	0.345±0.01	0.442±0.01	18.24±0.16	1.22±0.001
F_6	21.62±0.53	0.342±0.012	0.380±0.00	21.89±0.56	1.23±0.021
F_7	26.89±0.92	0.319±0.024	0.377±0.00	16.62±0.32	1.201±0.019
F_8	28.47±0.92	0.334±0.01	0.4527±0.00	19.88±0.33	1.24±0.04
F_9	28.97±0.86	0.3330±0.01	0.410±0.01	20.24±1.49	1.26±0.019
F_{10}	27.78±0.78	0.362±0.01	0.4712±0.01	20.82±0.07	1.28±0.07
F_{11}	28.58±0.94	0.334±0.01	0.428±0.003	22.16±1.20	1.30±0.09
F_{12}	24.62±0.90	0.325±0.00	0.399±0.00	17.20±0.12	1.21±0.02

Post-Compression Studies

Table 4: Post-Compression Parameters

Formulation codes	Average Weight (%)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Total Floating Time (hrs)	Floating Lag time (sec)	Swelling index (%)
F_1	2	4.8±0.86	0.58±0.21	2.3±0.8	98.84	6	42	39.20±0.26
F_2	0.8	4.5±0.37	0.56±0.28	2.1±0.17	96.59	7	45	35.16±0.19
F_3	0	4.3±0.68	0.53±0.34	2.4±0.24	98.88	8	44	48.64±0.40
F_4	0.4	4.9±0.74	0.57±0.19	1.8±0.39	99.71	9	43	61.22±0.56
F_5	1.6	4.1±0.95	0.57±0.55	2.0±0.84	95.28	7	41	44.76±0.44
F_6	0.4	4.6±0.25	0.46±0.27	2.2±0.45	98.77	10	40	37.84±0.81
F_7	1.2	5.9±0.67	0.59±0.95	2.0±0.67	9738	11	42	58.96±0.54
F_8	2	5.8±0.89	0.48±0.17	2.1±0.88	99.47	>12	38	50.11±0.45
F_9	2.8	5.3±0.93	0.57±0.28	2.6±0.51	96.53	12	45	45.12±0.10
F_{10}	2.4	5.8±0.76	0.59±0.66	1.8±0.26	98.76	12	47	38.15±0.33
F_{11}	3.2	5.6±0.67	0.48±0.38	2.5±0.18	97.83	12	42	40.76±0.7
F_{12}	2.8	5.2±0.96	0.56±0.84	2.7±0.44	99.35	12	46	65.11±0.43

In vitro Drug Release

Table 5: Dissolution Data of Floating Tablets

TIME	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	15.26	30.36	20.15	18.41	24.12	28.19	15.41	9.23	19.25	04.31	13.50	6.47
1	30.34	43.52	34.99	24.62	38.64	36.77	20.98	15.69	22.11	11.29	25.62	14.56
2	46.18	56.88	48.26	31.94	50.20	45.82	26.55	30.04	25.09	16.27	38.97	25.24
3	53.64	68.97	57.38	42.76	69.56	57.59	32.84	49.08	29.54	20.34	43.54	29.09
4	62.22	73.43	66.75	55.29	75.43	63.26	39.39	57.71	33.36	28.09	50.93	33.24
5	84.23	86.28	70.19	63.48	83.01	71.14	44.71	59.61	39.67	32.48	58.17	38.09
6	98.97	93.33	85.44	70.52	95.57	75.96	53.05	65.05	44.36	40.85	66.22	43.15
7	98.97	96.88	91.96	78.87	98.69	83.58	60.87	69.94	50.77	49.02	72.31	51.28
8	98.97	96.88	97.57	85.37	98.69	89.45	67.02	71.78	56.42	58.92	79.07	58.42
9	98.97	96.88	97.57	99.33	98.69	94.74	74.15	74.02	60.02	62.21	83.12	62.70
10	98.97	96.88	97.57	99.33	98.69	97.99	89.24	79.66	64.46	69.95	87.75	70.36
11	98.97	96.88	97.57	99.33	98.69	97.99	97.54	81.23	79.39	70.68	91.01	72.03
12	98.97	96.88	97.57	99.33	98.69	97.99	97.54	84.93	86.14	74.85	96.68	78.98

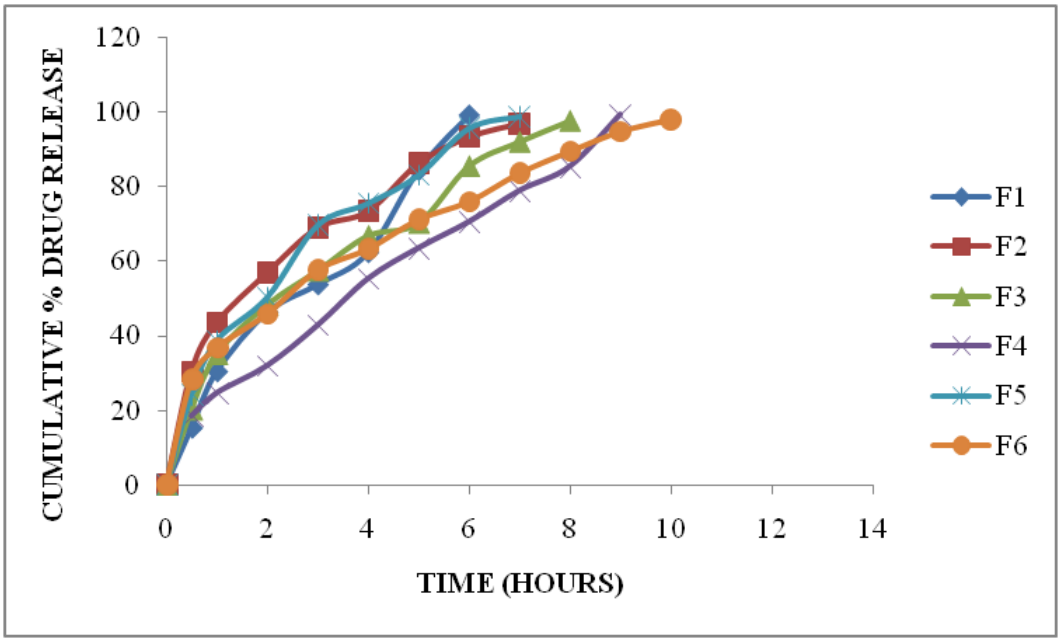

Fig 3: Dissolution Data of Captopril Floating Tablets by Direct Compression Method.

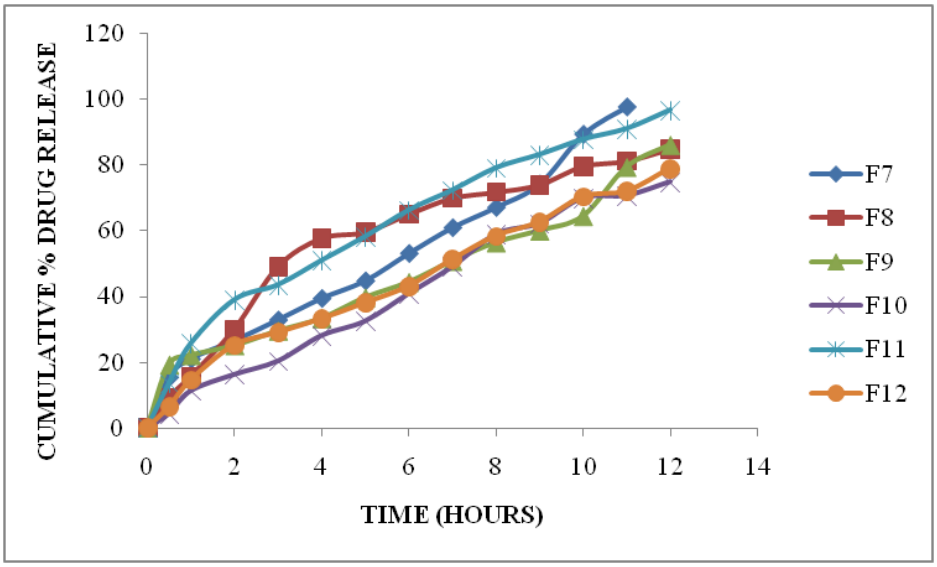

Fig 4: Dissolution Data of Captopril Floating Tablets by Wet Granulation Method

Kinetic Studies

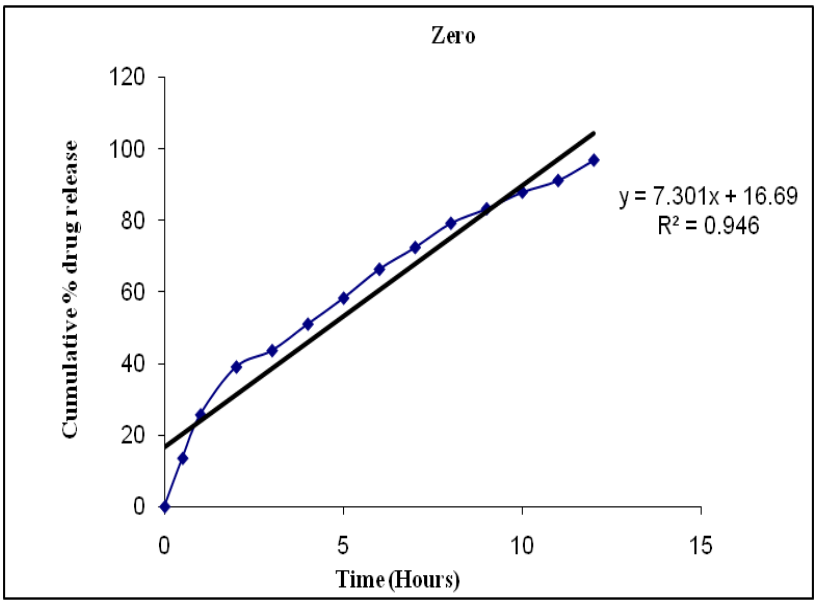

Fig 5: Zero Order Rlease Kinetics

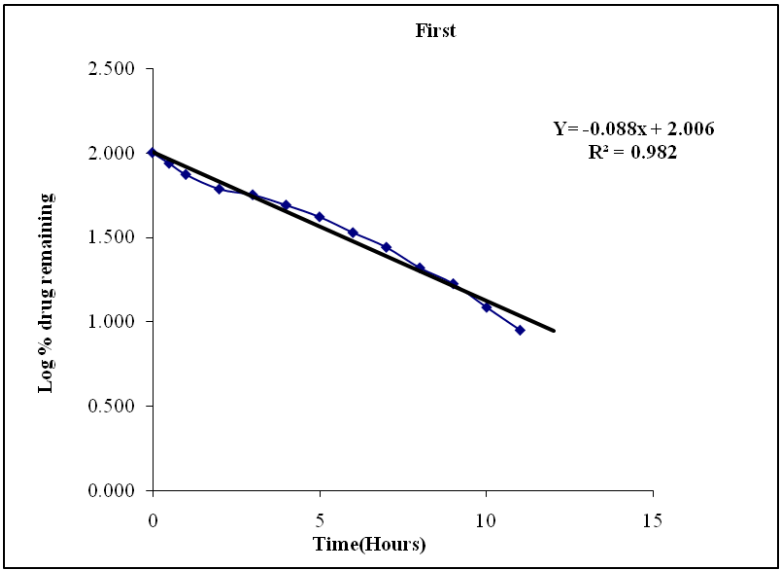

Fig 6: First Order Release Kinetics

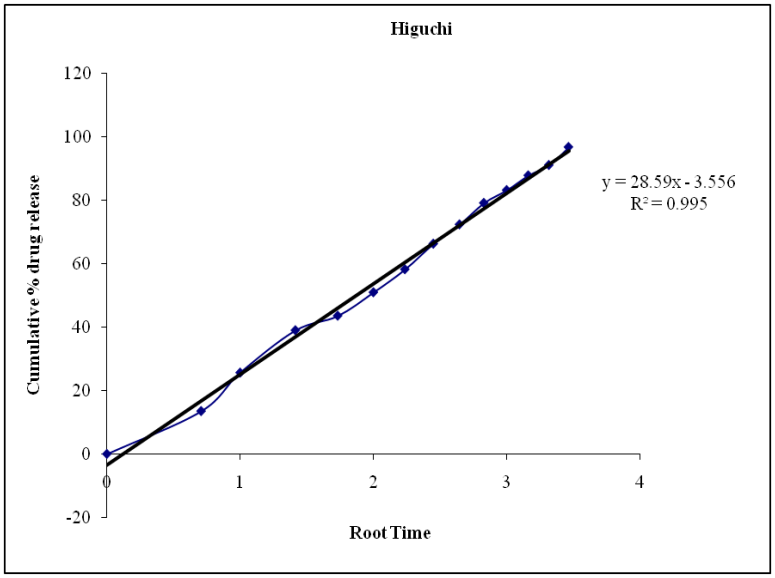

Fig 7: Higuchi Release Kinetics

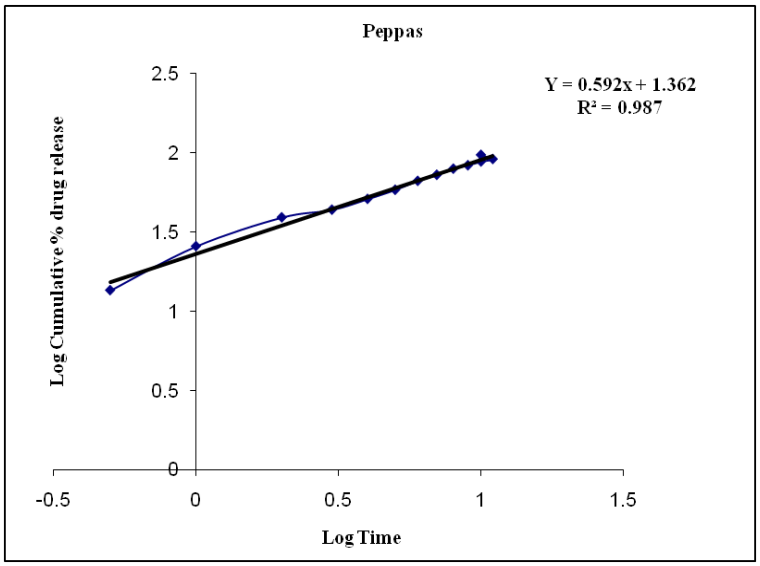

Fig 8: Korsmeyer- Peppas Release Kinetics

Table 6: *In-Vitro* Drug Release Data of the Stability Formulation –F_{11}

S. No	Formulation code	1st day	30th day	60th day	90th day
1.	F_{11}	96.68±0.93	96.70±0.59	96.65±0.42	96.66±0.39

All values are expressed as mean ± SD, n=3

Table 7: Drug Content Data of the Stability Formulation –F_{11}

S. No	Formulation code	1st day	30th day	60th day	90th day
1.	F_{11}	97.83±0.85	97.85±0.49	97.75±0.93	97.81±0.72

All values are expressed as mean ± SD, n=3

In the present study floating drug delivery of Captopril tablets has been developed, to provide the drug action up to 12 hours. Floating tablets were prepared by direct compression and wet granulation methods using various polymers like Karaya gum, Badam Gum alone and in combination. The formulated floating tablets were evaluated for different parameters such as drug excipient compatablity studies and was done using FTIR; results revealed that there was no interaction betweeen drug and other excipients (fig.1,2), pre-compression parameters was found to be within the prescribed limit (table 3). The post-compression evaluation was done (table 4). Hardness test indicates good mechanical strength. Friability of all formulations was less than 1%, which indicates that the tablets has good mechanical resistance. weight variation, thickness, content uniformity, *in vitro* drug release studies performed in 0.1 N HCl for 12 hrs and the data was subjected to various mathematical models like zero order, first order, higuchi, korsmeyer-peppas release kinetics. Swelling index for the formulations from F_1 to F_{12} was found to be in the range of 35.20 to 65.11%. The in-vitro buoyancy of formulations from F_1 to F_{12} was found to be in the range of 6 to 12 hours. From the dissolution data it was evident that the formulations prepared with direct compression technique were not retarding the drug release upto 12 hours. Whereas

the formulations prepared with wet granulation technique retarded the drug release up to 12 hours. In lower concentrations the polymer was unable to retard the drug release (Figure3). Direct Compression technique yielded a faster initial burst effect. The formulations prepared with combination of polymers showed more retardation capacity, controlled and maximum drug release. Hence from the above dissolution data it was concluded that F_{11} formulation was considered as an optimised formulation because of controlled drug release (96.68%) in 12 hours. Short term stability studies of the promising formulation F_{11} indicated that there are no significant changes in drug content and dissolution parameter values after 3 months at 40 ± 2 ^{0}C / 75 ± 5% RH, are shown in table 6 & 7.

5. Conclusion

Captopril is an anti-hypertensive drug, it was prepared using different natural polymers – karaya gum and badam gum alone and in combination, sodium bicarbonate, aerosil, MCC, Na. Stearyl Fumarate and PVP K_{30} were used as other excipients, formulations was developed by both direct compression and wet granulation. Tablets were evaluated for various physical parameters floating properties, swelling ability and drug release. Hence from the dissolution data it was concluded that F_{11} formulation was considered as optimized formulation because of controlled and maximum drug release (96.68%) in 12 hours. F_{11} formulation contains, drug (50mg), karaya gum (15mg) badam gum (10mg), sodium bicarbonate (20mg), sodium stearyl fumarate (2.5 mg), aerosil (2.5), PVP K_{30} in isopropyl alcohol (Q.S) MCC (150mg). The dissolution data was subjected to release rate kinetics and it was found that the optimized formulation F_{11} follows Higuchi release mechanism.

6. Acknowledgements

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