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Development and *In vitro* Evaluation of Gastro retentive matrix tablets: an approach using natural gums and polymers

Sreenivasa Reddy N[1*], Mahendra Kumar CB[2], Ramesh A[3], Chandrashekhar M S[1]

[1] Government College of Pharmacy, Drugs Control Department, P.Kalingarao Road, Bangalore-560027. India.
[2] Professor and Principal, St. Mary's College of Pharmacy, St.Francis Street, Secunderabad-India.
[3] Professor and Principal, SITHA Institute of Pharmaceutical Sciences, Bachupally, Hyderabad, India.

ABSTRACT

The purpose of this research was to prepare gastro retentive matrix tablets of Captopril as model drug. These floating matrix tablets are primarily controlled release drug delivery systems, which gets retained in the stomach for longer period of time. Captopril, is an ACE inhibitor is used to treat hypertension, congestive heart failure, and renal syndromes. Due to short half life of Captopril which stimulited for the development of modified formulations using Captopril as a model drug. The Captopril matrix tablets were prepared by direct compression technique using different polymers and natural gums. Formulations designed by varying the concentrations of Karaya gum, Gellan gum, Pullulan gum & HPMC. Formulations F1, F2, F3, F4, F7 & F8 contain Karaya gum and other polymers in two different concentrations (1:2 &1:3), where as F5, F6 &F9 contain equal amount of Gum karaya and other polymers (1:1). And F10, F11 & F12 contain Karaya gum & HPMC K15M in 3 different concentrations (1:1, 1:2, and 1:3). The Comparable drug release profile of twelve formulations studied (*In vitro),* the formulations containing Pullulan gum and Gum karaya (3:1) as polymer matrix exhibits better release of drug. The present research revealed amongst the twelve (F1-F12) formulations studied, F9 was found to be suitable for gastric retention based on *in vitro* evaluation parameters.

Keywords: Captopril, Pullulan gum, sustained release, intragastric floating tablet

Corresponding author
Email: sreenureddyn@gmail.com

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INTRODUCTION

Oral sustained release dosage forms have been developed for past few decades, due to their considerable therapeutic advantages. These dosage forms for gastric retention have drawn high attention for their theoretical advantages in permitting control over the time and site of drug release.[1] The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired period of time.[2] Gastro retentive drug delivery devices are primarily controlled release drug delivery systems, which gets retained in the stomach for longer period of time, thus helping in absorption of drug for the intended duration of time. This in turn improves bioavailability, reduces drug wastage, and improves solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drugs like captopril, domperidone,). It also helps in achieving local delivery of drug to the stomach and proximal small intestine. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs.[3] Many drugs categorized as once a day delivery have demonstrated to have sub optimal absorption due to dependence on transit time of the dosage form. Therefore, a system designed for longer gastric retention will extended the time within which drug absorption can occur in small intestine [4]. Thus it has been suggested that compounding the drugs with narrow absorption window in a unique dosage form prolongs gastric residence time and would enable an extended absorption phase of these drugs. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems or by the simultaneous administration of pharmacological agents that delay gastric emptying. [5]

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. [6]

Captopril, an angiotensin-converting enzyme (ACE) inhibitor, is used to treat hypertension, congestive heart failure, and renal syndromes such as diabetic nephropathy and scleroderma [7-9]. The adverse effect and pharmacokinetic limitations of captopril stimulated the development of subsequent ACE inhibitors. 75% without food (the presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent

MATERIALS AND METHODS

Materials

Captopril was received as gift samples from Charaka Pharma(p) Ltd, Mumbai, & HPMC, Aerosil, sodium bi carbonate, magnesium stearate, purified talc and the polymers like karaya gum, pullulan gum, gellan gum as gift samples from Varsha laboratories,

Bangalore, Embiotics pharmaceuticals, CP Kelco laboratories, German & Lucid Chemicals, Mumbai.

Methods

Preparation of floating matrix tablets

The powder mixture containing drug, polymers and other excipients were weighed as per required quantity as mentioned in (TABLE 01) along with other excepients fed manually into the die of an instrument Rimek RS B-4, 10 station mini press tablet punching machine using flat-faced die to get tablets of average weight 250 mg.

Evaluation of physical properties of floating matrix tablets

Hardness: The crushing strength of the tablets was measured using Monsanto hardness tester. Three tablets from each formulation were tested randomly and average reading noted.

Friability: The friability of a sample of 20 tablets were measured using ROCHE Friabilator (Electro lab) 20 previously weighed tablets were rotated at 25 RPM for 4 minutes. The thickness using a screw gauge micrometer, hardness (n = 6, Monsanto hardness tester), weight uniformity (n = 20) and % friability (n = 20, Roche friabilator) were determined in a similar manner as stated for conventional oral tablets in the accredited pharmacopoeia [5,8].

Uniformity of drug content: Ten tablets were randomly sampled from each formulation batch, finely powdered and individually estimated for the drug content after suitable dilution using UV-VIS Spectophotometer (UV Shimadzu) at 212 nm [5,8,9].

***In vitro* buoyancy study:** The *in vitro* buoyancy was carried out by determining floating lag time .The tablets were placed in a 100 ml glass beaker containing 0.1N HCl. The time required for the matrix tablet to rise from bottom to the surface of the glass beaker and float on surface was determined. Total floating time was measured as buoyancy lag time during *in vitro* dissolution studies [5, 10, 11].

***In vitro* drug release study:** The release rate of Captopril from floating matrix tablets (n = 6) was determined using dissolution testing apparatus USP II type (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl at 37±0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at regular interval for 8 hours and the samples were replaced with fresh dissolution medium (0.1N HCl). The samples were filtered through 0.42 µ membrane filter and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 212 nm using a Shimadzu UV-visible spectrophotometer. Duration of time, i.e. the tablet which was floating constantly on dissolution medium was noted as total floating time [5, 8].

Stability Studies: The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of 40±2°C/75±5% RH and a control sample (real time) was placed at an ambient condition. Both test and control samples were withdrawn at the end of every ONE month for a period of 12 months & evaluated for active drug content*, in vitro* buoyancy and drug release profile.

RESULTS AND DISCUSSION

Preformulation Studies

Calibration Curve

In pre formulation studies it was found that, the estimation of captopril by spectrophotometric method at 212 nm had good reproducibility. Correlation between the concentration and the absorbance was found to be nearer to 1, with slope = 0.0038 and intercept = – 0.0025 (Graph 03)

Drug Excipient Compatibility Study

Thin layer chromatography was carried out to check for the possible Drug excipient interaction. The R_f values with TLC of the drug and the drug-excipient were almost similar indicating that there was no interaction. IR spectra's of Drug and excipients also revealed similar results indicating no change. Hence, it can be concluded that the drug Captopril was found to be compatible with the excipients used in the designed formulation. [Figure 01]

Formulation development

In the development of formulation of oral floating dosage form of captopril various polymers were included such as; Gellan gum, Xanthan gum, Gum karaya, Pullulan gum and HPMC. A direct compression method was adopted for the preparation of tablets. According to variability of polymers totally 12 set of formulations were prepared and evaluated for various in vitro studies. [Table 01]

As a part of pre-compression studies, the powder blends were subjected to bulk density, tapped density, cars index and angle of repose in order to estimate the flow properties. The results of pre-compression parameters revealed that all the studied parameters were found to be with in the Pharmacopoeia limits. Similarly post-compression parameters for all the set of formulations were performed. Based on the results it may be concluded that all the studied parameters were found to be with in the limits of Pharmacopoeia.

Buoyancy studies

The time required for the tablet to go from bottom of the beaker to the surface was ranged from 3 to 12 min [Table 07 & Graph 04] Amongst 12 set of formulations, F9 exhibited

a shortest lag time, while formulation F1 exhibited longest lag time. Such behavior may be due to change in the polymer composition leading to variability in floating capacity. Except formulation F8, all the other formulations exhibited a floating time more than 12hrs.

***In vitro* Drug Release Studies**

The drug release profile of F7 is compared with F1 [figure 01], it was found that F1 has shown decrease in the release marginally with 73.02 % at 8^{th} hour against F7 with 97.07% (with in 5 hours). The drug release behavior of different formulations follows the order F1<F10<F3<F9<F12<F5<F11<F6<F4<F8<F2<F7 (Table05&06; Graph 01 &02).

Above studies revealed that formulation F7 releases the drug at better rate than any other formulations, this can be attributed to the hydrophilic nature of polymer and pores formed by the release of CO_2.

Whereas, Formulations F5, F6 , F9 and F12 which contains Gum karaya with Xanthan gum, Gellan gum Pullulan gum and HPMC M15K in the ratio 1:1 have shown 93.98%, 97.07%, 92.09% & 93.27% drug release respectively. The drug release retardation of F5, F6, F9 & F12 follows the order F9<F12<F5<F6.

KINETIC MECHANISM (CURVE FITTING)

The curve fitting results of the release rate profile of the designed formulations gave an idea on the release rate and mechanism of drug release.

Fitting of the release data to the Korsmeyer and Peppas equation and found that, the regression coefficient is 0.9912 and the diffusion coefficient (n) ranges from 0.5167±0.01913 to 0.6752±0.01744. The Higuchi regression coefficient is 0.9899. These results indicated that, the release mechanism is by diffusion and erosion. The diffusion coefficient values indicate that the drug release follows non-Fickian transport [19-21].

These results are encouraging because the longer gastric residence time is an important factor which influences the bioavailability of the drugs included in the prolonged/controlled release dosage

STABILITY STUDIES

The optimized formulation subjected to stability study for 12 months at storage conditions of 40^0C AT 75 % RH; the tablets were analyzed for physical appearance and drug content. The residual drug content of optimized formulation was found to be within the permissible limits. The tablets were also subjected to Thin Layer Chromatography (TLC) and Infra red spectra by using FTIR to determine compatibility of the drug with the adjuvants used in the tablets. [Graph 01 & 02] The TLC profiles showed that the R_f values of the drug did not change, and IR spectra also showed no change which indicates no interaction between the drug and adjuvants [16].

The tablets showed satisfactory physical stability at 40^0C at 75 % RH. And physical appearance did not change considerably.

There was no significant difference in drug content among different batches, though the experimental parameters were changed i.e. change in the polymer, and polymer concentrations. However when the release of F7 is compared with F1 [figure 01], it was found that F1 has shown decrease in the release marginally with 73.02 % at 8^{th} Hour, against F7 with 97.07% (with in 5 hours). The drug release behavior of different formulations follows the order F1<F10<F3<F9<F12<F5<F11<F6<F4<F8<F2<F7.

Above studies revealed that formulation F7 releases the drug at better rate than any other formulations, this can be attributed to the hydrophilic nature of polymer and pores formed by the release of CO_2.

Whereas Formulations F5, F6 , F9&F12 which contains Gum karaya with Xanthan gum, Gellan gum Pullulan gum& HPMC M15K in the ratio 1:1 have shown 93.98%, 97.07%, 92.09% & 93.27 drug release respectively. The drug release retardation of F5, F6, F9 & F12 follows the order F9<F12<F5<F6. The stability studies for period of 12 months revealed that there was no change in buoyancy property, as well as drug content, indicating that, indicating that formulations are stable.

CONCLUSION

The Formulation F9 designed with gum karaya and pullulan gum in the ratio (1:1) took 3 minutes to become buoyant and showed better floating property along with controlled drug release in comparison to all other formulations. The gastro retentive floating drug delivery is a promising approach to achieve *in vitro* buoyancy and thereby longer gastric retention time for weakly basic drug. By using gel-forming as well as low density polymers like xanthan ,gum karaya, gellan gum, pullulan gum, HPMC and gas-generating agent sodium bicarbonate the floating matrix tablet dosage forms can be designed. From the above findings the formulation F9 was found to be suitable for gastric retention based on evaluation parameters, which was considered desirable for the drugs with absorption window in upper GIT. These results are encouraging because the longer gastric residence time is an important factor which influences the bioavailability of the drugs included in the prolonged/controlled release dosage to develop floating matrix tablets using Captopril as model drug.

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Table01: Composition of Captopril matrix tablets (F1-F12)

INGREDIENTS (in milligrams)	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F11	F12
Captopril	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Xanthan Gum	75	50	--	--	50	--	--	--	--	--	--	--
Gum Karaya	25	25	25	25	50	50	25	25	50	25	25	50
Gellan Gum	--	--	75	50	--	50	--	--	--	--	--	--
Pullulan Gum	--	--	--	--	--	--	75	50	50	--	--	--
HPMC 15K	-	-	-	-	-	-	-	-	-	75	50	50
Aerosil	20	20	20	20	20	20	20	20	20	20	20	20
HPMC 4K	50	50	50	50	50	50	50	50	50	50	50	50
PVP K-30	20	20	20	20	20	20	20	20	20	20	20	20
Di Calcium Phosphate	14.5	39.5	14.5	39.5	14.5	14.5	14.5	39.5	14.5	14.5	39.5	14.5
Sodium bicarbonate	30	30	30	30	30	30	30	30	30	30	30	30
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1	1	1
Purified Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total	250	250	250	250	250	250	250	250	250	250	250	250

*Quantities given for each tablet in mg

Graph (1) I.R. Spectra of Captopril

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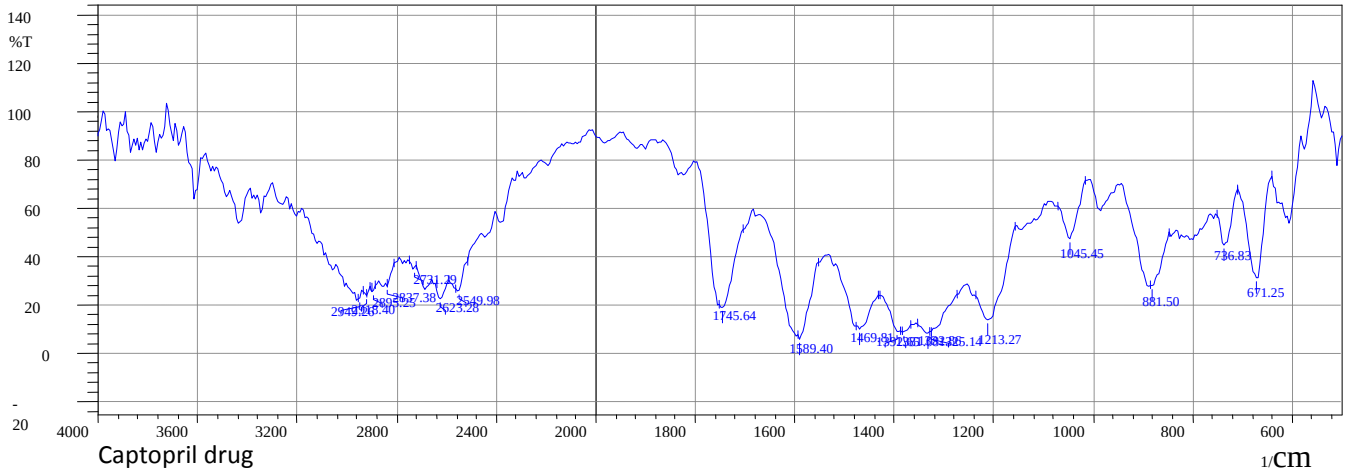
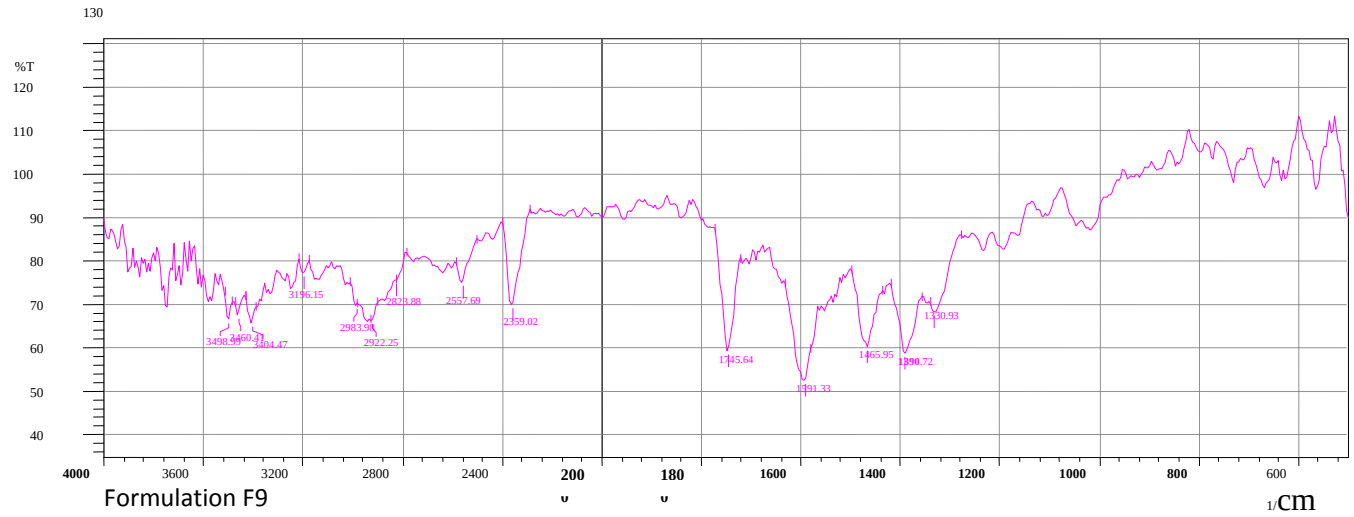


Graph (2): I.R. Spectra of Formulation F9.



Graph 03: Standard calibration curve of Captopril

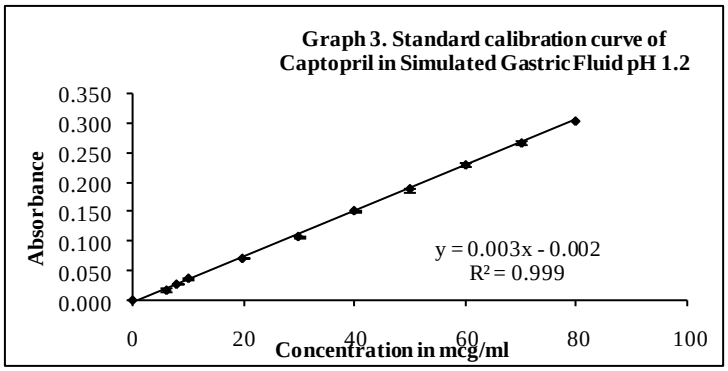


Figure 01 : Photograph of Compatibility studies Drug and excipient (TLC Plate)

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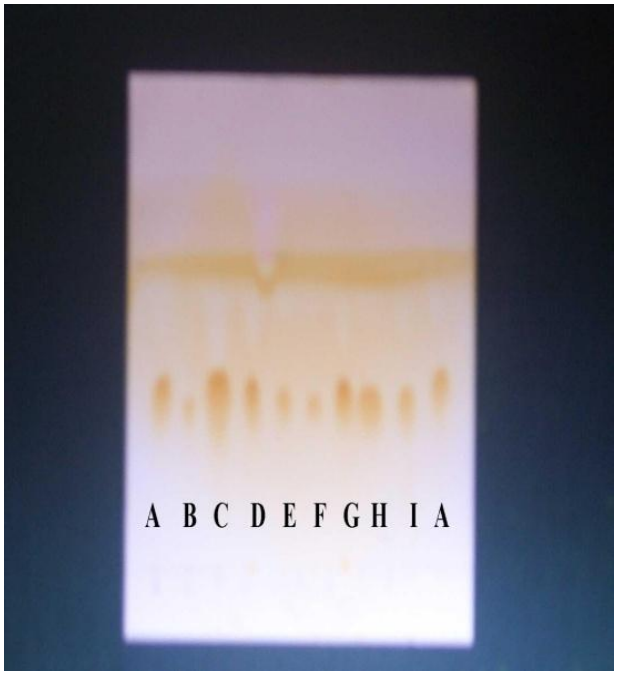

Table: 02 Evaluation parameters for formulations F1-F12

PARAMETERS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Bulk Density (g/cc)	0.7632	0.7241	0.5840	0.6066	0.5453	0.5127	0.5225	0.5210	0.4606	0.5449	0.5456	0.5240
Tapped Density (g /cc)	0.8904	0.8119	0.7069	0.7800	0.6991	0.6320	0.6923	0.6735	0.6008	0.6985	0.6995	0.6635
Angle of Repose (θ)	25.35	24.33	27.70	28.22	29.17	29.33	29.17	30.34	35.17	30.17	32.74	3434
Carr's Index (%)	14.29	10.81	17.39	22.22	22.00	18.87	24.53	22.64	23.33	22.00	22.00	23.68

Table No 03 . Post compression parameters of designed formulations

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PARAMETERS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Hardness (Kg / cm^2)	4.6	4.4	5.4	4.8	5.2	6.2	4.8	5.7	5.4	5.2	5.3	4.9

Table 04: Post compression parameters

PARAMETERS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Hardness (Kg / cm2)	4.9	5.4	5.6	4.9	5.1	5.9	5.7	5. 9	5.6	6.2	5.6	4.9
Friability (%)	0.21	0.19	0.19	0.20	0.18	0.21	0.20	0.18	0.16	0.19	0.20	0.23
Thickness (mm)	3.65±0.1	3.71±0.1	3.66±0.1	3.68±0.1	3.69±0.1	3.67±0.1	3.69 ±0.1	3.70 ±0.1	3.71±0.1	3.69±0.1	3.64±0.1	3.68 ±0.1
Weight Variation	245-255 mg(I.P. limit 240-260 mg)											

Graph 04: Floating lag time of formulations F1-F12

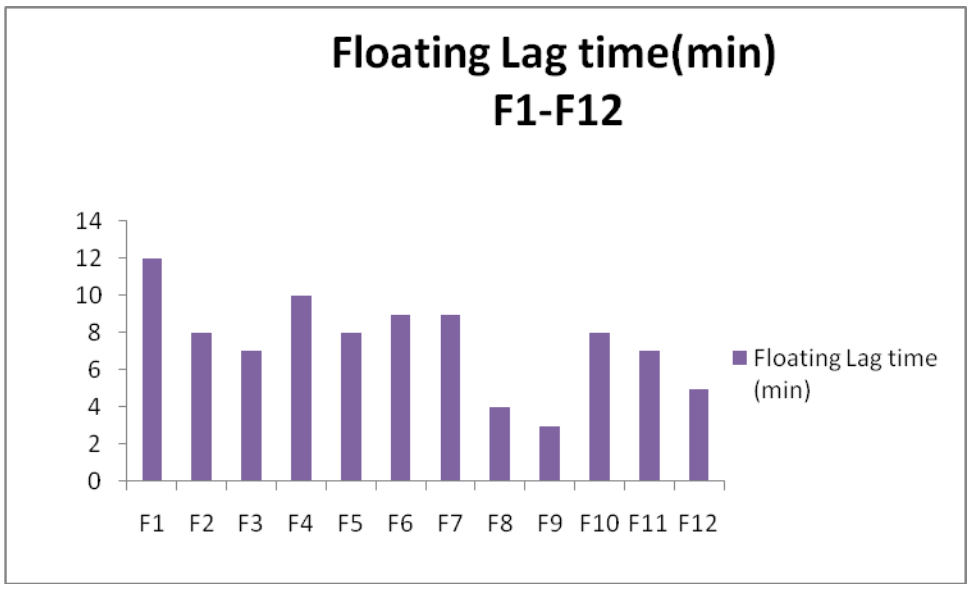

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Table: 05: Percentage Cumulative Drug Release Formulation F1-F6

Time in Hours	F1	SEM±	F2	SEM±	F3	SEM±	F4	SEM±	F5	SEM±	F6	SEM±
0	0		0		0		0		0		0	
1	35.73	0.9506	37.97	0.7588	46.33	0.0158	44.67	0.7726	35.22	0.2808	45.36	2.6811
2	47.25	4.6852	45.53	2.8994	57.41	0.7891	58.41	0.1331	46.04	0.1388	62.02	1.4045
3	50	4.8583	52.74	1.8472	67.7	0.1588	64.94	0.5136	53.26	0.2808	68.38	1.0952
4	59.68	4.4439	64.26	2.0099	70.2	0.4771	76.97	0.5193	54.12	0.1412	78.35	2.2115
5	60.48	4.6153	70.79	0.6475	75.97	0.1551	78.35	0.7726	72.33	0.4243	82.13	2.2237
6	63.23	3.6111	77.14	2.9399	77.84	0.7909	82.81	0.7769	84.87	0.1443	93.12	0.3329
7	63.91	2.8953	90.03	0.8195	79.87	0.3158	91.23	2.4644	93.12	0.8431	95.87	1.1276
8	73.02	5.1166	98.62	0.0607	88.76	1.9048	97.59	0.5	93.98	0.8462	97.07	2.9895

Graph 01: Percentage Cumulative Drug Release F1-F6

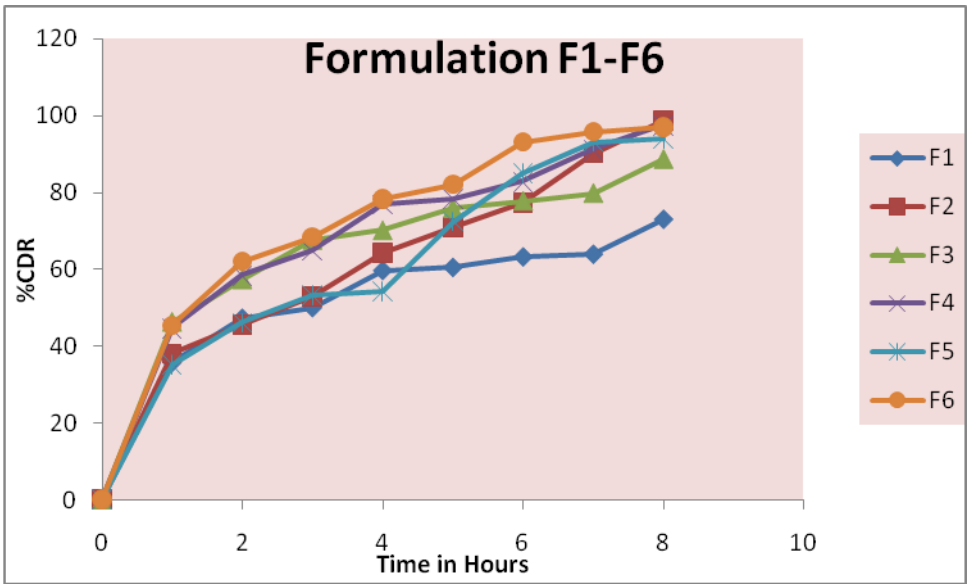

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Table06: Percentage Cumulative Drug Release (F7-F12)

Time in Hours	F7	SEM±	F8	SEM±	F9	SEM±	F10	SEM±	F11	SEM±	F12	SEM±
0	0		0		0		0		0		0	
1	50.98	0.1579	32.98	0.3082	23.19	1.243	40.32	1.243	29.93	0.6181	21.22	0.2409
2	77.86	0.4727	43.29	2.9293	28	0.3039	47.46	0.3039	37.29	0.7778	26.02	0.3039
3	91.14	0.9532	55.67	0.7764	39.69	0.6181	57.79	0.6181	48.64	1.0946	38.48	0.5681
4	98.42	1.1172	64.26	0.3039	60.3	0.7778	69.21	0.7778	62.26	3.288	59.36	0.7778
5	99.67	1.1234	70.79	1.7086	72.33	1.0946	74.96	1.0946	68.71	1.275	79.63	1.0946
6	-	-	77.14	0.4785	75.42	3.288	78.82	3.288	73.18	2.2194	82.53	3.6288
7	-	-	90.03	2.3404	84.53	1.275	80.87	1.275	88.03	0.8252	85.31	1.8275
8	-	-	98.62	0.4939	92.09	2.2194	87.63	2.2194	96.02	1.142	93.27	2.2194

Graph 02: Cumulative drug Release F7-F12

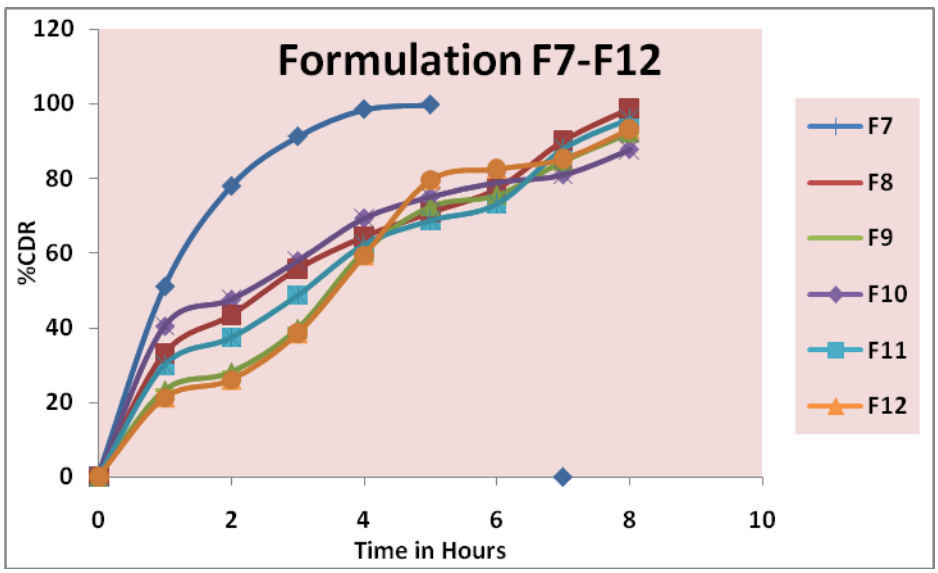

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Table 07: Floating lag time; total floating time; %CDR at 4th & 8th hour

Formulation	Floating lag time (min)	Total floating time (hrs)	%CDR* after 4 hours	% CDR* after 8 hours
F1	12	>24	59.62	73.02
F2	8	>14	64.26	98.62
F3	7	>14	70.20	88.76
F4	10	>14	76.97	97.59
F5	8	>24	54.12	93.98
F6	9	>14	78.35	97.07
F7	9	>12	98.52	99.67
F8	4	>10	64.26	98.62
F9	3	>24	60.30	92.09
F10	8	>14	69.20	87.63
F11	7	>18	62.26	96.02
F12	5	>20	59.36	93.27

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Table 08: Curve fitting data of release profile of formulations F1-F12

KORSMEYER AND PEPPAS MODEL												
Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
K (h^{-n})	20.28	21.11	25.89	13.31	16.99	26.98	14.61	19.06	27.16	21.44	18.98	19.34
N	0.5365	0.5912	0.5563	0.6605	0.6285	0.5334	0.6752	0.6093	0.5167	0.5843	0.5467	0.6195
SEM (K)	0.533	0.7371	1.476	0.5323	0.8222	1.37	0.5455	0.7258	1.087	0.5927	0.5624	0.6797
SEM (n)	0.01252	0.0165	0.02707	0.01871	0.02274	0.02421	0.01744	0.01794	0.01913	0.01307	0.01456	0.01654
$T_{50\%}$ (hr)	5.378	4.3	3.264	7.418	5.571	3.179	6.188	4.869	3.258	4.26	4.987	4.634
R^2	0.9964	0.9951	0.9854	0.995	0.9918	0.9867	0.9959	0.9945	0.9912	0.9968	0.9845	0.9955
HIGUCHI MODEL												
Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
K ($h^{-1/2}$)	0.1279	0.1686	0.2273	0.09621	0.1292	0.2251	0.1172	0.1483	0.2145	0.169	0.275	0.158
SEM	0.004828	0.005385	0.006834	0.002553	0.0037	0.00883	0.002911	0.004436	0.00482	0.006122	0.03812	0.005753
R^2	0.9466	0.9765	0.9857	0.9745	0.9761	0.9728	0.982	0.9766	0.9899	0.9689	0.8891	0.9685

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Table 09: Curve fitting data of release profile for formulations F1-F12

ZERO-ORDER RELEASE KINETICS												
Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
K (h^{-1})	7.442	8.707	9.904	6.371	7.592	9.831	7.215	8.173	9.549	8.715	8.345	8.477
SEM	0.4136	0.4198	0.5504	0.2459	0.3296	0.5679	0.2659	0.373	0.5753	0.4229	0.4532	0.3715
R^2	0.6563	0.7749	0.6926	0.873	0.8301	0.6363	0.8878	0.8043	0.5919	0.7651	0.6345	0.8218
FIRST ORDER RELEASE KINETICS												
Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
K (h^{-1})	0.1279	0.1686	0.2273	0.09621	0.1292	0.2251	0.1172	0.1483	0.2145	0.169	0.234	0.158
SEM	0.004828	0.005385	0.006834	0.002553	0.0037	0.00883	0.002911	0.004436	0.00482	0.006122	0.0087	0.005753
R^2	0.9466	0.9765	0.9857	0.9745	0.9761	0.9728	0.982	0.9766	0.9899	0.9689	0.9456	0.9685

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Table 10: Zero order & first order kinetics: F1- F12

Formulation Code	Zero Order	First Order	Higuchi Model	Korsmeyer model (n values)
F1	0.9728	0.7787	0.9731	0.9671
F2	0.9678	0.7231	0.9713	0.8789
F3	0.9881	0.9569	0.9701	08762
F4	0.9875	0.9255	0.9660	0.9018
F5	0.9902	0.9618	0.9745	0.9225
F6	0.9924	0.9123	0.9881	08743
F7	0.9878	0.8976	0.9887	0.9621
F8	0.9975	0.8657	0.9891	0.9189
F9	0.9831	0.8745	0.9674	08554
F10	0.9923	0.9517	0.9736	0.9241
F11	0.9913	0.9163	0.9827	08853
F12	0.9807	0.8870	0.9809	0.9604

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Figure 02: Floating properties of gastro retentive Captopril matrix tablets

(A)at 0 hour,(B) at 30 minutes,(C) after 1 hour, (D)3 hours, (E)5 hours & (F) 8 hours;

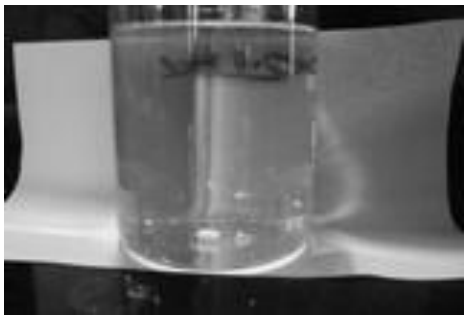

Figure (A) at 0 hour

Figure (B) at 30 minutes

Figure (C). at 1 hour

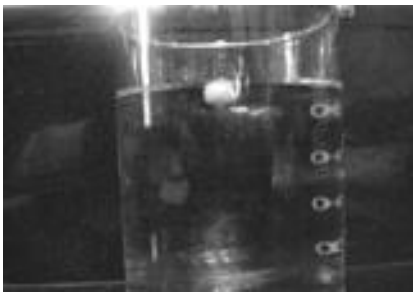

Figure (D). at 3rd hour

Figure(E) at 5th hour

Figure (F) at 8th hour

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STABILITY STUDIES

Table no.11 Stability data of F9 formulations at 40^{O} C/75%RH and

Time in months	Physical Appearance		Floating time (min) lag		Drug Content*%	
	RT	40^{O} C/75%RH	RT	40^{O} C/75%RH	RT	40^{O} C/75%RH
0	+++	+++	3	3	96.67	96.62
1	+++	+++	3	3	96.38	96.31
3	++	++	3.01	3.04	95.87	95.47
6	++	++	3.03	3.09	95.54	95.24
12	++	-	3.05	-	95.03	-

*n = 3

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