CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.2650760

Available online at: http://www.iajps.com ***Research Article***

FORMULATION OF GASTRO RETENTIVE MATRIX TABLETS FOR ANTIHYPERTENSIVE DRUGS USING NATURAL GUMS AND LOW-DENSITY POLYMERS: EFFECT OF FORMULATION FACTORS ON IN VITRO DISSOLUTION RATES

[1]Sreenivasa Reddy N, [2]Mahendra Kumar CB, [3]Ramesh A

[1]Department of Pharmaceutical Sciences, Jawaharlal Technological University, Hyderbad-85, Telangana State, India.

Article Received: January 2019 **Accepted:** March 2019 **Published:** April 2019

Abstract:

The objective of the study was to develop Gastro retentive matrix tablets for antihypertensive drugs. The matrix tablets of antihypertensive drug captopril with 12 formulations coded as F1 to F12 with variant ratios of polymer were prepared in the preliminary studies by direct compression method. Hydrophilic and hydrophobic low density polymers like HPMC M15K and HPMC M4K and natural gums like Karaya gum, Xanthan gum, Pullulan gum, Gellan gum and Guar gum were used. The pre-compression parameters, and compatibility of drug with various excipient was studied using HPTLC, FTIR and DSC. The tablets were directly compressed and evaluated for compliance with pharmacopeia limits.

The results of floating lag time (FLT), total floating lag time (TFT), and in vitro dissolution studies indicated that formulation F9 was shown better drug release, floating lag time characteristics compared to other formulations. The decrease in release kinetics of the drug was observed on increasing polymer ratio. Based on the preliminary formulation (F1-F12) and evaluation, optimization technique was adopted using 3^2 factorial design and statistical ANOVA (software). Ten formulations designed and formulated with code R1 to R10.

The pre-compression, post-compression parameters including buoyancy of R1 to R10 were investigated, and optimized formulae were developed with predicted values. The optimized matrix tablets coded as FC were prepared by direct compression, evaluated for pre & post compression parameters, buoyancy, and in vitro cumulative drug release. The predicted values of optimized technique, and actual values of formulation FC after evaluation were found nearer. The in vitro drug release curve fitting kinetics was studied. and found to be non-fickian, and by diffusion .

Key words: *Captopril, Karaya gum, Xanthan gum, Pullulan gum, Gellan gum, Floating lag time.*

Corresponding author:

Sreenivasa Reddy N,

Department of Pharmaceutical Sciences,

Jawaharlal Technological University, Hyderbad-85, Telangana State, India.

sreenureddyn@gmail.com

QRcode

Please cite this article in press Sreenivasa Reddy N et al., ***Formulation of Gastro Retentive Matrix Tablets for Antihypertensive Drugs Using Natural Gums and Low Density Polymers: Effect of Formulation Factors on in Vitro Dissolution Rates.,*** *Indo Am. J. P. Sci, 2019; 06(04).*

INTRODUCTION:

The novo design of an oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the DDS within desired regions of the gastrointestinal (GI) tract and the highly variable nature of gastric emptying process. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 h. Furthermore, the relatively brief Gastric Emptying Time in humans, which normally averages 2–3 h through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose. Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem. The role of ideal drug delivery system is to provide proper amount of drug at regular time of interval & at right site of action to maintain therapeutic range of drug in blood plasma. In the present work, attempts made to formulate gastroretentive floating systems of captopril.

Captopril, (1[(2S)-3-mercapto-2-methylpropionyl]-L-proline, is an angiotensin-converting enzyme (ACE) inhibitor used to treat hypertension, congestive heart failure and renal syndromes such as diabetic nephropathy and scleroderma. The half-life of Captopril is only about 2-3 hours, the multiple doses of the drug is required to maintain a constant plasma concentration for good therapeutic response. Hence, clinically acceptable sustained release dosage forms of Captopril prepared with conventional technology may not be useful. So, the gastro retentive matrix tablets were prepared and evaluated for physical properties, content uniformity, hardness, friability, floating lag time and *in vitro* drug release.

The matrix tablets of antihypertensive drug captopril with 12 formulations coded as F1 to F12 with variant ratios of polymer were prepared in the preliminary studies by direct compression method Based on the results, the optimization technique was adopted. In the trial and error method, a lot of formulations have to be prepared to get a conclusion, which involves lot of money, time and energy. These can be minimized by the use of optimization technique.

Optimization

The word optimize is defined as, to make as perfect, effective or functional as possible. Optimization technique may be interpreted as to find out the values of controllable independent variables, that gives the most desired value of dependent variables.

Experimental design

Experimental design is a statistical design that prescribes or advises a set of combination of variables. The number and layout of these design points within the experimental region, depends on the number of effects that must be estimated, depending on the number of factors, their levels, possible interactions and order of the model

MATERIALS AND METHODS:

The drug Captopril was obtained from Charaka Pharma (P) Ltd.,Mumbai Enlapril maleate from Varsha Labs, Xanthan gum,Karaya gum, Pullulan gum, gellan gum from CP Kelco & Lucid chemicals, India and other excipients from Ce-chem pharmaceuticals, & varsha labs, India as a gift samples.

Table 1: Formulations for screening of polymers and excipients

INGREDIENTS	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
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 K15	--	--	--	--	--	--	--	--	--	75	50	50
Aerosil	20	20	20	20	20	20	20	20	20	20	20	20
HPMC K4	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
Dicalcium 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
Sodiumbi Carbonate	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 weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

*All weights are in mgs.

The Gastro retentive matrix tablets for antihypertensive drug captopril were prepared by direct compression technique. All the Excipients and drug are sieved individually through mesh #80. The sifted ingredients are then individually weighed and blended. The blended mixture is then punched in to 250 mg tablets, using 9mm flat-faced punche using 10 station mini punching machine. The tablets are stored in a desiccator. In the Preliminary studies 12 formulations (as shown in Table (1) were prepared by direct compression method without granulation.

COMPATIBILITY STUDIES:

Micrometric and physico chemical properties:
The physical mixture of drug and polymers with1:1 ratio were evaluated for assessment of drug content on 7th,14th,21st day and for the physical appearance.

High Performance Thin Layer Chromatography (HPTLC): The compatibility studies of Drug and Excipients in 1:2 ratios were mixed and stored in glass vials at 50^0C. The Drug and the excipients were analyzed for compatibility.

Fourier Transfer Infra Red (FTIR) analysis: The FTIR analysis of drug and excipients used in the formulation of matrix tablets were analyzed by using FTIR

Differential Scanning Colorimeter (DSC):
The Differential Scanning Colorimeter analysis was undertaken to characterize the changes if any during thermal exposure of samples. The Test was conducted using a thermal analysis system (DSC).The instrument automatically calculate onset of melting point and enthalpy of fusion.

EVALUATION PARAMETERS:

Pre-compression parameters
The prepared matrix tablets of Gastro retentive matrix tablets of antihypertensive drug were evaluated for Bulk Density (D_b),Tapped Density (D_t), Hausners ratio (HR) , Carr's Index (I) and Angle of Repose Micrometric and Physico chemical parameters.

Post compression parameters
The post-compression parameters were evaluated for Friability (F), Weight Variation, Thickness, Floating lag time and Duration of Buoyancy.

Assay of FC formulation by HPLC method: The assay of the Optimized formulation of Captopril (FC) is carried out by HPLC method too. The triturate of the formulation FC equivalent to 50 mg is of the drug was weighed accurately, dissolved in Mobile Phase containing mixture of 55 volumes methanol and 45 volumes water containing 0.05 volumes of Phosphoric acid. The Captopril RS is prepared (0.1 % solution) in mobile phase. using column= 25cm X 4.6mm, packed with Octadecylsilane (C18)bonded to porous silica (3 to 10 micro meter) with flow rate of 1ml/min, at wave length 220 nm. and the concentrations of Captopril formulation(FC) in mcg / ml was determined by using the regression equation.

In vitro Dissolution Studies:
The *In vitro* dissolution study was carried out in USP Dissolution Test Apparatus, Type 2 (paddle type). 900ml of simulated gastric fluid pH 1.2 (without enzymes) was used as dissolution medium. The temperature of dissolution media was maintained at 37 ± 0.5^{O} C. The paddle rotation speed was kept at 50 rpm. 5ml of the sample was with drawn at every 1-hour interval for 8 hours and the same volume was replaced with pre warmed fresh dissolution media. The sample withdrawn was diluted to suitable volume with simulated gastric fluid, filtered through 0.45µ filter paper and the absorbance was recorded at 212 nm using UV-VIS spectrophotometer.

Drug release kinetics
To analyze the mechanism of drug release and release rate kinetics from the dosage form, the data obtained were fitted into zero order, first order, Higuchi release and Korsmeyer and Peppas release model using Prism® and Sigma plot® software, which is specially meant for curve fitting and statistical data analysis.

Zero-Order release kinetics: To study the zero-order release kinetics the release rate data are fitted to the fallowing equation.$F = K.t$ ----------1 Where, 'F' is the fraction of drug release, 'K' is the release rate constant and 't' is the release time.

First order release kinetics: To study the first-order release kinetics the release rate data are fitted to the fallowing equation. $F = 100*(1 - e^{-Kt})$ ----------2 Where, 'F' is the fraction of drug release, 'K' is the release rate constant, 'e' is exponent coefficient and 't' is the release time.

Higuchi release model: To study the Higuchi release model the release rate data are fitted to the fallowing equation=$K.t^{1/2}$.3 Where, 'F' is the fraction of drug release, 'K' is the release rate constant and 't' is the release time.

Korsmeyer and Peppas release model : To study the Korsmeyer and Peppas release model the release rate data are fitted to the fallowing equation.$M_t / M_\infty = K.t^n$ --------4
Where, M_t / M_∞ is the fraction of drug release, 'K' is the release rate constant, 't' is the release time and 'n' is the diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form.

Optimization technique: The runs or formulations, which are designed based on 3^2 full factorial designs, are evaluated for the response variables. The response values are subjected to multiple regression analysis to find out the relationship between the independent factors used and the response values obtained.

Statistical analysis: The effect of formulation variables on the response variables were statically evaluated by applying one-way ANOVA at 0.05 level using a commercially available software package Design of Experiments® 6.05 (Stat Ease, USA).

Scanning Electron Microscopy(SEM):
Scanning electron microscopy of optimized formulation was done at different time intervals after the dissolution. The morphological characters of optimized tablet were compared to know the mechanism of drug release and floating. The surface of the Optimized formulation(tablet) was studied by placing the intact tablets before and after 1st,3rd, 5th , 8th hour after 24 hours of dissolution by drying them to remove water content.

Stability Studies
In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. The International Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America.ICH specifies the length of study and storage conditions. The specifications are 25^0 C ± 2^0 C / 60% RH ± 5% , 30^0 C ± 2^0 C / 65% RH ± 5%(intermediate) and 40^0 C ± 2^0 C / 75% RH ± 5% (accelerated).

RESULTS & DISCUSSIONS:

Compatibility studies FTIR analysis

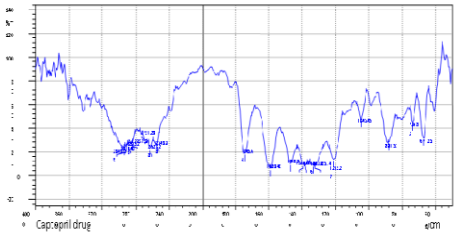


Figure 1: FTIR SPECTRUM OF CAPTOPRIL

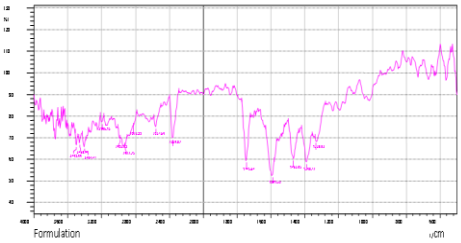


Figure 2 FTIR spectrum of drug & excipients-optimized formulation(FC)

Some of the important peaks in the spectrum were noted from FTIR spectra of the pure Captopril, & excipients of Optimized formulation(FC), The Characteristic peaks of 1747 and 1593(Stretching vibration band –COOH & amide band.), 2920 to 2851(Stretching vibration of CH2-CH3), 2561 (Characteristic peak for –SH group), 1575 & 1461(Symmetric stretching of -COO group), 2978 &2870 (Corresponds to –CH2 group). Thus, indicates that there was absence of chemical interaction between drug and excipients.(Shimadzu FTIR, Kbr pellet technique)

DIFFERENTIAL SCANNING COLORIMETRIC (DSC) STUDIES:

Differential scanning colorimetric analysis was performed for captopril drug with excipients in order to study the compatibility.

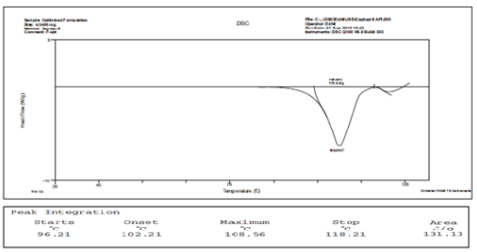


Figure 3 DSC thermograph of Captopril

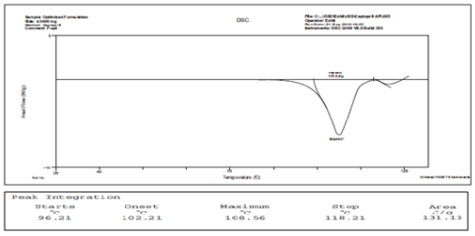


Figure 4 DSC thermograph of Drug & Excipients

Differential scanning calorimetric analysis was performed for captopril drug with excipients in order to study the compatibility. The melting points in the DSC thermographs revealed that the 107.98ºC of

mixture of Drug Captopril and excipients, when compared with that of Captopril pure 107.48ºC showing not much changes in melting point. Hence the drug and excipients are proven compatible.

Table 2. Pre-compression parameters for F1 to F12

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Bulk Density (g/cc)	0.763 ±0.11	0.724 ±0.12	0.584 ±0.09	0.606 ±0.11	0.545 ±0.12	0.512 ±0.45	0.522 ±0.14	0.521 ±0.13	0.460 ±0.14	0.544 ±0.16	0.545 ±0.11	0.524 ±0.12
Tapped Density(g /cc)	0.890 ±0.04	0.811 ±0.04	0.706 ±0.05	0.780 ±0.01	0.699 ±0.07	0.632 ±0.08	0.692 ±0.03	0.673 ±0.04	0.600 ±0.02	0.698 ±0.06	0.699 ±0.04	0.663 ±0.01
Angle of Repose(θ)	25.35 ±0.9	24.33 ±0.10	27.70 ±0.12	28.22 ±0.15	29.17 ±0.13	29.33 ±0.14	29.17 ±0.15	30.34 ±0.13	35.17 ±0.14	30.17 ±0.15	32.74 ±0.13	34.34 ±0.09
Carr's Index (%)	14.29 ±0.05	10.81 ±0.07	17.39 ±0.08	22.22 ±0.05	22.00 ±0.04	18.87 ±0.02	24.53 ±0.04	22.64 ±0.12	23.33 ±0.01	22.00 ±0.04	22.00 ±0.05	23.68 ±0.01
Hausner's Ratio	1.23 ±0.05	1.24 ±0.08	1.21 ±0.11	1.25 ±0.01	1.23 ±0.07	1.24 ±0.08	1.25 ±0.13	1.25 ±0.06	1.25 ±0.14	1.24 ±0.17	1.24 ±0.11	1.25 ±0.05

Table 3. Post-compression parameters for F1 to F12

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Hardness (Kg / cm2)	4.9 ±0.27	5.4 ±0.14	5.6 ±0.11	4.9 ±0.24	5.1 ±0.17	5.9 ±0.51	5.7 ±0.1	5.9 ±0.16	5.6 ±0.05	6.2 ±0.13	5.6 ±0.42	4.9 ±0.05
Friability (%)	0.21 ±0.11	0.19 ±0.10	0.19 ±0.17	0.20 ±0.13	0.18 ±0.14	0.21 ±0.15	0.20 ±0.12	0.18 ±0.12	0.16 ±0.17	0.19 ±0.14	0.20 ±0.16	0.23 ±0.17
Thickness (mm)	3.65 ±0.07	3.71 ±0.04	3.66 ±0.07	3.68 ±0.09	3.69 ±0.01	3.67 ±0.02	3.69 ±0.05	3.70 ±0.04	3.71 ±0.01	3.69 ±0.07	3.64 ±0.04	3.68 ±0.06
Weight Variation 250 ± 7.5% (IP limit 231.25-268.5 mg)	249.01 ±1.02	248.18 ±0.44	248.01 ±1.04	251.01 ±0.98	249.12 ±1.71	248.31 ±1.01	249.12 ±1.17	248.18 ±0.84	249.01 ±1.47	250.61 ±1.16	249.11 ±1.43	248.61 ±1.74

Table4.% Drug content, buoyancy of

Formulations	% Drug Content	Floating Lag time (in min/sec)	Total floating time(in hour)
F1	98.78 ± 0.07	12 ±0.27	24±1.46
F2	98.75 ± 0.11	8 ±0.16	24±0.19
F3	98.12 ± 0.03	7 ±0.38	24±0.41
F4	98.99 ± 0.12	10 ±0.48	24±1.19
F5	99.01 ± 0.15	8 ±0.33	24±0.24

F6	97.34 ± 0.01	9 ±0.63	24±.014
F7	98.47 ± 0.17	9 ±0.56	24±0.08
F8	98.15 ± 0.04	4 ±1.11	24±1.01
F9	97.07 ± 0.17	3 ±0.10	24±1.40
F10	98.11 ± 0.03	8 ±0.33	24±0.12
F11	97.35 ± 0.18	7 ±1.45	24±0.14
F12	98.49 ± 0.16	5 ±0.02	24±0.28

The formulation F9 demonstrated better floating lag time (buoyancy). Total float time of the formulations were more than 24±1.40 hours, except F7, which is attractive for creating floating tablets.

SWELLING INDEX STUDY:

Swelling proportion depicts the measure of water that was contained inside the hydrogel at harmony and is a component of system structure, hydrophylicity of the practical groups. Swelling study was performed on every one of the clusters for 6 hours

Table 5 Swelling in weight of F1-F12

Sl No	Formulation	Swelling in weight of formulation-water retained (time in hours)						
		0	1	2	3	4	5	6
1	F1	0.25	1.5405	1.6778	1.7642	1.8883	2.0074	2.275
2	F2	0.25	1.5317	1.6826	1.8694	1.9199	1.9365	1.9852
3	F3	0.25	1.6043	1.7591	1.7353	1.8728	1.9511	2.0568
4	F4	0.25	1.5109	1.5126	1.6271	1.6291	1.6467	1.7922
5	F5	0.25	1.5212	1.6812	1.7792	1.8544	1.9517	2.0612
6	F6	0.25	1.5354	1.6481	1.7678	1.8611	2.0013	2.2135
7	F7	0.25	1.4699	1.6321	1.6456	1.7253	1.7435	1.7813
8	F8	0.25	1.4736	1.6534	1.7242	1.7743	1.8034	1.8523
9	F9	0.25	1.4824	1.5836	1.7116	1.7534	1.7927	1.8623
10	F10	0.25	1.4786	1.6089	1.7114	1.7584	1.8014	1.8145
11	F11	0.25	1.4813	1.5543	1.7245	1.7402	1.8245	1.8399
12	F12	0.25	1.4876	1.5915	1.7268	1.7914	1.8241	1.8396

7. *In Vitro* %CDR of -F1 to F12

The percentage drug release for the formulations F1 to F6 are presented here with their SD values in the table 7 and the corresponding graph is given(Fig 6) below.

Table 7. *In Vitro* %CDR of F1-F6

Time (Hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.25	15.42±0.41	14.11±0.58	12.75±0.11	16.74±0.71	20.75±0.41	19.75±1.75
0.50	22.75±0.84	18.16±0.74	17.05±0.10	19.42±0.81	24.01±0.24	21.77±0.94
0.75	27.16±0.78	31.41±0.76	35.41±0.01	30.49±0.70	28.76±0.21	30.26±0.75
1	35.73±0.95	37.97±0.75	46.33±0.01	44.67±0.77	35.22±0.28	45.36±1.68
2	47.25±1.68	45.53±2.89	57.41±0.78	58.41±0.13	46.04±0.13	62.02±1.40
3	50.00±1.85	52.74±1.84	67.7±0.15	64.94±0.51	53.26±0.28	68.38±1.09
4	59.68±1.44	64.26±2.04	70.2±0.47	76.97±0.51	54.12±0.14	78.35±1.21
5	60.48±4.61	70.79±0.64	75.97±0.15	78.35±0.77	72.33±0.42	82.13±2.22
6	63.23±3.61	77.14±2.93	77.84±0.79	82.81±0.77	84.87±0.14	93.12±0.33
7	63.91±1.89	90.03±0.81	79.87±0.31	91.23±2.46	93.12±0.84	95.87±1.12
8	73.02±1.11	98.62±0.06	88.76±1.90	97.59±0.51	93.98±0.84	97.07±2.98

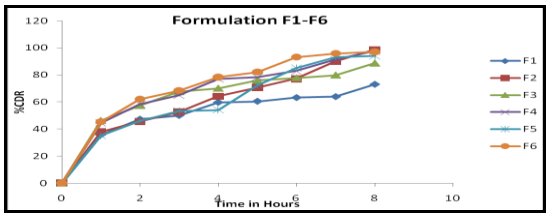


Figure 6 : *In vitro* %CDR of F1-F6

The Percentage of drug release of the next 6 formulations i.e., F7-F12 with their corresponding graphs is given below in the table 8 and figure. 7.

Table 8: *In Vitro* %CDR of formulations F7-F12

Time (Hr)	7	8	9	10	11	12
0.25	14.42±0.40	13.11±0.51	18.75±0.10	17.74±0.87	20.01±0.12	19.05±1.74
0.50	21.75±0.84	19.46±0.70	21.05±0.18	20.14±0.82	23.01±0.31	22.77±0.94
0.75	33.16±0.70	31.41±0.76	22.01±0.01	30.49±0.70	21.26±0.21	27.01±0.75
	0.98±0.15	2.98±0.30	3.19±1.24	0.32±1.24	9.93±0.61	1.22±0.24
	7.86±0.47	3.29±2.92	8.01±0.30	7.46±0.30	7.29±0.77	6.02±0.30
	1.14±0.95	5.67±0.77	9.69±0.61	7.79±0.61	8.64±1.09	8.48±0.56
	8.42±1.11	4.26±0.30	0.30±0.74	9.21±0.77	2.26±3.28	9.36±0.77
	9.67±1.12	0.79±1.70	2.33±1.09	4.96±1.09	8.71±1.27	9.63±1.09
		7.14±0.47	5.42±1.28	8.82±3.28	3.18±2.21	2.53±3.62
		0.03±2.34	4.53±1.27	0.87±1.27	8.03±0.82	5.31±1.82
		8.62±0.49	2.09±1.21	7.63±2.21	6.02±1.142	3.27±2.21

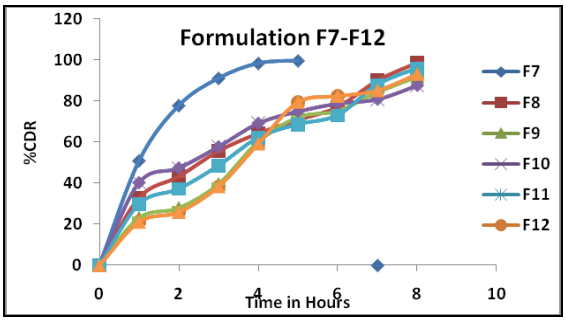


Figure 7: Graph -*In vitro* %CDR of F7-F1

The cumulative drug release of formulation F1 to F12 introduced in the Table 7 and 8, Figure 6 and 7. This might be due to the slower rate of medication dispersion(drug release) from these GRDS tablets in to the disintegration media because of expanded thickness of polymeric lattice-matrix

CURVE FITTING ANALYSIS (FOR F1- F12 FORMULATIONS):

The Korsmeyer and Peppas show information and Higuchi display information for formulations F1 to F12 have been determined

Table 9 Curve fitting analysis (for F1- F12 formulations

KORSMEYER AND PEPPAS MODEL												
Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
K (h^{-n})	20.28± 0.53	21.11± 0.73	25.89± 1.47	13.31±0 .53	16.99± 0.82	26.98±1 .37	14.61±0 .54	19.06± 0.72	27.16±1 .08	21.44± 0.59	18.98±0 .56	19.34± 0.67
n	0.536±0. 012	0.591± 0.016	0.556± 0.02	0.66± 0.02	0.628 ±0.02	0.533 ±0.02	0.675 ±0.01	0.609 ±0.02	0.516 ±0.019	0.584 ±0.012	0.546 ±0.01	0.619 ±0.011
$T_{50\%}$ (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 ($h^{-1/2}$)	0.127±0. 01	0.168± 0.01	0.227± 0.01	0.096±0 .01	0.129± 0.07	0.225±0 .05	0.117±0 .02	0.148± 0.04	0.214±0 .03	0.169± 0.04	0.148±0 .04	0.158± 0.05
R^2	0.9466	0.9765	0.9857	0.9745	0.9761	0.9728	0.982	0.9766	0.9899	0.9689	0.974	0.9685

ZERO ORDER MODEL												
Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
K ($h^{-1/2}$)	14.41 ± 0.7014	13.15± 0.7025	13.08± 0.716	13.68 ± 0.7284	13.47± 0.7214	13.09± 0.7145	13.37± 0.7276	13.19± 0.7301	13.41± 0.7146	13.61±0. 72	13.23 ± 0.714	13.11± 0.7146
R^2	0.904	0.9071	0.9079	0.9102	0.9013	0.9011	0.9041	0.9012	0.9021	0.901	0.909	0.904
FIRST ORDER MODEL												
Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
K ($h^{-1/2}$)	0.1912 ±0.032	0.1986±0. 015	0.1974±0. 006	0.1961±0. 002	0.199 ±0.037	0.1945±0. 008	0.1931±0. 002	0.1942±0. 004	0.1975±0. 017	0.1919±0. 016	0.1971±0. 014	0.198±0.0 047
R^2	0.9414	0.9569	0.9756	0.9754	0.9745	0.9717	0.9784	0.9749	0.9710	0.9687	0.9470	0.9751

The values of n ranged between 0.516 to 0.675 indicating anomalous (non-fickian) diffusion mechanism for the drug release. The peculiar diffusion mechanism of drug release demonstrates both diffusions controlled and swelling controlled

Stability studies of the F9 formulations are important in order to find out the drug content of the formulations at extremities, such as different temperatures, humidity etc. and found satisfactory.

Based on the preliminary twelve formulation (F1-F12) and evaluation, optimization technique was adopted using 3^2 factorial design and statistical ANOVA (software). Ten formulations designed and formulated with code R1 to R10.

medication discharge from floating tablets of definitions.

The results revealed that amongst the F1- F12 formulations, F9 found to be good with better buoyancy, *in vitro % CDR*, % drug content and good characteristics suitable for developing GRDS tablets.

OPTIMIZATION TECHNIQUE-EXPERIMENTAL DESIGN:

Factorial design is an experimental design technique, by which the factor involved and their relative importance can be assessed. In the present study, the formulations, which are designed based on 3^2 full factorial design containing 2 factors evaluated at three-dimension levels and the experimental trials were performed at all possible combinations.

Factor A: Distinctive Ratios of Polymers (X1) (Karaya gum: Pullulan Gum) (25:25, 25:50, 37.5:37.5, 50:50, 50:25) (in mg).
Factor B: Amount of HPMC M4K, HPMC M15K (X_2) (0:20, 20:0, 20; 0) in %). 3^2 full factorial design was considered.

Table 10. Actual and coded values of the factor

Model	Actual values			Coded values		
Factor	Low level	Mid level	High level	Low	Mid	High
Factor A = Gum Karaya & Pullulan (X_1)	0:50	37.5:37.5	50:0	-1	0	+1
Factor B= HPMC K 15M/ HPMC K4M (X_2)	0	50	50	-1	0	+1

Table 11 Formulations based on 3^2 full factorial design

Ingredients	R1	R 2	R3	R 4	R5	R 6	R7	R 8	R 9	R 10
Captopril	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Gum Karaya	37.5	25	50	50	37.5	50	25	50	25	25
Pullan Gum	37.5	25	25	50	37.5	50	25	25	25	50
HPMC K15M	-	50	50	50	50	-	50	-	-	-
HPMC K4M	50	--	--	--	--	50	--	50	50	50
Aerosil	20	20	20	20	20	20	20	20	20	20
PVP K-30	20	20	20	20	20	20	20	20	20	20
Dicalcium Phosphate	20	0	0	20	20	0	0	20	20	0
Sodium bicarbonate	30	30	30	30	30	30	30	30	30	30
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2
Total Weight	250	250	250	250	250	250	250	250	250	250

The medication discharge(drug release) example of definitions of plans R1 to R10 of GRDS tablets arranged and assessed. The in vitro medication discharge profile is performed for every one of the details. The in vitro medication discharge profile is displayed, curve fitting investigation

The R1 –R10 results are introduced here in the compelled table underneath, with the upper and lower limits acquired at at different times of evaluation.

Table 12 : Composition of formulation (FC)

Sl.No	Ingredients	Quantity (in mg)
1	Captopril Drug	12.5
2	Karaya gum	25.59
3	Pullulan Gum	49.39
4	HPMC4K	20
5	PVP K-30	20
6	Aerosil	20

7	Sodium Bi Carbonate	30
8	Di calcium Phosphate	69.52
9	Magnesium Stearate	1
10	Purified Talc	2

The measurable methodology for definition streamlining is a helpful apparatus especially in an all the while assessing a few factors. The watched reactions were in close concurrence with the anticipated estimations of the advanced detailing.

The watched reactions were in close concurrence with the anticipated estimations of the advanced detailing. Exhibiting the plausibility of the advancement methodology(optimization procedure) in the developing the floating tablets of Captopril(FC)

Table .13. Pre compression parameters of formulation FC

Bulk Density (g/cc)	0.4614 ± 0.14
Tapped Density (g /cc)	0.6013 ± 0.12
Angle of Repose (θ)	34.19 ± 0.91
Carr's Index (%)	23.02 ± 0.05
Hausner's ratio	1.24 ± 0.11

Table .14. Post compression parameters of formulation FC

Hardness (Kg / cm2)	5.6 ± 0.47
Friability (%)	0.16 ± 0.12
Thickness (mm)	3.71 ± 0.10
Weight Variation(in mg/tablet)	249.01 ± 1.31

IN VITRO %CDR OF FORMULATION (FC):

The *In vitro* drug release consider was completed in USP Dissolution Test

Apparatus, Type 2 (paddle type). 900ml of recreated gastric liquid pH 1.2 (without compounds) was utilized as disintegration medium. The temperature of disintegration media was kept up at 37 ± 0.5^{O} C. The oar turn speed was kept at 50 rpm. One tablet at any given moment was gauged and taken for study. 5ml of the example was pulled back at 0.25,0.50,0.75 hour and there after each 1-hour interim for 8 hours and a similar volume was supplanted with pre warmed new disintegration media and the absorbance was measured and recorded at 212 nm utilizing UV-VIS spectrophotometer.

Table 15 : % CDR of the (FC) stored at 25^{0}C /60% RH

Time(Hrs) ⇨ Duration (Months)⇩	0	0.25	0.50	0.75	1	2	3	4	5	6	7	8
0	0	2.31	4.09	18.33	25.27	42.16	57.27	63.84	67.43	80.07	86.98	97.21
1	0	2.32	4.10	18.29	25.28	42.33	57.23	63.75	67.41	80.11	86.47	97.19
3	0	2.32	4.21	18.14	25.39	42.17	57.02	63.61	67.84	80.04	86.35	97.12
6	0	2.34	4.17	18.91	25.43	42.16	56.79	63.93	68.76	80.95	87.22	96.33

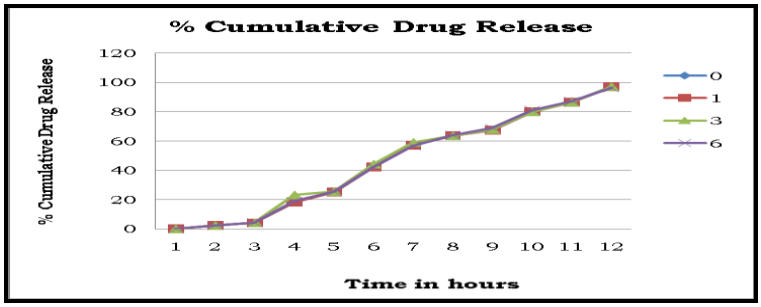
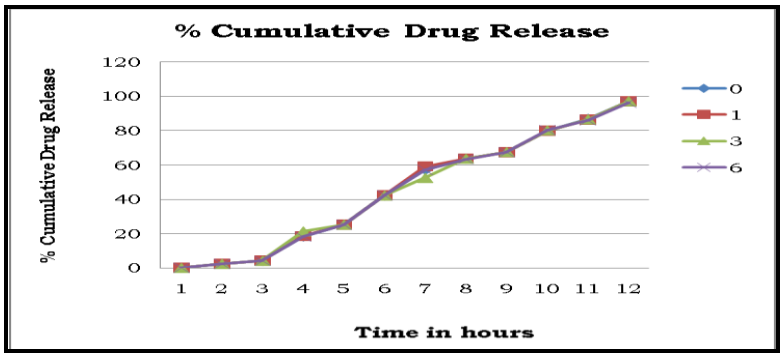


Table 16 *In vitro* % CDR of (FC) stored at 40^{0}C /75% RH

Time(Hrs) ⇨ Duration (Months)⇩	0	0.25	0.50	0.75	1	2	3	4	5	6	7	8
0	0	2.31	4.09	18.33	25.27	42.16	57.27	63.84	67.43	80.07	86.98	97.21
1	0	2.32	4.18	18.51	25.28	42.33	57.23	63.75	67.41	80.11	86.47	97.21
3	0	2.32	4.15	18.27	25.26	42.19	57.24	63.58	67.50	80.13	86.53	97.09
6	0	2.39	4.04	18.22	25.21	42.21	57.03	63.41	67.49	80.28	85.98	96.37



Time in months	Formulation Stored at Intermediate 30ºC/65%RH		Formulation Stored at 25ºC /60%RH		Formulation Stored at 40ºC /75%RH	
	Floating lag time (seconds)	Total Floating Time(Hours)	Floating lag time (seconds)	Total Floating Time (in Hours)	Floating lag time (seconds)	Total Floating Time(in Hours)
0	98 ± 0.14	24 ± 1.47	98 ± 1.14	24 ± 1.47	98 ± 1.14	24 ± 1.47
1	99 ± 0.25	24 ± 1.33	99 ± 0.11	24 ± 1.18	99 ± 0.25	24 ± 1.21
3	101 ± 0.37	24 ± 1.24	102 ± 0.81	24 ± 1.08	102 ± 0.37	24 ± 1.13
6	102 ± 0.49	24 ± 1.19	103± 0.64	24 ± 1.02	103 ± 0.49	24 ± 1.01

Figure 9.Graph % CDR of (FC) stored at 40^{0}C /75% RH

CURVE FITTING DATA:

Table 17. Curve fitting data for formulation FC

Kinetic Models	Optimized Formulation
Peppas Model	
K (h^{-n})	25.42 ± 1.821
n	0.5438 ± 0.0409
R^2	0.991
$T_{50\%}$ (hr)	3.963
Higuchi Model	
K($h^{-1/2}$)	31.99 ± 1.084
R^2	0.992
Zero order release kinetics	
K(h^{-1})	13.49 ± 0.7255
R^2	0.974
First order release kinetics	
K(h^{-1})	0.1967
R^2	0.882

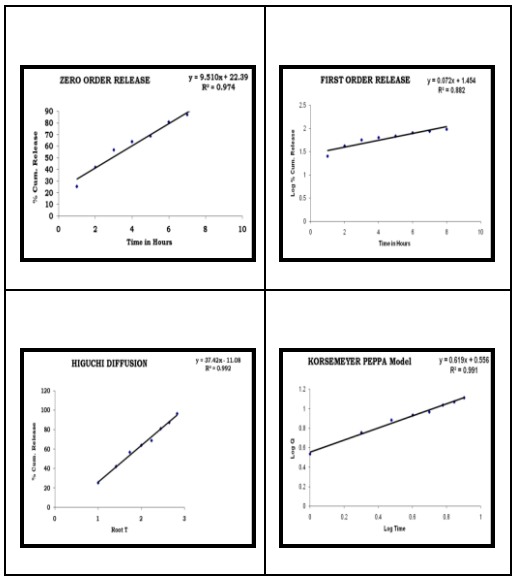


Figure 10. Graph for Kinetic models for the formulation(FC)

The float slack(lag) time was between 98 ± 0.14 seconds to 104 ± 0.49 seconds and TFT was >24 ± 1.01 hours on sixth month. The investigations of the FC demonstrated great Floating lag time (FLT) and absolute(total) coasting lag time (TFT).

Table 19: Stability Data of Formulation(FC)

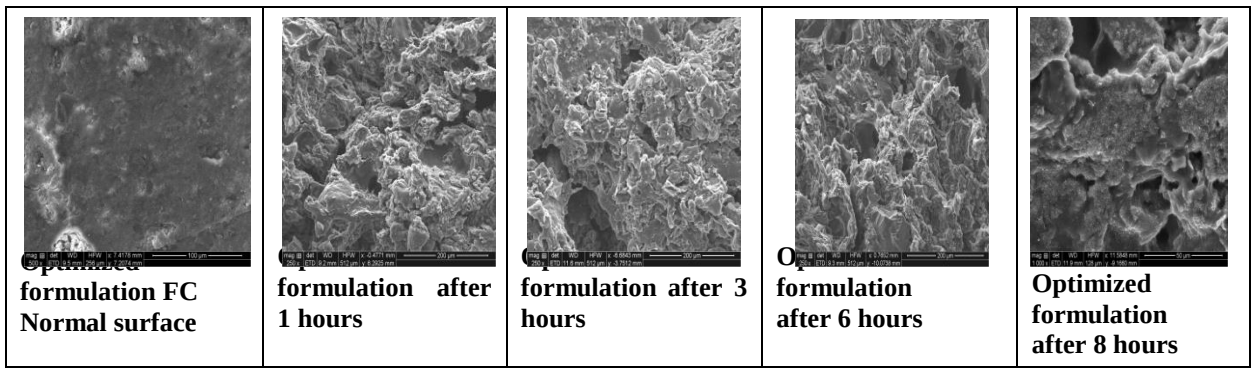
Time in months	Formulation Stored at Intermediate 30ºC ± 2ºC /65%RH		Formulation Stored at 25ºC± 2ºC /60%RH		Formulation Stored at 40ºC ± 2ºC /75%RH	
	Physical Appearance	% Drug Content*	Physical Appearance	% Drug Content	Physical Appearance	% Drug Content
0	+++	98.88	+++	98.88	+++	98.88
1	+++	98.84	+++	98.83	+++	98.41
3	+++	98.80	+++	98.78	+++	98.03
6	+++	98.00	+++	98.02	+++	97.65

*n = 3 +++ Same as on zero day

Accelerated stability investigations of Optimized detailing FC stored did not demonstrate (show) any adjustments (changes) in the Physical appearance and discovered stable. Plans put away at various conditions were come about between 97.07% to 98.88% at 0 day, first month, third month and sixth month. Also, were within specifications of IP compendia (90%-110%)

MORPHOLOGICAL STUDY OF SOAKED MATRIX TABLETS:

The FC formulation selected was observed under the scanning electron microscope and the morphological characters were compared to know the mechanism of drug release and floating.



Optimized formulation FC Normal surface | **Optimized formulation after 1 hours** | **Optimized formulation after 3 hours** | **Optimized formulation after 6 hours** | **Optimized formulation after 8 hours**

Figure 11. Scanning Electronic Microscopic study of the optimized formulation (FC):

CONCLUSION:

Gastro retentive matrix tablets for antihypertensive drug captopril was prepared by direct compression method using Xanthan gum, pullulan gum, gum karaya and gellan gum in different ratios along with HPMC 4K.

The prepared matrix tablets were evaluated for hardness, friability, FTIR analysis, DSC analysis, buoyancy, swelling index study, drug content and *in vitro* cumulative drug release. All the prepared Formulations were found to be good without chipping and capping. The FTIR and DSC analysis study indicated no drug-excipient interactions. Formulation F9 was found better than others out 12 formulations with good characteristics of gastro retentive floating properties and *in vitro* cumulative drug release. The decrease in release kinetics of the drug was observed on increasing polymer ratio. Based on the preliminary formulation (F1-F12) and evaluation, optimization technique was adopted using 3^2 factorial design and statistical ANOVA (software).

Ten formulations designed and formulated with code R1 to R10. The pre-compression, post-compression parameters including buoyancy of R1 to R10 were investigated, and optimized formulae was developed with predicted values. The optimized matrix tablets coded as FC were prepared by direct compression.

The formulation FC with Karaya gum and pullan gum along with HPMC M4K were shown good retarding characteristics, which was need for sustained release of antihypertensive drug for longer duration.The evaluation results of optimized formulation FC for pre & post compression

parameters, buoyancy, swelling index, stability, drug content and *invitro* cumulative drug release, indicates the optimized formulation holds good for preparation of Gastro retentive matrix tablets for antihypertensive drug.

Acknowledgements

The authors are thankful to the Pharma industry who have provided drug, polymers, and excipients as a gift samples for the research work. And also thankful to the Principal and staff of Govt. College of Pharmacy, Bangalore for the facility.

REFERENCES:

1. Pankit M, et al Formulation & evaluation of sustained matrix tablets of captopril, Indo American J of Pharm Res, 2011;2(1):69-83.
2. Brahma N, Kwon HK. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Contr Rel 2000; 63: 235–259.
3. Swarbrick J, Boylan JC. Optimization techniques in formulation and processing pharmaceutical encyclopedia, vol12: marcel dekker (NY); 1990.
4. Hoffman A, David S, Eran L, Sara E, Eytan K, Michael F. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. Int J Pharm 2004; 277: 141–153.
5. Indian Pharmacopeia 2007; Indian Pharmacopeia 2014
6. Sreenivasa Reddy N, Mahendra Kumar CB, Ramesh A *et al*., Development and in vitro evaluation of Gastro retentive matrix tablets: an approach using natural gums and polymers; Research J of Pharm Bio and Chem Sci ,2011; 2 (1); 0975-8585.
7. Brijesh SD, Avani FA, Madhabhai MP. Gastroretentive drug delivery system of ranitodine hydrochloride formulation and in vitro evaluation. AAPS Pharm Sci Tech 2004; 5(2): 1-6.
8. Srinath MS, Narendra C, Prakash BR, Formulation and evaluation of a sublingual tablet containing terbutaline sulphate: optimisation and in vivo studies. Ars Pharm 2005; 46 (2): 139-158.
9. Sasa B, Julijana K, Franc V, Polona V, Bojan Z. Optimisation of floating matrix tablets and evaluation of their gastric residence time Int J Pharm 2000; 195: 125–135.
10. Foye. Analytical profiles of drug substances. Vol 15: 3rd ed: American pharmaceutical association; 1986: 533-561.