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RESEARCH ARTICLE

Optimization of Floating Microspheres of Captopril Using Full Factorial Design

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ABSTRACT

Captopril is an angiotensin converting enzyme inhibitor, widely used in management of hypertension. It has very short half life of 2 h and oral bioavailability of 70%. The present investigation is concerned with the development of the floating microspheres of Captopril to target the drug to its absorption site by increasing the residence time of drug in stomach and to control drug release in therapeutic range for longer period of time. Floating microspheres of Captopril were prepared by Non-aqueous solvent evaporation technique using 3^2- Full factorial design. In this dosage form, hydrophobic water impermeable polymer (EC) for controlling the release of drug and hydrophobic water permeable polymer (Eudragit RL-100) were used for initial release of drug. Optimization process was carried out with respect to various dependent variables like $T_{50\%}$(h),$T_{80\%}$ (h), log K of Pappas eq., release at 12 h, release at 18 h, K of 1st order etc. and optimized formulations were developed. Among three optimized formulations, results of OF1 and OF2 closely met to targeted data while OF3 was found to be best formulation as per cost-effectiveness which also showed significant results to targeted data. Two months of stability study was carried out at room temperature for all three optimized formulations and results showed no significant changes in percentage drug entrapment efficiency and *in-vitro* drug release study after stability study. So the all three optimized formulation containing 50 mg of Captopril, released drug for 24 h within desired therapeutic concentration.

Keywords: Captopril, Floating drug delivery system, Floating microspheres, Optimization process, Stability study.

1. INTRODUCTION

Development of oral controlled-release systems has been a challenge to formulation scientists because of their inability to restrain and localize the system in the targeted area of the gastrointestinal tract. Controlled/sustained release preparations using alternative routes have been formulated but the oral route still remains preferable. Floating Drug Delivery Systems (FDDS) or Hydrodynamically Balanced Systems (HBS) are among the several approaches that have been developed in order to increase the gastric residence time (GRT) of dosage forms. Both single and multiple unit systems have been developed. The single-unit floating systems are more popular but have a disadvantage owing to their 'all-or-nothing' emptying process leading to high variability of the gastrointestinal transit time. Still, the multiple-unit dosage forms may be better suited because they are claimed to reduce the intersubject variability in absorption and lower the probability of dose dumping. Such a dosage form can be distributed widely throughout the gastrointestinal tract (GIT), affording the possibility of a longer lasting and more reliable release of the drug from the dosage form[1,2,3]. Captopril, an antihypertensive agent, has been widely used for the treatment of hypertension and congestive heart failure. It has been reported, however, that the duration of antihypertensive action after a single oral dose of captopril is only 6–8 h, so clinical use requires a daily dose of 37.5–75 mg to be taken three times[4,5,6] (6). It is most stable at pH 1.2 and as the pH increases; it becomes unstable and undergoes a degradation reaction (7). The virtue of the prolonged

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release dosage form of captopril has been reviewed (8). Researchers have developed a floating tablet of captopril (9). In comparison with the tablet, floating microspheres

MATERIALS AND METHODS

Materials:

Sr. No.	Materials	Source
1	Captopril	Worckhardt pharmaceuticals, Maharashtra
2	Ethyl Cellulose	Central Drug House (P) Ltd.
3	Eudragit RL 100	Sun Pharmaceuticals, Baroda.
4	Liquid Paraffin	Central Drug House (P) Ltd.
5	Acetone	Central Drug House (P) Ltd.

Table 1: List of materials

Equipments:

Sr. No.	Equipments	Model/ Company
1	UV-Visible Spectrophotometer	Spectrophotometer UV-1701, Shimandzu,Japan
2	Electronic Analytical balance	Electronic balance, Shimandzu, Japan
3	FTIR	IISC, Bangalore.
4	USP dissolution apparatus	Scientific USP Standard DA-60s, Elecrolab, Ahmedabad

Table 2: List of equipments

Theoretical release profile of Captopril:

Calculation of Immediate Release profile:

IRP = Css * Vd /F

Where C_{ss} = Concentration at steady state

V_d = Volume of distribution

F = fraction of bioavailable dose

Calculation of dose:

Dose = IRP ([1+0.693t]/ $t_{1/2}$)

Where t=time upto sustain release required

$t_{1/2}$ = half life of drug

Time(h)	Theoretical drug release(mg)	% Theoretical drug release
1	4.808	9.602
2	6.776	13.533
3	8.744	17.464
4	10.712	21.395
5	12.680	25.325
	14.648	29.256
9	20.553	41.048
12	26.457	52.840
18	38.266	76.425
24	50.074	100.009

Table 4: Theoretical release profile of Captopril

float in stomach for longer period of time and release drug at desired rate without much intersubject variability[7, 8,9,10].

PREFORMULATION STUDY:

Preformulation study is one of the important prerequisite in development of any drug delivery system. Thus, a preformulation study was carried out to check the compatibility between drug and various polymers and development of analytical method of drug.

DEVELOPMENT OF ANALYTICAL METHOD OF DRUG:

Calibration curve of drug Captopril was prepared in simulated gastric fluid (pH 1.2)

PREPARATION OF STANDARD CURVE:

Standard stock solution of Captopril in Simulated Gastric Fluid (pH 1.2):

100 mg of Captopril was dissolved in 100 ml 0.1N HCL, from this stock solution 10ml was withdrawn and transferred into 100ml volumetric flask. Volume was made with 0.1N HCL in order to get standard stock solution containing 100 µg/ml.

Calibration curve of Captopril in Simulated Gastric Fluid (pH 1.2):

From standard stock solution, a series of diluents were prepared using 0.1N HCL containing 1% Tween 80. The absorbance of these solutions was measured against blank of 0.1N HCL containing 1% Tween 80 at 212nm for Captopril.

Drug polymer compatibility studies:

Drug polymer compatibility studies were carried out using FTIR.

PREPARATION OF MICROSPHERES:

Microspheres containing anti-hypertensive drug as a core material were prepared by a Non-aqueous Solvent Evaporation method. Briefly, drug and different ratio of polymers (Ethyl Cellulose and Eudragit-RL) shown in table, were mixed in 30 ml acetone. The slurry was slowly introduced into 30ml of liquid paraffin while being stirred at 500 rpm by a mechanical stirrer equipped with a three bladed propeller at room temperature. The solution was stirred for 2 h to allow the solvent to evaporate completely and the microspheres were collected by filtration. The microspheres were washed repeatedly with petroleum ether (40-60ºC) until free from oil. The collected microspheres were dried for 1 h at room temperature and subsequently stored in desiccators over fused calcium chloride[36].

CODE	Level		
	-1	0	1
Total amount of polymer (mg) X_1	150	300	450
% of Ethyl cellulose (mg) X_2	50	66.66	100

Table 5: INDEPENDENT VARIABLES AND THEIR LEVELS

Batch	Amount of Drug (mg)	Total amount of Polymer (mg) (X_1)	Amount of Ethyl Cellulose (X_2)		Amount of Eudragit RL100		Amount of Acetone (ml)	Amount of liquid Paraffin (ml)
			%	mg	%	Mg		
F1	200	1800	100	1800	0	0	30	30
F2	200	1200	100	1200	0	0	30	30
F3	200	600	100	600	0	0	30	30
F4	200	1800	66.66	1200	33.33	600	30	30
F5	200	1200	66.66	800	33.33	400	30	30
F6	200	600	66.66	400	33.33	200	30	30
F7	200	1800	50	900	50	900	30	30
F8	200	1200	50	600	50	600	30	30
F9	200	600	50	300	50	300	30	30

TABLE 6: FORMULATION CHART (FULL FACTORAIL DESIGN[10, 11, 12])

Note: Each formulation contains 4 replicate of Floating microspheres equivalent to 50 mg drug in each.

EVALUATION OF FLOATING MICROSPHERES:

1) Yield of Microspheres:

The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

% Yield = (Actual weight of product / Total weight of excipient and drug) × 100

2) Particle size analysis:

Size distribution was determined by optical microscopy using stage micrometer slide and calibrated eyepiece by counting at least 100 microspheres per batch.

3) Percentage Drug Entrapment Efficiency (%DEE)[37]:

Microspheres equivalent to 10 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, Japan) at 212 nm against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula.

%Drug Entrapment Efficiency = (Amount of drug actually present / Theoretical drug load expected) × 100

4) Surface Topography (SEM):

The surface morphology of the microspheres was examined by Scanning Electron Microscopy (SEM).

5) *In vitro* Evaluation of Floating Ability (% Buoyancy)[38]:

An *in vitro* floating study was carried out using simulated gastric fluid USP as a dispersing medium. Microspheres were spread over the surface of 500 ml of dispersing medium at 37 ± 0.5°C. A paddle rotating at 100 rpm agitated the medium. Each fraction of microspheres floating on the surface and those settled down were collected at a predetermined time point (24 h). The collected samples were weighed after drying.

% Buoyanc**y** = (Weight of floating microspheres/ Initial weight of microspheres) × 100

6) *In vitro* Drug Release Study[39,40]:

In vitro drug release studies were carried out in USP type II dissolution test apparatus. Microspheres equivalent to 50 mg of the pure drug were used for dissolution study. Two ml of the aliquot was withdrawn at predetermined intervals and filtered. The required dilutions were made with 0.1N HCl (Simulated gastric fluid) and the solution was analyzed for the drug content spectrophotometrically at 212 nm against suitable blank. Equal volume of the

dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. Three trials were carried out for all formulations. From this percentage drug release was calculated and plotted against function of time to study the pattern of drug release. The similarity of dissolution profile of the prepared formulations was compared with that of the predicted theoretical value to arrive at the optimum profile.

7) Stability studies:

Stability studies were carried out on most satisfactory formulation as per ICH Guidelines Q1C. The most satisfactory formulation stored in sealed in aluminum foil. These were stored at room temperature for 2 months. After 2 months % Drug entrapment efficiency of most satisfactory formulation was determined *In vitro* release study was also carried out of best formulation.

DISCUSSION

Captopril is ACE inhibitors, used in management of hypertension. The bioavailability of Captopril is 70%, its half-life is less than 2 h and it is absorbed in stomach. So in the present study, an attempt was made to formulate floating microspheres of Captopril in order to increase residence time in stomach for better absorption. Floating microspheres of Captopril were prepared by Non-aqueous solvent evaporation technique using 3^2-Full Factorial design. Evaluation of its physicochemical properties, investigation of release kinetics, optimization of the release pattern at 6 h, 12 h, and 18 h, $T_{50\%}$ (h), $T_{80\%}$ (h) and release kinetics were carried out and find out optimized formulation.

Preformulation study:

Any formulation development work has to be preceded by preformulation studies. This preformulation study includes selection of method of preparation, selection of polymers, Drug- polymer compatibility study and analytical investigation of drug.

Floating microspheres of Captopril were prepared by Non-aqueous solvent evaporation technique using 3^2-Full Factorial design. As per review of literature, hydrophobic water impermeable polymer Ethyl cellulose and hydrophobic water permeable polymer Eudragit RL-100 were selected because Eudragit RL-100 is required for initial release of drug and Ethyl cellulose is required for retarding drug release. Both polymers are soluble in acetone, so acetone was used as solvent and Liquid paraffin was used as dispersion medium.

FT-IR study showed that there is no interaction between drug and polymer so the drug and polymer are compatible.

Estimation of Captopril was carried out by SHIMADZU-1701 UV spectrophotometer at λ_{max} 212 nm in simulated gastric fluid. The linear co-efficient was found to be closer to 1 (i.e. 0.9946) at concentration range between 5-30µg/ml.The regression equation generated was **y=0.0214x**. By using this regression co-efficient equation the assay and % CDR were calculated.

Formulation study:

Floating microspheres of Captopril were prepared by Non-aqueous solvent evaporation technique using 3^2-Full Factorial design. In this design total amount of polymer and amount of Ethyl cellulose were kept as independent variables. Amount of acetone and liquid paraffin were kept constant.

Evaluation:

1. Percentage Yield:

As the concentration of total amount of polymer was increased, the % yield was also found to be increased. So the F1, F4, F7 batches showed good % yield (93.56±2.79), (92.11±2.79) and (91.71±1.23) respectively.

2. Percentage Drug entrapment efficiency:

As the total amount of polymer is increased, the % DEE was also found to be increased. So F1, F4, F5 batches showed (92.74±1.24 %), (90.61±2.21%) and (88.65±2.35%) respectively.

3. Percentage Buoyancy:

As the amount of hydrophobic polymer (EC) is increased, % Buoyancy was found to be increased. So the F1 batch showed highest % Buoyancy (98.75±3.62) while F9 batch showed lowest % Buoyancy (91.12±2.87). Because as the amount of water permeable polymer Eudragit-RL 100 increases, the microspheres got sunk readily.

4. Particle size: Particle sizes of all batches were found to be between 175-350 µm.

5. *In-Vitro* drug release study:

The formulation in full factorial design was having wide range of release both over and below targeted release. As the amount of hydrophobic polymer (Ethyl cellulose) increases, release of drug was found to be retarded. So F6 batch showed maximum drug release (99.78± 0.20) while F1 batch showed lowest drug release (75.20± 2.63).

OPTIMIZATION RESULTS:

1) $T_{50\%}$ (h):

Equation:

$$Y = 0.00139*X_1 + 0.03452*X_2 + 0.00032*X_1X_2 - 0.000012*X_1^2 - 0.00061*X_2^2$$

β_1: Positive co-efficient (0.00139) of total amount of polymer suggests that as total amount of polymer increases, the value of **$T_{50\%}$** is increased.

β_2; Positive co-efficient (-0.03452) of amount of Ethyl cellulose suggests that as amount of ethyl cellulose, increases**,** $T_{50\%}$ is decreased.

β_3: Positive co-efficient (+0.00032) of X_1 and X_2 suggests that as total amount of polymer and amount of ethyl

cellulose increase, $T_{50\%}$ is increased rapidly. So no significant interaction was found.

β_4: Negative co-efficient (– 0.000012) of X_1^2 suggests that as total amount of polymer increases, $T_{50\%}$ is increased slowly**.**

β_5: Negative co-efficient (- 0.00061) of X_2^2 suggests that as amount of Ethyl cellulose increases, $T_{50\%}$ is increased slowly.

2) $T_{80\%}$ (h**):**

Equation:

$Y = 0.0235971*X_1+0.0843998*X_2 + 0.0001666*X_1X_2 – 0.000028*X_1^2 - 0.000505*X_2^2$

β_1: Positive co-efficient (0.0235971) of total amount of polymer suggests that as total amount of polymer increases, the value of $T_{80\%}$ is increased.

β_2: Positive co-efficient (+0.0843998) of amount of Ethyl cellulose suggests that as amount of ethyl cellulose, increases, $T_{80\%}$ increased.

β_3: Positive co-efficient (+0.0001666) of X_1 and X_2 suggests that as total amount of polymer and amount of ethyl cellulose increase, $T_{80\%\ is}$ increase rapidly. So, significant interaction was found.

β_4: Negative co-efficient (–0.000028) of X_1^2 suggests that as total amount of polymer increases, $T_{80\%}$ increases slowly.

β_5: Negative co-efficient (-0.000505) of X_2^2 suggests that as amount of Ethyl cellulose increases, $T_{80\%}$ increases slowly.

3) 'Log K' of Pappas Equation:

Equation:

$Y =2.26824 -0.00095*X_1 - 0.01138*X_2 - 0.000012*X_1X_2+0.000001*X_1^2 + 0.000055*X_2^2$

β_1: Negative co-efficient (**-0.00095**) of total amount of polymer suggests that as total amount of polymer increases, the value of **'Log K' of Pappas Equation** is decreased. This shows that release kinetics moves from 1st order to zero order.

β_2: Negative co-efficient (**- 0.01138**) of amount of Ethyl cellulose suggests that as amount of ethyl cellulose increases, **'Log K' of Pappas Equation** is decreased.

β_3: Negative co-efficient (-**0.000012**) of X_1 and X_2 suggests that as total amount of polymer and amount of ethyl cellulose increase, **'Log K' of Pappas Equation** increases rapidly. So due to interaction release kinetics move towards 1st order.

4) K of 1st order:

Equation:

$Y = –0.542161+0.00063*X_1 +0.00634*X_2–0.000002*X_1X_2 – 0.0000003*X_1^2–0.000023*X_2^2$

β_1: Positive co-efficient (+0.00063) of total amount of polymer suggests that as total amount of polymer increases, the value of **K of 1st order** is increased. This shows that release kinetics is based on 1st order reaction.

β_2: Positive co-efficient (+0.00634) of amount of Ethyl cellulose suggests that as amount of ethyl cellulose increases, **K of 1st order** is increased.

β_3: Negative co-efficient (–0.000002) of X_1 and X_2 suggests that as total amount of polymer and amount of ethyl cellulose increase, **K of 1st order** decreases slowly.

5) Release at 12 h**:**

Equation:

$Y = 101.08196 – 0.0151978*X_1- 0.0752996*X_2 – 0.000769*X_1X_2 + 0.0000254*X_1^2 +0.00018257*X_2^2$

β_1: Negative co-efficient (**–0.0151978**) of total amount of polymer suggests that as total amount of polymer increases, release of drug at 9 h is decreased.

β_2: Negative co-efficient (-**0.0752996**) of amount of Ethyl cellulose suggests that as amount of ethyl cellulose increases, release of drug at 9 h is decreased.

β_3: Negative co-efficient (-**0.000769**) of X_1 and X_2 suggests that as total amount of polymer and amount of ethyl cellulose increase, due to interaction between polymers release of drug at 9 h is further retarded.

β_4 : Positive co-efficient (**0.0000254**) of X_1 and X_2 suggests that as total amount of polymer and amount of ethyl cellulose increase, due to interaction between polymers release of drug at 12 h is slowly is decreased (at higher concentration).

β_5 : Positive co-efficient (**0.00018257**) of X_1 and X_2 suggests that as total amount of polymer and amount of ethyl cellulose increase, due to interaction between polymers release of drug at 12 h is slowly decreased.

6) Release at 18 h**:**

Equation:

$Y =96.318548 -0.0347161*X_1 - 0.4300386*X_2 – 0.0005847*X_1X_2 + 0.00005477*X_1^2 +0.0048155*X_2^2$

β_1: Negative co-efficient (**–0.0347161**) of total amount of polymer suggests that as total amount of polymer increases, release of drug at 18 h is decreased.

β_2: Negative co-efficient (**-0.4300386**) of amount of Ethyl cellulose suggests that as amount of ethyl cellulose increases, release of drug at 18 h is decreased.

β_3: Negative co-efficient (-**0.0005847**) of X_1 and X_2 suggests that as total amount of polymer and amount of ethyl cellulose increase, due to interaction between polymers release of drug at 18 h is further retarded.

β_4 : Positive co-efficient (**0.00005477**) of X_1 and X_2 suggests that as total amount of polymer and amount of ethyl cellulose increase, due to interaction between polymers release of drug at 18 h is slowly is decreased (at higher concentration).

β_5 : Positive co-efficient (**0.0048155**) of X_1 and X_2 suggests that as total amount of polymer and amount of ethyl cellulose increase, due to interaction between polymers release of drug at 18 h is slowly decreased.

OPTIMIZED FORMULATION:

On the basis of above derived equation and % similarity, 3 optimized formulations were derived. Among 3 optimized formulation OF1 and OF2 having maximum similarity with standard formulation .for all evaluated variables while OF3 is on the basis of cost-effectiveness and it also showing relatively high degree of similarity with desired data.

EVALUATION OF OPTIMIZED FORMULATION:

1) Percentage Yield:

Percentage yield for all thee optimized formulation were found to be between 87 to 90% which is higher level of yield and also within the desirable range.

2) Percentage Drug entrapment efficiency:

Percentage Drug entrapment efficiency for all thee optimized formulation were found to be between 83 to 87% which is within the desirable range.

3) Percentage Buoyancy:

Percentage buoyancy of all thee optimized formulation were found to be between 96 to 99% which is most significant value to localize drug in stomach upto 24 h.

4) Particle size:

Particle sizes of floating microspheres were found to be between 180 to 250 µm which is quite significant.

5) *In-Vitro* drug release:

Figure 12 showed that *In-Vitro* release of optimized formulation was found to be near to targeted release of drug.

STATISTICAL ANALYSIS:

Table 43 and 44 showed that experimental values of $T_{50\%}$ (h), $T_{80\%}$(h), 'Log K' of Pappas eq., K of 1st order, release at 12h, release at 18 h of OF1, OF2 and OF3 were near to expected values of OF1, OF2 and OF3 respectively and also significant to desirable data.

Stability study:

Table 39,40,41 and 42 showed that there were no significant changes found in Percentage drug entrapment efficiency and *in-vitro* drug release profile of all thee optimized formulation after stability study.

SCANNING ELECTRON MICROSCOPE (SEM):

Surface topography of optimized formulation OF1 was carried out. SEM study (Figure13 and 14) showed that pores were found on the surface of microspheres which indicates that drug is released by diffusion mechanism.

Therefore, objective of design and development of floating drug delivery system of Captopril was completely achieved. This formulation having release pattern closer to theoretical release profile, being floating drug delivery system, drug will be released in stomach. So that drug administration should be with glass of water to provide suitable floating capability.

The model equation developed has not only led us to present optimum formula, but can be used to achieve any target data within effective concentration range.

RESULTS

FT-IR Peak of Pure drug

Wave no.	Assignment
1743 cm^{-1}	C=O (- COOH group)
1725 cm^{-1}	C=O (- COOH group)
1640 cm^{-1}	C=O (Amide Group)
2560 cm^{-1}	S-H

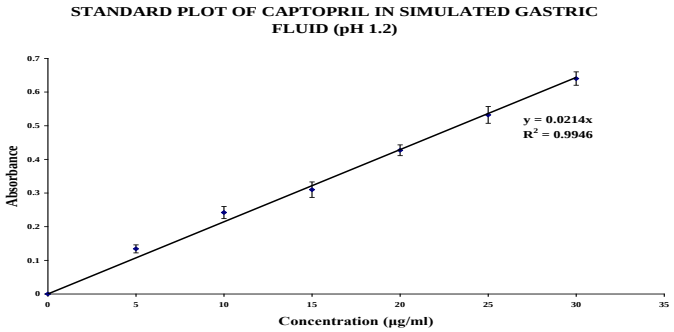


Figure 1: Standard Plot of Captopril in Simulated Gastric Fluid (pH 1.2)

SUMMARY

- UV-spectrophotometeric method was used for determination of Captopril in Simulated gastric fluid (pH 1.2) at 212nm
- IR spectrum of pure drug and drug-polymer mixture revealed no chemical interaction.
- Floating microspheres of Captopril were prepared by Non- aqueous solvent evaporation technique using 3^2-Full factorial design.
- Various physicochemical properties like % Yield, % DEE ,% Buoyancy and Particle size were evaluated. *In-vitro* drug dissolution was also performed for drug release study.
- Optimization process was carried out and optimized formulations were selected on the basis of desirable values of dependent variables and also on the basis of cost effectiveness.
- Accelerated stability study of optimized formulation OF1, OF2 and OF3 were performed which showed slight change in % DEE and drug release profile.
- All three optimized formulation (OF1, OF2 and OF3) containing 50mg drug release drug for 24 Hr. with desired therapeutic concentration.

CONCLUSION

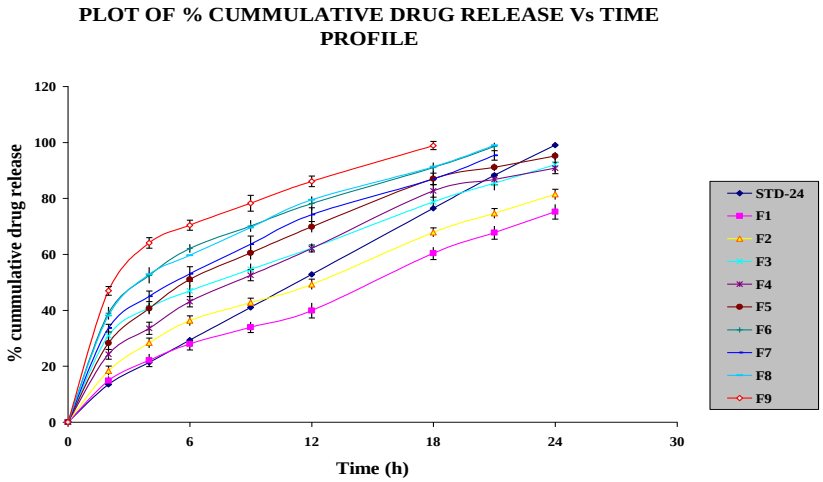
In the present study, an attempt was made to design floating microspheres of Captopril for treatment/ management of hypertension. The main interest in such a dosage form was to target the drug to its absorption site by increasing the residence time of drug in stomach and to control drug release in therapeutic range for longer period of time.

Floating microspheres of Captopril were prepared by Non-aqueous solvent evaporation technique using 3^2- Full factorial design. In this dosage form, hydrophobic water impermeable polymer (EC) for controlling the release of drug and hydrophobic water permeable polymer (Eudragit RL-100) were used initial release of drug. Optimization process was carried out and optimized formulations were developed. Among three optimized formulations, results of OF1 and OF2 closely met to targeted data while OF3 was found to be best formulation as per cost-effectiveness which also showed significant results to targeted data. All three optimized formulation containing 50 mg of Captopril, released drug for 24 h within desired therapeutic concentration.

TABLE 7: PHYSICO-CHEMICAL PROPERTIES OF VARIOUS FORMULATIONS

Batch	Percentage Yield ±S.D	Percentage Drug Entrapment Efficiency ±S.D	Percentage Buoyancy ±S.D	Particle size ±S.D (µm)
F1	93.56±2.79	92.74±1.24	98.75±3.62	220 ± 47
F2	86.14±1.43	89.17±1.63	97.90±3.79	290 ± 53
F3	79.37±1.69	85.28±1.65	96.21±3.92	235 ± 23
F4	92.11±1.27	90.61±2.21	97.56±3.86	184 ± 29
F5	85.49±2.12	87.09±1.92	96.95±3.47	244 ± 37
F6	80.19±1.37	86.49±2.12	94.21±2.53	210 ± 22
F7	91.71±1.23	88.65±2.35	97.05±3.29	236 ± 56
F8	83.94±2.35	86.97±2.41	95.26±2.37	289 ± 55
F9	78.21±1.09	84.89±2.19	91.12±2.87	271 ± 34

TABLE 8: *IN-VITRO* DRUG RELEASE OF VARIOUS FORMULATIONS



STD-24: Percentage theoretical drug release profile
F1: Batch 1
F2: Batch 2
F3: Batch 3
F4: Batch 4
F5: Batch 5
F6: Batch 6
F7: Batch 7
F8: Batch 8
F9: Batch 9

Figure 2: *In-vitro* drug release study of various formulations

TABLE 9: RELEASE KINETIC STUDY OF VARIOUS FORMULATIONS

Kinetic Profile of formulations	For Pappas Korsmayer Equation		For 1st Order Equation		
	n	Log K	n	R^2	K
Desirability	0.73	0.95	-0.05	0.75	-0.12
F1	0.58	1.02	-0.02	0.97	-0.05
F2	0.53	1.15	-0.03	0.98	-0.07
F3	0.39	1.39	-0.04	0.96	-0.10
F4	0.49	1.27	-0.04	0.99	-0.10
F5	0.45	1.36	-0.05	0.98	-0.12
F6	0.34	1.53	-0.07	0.95	-0.16
F7	0.38	1.45	-0.06	0.97	-0.13
F8	0.34	1.52	-0.07	0.97	-0.17
F9	0.29	1.63	-0.09	0.90	-0.22

Regression Statistics	
Multiple R	0.9999667
R Square	0.9999334
Adjusted R Square	0.7498668
Standard Error	0.0986323
Observations	9

ANOVA					
	Degree of Freedom	**Sum Square**	**Mean Square**	**F**	**Significance F**
Regression	5	584.12414	116.82483	12008.725	1.199E-06
Residual	3	0.0389133	0.0097283		
Total	8	584.16306			

ANOVA					
	Degree of Freedom	**Sum Square**	**Mean Square**	**F**	**Significance F**
Regression	5	584.12414	116.82483	12008.725	1.199E-06
Residual	3	0.0389133	0.0097283		
Total	8	584.16306			

	Coefficients	**Standard Error**	**t Stat**	**P-value**
Intercept	0	-	-	-
X_1	0.0013937	0.0018919	0.7366709	0.0502193
X_2	0.0345253	0.007349	4.6979268	0.0093227
X_1X_2	0.0003204	1.207E-05	26.539935	0.0000120
X_1^2	-1.27E-05	2.962E-06	-4.2883014	0.0127633
X_2^2	-0.0006188	6.34E-05	-9.7604506	0.0006173

$$Y = 0.00139*X_1 + 0.03452*X_2 + 0.00032*X_1X_2 - 0.000012*X_1^2 - 0.00061*X_2^2$$

Table 10: Percentage similarity between experimental and predicted $T_{50\%}$ (h)

Form. Code	Amount of Drug	Total Amount of Polymer	% of Ethyl cellulose	$T_{50\%}$ (h)		Resi.	% Similarity
		X_1	X_2	EXP. Y	PRED. Y		
F1	50	450	100	15	34	-18.97	302.71
F2	50	300	100	12	39	-27.54	348.39
F3	50	150	100	7	44	-36.90	392.80
F4	50	450	66.66	8	59	-51.21	525.89
F5	50	300	66.66	6	66	-60.16	587.55
F6	50	150	66.66	4	73	-69.43	647.93
F7	50	450	50	5	91	-86.20	810.04
F8	50	300	50	4	100	-96.29	887.66
F9	50	150	50	2	109	-106.5	964.01

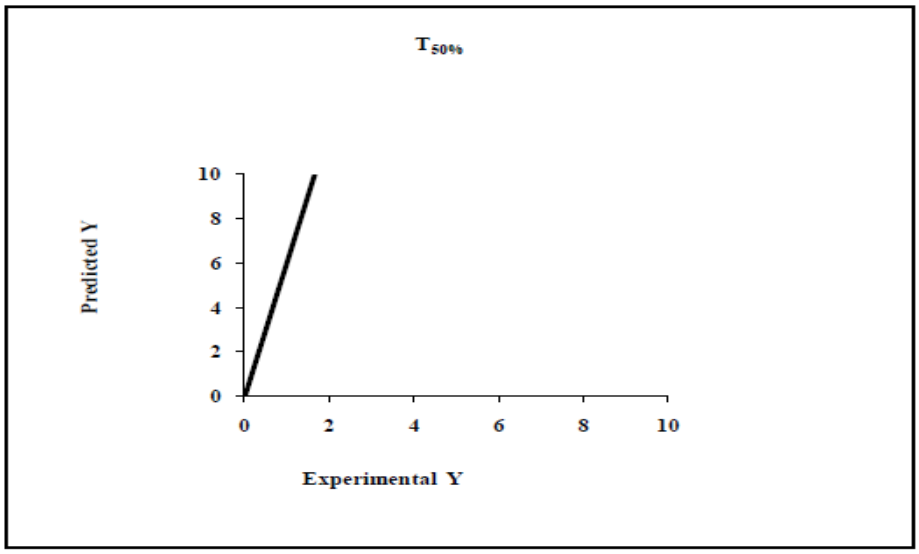
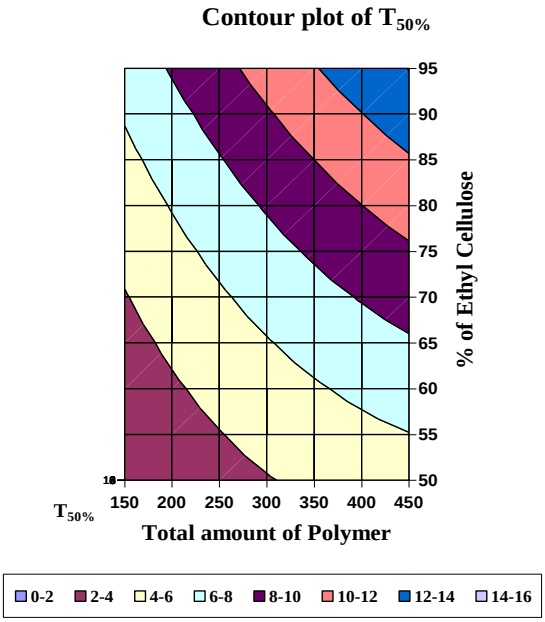


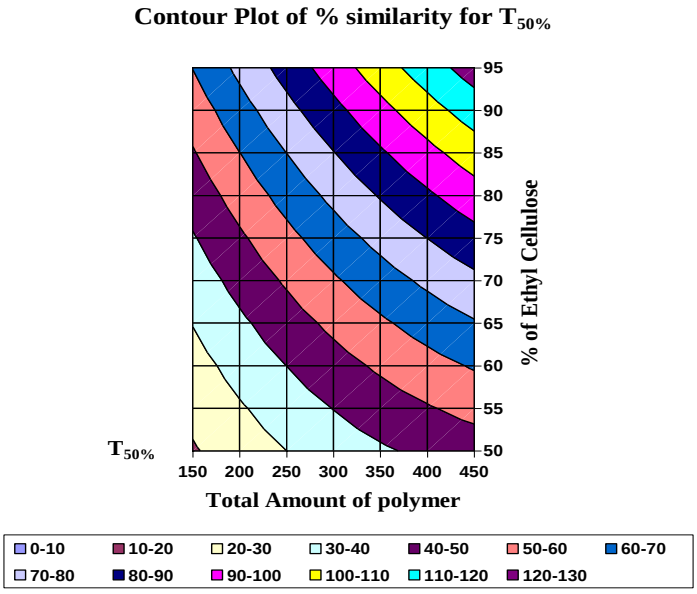
TABLE 11: Statistically predicted values of $T_{50\%}$ (h)

		Percentage of Ethyl cellulose									
		50	55	60	65	70	75	80	85	90	95
Total amount of Polymer	150	2.147	2.540	2.963	3.418	3.903	4.419	4.967	5.545	6.154	6.794
	200	2.796	3.268	3.772	4.307	4.872	5.469	6.096	6.754	7.443	8.164
	250	3.381	3.934	4.517	5.132	5.778	6.454	7.162	7.900	8.669	9.470
	300	3.902	4.535	5.199	5.894	6.619	7.376	8.164	8.982	9.832	10.712
	350	4.360	5.073	5.817	6.592	7.398	8.235	9.102	10.001	10.931	11.891
	400	4.755	5.548	6.372	7.227	8.113	9.030	9.977	10.956	11.966	13.007
	450	5.086	5.959	6.863	7.798	8.764	9.761	10.789	11.848	12.938	14.059

TABLE 12: Percentage Similarity for the predicted values of $T_{50\%}$(h)

		Percentage of Ethyl cellulose									
		50	55	60	65	70	75	80	85	90	95
Total amount of Polymer	150	19.04	22.52	26.28	30.31	34.61	39.19	44.04	49.17	54.57	60.24
	200	24.79	28.98	33.45	38.19	43.20	48.49	54.05	59.89	66.00	72.39
	250	29.98	34.88	40.06	45.51	51.23	57.23	63.50	70.05	76.87	83.97
	300	34.60	40.21	46.10	52.26	58.70	65.40	72.39	79.65	87.18	94.99
	350	38.66	44.98	51.58	58.45	65.60	73.02	80.71	88.68	96.92	105.44
	400	42.16	49.19	56.50	64.08	71.94	80.07	88.47	97.15	106.10	115.33
	450	45.09	52.84	60.86	69.15	77.71	86.55	95.67	105.06	114.72	124.66





OPTIMIZATION OF $T_{80\%}$ (h)

Regression Statistics	
Multiple R	0.9999972
R Square	0.9999945
Adjusted R Square	0.749989
Standard Error	0.0613267
Observations	9

ANOVA					
	Degree of Freedom	Sum Square	Mean Square	F	Significance F
Regression	5	2731.1111	546.22223	145234.62	2.851E-08
Residual	3	0.0150439	0.003761		
Total	8	2731.1262			

	Coefficients	Standard Error	t Stat	P-value
Intercept	0	-	-	-
X_1	0.0235971	0.0011763	20.059766	0.0000364
X_2	0.0843998	0.0045694	18.47056	0.0000506
X_1X_2	0.0001666	7.507E-06	22.194086	0.0000244
X_1^2	-2.808E-05	1.842E-06	-15.244444	0.0001080
X_2^2	-0.0005053	3.942E-05	-12.819368	0.0002134

$Y = 0.0235971*X_1+0.0843998*X_2 + 0.0001666*X_1X_2 – 0.000028*X_1^2 - 0.000505*X_2^2$

Table 13: Percentage similarity between experimental and predicted $T_{80\%}$ (h)

Form. Code	Amount of Drug	Total Amount of Polymer	% of Ethyl cellulose	$T_{80\%}$(h)		Resi.	% Similarity
		X_1	X_2	EXP. Y	PRED. Y		
F1	50	450	100	25.940	25.924	0.016	137.09
F2	50	300	100	23.071	23.044	0.027	121.86
F3	50	150	100	18.872	18.900	-0.028	99.95
F4	50	450	66.66	17.729	17.803	-0.074	94.14
F5	50	300	66.66	15.748	15.756	-0.008	83.32
F6	50	150	66.66	12.458	12.445	0.012	65.81
F7	50	450	50	14.231	14.166	0.065	74.91
F8	50	300	50	12.492	12.535	-0.043	66.29
F9	50	150	50	9.679	9.641	0.039	50.98

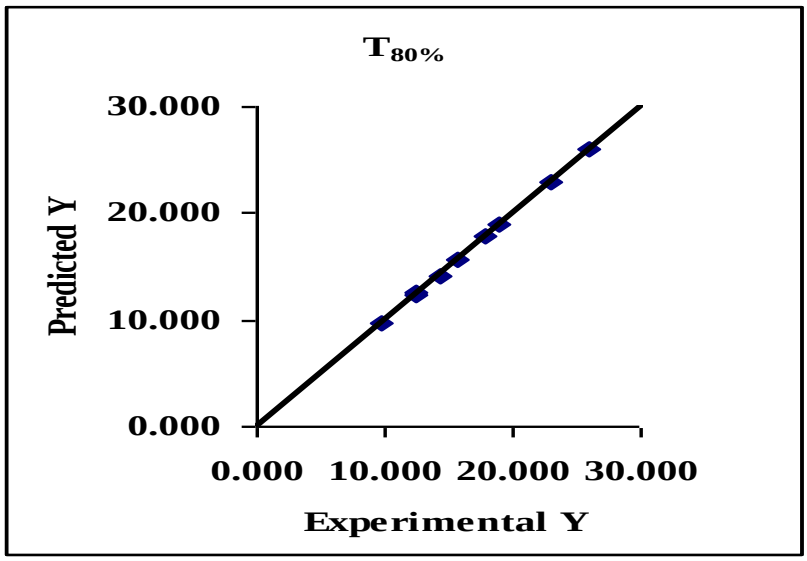
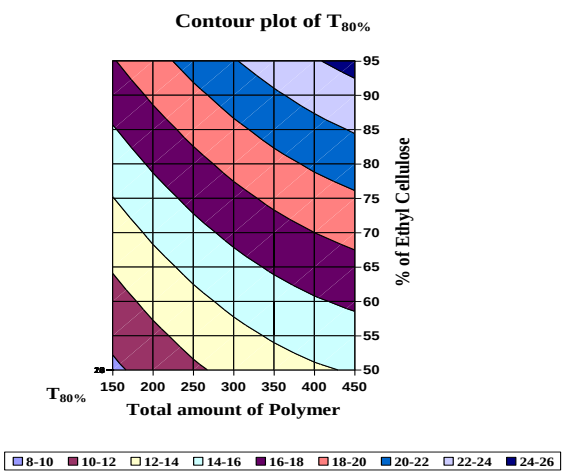


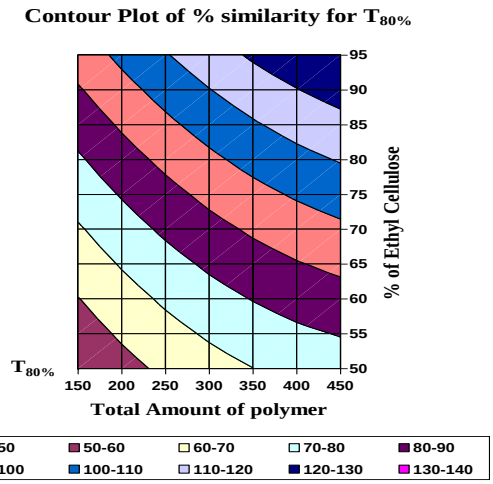
TABLE 14: Statistically predicted values of $T_{80\%}$

		Percentage of Ethyl cellulose									
		50	55	60	65	70	75	80	85	90	95
Total amount of Polymer	150	9.641	10.453	11.291	12.153	13.041	13.955	14.893	15.857	16.846	17.861
	200	10.746	11.600	12.479	13.383	14.313	15.268	16.248	17.254	18.285	19.341
	250	11.711	12.606	13.527	14.473	15.444	16.441	17.463	18.510	19.582	20.680
	300	12.535	13.472	14.435	15.422	16.435	17.474	18.537	19.626	20.740	21.879
	350	13.219	14.198	15.202	16.231	17.286	18.366	19.471	20.601	21.757	22.938
	400	13.762	14.783	15.829	16.900	17.996	19.118	20.264	21.437	22.634	23.857
	450	14.166	15.228	16.315	17.428	18.566	19.729	20.918	22.131	23.370	24.635

TABLE 15: Percentage Similarity for the predicted values of $T_{80\%}$

		Percentage of Ethyl cellulose									
		50	55	60	65	70	75	80	85	90	95
Total amount of Polymer	150	50.98	55.28	59.71	64.27	68.97	73.79	78.76	83.86	89.09	94.45
	200	56.83	61.34	65.99	70.77	75.69	80.74	85.92	91.24	96.69	102.28
	250	61.93	66.66	71.53	76.54	81.67	86.94	92.35	97.88	103.56	109.36
	300	66.29	71.24	76.33	81.56	86.91	92.40	98.03	103.79	109.68	115.70
	350	69.90	75.08	80.39	85.83	91.41	97.12	102.97	108.94	115.06	121.30
	400	72.78	78.17	83.70	89.37	95.17	101.10	107.16	113.36	119.69	126.16
	450	74.91	80.53	86.28	92.16	98.18	104.33	110.62	117.03	123.59	130.27





Optimization of Log (K) of Pappas Eq.

Regression Statistics	
Multiple R	0.9991086
R Square	0.998218
Adjusted R Square	0.9952481
Standard Error	0.0132874
Observations	9

ANOVA					
	Degree of Freedom	**Sum Square**	**Mean Square**	**F**	**Significance F**
Regression	5	0.2967067	0.0593413	336.10844	0.000255
Residual	3	0.0005297	0.0001766		
Total	8	0.2972364			

	Coefficients	**Standard Error**	**t Stat**	**P-value**
Intercept	2.2682401	0.1062644	21.345255	0.0002250
X_1	-0.0009538	0.0002826	-3.3751258	0.0432467
X_2	-0.0113811	0.0026848	-4.2390362	0.0240354
X_1X_2	-1.242E-05	1.74E-06	-7.1389797	0.0056586
X_1^2	1.592E-06	4.176E-07	3.8120727	0.0317434
X_2^2	5.511E-05	1.723E-05	3.1993515	0.0493563

$Y = 2.26824 - 0.00095*X_1 - 0.01138*X_2 - 0.000012*X_1X_2 + 0.0000015*X_1^2 + 0.000055*X_2^2$

Table 16: Percentage similarity between experimental and predicted Log (K) of Pappas Eq.

Form. Code	**Amount of Drug**	**Total Amount of Polymer**	**% of Ethyl cellulose**	**Log (K) of Pappas Eq.**		**Resi.**	**% Similarity**
		X_1	**X_2**	**EXP. Y**	**PRED. Y**		
F1	50	450	100	1.023	1.016	0.008	107.200
F2	50	300	100	1.153	1.166	-0.013	123.064
F3	50	150	100	1.393	1.388	0.005	146.491
F4	50	450	66.66	1.271	1.275	-0.005	134.598
F5	50	300	66.66	1.364	1.363	0.001	143.906
F6	50	150	66.66	1.527	1.523	0.004	160.776
F7	50	450	50	1.447	1.451	-0.003	153.135
F8	50	300	50	1.520	1.508	0.012	159.167
F9	50	150	50	1.628	1.637	-0.009	172.761

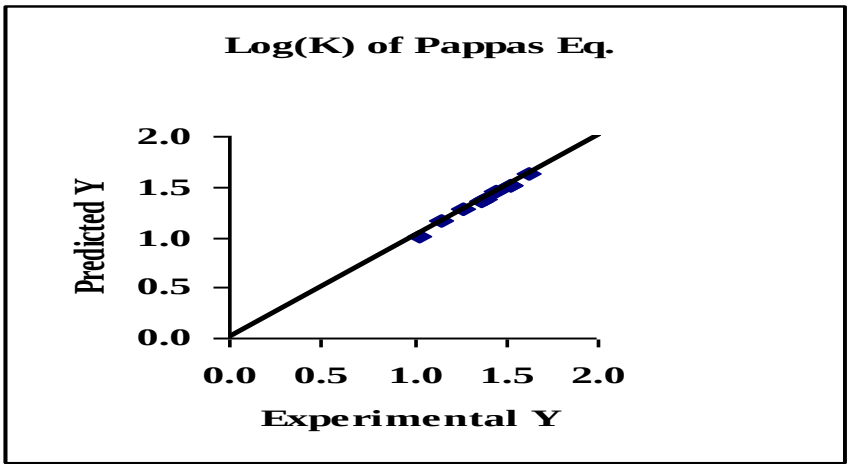


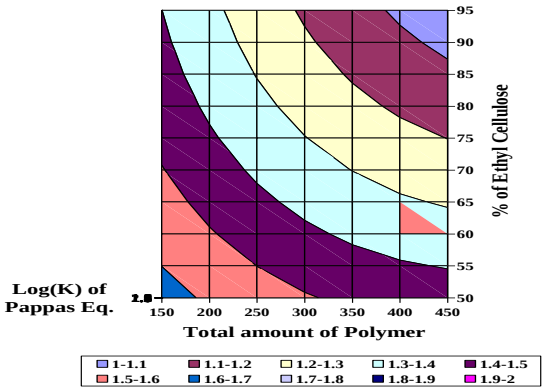
TABLE 17: Statistically predicted values of Log (K) of Pappas Eq.

		Percentage of Ethyl cellulose									
		50	55	60	65	70	75	80	85	90	95
Total amount of Polymer	150	1.637	1.599	1.565	1.533	1.504	1.478	1.454	1.433	1.415	1.400
	200	1.586	1.545	1.508	1.473	1.441	1.411	1.385	1.361	1.340	1.321
	250	1.543	1.499	1.459	1.421	1.385	1.353	1.323	1.296	1.272	1.250
	300	1.508	1.461	1.417	1.376	1.338	1.302	1.270	1.239	1.212	1.188
	350	1.481	1.431	1.384	1.340	1.298	1.260	1.224	1.191	1.160	1.133
	400	1.462	1.409	1.359	1.312	1.267	1.225	1.186	1.150	1.116	1.086
	450	1.451	1.395	1.342	1.291	1.244	1.199	1.156	1.117	1.080	1.047

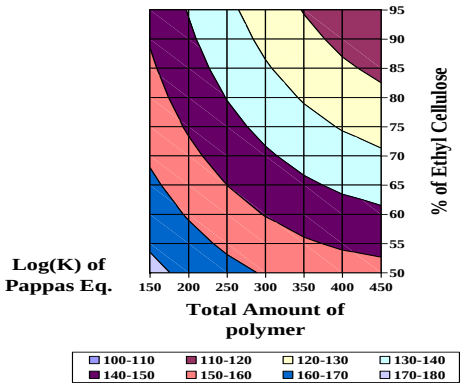
TABLE 18: Percentage similarity for the predicted values of Log (K) of Pappas Eq.

		Percentage of Ethyl cellulose									
		50	55	60	65	70	75	80	85	90	95
Total amount of Polymer	150	172.76	168.82	165.18	161.83	158.76	155.99	153.51	151.32	149.42	147.81
	200	167.39	163.13	159.15	155.47	152.08	148.98	146.17	143.65	141.42	139.49
	250	162.86	158.27	153.97	149.96	146.24	142.81	139.67	136.83	134.27	132.01
	300	159.17	154.25	149.62	145.28	141.24	137.48	134.01	130.84	127.96	125.37
	350	156.32	151.07	146.11	141.45	137.07	132.99	129.20	125.70	122.48	119.56
	400	154.31	148.73	143.45	138.45	133.75	129.34	125.22	121.39	117.85	114.60
	450	153.14	147.23	141.62	136.30	131.27	126.53	122.08	117.93	114.06	110.48

Contour plot of Log(K) of Pappas Eq.



Contour Plot of % similarity for Log(K) of Pappas Eq.



Optimization of K of 1st order

Regression Statistics	
Multiple R	0.9988697
R Square	0.9977407
Adjusted R Square	0.9939753
Standard Error	0.0040847
Observations	9

ANOVA					
	Degree of Freedom	**Sum Square**	**Mean Square**	**F**	**Significance F**
Regression	5	0.0221053	0.0044211	264.97199	0.0003639
Residual	3	5.006E-05	1.669E-05		
Total	8	0.0221554			

	Coefficients	**Standard Error**	**t Stat**	**P-value**
Intercept	-0.5421618	0.0326672	-16.596516	0.0004762
X_1	0.0006359	8.688E-05	7.3190773	0.0052682
X_2	0.0063475	0.0008254	7.6905795	0.0045685
X_1X_2	-2.994E-06	5.348E-07	-5.5979045	0.0112622
X_1^2	-3.344E-07	1.284E-07	-2.6046564	0.0080053
X_2^2	-2.301E-05	5.296E-06	-4.3455704	0.0224992

$Y = - 0.542161 + 0.000635*X_1 + 0.0063475*X_2 – 0.0000029 *X_1X_2 – 0.00000033*X_1^2 – 0.000023*X_2^2$

Table 19: Percentage similarity between experimental and predicted K of 1st order

Form. Code	**Amount of Drug**	**Total Amount of Polymer**	**% of Ethyl cellulose**	**K of 1st order**		**Resi.**	**% Similarity**
		X_1	**X_2**	**EXP. Y**	**PRED. Y**		
F1	50.00	450.00	100.00	-0.05	-0.05	0.00	43.93
F2	50.00	300.00	100.00	-0.07	-0.07	0.00	54.43
F3	50.00	150.00	100.00	-0.10	-0.09	0.00	77.20
F4	50.00	450.00	66.66	-0.10	-0.09	0.00	75.64
F5	50.00	300.00	66.66	-0.12	-0.12	0.00	98.35
F6	50.00	150.00	66.66	-0.16	-0.16	0.00	133.35
F7	50.00	450.00	50.00	-0.13	-0.13	0.00	107.12
F8	50.00	300.00	50.00	-0.17	-0.17	0.00	135.94
F9	50.00	150.00	50.00	-0.22	-0.22	0.00	177.05

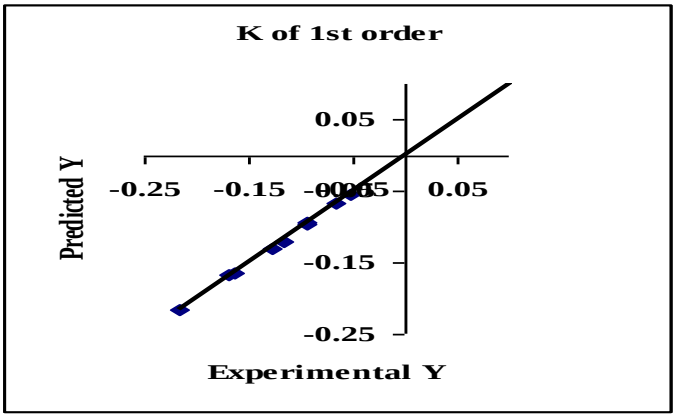
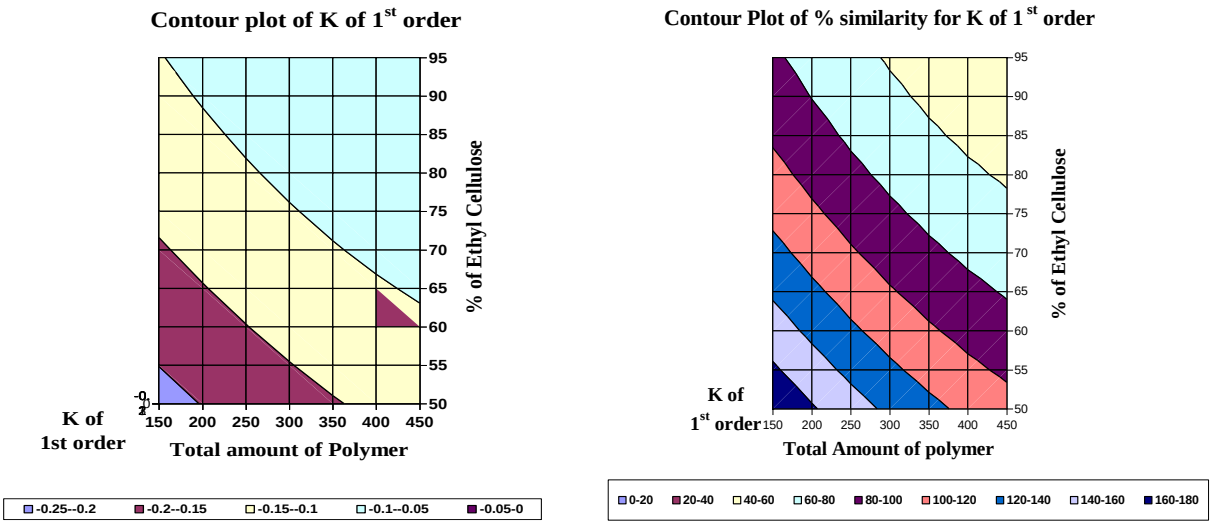


TABLE 20: Statistically predicted values of K of 1st order

		Percentage of Ethyl cellulose									
		50	55	60	65	70	75	80	85	90	95
Total amount of Polymer	150	-0.217	-0.200	-0.183	-0.168	-0.154	-0.141	-0.130	-0.119	-0.110	-0.102
	200	-0.198	-0.182	-0.166	-0.152	-0.139	-0.127	-0.116	-0.106	-0.097	-0.090
	250	-0.182	-0.166	-0.151	-0.137	-0.125	-0.114	-0.103	-0.094	-0.087	-0.080
	300	-0.167	-0.151	-0.137	-0.125	-0.113	-0.102	-0.093	-0.085	-0.077	-0.071
	350	-0.153	-0.139	-0.125	-0.113	-0.102	-0.093	-0.084	-0.076	-0.070	-0.065
	400	-0.141	-0.128	-0.115	-0.104	-0.094	-0.085	-0.077	-0.070	-0.064	-0.060
	450	-0.131	-0.118	-0.107	-0.096	-0.086	-0.078	-0.071	-0.065	-0.060	-0.056

TABLE 21: Percentage similarity for the predicted values of K of 1st order

		Percentage of Ethyl cellulose									
		50	55	60	65	70	75	80	85	90	95
Total amount of Polymer	150	177.05	162.84	149.56	137.23	125.84	115.39	105.87	97.29	89.66	82.96
	200	161.98	148.38	135.72	124.00	113.22	103.37	94.47	86.51	79.48	73.39
	250	148.28	135.29	123.24	112.13	101.96	92.73	84.44	77.08	70.67	65.19
	300	135.94	123.57	112.13	101.63	92.07	83.45	75.76	69.02	63.22	58.35
	350	124.97	113.21	102.38	92.49	83.54	75.53	68.46	62.33	57.13	52.88
	400	115.37	104.21	93.99	84.72	76.38	68.98	62.52	57.00	52.41	48.77
	450	107.12	96.58	86.97	78.31	70.58	63.79	57.94	53.03	49.06	46.03



Optimization of Release at 12 h

Regression Statistics	
Multiple R	0.9999987
R Square	0.9999974
Adjusted R Square	0.9999932
Standard Error	0.038924
Observations	9

ANOVA					
	Degree of Freedom	Sum Square	Mean Square	F	Significance F
Regression	5	1779.6558	355.93115	234925.68	1.386E-08
Residual	3	0.0045452	0.0015151		
Total	8	1779.6603			

	Coefficients	Standard Error	t Stat	P-value
Intercept	101.08196	0.3112909	324.71863	0.0000001
X_1	-0.0151978	0.0008279	-18.357554	0.0003527
X_2	-0.0752996	0.007865	-9.5740602	0.0024176
X_1X_2	-0.000769	5.096E-06	-150.8907	0.0000006
X_1^2	2.546E-05	1.223E-06	20.809533	0.0002427
X_2^2	0.0018257	5.046E-05	36.179237	0.0000464

$$Y = 101.08196 – 0.0151978*X_1 - 0.0752996*X_2 – 0.000769*X_1X_2 + 0.0000254*X_1^2 + 0.00018257*X_2^2$$

Table 22: Percentage similarity between experimental and predicted values of Release at 12h

Form. Code	Amount of Drug	Total Amount of Polymer	% of Ethyl cellulose	Release at 12 h		Resi.	% Similarity
		X_1	X_2	EXP. Y	PRED. Y		
F1	50	450	100	39.020	39.007	0.013	73.822
F2	50	300	100	49.948	49.958	-0.009	94.546
F3	50	150	100	62.050	62.053	-0.003	117.438
F4	50	450	66.66	63.158	63.199	-0.041	119.605
F5	50	300	66.66	70.337	70.304	0.033	133.051
F6	50	150	66.66	78.562	78.554	0.008	148.665
F7	50	450	50	73.795	73.767	0.028	139.605
F8	50	300	50	78.926	78.950	-0.024	149.414
F9	50	150	50	85.274	85.279	-0.005	161.392

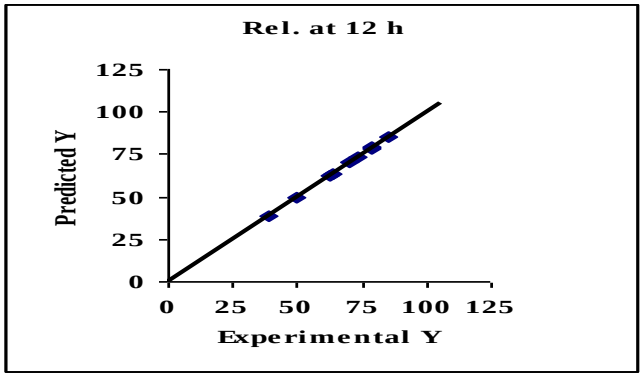
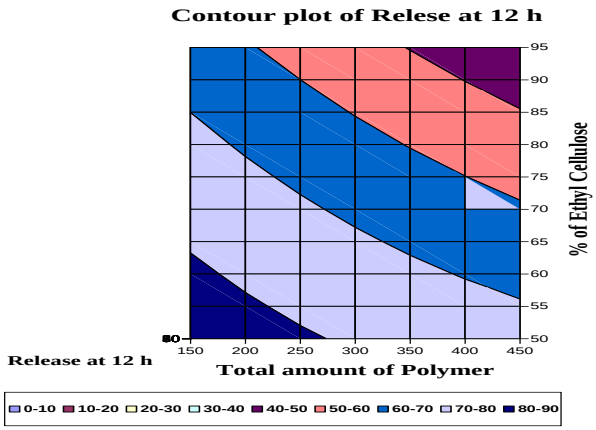


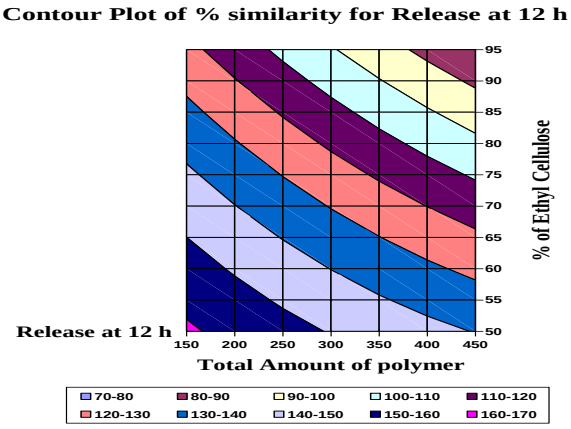
TABLE 23: Statistically predicted values of Release at 12 h

		Percentage of Ethyl cellulose									
		50	55	60	65	70	75	80	85	90	95
Total amount of Polymer	150	85.279	83.367	81.364	79.270	77.084	74.807	72.439	69.979	67.429	64.787
	200	83.042	80.938	78.742	76.456	74.078	71.609	69.049	66.397	63.654	60.820
	250	80.932	78.636	76.248	73.770	71.200	68.538	65.786	62.942	60.006	56.980
	300	78.950	76.461	73.882	71.211	68.448	65.595	62.650	59.614	56.486	53.268
	350	77.095	74.414	71.642	68.779	65.824	62.779	59.641	56.413	53.093	49.682
	400	75.367	72.494	69.530	66.474	63.328	60.090	56.760	53.340	49.828	46.224
	450	73.767	70.701	67.545	64.297	60.958	57.528	54.006	50.393	46.689	42.894

TABLE 24: Percentage similarity for the predicted values of Release at 12 h

		Percentage of Ethyl cellulose									
		50	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**
Total amount of Polymer	**150**	161.39	157.77	153.98	150.02	145.88	141.57	137.09	132.44	127.61	122.61
	200	157.16	153.18	149.02	144.69	140.19	135.52	130.68	125.66	120.47	115.10
	250	153.17	148.82	144.30	139.61	134.75	129.71	124.50	119.12	113.56	107.84
	300	149.41	144.70	139.82	134.77	129.54	124.14	118.57	112.82	106.90	100.81
	350	145.90	140.83	135.58	130.17	124.57	118.81	112.87	106.76	100.48	94.02
	400	142.63	137.20	131.59	125.80	119.85	113.72	107.42	100.95	94.30	87.48
	450	139.61	133.80	127.83	121.68	115.36	108.87	102.21	95.37	88.36	81.18





Optimization of Release at 18 h

Regression Statistics	
Multiple R	0.9993927
R Square	0.9987858
Adjusted R Square	0.996762
Standard Error	0.6950513
Observations	9

ANOVA					
	Degree of Freedom	**Sum Square**	**Mean Square**	**F**	**Significance F**
Regression	**5**	1192.1262	238.42524	493.53559	0.0001435
Residual	**3**	1.4492891	0.4830964		
Total	**8**	1193.5755			

	Coefficients	Standard Error	t Stat	P-value
Intercept	**96.318548**	**0.5586018**	**17.327837**	**0.0004188**
X_1	-0.0347161	0.014783	-2.3483753	0.0100454
X_2	-0.4300386	0.1404415	-3.062047	0.0549045
X_1X_2	-0.0005847	9.1E-05	-6.4256143	0.0076401
X_1^2	5.477E-05	2.184E-05	2.5073901	0.0087137
X_2^2	0.0048155	0.0009011	5.344046	0.0128131

$$Y = 96.318548 - 0.0347161*X_1 - 0.4300386*X_2 - 0.0005847*X_1X_2 + 0.00005477*X_1^2 + 0.0048155*X_2^2$$

Table 25: Percentage similarity between experimental and predicted values of Release at 18h

Form. Code	Amount of Drug	Total Amount of Polymer	% of Ethyl cellulose	Release at 18 h		Resi.	% Similarity
		X_1	X_2	EXP. Y	PRED. Y		
F1	50	450	100	60.338	60.323	0.015	78.933
F2	50	300	100	67.819	68.140	-0.321	89.161
F3	50	150	100	78.728	78.421	0.306	102.614
F4	50	450	66.66	81.644	81.515	0.129	106.663
F5	50	300	66.66	87.024	86.408	0.616	113.065
F6	50	150	66.66	93.020	93.765	-0.745	122.692
F7	50	450	50	87.950	88.094	-0.144	115.271
F8	50	300	50	91.230	91.525	-0.295	119.761
F9	50	150	50	97.860	97.421	0.439	127.476

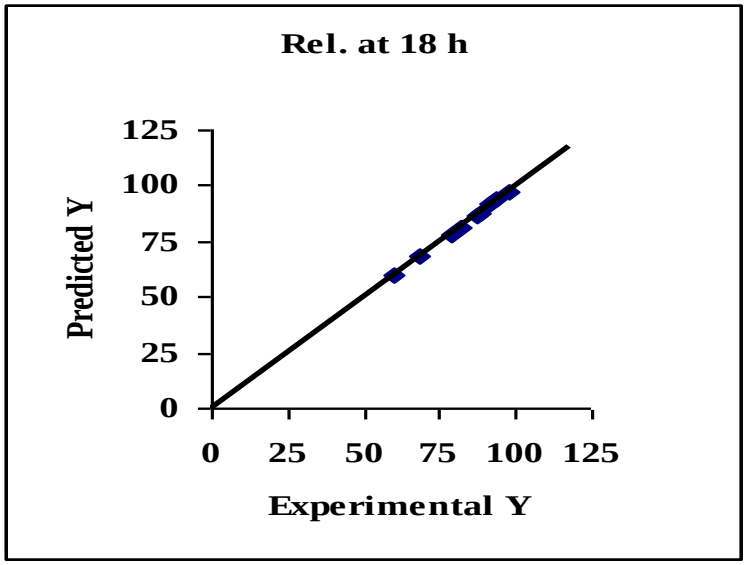
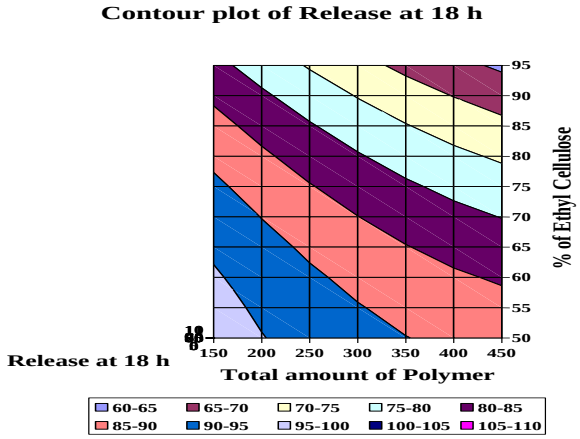


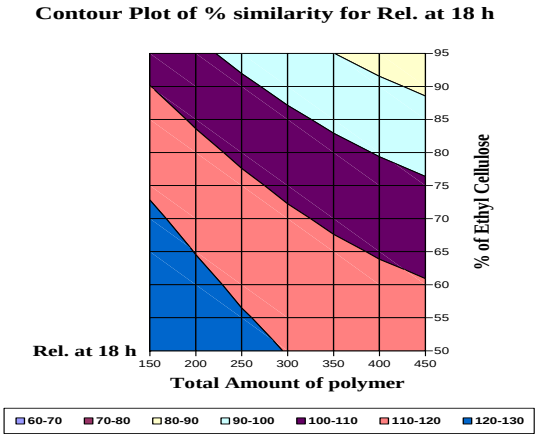
TABLE 26: Statistically predicted values of Release at 18 h

		Percentage of Ethyl cellulose									
		50	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**
Total amount of Polymer	**150**	97.421	96.605	95.547	94.249	92.710	90.931	88.911	86.649	84.147	81.405
	200	95.182	94.219	93.016	91.572	89.887	87.961	85.794	83.387	80.739	77.850
	250	93.217	92.108	90.758	89.168	87.336	85.265	82.952	80.398	77.604	74.569
	300	91.525	90.270	88.774	87.038	85.060	82.842	80.383	77.684	74.743	71.562
	350	90.107	88.706	87.064	85.181	83.058	80.694	78.088	75.243	72.156	68.829
	400	88.964	87.416	85.628	83.599	81.329	78.819	76.068	73.076	69.843	66.369
	450	88.094	86.400	84.466	82.291	79.875	77.218	74.321	71.182	67.803	64.183

TABLE 27: Percentage Similarity for the predicted values of Release at 18 h

		Percentage of Ethyl cellulose									
		50	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**
Total amount of Polymer	**150**	127.48	126.41	125.02	123.33	121.31	118.98	116.34	113.38	110.11	106.52
	200	124.55	123.29	121.71	119.82	117.62	115.10	112.26	109.11	105.65	101.87
	250	121.97	120.52	118.76	116.68	114.28	111.57	108.54	105.20	101.54	97.57
	300	119.76	118.12	116.16	113.89	111.30	108.40	105.18	101.65	97.80	93.64
	350	117.91	116.07	113.92	111.46	108.68	105.59	102.18	98.46	94.42	90.06
	400	116.41	114.38	112.04	109.39	106.42	103.13	99.53	95.62	91.39	86.84
	450	115.27	113.05	110.52	107.68	104.52	101.04	97.25	93.14	88.72	83.98





OPTIMIZED FORMULATIONS:

Table 28: Formula of optimized formulations which have met the data of all desired variables

Code	Amount of Drug (mg)	Total amount of Polymer (mg)	% of Ethyl Cellulose	% of Eudragit RL100	Vol. of acetone (ml)	Vol. of Liquid Paraffin (ml)
OF1	200	1800	80	20	30	30
OF2	200	1600	85	15	30	30

OF1= Optimized Formulation 1; OF2 Optimized Formulation 2

Table 29: Formula of optimized formulation according to Cost Effectiveness

Code	Amount of Drug (mg)	Total amount of Polymer (mg)	% of Ethyl Cellulose	% of Eudragit RL100	Vol. of acetone (ml)	Vol. of Liquid Paraffin (ml)
OF3	200	1200	95	5	30	30

OF3= Optimized Formulation 3

Table 30: Physico-Chemical Properties of Optimized Formulations

Batch	% Yield ±S.D	%Drug Entrapment Efficiency ±S.D	% Buoyancy ±S.D	Particle size ±S.D (µm)
OF1	91.73±2.13	86.34±1.19	98.32±3.41	189 ± 39
OF2	89.14±1.64	84.36±1.61	97.19±3.23	238 ± 59
OF3	87.93±1.79	83.11±1.27	96.56±2.92	221 ± 27

Table 31: *In-Vitro* Drug Release of Optimized Formulations

Name of Parameter	% Cumulative Drug Release						
	2 h	**4 h**	**6 h**	**9 h**	**12 h**	**18 h**	**24 h**
OF1	16.62 ±1.51	26.22 ±1.84	39.42 ±2.30	49.57 ±2.63	56.26 ±1.70	78.69 ±2.22	93.27 ±1.56
OF2	14.61 ±1.54	24.17 ±1.65	38.65 ±1.59	48.73 ±2.17	54.16 ±1.98	74.32 ±2.69	89.46 ±2.55
OF3	14.92 ±1.60	26.19 ±1.97	38.86 ±1.65	48.43 ±1.93	54.65 ±2.38	73.26 ±1.91	87.74 ±2.05

Table 32: Stability Studies of Optimized Formulations

Batch	%Drug Entrapment Efficiency ±S.D	% Buoyancy ±S.D
OF1	85.94±1.29	97.62±3.89
OF2	83.74±1.68	96.53±3.91
OF3	83.03±1.46	94.12±2.42

Table 33: *In-Vitro* Drug Release of Optimized Formulations

Name of Parameter	% Cumulative Drug Release						
	2 h	**4 h**	**6 h**	**9 h**	**12 h**	**18 h**	**24 h**
OF1	17.22 ±1.37	28.63 ±1.46	40.37 ±1.74	51.29 ±1.98	55.82 ±2.55	77.86 ±2.84	91.59 ±1.83
OF2	15.72 ±2.45	26.39 ±1.81	39.67 ±1.91	50.09 ±2.85	53.92 ±2.47	76.49 ±1.54	87.73 ±2.05
OF3	14.92 ±1.60	26.19 ±1.97	38.86 ±1.65	48.43 ±1.93	54.65 ±2.38	73.26 ±1.91	88.74 ±2.47

Table 34: Comparison between Predicted and Experimental Of Various Dependent Variables of Optimized Formulation

Parameters	Total Amount of polymer (mg)	% of Ethyl Cellulose	$T_{50\%}$	$T_{80\%}$	Log(k) of Pappas	Rel at 12 hr	Rel at 18 hr	K of 1st order
Codes	X_1	X_2	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6
Desirability	-	-	**11.278**	**18.890**	**0.973**	**39.02**	**60.338**	**-0.123**
Predicted OF1	450	80	10.79	20.92	1.16	54.01	74.32	-0.071
Predicted OF2	400	85	10.96	21.44	1.15	53.34	73.08	-0.070
Predicted OF3	300	95	10.71	21.88	1.19	53.27	71.56	-0.071
Experimental OF1	450	80	9.82	19.12	1.23	56.26 ±1.70	78.69 ±2.22	-0.069
Experimental OF2	400	85	19.56	19.56	1.19	54.16 ±1.98	74.32 ±2.69	-0.066
Experimental OF3	300	95	9.73	19.34	1.20	54.65 ±2.38	73.26 ±1.91	-0.067

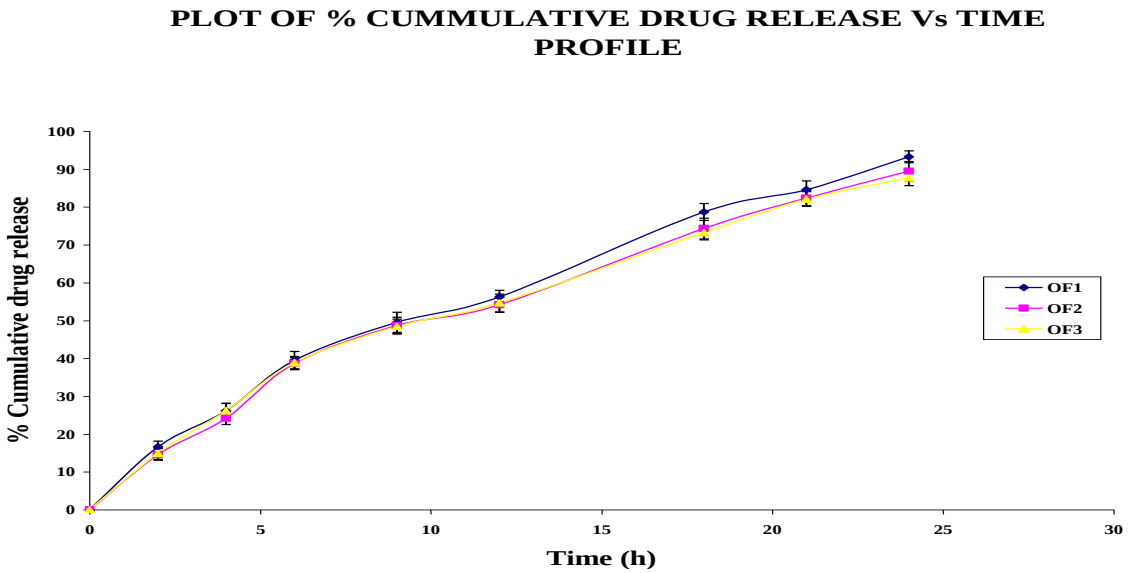


Figure 3: *In-vitro* drug dissolution of optimized formulations

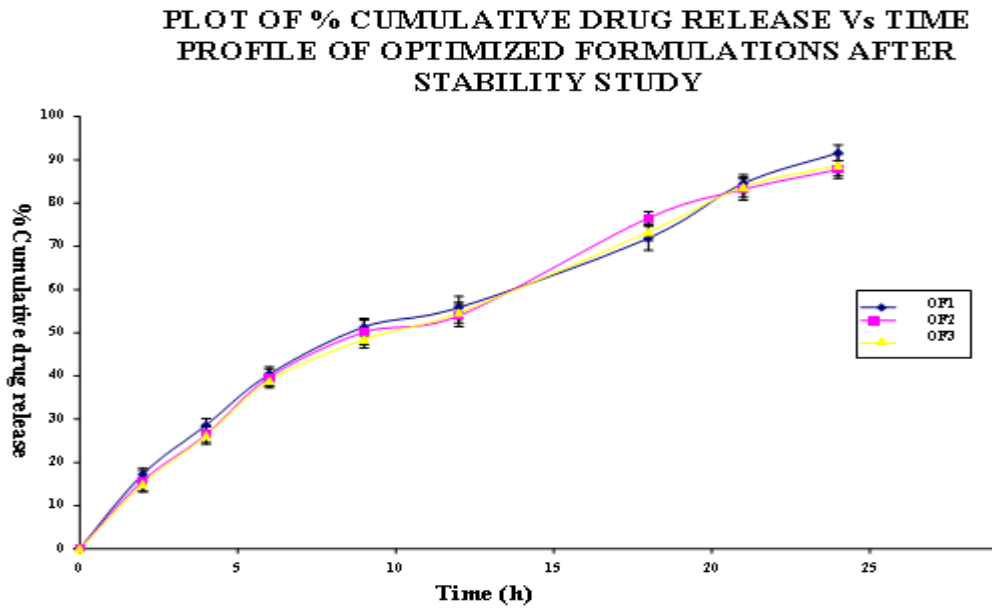


Figure 4: *In-vitro* drug release study of optimized formulations (Stability study)

Scanning electron microscopy of optimized formulation:

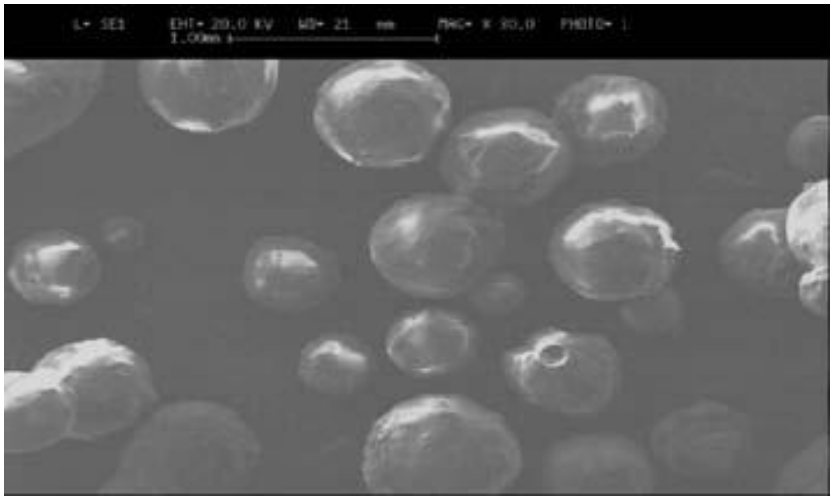


Figure 5: SEM of Optimized formulation OF1 (Before dissolution study)

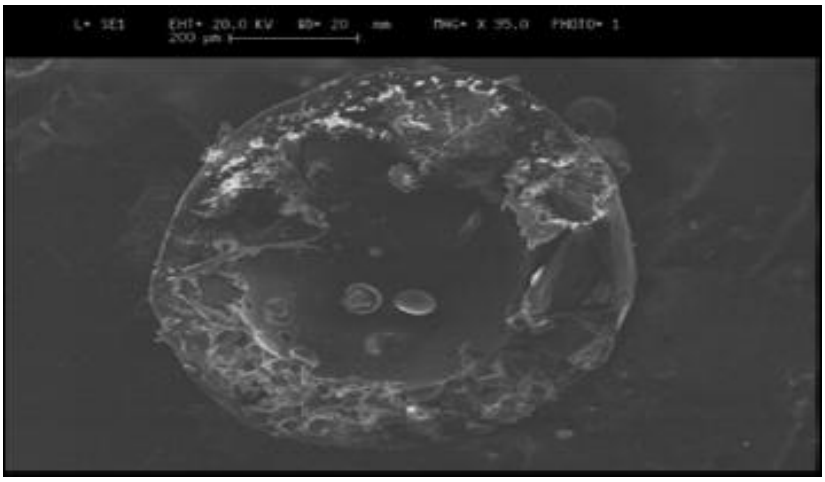


Figure 6: SEM of Optimized formulation OF1 (After dissolution study)

REFERENCES

1. Joel G. Hardman, Lee E.Limbird, Alford Goodman Gilman, Goodman and Gilman's the Pharmacological Basis of Therapeutics**,** Tenth Edition (International Edition), McGraw-Hill. Medical Publishing Division, New York, Chicago, New Delhi; 2001:870-932.
2. Yeole P, Khan S, Patel V, Floating drug delivery system: Need and development, Ind J Pharm. Sci; 2005: 67(3): 265-272.
3. Matharu, R. S. and Sanghavi, N. M., Novel drug delivery system for Captopril. Drug Development and Industrial Pharmacy: 1992:18:1567–1574.
4. Gangadharappa H.V, Pramod Kumar T.M, Shiv Kumar H.G, Gastric Floating Drug Delivery Systems: A Review, Ind J Pharm. Edu Res; 2007:41(4):295-305.
5. Streuble A, Siepmann J, Bodmeirer R, Floating micrparticulate based on low density foam powder. Int J Pharm.2002; 241-292.
6. Shweta Arora, Javed Ali, Alka Ahuja, Roop K. Khar, Sanjula Baboota, Floating Drug Delivery System: A Review, AAPS Pharm Sci Tech; 2005: 6 (3):E372-390.
7. Hilton AK. Deasy PB, In-vitro and in vivo evaluation of an oral sustain release dosage form of amoxicillin trihydrate. Int J Pharm. 1992;86:79-88.
8. Timmermans J, Andre JM, Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: New data for reconsidering the controversy. J Pharm Sci.1994;83:18-24.
9. Li S, Lin S, Daggy BP,Mirchndani HL,Chein TW. Effect of formulation variables on floating properties of gastric floating delivery system. Drug Dev Ind Pharm. 2002;28:783-793.
10. Schwarrthz et al. Optimization techniques in pharmaceutical formulation and processing, in modern pharmaceutics, G.S. Banker and C.T Rhodes, Editors 1996, Marcel Dekker: New York, 727-752.
11. Bolten S, Pharmaceutical statistics practical and clinical application. 2nd ,New York:Marcel Dekker.1990;308-337.
12. Swarbrick J et al. Optimization techniques in formulation and processing pharmaceutical encyclopaedia, Vol 12.Marcel Dekker,1990;77-160.
13. El-Kamel, A.H., Sokar, M.S., Naggar, V.F. "Preparation and evaluation of Ketoprofen floating oral drug delivery system". Int. J. Pharm; 2001: 220,13-21.
14. Kawashima, Y., Niwa, T., Takeuchi, H., Hino, T., Ito, Y. "Preparation of multiple unit hollow microspheres (microballoons) with acrylic resins containing Tranilast and their drug release characteristics (*In vivo*)". J. Control Rel; 1991:16; 279-290.
15. Sato, Y., Kawashima, Y., Takeuchi H.,Yamamoto, H.,. *In vitro* evaluation of floating and drug releasing behavior of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. Eur J Pharm Biopharm; 2004: 57,235-243.
16. Lee, J.H., Park, T.G., Lee, Y.B., Shin, S.C., Choi, H.K. "Effect of adding non-volatile oil as a core material for the floating microspheres prepared by emulsion solvent diffusion method". J. Microencap.; 2001: 18, 65-75.
17. Kumaresh, S, "Development of Hollow Microspheres as Floating Controlled-Release Systems for Cardiovascular Drugs: Preparation and Release Characteristics". Drug Dev. Ind. Pharm; 2001:27:507-515.
18. Joseph, N.J., Lakshmi, S., Jayakrishnan, A., "A floating type oral dosage form for Piroxicam based on hollow polycarbonate microspheres: in vitro and in vivo evaluation in rabbits". J. Control. Rel.; 2002:79:71-79.
19. Jain, D., Panda, A.K., Majumdar D.K., "Eudragit S100 Entrapped Insulin Microspheres for Oral Delivery". AAPS Pharm SciTech; 2005: 6(16).
20. Haznedar, S., Dortunc, B, "Preparation and *in vitro* evaluation of Eudragit microspheres containing Acetazolamide". Int. J. Pharm.; 2004:269:131-140.
21. Tike, C.A., et al., "Bioequivalence of ACE inhibitors: Part VII-pharmacokinetic interaction between Captopril and Hydrochlorothiazide." Indian drugs, 1995; 32(5):217-224.
22. Testa, A.M.et al.,"Quality of life and antihypertensive therapy in men- A comparison of Captopril with Enalapril"N.Engl.J.Med, 1993; 328(13):907-913.
23. Pandey, s.et al.,"Mucoadhesive formulation of Captopril": Pharmag, 1992;(3):12-15.
24. Karachalios, G.N et. Al., "Treatment of hypertensive crisis with sublingual Captopril." Curr Ther Res , 1990;(48): 5-9.
25. Jayaswal SB, Reddy, TSR, Vijay Kumar Gupta. "Preparation and Evaluation of Captopril microspheres by spherical crystallization".Indian Drugs: 32 (9):454-457.
26. P.M.Dandagi, V.S.Mastiholimath, M.B.Patil, M.K.Gupta.,Biodagradable microparticulate system of Captopril; Int J Pharm; 2006:307:83-88.
27. Kagkadis KA, Rekkas DM, Dallas PP, Choulis NH. A freeze dried injectable form of Flubriprofen: development and optimization using response surface methodology. Int J Pharm 1998; 61: 87-94.
28. Velasco MV, Ford JL, Rowe P, Rajabi Siahboomi AR. Influence of drug: hydroxypropyl methylcellulose ratio, drug and polymer size

and compression force on the release of Diclofenac sodium from HPMC tablets. J control Rel 1999; 57: 75-85.
29. Juarez H, Rico G, Villafuerte L. Influence of admixed carboxymethyl cellulose on release of 4- aminopyridine from hydroxy propyl methyl cellulose matrix tablets. Int J Pharm 201; 216: 115-125.
30. Siepmann J, Peppas NA. modeling of drug release from delivery systems based on hydroxy propyl methyl cellulose. Adv Drug Del Reviews 2001; 48: 139-157.
31. Lafuente CS, Teresa Faucci T, Mura P, Rabasco AM. Development of sustained release release matrix tablets of didanosine containing methacrylic and ethyl cellulose polymers. Int J Pharm 2002; 234: 213-321.
32. Giannakou SA, Dallas PP. *In vitro* evaluation of Nimodipine permeation through human epidermis using response surface methodology. Int J Pharm 2002; 241: 27-34.
33. Raymond C Rowe. Handbook of pharmaceutical Excipient. 4th edition, pharmaceutical press (LONDON) 2003. 237-242.
34. McGinity JW. Polymethycrylate, Handbook of Pharmaceutical Excipient American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.1986: 138-140
35. Deasy PB. Microencapsulation and related drug processes. Marcel Dekker Inc; 1984.
36. Jain S.K., Awasthi, A.M.Jain, N.K., Agrawal G.P, Calcium silicate based microsphere of repaglinide for gastroretentive drug delivery system: Preparation and *in-vitro* characterization. J Control Rel.2005, 107, 300-309.
37. Joseph N.J., Lakshmi S., Jayakrishnan, A floating type oral dosage form for piroxicam based on hollow polycarbonate microspheres: In-vitro and in-vivo evaluation in rabbits. J Control Rel.2005(79);71-79.
38. Iannuccelli V, Coppi G, Bernabei MT, Cameroni R. Air compartment multiple unit system for prolonged residence. Part I. formulation study. Int J Pharm 1998;174:47-54.
39. Costa P, Modeling and comparision of dissolution profile. Eur J Pharm Sci.2001;13:123-133.
40. Asha Patel, Subhabrata Ray, Ram Shankar Thakur, *In-vitro* evaluation and optimization of controlled release floating drug delivery system of Metformin hydrochloride. DARU;2006:14(2):57-64.

Conflict of Interest: None Declared

