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Optimization And Evaluation Of Prazosin Hydrochloride Floating Microspheres Using Response Surface Methodology

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Abstract:*The purpose of the present study was to get the floating microspheres of Prazosin hydrochloride and to sustain the drug to overcome the side effects as postural hypotension.A central composite design based on the response surface method was used.The preparations were made by emulsion-solvent evaporation method.In this study, a three-factors, three levels Central composite design with drug-polymer ratio (X1), Solvent ratio (X2) and Speed (X3) as independent variables were chosen for the formulation. The microspheres were evaluated for physicochemical parameters as shape, size, buoyancy percentage and drug entrapment efficiency. SEM studies showed good topology of microspheres. The cumulative % drug release of optimized formulation after 24 hours was 99.87%. Model fitting analysis revealed the release pattern followed Korsmeyer.The results demonstrated a good relationship between the predicted and experimental values, supporting the validity of the model.FTIR and DSC studies showed that there was no interaction between drug and polymers. The optimized formulation was found to be stable when subjected to accelerated stability studies. The results obtained indicated that response surface methodology may be successfully used to analyze the effect of formulation variables and develop an optimized formulation thereby reducing the severaltrials, time and cost of formulation development.*

Key words: *floating microspheres ,FTIR,HPMC K100,Prazosin hydrochloride, solvent evaporation*.

I. Introduction

One of the most important approaches for achieving a prolonged drug delivery in the GI tract is to run in the gastric residence time by using gastro-retentive dosage forms (GRDFs).Gastro retentive floating drug delivery systems (GRFDDS) have a bulk density lower than that of gastric fluids and thus remains buoyant in the stomach without change in gastric emptying rate for a lengthy period of time[1].It has several advantages over immediate release dosage forms including the reducing of fluctuations in drug concentration in plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduce the side effect. Reduction of total dose administered and minimization of administration frequency leading to better patient compliances [2,3].Both single and multiple unit systems have been developed, the single unit floating system is more popular but has the disadvantage that its purpose would not be achieved if it fails to float, or is rapidly emptied from the stomach since there is high variability of gastrointestinal transit time[4]. On the other hand, a floating system made up of multiple units may be better suited because they are claimed to reduce intersubject variability in absorption and also lower the probability of dose dumping [5]. Floating microspheres are non-effervescent gastro retentive drug delivery systems. These microspheres having a size less than 200 μm, free flowing powders and remain buoyant over gastric contents and for prolonged periods.The drug is released slowly from the floating system at the desired rate, resulting increased gastric retention and reduced fluctuations in plasma drug concentration[6,7]. Prazosin is a selective α-$_1$-adrenergic receptor antagonist used to treat hypertension. Prazosin acts by inhibiting the postsynaptic alpha1-adrenoceptors on vascular smooth muscle. It inhibits the vasoconstrictor effect of catecholamines (epinephrine and norepinephrine), resulting in peripheral vasodilation. It has a mean plasma half -life of 2-3 hour.Prazosin has a shorthalflife and low bioavailability in the upper part of the GIT hence it is suitable for gastro-retentive system[8]. The aim of the present work was to develop a new drug delivery system that provides gastric retention, increase the efficiency and reduces the side effects like postural hypotension which may lead to precipitation of congestive heart failure. Floating microspheres of Prazosin hydrochloride was optimized by using central composite design. In this study, a three-factors, three levels Central-composite design with drug-polymer ratio(X1), Solvent ratio(X2) and Speed (X3) as independent variables and particle size (Y1) and percent drug released (Y2) were the dependent variables. Drug-excipient compatibility was studied by Fourier transform infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC).

II. Materials and Methods

2.1 Materials:

Prazosin hydrochloride (PH) was obtained as a gift sample from Synthokem labs, Hyderabad. HPMC K100M, ethyl cellulose and Eudragit were provided by Dr. Reddy's laboratories, Hyderabad and all solvents used were of analytical grade.

2.2 Experimental Design:

In the preliminary studies, eight formulations with different drug/polymer ratios were formulated based on a 2^3factorial design[9]. The design included three factors, each evaluated at two levels. The proportion of the retardant materials drug: polymer (X1), solvent ratio (X2) and speed (X3) as independent variables are selected, Drug entrapment efficiency (Y1), %Yield (Y2), Buoyancy (Y3), Drug release (Y4) were the dependent variables. The plan of the experiment is given in Table 1, 2 and 3. Drug-polymer ratios of 1:2, 1:2.5, and 1:3. While solvent ratios of 1:1.5,1:1.75,1:2. Three levels of speed used are 600-1000rpmequal to -1,0 and +1 values for the above design. The 4 dependent variables were analyzed by Analysis of Variance (ANOVA).

Y = bo+b1x1+b2x2+b12x1x2+b11x12+b22x22

Table 1: Coded Values And Actual Values For The Independent Variables

Coded Values	X1	X2	X3
-1	1:2	1:1.5	700
0	1:2.5	1:1.75	800
+1	1:3	1:2	900

Where X_1 = Drug **:** polymer X_2=Solvent ratio X_3 = Speed

Table 2: Factorial design batches of Prazosin HCL floating microspheres

Variables	F1	F2	F3	F4	F5	F6	F7	F8
X_1	-1	+1	-1	+1	-1	+1	-1	+1
X_2	-1	-1	+1	+1	-1	-1	+1	+1
X_3	-1	-1	-1	-1	+1	+1	+1	+1

Y = bo+b1x1+b2x2+b12x1x2+b11x12+b22x22

Table 3: Various processing variables investigated by optimization

Formulation	X1(Drug:polymer)	X2(Solvent ratio)	X3(RPM)
I	1:2	1:1.5	700
X1	1:3	1:1.5	700
X2	1:2	1:2	700
X1X2	1:3	1:2	700
X3	1:2	1:1.5	900
X1X3	1:3	1:1.5	900
X2X3	1:2	1:2	900
X1X2X3	1:3	1:2	900
MID POINT	1:2.5	1:1.75	800
MID POINT	1:2.5	1:1.75	800
MIDPOINT	1:2.5	1:1.75	800
MID POINT	1:2.5	1:1.75	800
AVGMID POINT	1:2.5	1:1.75	800
X1At-2L	1:1.5	1:1.75	800
X1At+2L	1:3.5	1:1.75	800
X2At-2L	1:2.5	1:1.25	800
X2At+2L	1:2.5	1:2.25	800
X3At-2L	1:2.5	1:1.75	600
X3At+2L	1:2.5	1:1.75	1000

2.3 Preparation Of Microspheres:

Microspheres containing Prazosin hydrochloride as a core material were prepared by a Non-aqueous Solvent Evaporation method[10,11]. Drug and polymers (HPMC, ethyl cellulose and eudragit) were mixed in dichloromethane and chloroform at various ratios. The slurry was slowly introduced into 100ml of liquid paraffin containing 1% of Tween80 as emulsifying agent while being stirred at various rpm by a mechanical stirrer with a three bladed propeller at room temperature. The solution was stirred for 2 hours for complete evaporation of solvent and the microspheres were collected by filtration. The microspheres were washed three times with n-hexane and three times with 180 ml petroleum ether to remove the remaining oily phase and then dried overnight at room temperature for 24 hours and subsequently stored in a desiccator.Composition of microspheres as per central composite design is given in Table no.4.

Table 4: Formulation of Floating microspheres of Prazosin hcl

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Prazosin HCL(mg)	100	100	100	100	100	100	100	100	100	100
HPMC(mg)	100	100	100	100	100	100	100	100	100	100
EC(mg)	50	100	50	100	50	100	50	100	75	75
Eudragit(mg)	50	100	50	100	50	100	50	100	75	75
Heavyliquid Paraffin(ml)	100	100	100	100	100	100	100	100	100	100
Dichloromethane(ml)	10	10	10	10	10	10	10	10	10	10
Ethanol(ml)	15	15	20	20	15	15	20	20	17.5	17.5
Tween 80(%)	1	1	1	1	1	1	1	1	1	1
Petroleum ether(ml)	180	180	180	180	180	180	180	180	180	180

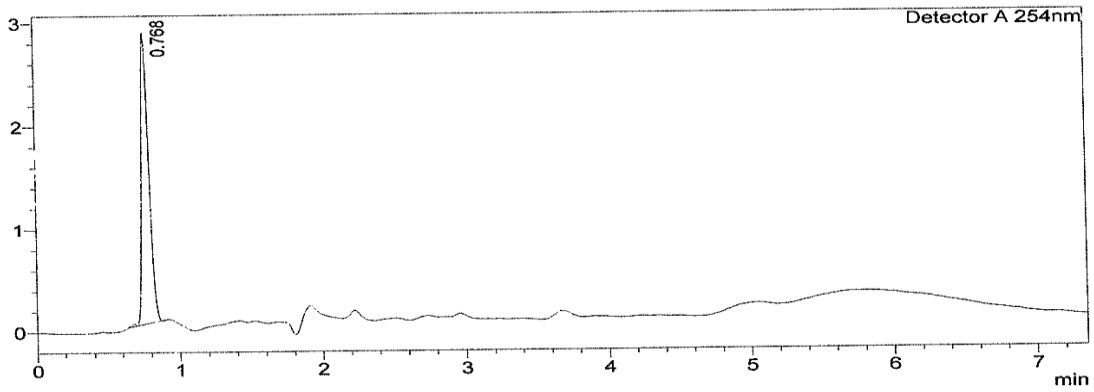
III. Determination Of Prazosin Hydrochloride By Hplc Method[12]

3.1 Preparation of Stock Solution

100 mg of pure prazosin hydrochloride was accurately weighed & dissolved in HPLC grade Acetonitrile: methanol: water (10:55:35) in100ml volumetric flask to get 1mg/ml stock solution

3.2 Separation Studies

The mobile phase was pumped from the solvent reservoir to the column – C18 at a flow rate 1ml/min. It was filtered through 0.45µm nylon membrane and degaussed before use. The injection volume was 5µl.The detection was carried out at 254 nm.The mobile phase composed ofacetonitrile: methanol: water (10:55:35).The temperature was maintained at 30±1°C.The standard graph of Prazosin hcl was shown in Fig:1



<Peak Table>
Detector A 254nm

Name	Area	Height	Ret. Time	Peak Start	Peak End
MOBILE PHASE ..	10197	2823	0.768	0.642	0.917
	10197	2823			

Fig.1 Standard Chromatogram of Prazosin Hcl

3.3 Drug Entrapment Efficiency (%)

Accurately weighed microspheres equivalent to 100mg of the drug was dissolved in 10ml of solvent system and made up to 100ml using simulated gastric fluid pH 1.2 and sonicated for 3 min. The solution was then filtered, diluted suitably and analyzed for drug content spectrophotometrically at 254 nm. The percentage drug entrapment was calculated as[13](1):

$$\text{Drugentrapmentefficiency}(\%) = \frac{\text{Actualdrugcontentinmicrosphers}}{\text{Theori ticaldrugcontentinmicrospheres}} \times 100 \text{-------“equation1”}$$

3.4Determination of size and shape of microspheres

The size of microspheres was determined using a microscope fitted with an ocular micrometer and stage micrometer. Scanning electron microscopy (SEM) was performed to characterize the surface of the formed microspheres[14].

3.5 Micromeritic properties of microspheres

The average particle size of the microspheres was determined by using an optical microscope. The flow properties and packing properties were investigated by measuring the angle of repose, Carr’s Index and Hausner ratio.

3.6 Percentage yield

The percentage of productionyield was calculated from the weight of driedmicrospheres recovered from each batch and the sum of the initial weight of startingmaterials.The percentage yield was calculated as follows(2):

$$\%\text{Yield} = \frac{\text{practicalmass (microsp heres)}}{\text{theoriticalmass (drug +polymer)}} \times 100 \text{ -----“equation2”}$$

3.7 Buoyancy percentage

Microspheres were spread over the surface of a USP XXIV dissolution apparatus (type II) filled with 900 ml 0.1 N HCl containing 0.01% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portion of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres[9,10] (3):

$$\%\text{ Buoyancy} = \frac{\text{Microspheresremainedfloating}}{\text{Totalmassofmicrospheres}} \times 100 \text{ -----“equation3”}$$

3.8 Dissolution studies

Dissolution test was performed in USP XXIII dissolution test apparatus by paddle method. The dissolution media used was 900ml of simulated gastric fluid maintained at 37±0.5^{0}C and rotated at 50 rpm/min. Aliquots samples were withdrawn at specified time intervals and replaced with the same volume of fresh media, filtered and analyzed spectrophotometrically at 254 nm for cumulative percentage drug release.

3.9 Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to zero order, first order, Higuchi, Korsemeyer and Peppas models to ascertain the kinetic modeling of drug release[16].

IV. Drug-Excipient Compatability Studies

4.1 FourierTransform-Infrared (FT-IR) Spectroscopy:

FT-IR was carried out to assess the interaction between drug and excipients. One milligram of substance in solid state was ground with 100mg of dry potassium bromide and scanned from 400-4000cm^{-1} using FT-IR spectrophotometer.

4.2 DSC analysis

Thermal analysis was carried out using a differential scanning calorimeter (Perkin Elmer DSC Pyris-1, Perkin Elmer Inc.).

4.3 Accelerated stability studies:

In order to determine the change in evaluation parameters and in vitro release profile on storage, stability study of optimized batch was carried out as per ICH guidelines at temperature 40° ± 2°C/75% ± 5% RH in a humidity chamber for 2 months.

V. Results And Discussion

Initially 2^3 full factorial design was followed for the formulation of floating microspheres. The two levels of the variables, I. e. lower level and higher level were selected for the optimization. After analysis of the responses of the factorial design, Central composite design was selected which had given 6 experiments.95% Confidence level of Curvature effect= 0.76 to 3.3 and the relationship between Y and X is Linear. Hence Central Composite Design is used to construct Quadratic process model which can be used for Robust Process Design.Six more experiments were conducted and added to the previous observations. By taking experiments at lower and higher values and mid points of variables explained in table1.By using Sigma tech software central composite designwas designed. Factorial design of experiments and observed values are given in table 5.

Table 5: Central composite Design of experiments and observed values

S. No	Combinations	X1	X2	X3	Y1 (DE)	Y2(B)	Y3 (%Y)	Y4(DR)
1	**I**	1:2	1:1.5	700	34%	84%	80%	99%
2	**X1**	1:3	1:1.5	700	47%	80%	78%	98%
3	**X2**	1:2	1:2	700	45%	83%	93%	99%
4	**X1X2**	1:3	1:2	700	53%	85%	77%	98%
5	**X3**	1:2	1:1.5	900	54%	79%	71%	95%
6	**X1X3**	1:3	1:1.5	900	87%	90%	97%	99%
7	**X2X3**	1:2	1:2	900	71%	73%	86%	95%
8	**X1X2X3**	1:3	1:2	900	82%	77%	91%	99%

9	**Midpoint**	1:2.5	1:1.75	800	82%	79%	98%	97%
10	**Midpoint**	1:2.5	1:1.75	800	79%	82%	92%	97%
11	**Midpoint**	1:2.5	1:1.75	800	81%	87%	87%	95%
12	**Midpoint**	1:2.5	1:1.75	800	78%	84%	89%	95%
13	**X1At -2L**	1:1.5	1:1.75	800	79%	85%	90%	95%
14	**X1At + 2L**	1:3.5	1:1.75	800	78%	81%	79%	97%
15	**X2At - 2L**	1:2.5	1:1.25	800	80%	79%	82%	95%
16	**X2At + 2L**	1:2.5	1:1.25	800	81%	82%	94%	95%
17	**X3At-2L**	1:2.5	1:1.75	600	83%	79%	88%	98%
18	**X3At + 2L**	1:2.5	1:1.75	1000	84%	84%	82%	98%

All 18 observations were used for statistical analysis. Software Sigma Tech was used for statistical analysis and constructing quadratic process Model which is given below.

Y= 97.33+0.625X1+0.0X2- 0.375 X3+0.0 X1X2+ 1.25 X1X3+0.0X2X3- 0.1667 X1^2-).4167 X2^2+ 0.3333X3^2

Statistical analysis and ANOVA were mentioned in the table. 6 and 7.The Contour diagram has been drawn based on this Quadratic process model to arrive at Robust Process and given at Fig-2.

Table 6: Statistical analysis of observations for factorial Design of Experiments for Y4

S. No	Coefficients(BS)	Coefficient values	F values	SS%	P values
1	Bo	97.75	-	-	-
2	B1	0.75	3.37	21	> 0.1
3	B2	0.00	0.00	0	0
4	B12	0.00	0.00	0	0
5	B3	-0.75	3.375	21	>0.1
6	B13	1.25	9.375	58	< 0.05
7	B23	0.00	0.00	0	0
8	B123	0.00	0.00	0	0

SS% = the % sum of the squares. P values lower than 0.05 are considered as significant

Table 7: ANOVA for Y4 (drug release)

S. No	Source of variance	SS = Sum of squares	DF = Degrees of freedom	MS= Mean square	F value	P values	
1	Model	21.5	6	3.5833	9.223372	>0.05	Significant
2	Error	0.00	5	0.0			
3	Total	21.5	11				

A number of alternative contours have been simulated (X1 X2, X1 X3, X2 X3) varying third factor from lowest to highest value for targeted values of 97-100% drug release.Out of these, the one which has given maximum area of higher outputs has been considered as optimal and robust design of the process.The Contour has resulted in Robust Process Design with the following parameters. The targeted values used for Contour are, 97%, 98%, 99% , 100% Drug release.

X1=D: P drug to polymer ratio: -2 to -1 coded level (absolute values are 1.5 to 2 D: P ratio) on the X axis

X2= Solvent ratio: -2 to 2 coded levels (absolute values are 1.25 to 2.25 solvent ratio) on the Y axis.

X3=600 RPM

The Y= Drug release is 99% to 100

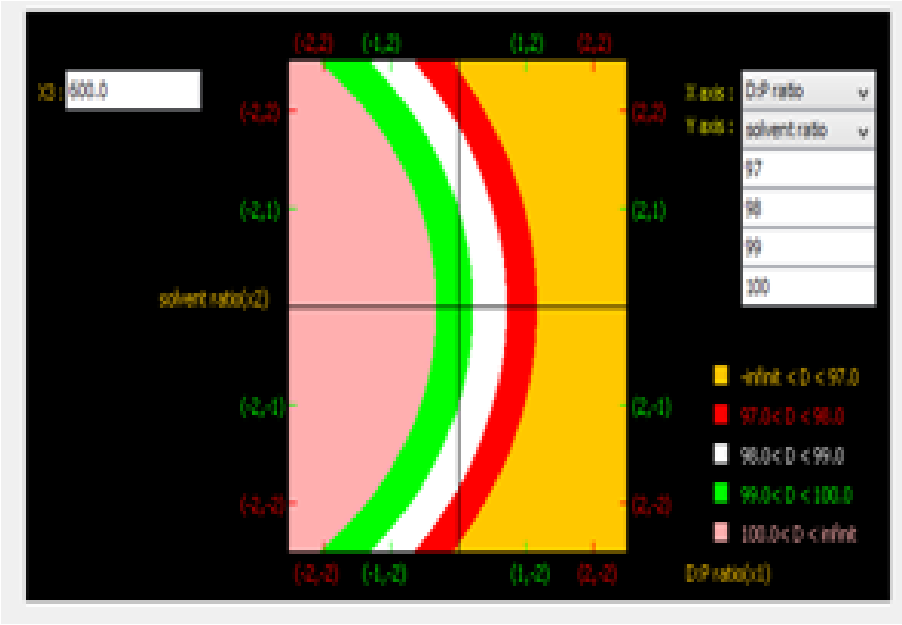


Fig 2: Contour Diagram

Colour code: Red=97%, White= 98%, Green=99%, Pink = 100%

5.1 Drug Entrapment Efficiency

The drug entrapment efficiencies of all formulated Prazosin HCL floating microspheres were determined and presented in Table 8. The measured drug entrapment efficiencies were within the range. It was also found that drug entrapment efficiencies of Prazosin HCL containing floating microspheres were increased with an increment of stirring speeds used during the formulation[13].

Table.8.Physicochemical characterization of Prazosin HCL floating microspheres

CODE	%Yield (±S.D)	Drug entrapment efficiency(%) (±S.D)	Mean particle size(µm) (±S.D)
F1	80±1.8	34.37%	364±4.32
F2	78±2.9	47.02%	394±4.34
F3	93±3.2	45.34%	275±3.42
F4	77±2.6	53.12%	388±7.46
F5	71±4.9	54.47%	350±8.80
F6	93±2.1	87.46%	275±6.65
F7	86±2.5	71.23%	400±3.30
F8	91±2.7	82.34%	374±8.64
F9	95±2.6	82.19%	250±9.24
F10	92±4.1	79.11%	320±7.12
F11	79±2.4	57.62%	294±1.34
F12	83±3.9	65.24%	300±6.42
F13	87±3.6	63.18%	400±5.36
F14	81±6.9	74.42%	330±8.10
F15	87±8.1	67.41%	250±4.65
F16	81±5.5	61.29%	370±2.35
F17	86±2.7	82.34%	350±8.21
F18	88±3.1	78.29%	325±6.23

5.2 Size and shape of microspheres

The mean particle size of Prazosin hcl floating microspheres was determined using the microscope fitted with an ocular micrometer[14] and stage micrometer and presented in Table 8. The determined mean particle size of all microspheres increasing the drug-polymer ratio and at high stirring speed in the preparation of these microspheres resulted in the formation of comparatively smaller particle size. This observation may be attributed to an increase in viscosity of the internal phase with the increasing amount of polymers. The higher the viscosity of the internal phase, the higher the amount of energy is required to break the drug-polymer droplets into smaller particles[17,18].

The SEM photographs of floating microspheres of Prazosin hcl are presented in Fig3. The shape of these microspheres was spherical and their surfaces were rough. In addition, these SEM photographs showed the

appearance of drug particles on their surface, which was responsible for the initial burst release of drug during dissolution[19].

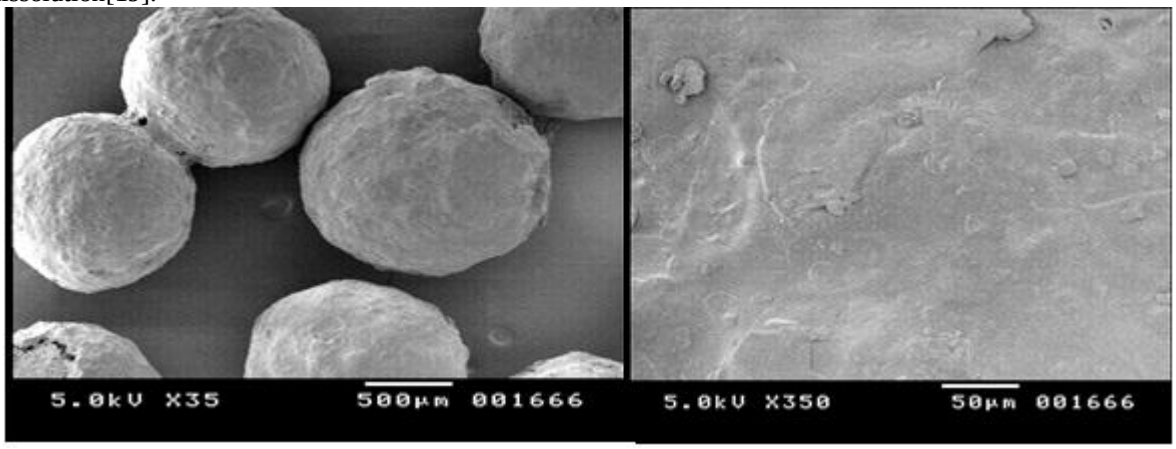


Figure 3: SEM photographs of floating microspheres of Prazosin hcl

5.3 Flow Property

The flowability of these microspheres was exemplified by Carr's index, Hausner ratio and angle of repose are presented in Table 9. The flowablity of these microspheres was found good. There was no significant effect of polymer content on flow properties of microspheres [17].

Table 9:Flowability and buoyancy results of Prazosin hcl floating microspheres

Code	Angleof repose(º)	Hausner ratio(HR)	Carr's index(%)	Buoyancy(%)
F1	25.01	1.13	13.12	84.91
F2	24.94	1.14	14.15	80.19
F3	23.62	1.115	13.34	83.04
F4	26.91	1.14	15.45	85.43
F5	27.18	1.13	14.08	79.54
F6	28.12	1.14	14.54	90.21
F7	28	1.12	12.37	73.45
F8	27	1.13	13.48	77.32
F9	26.42	1.12	13.08	79.21.
F10	28	1.14	14.31	82.43
F11	27.62	1.14	14.42	85.36
F12	25	1.15	13.38	78.40
F13	25.47	1.13	13.67	77.52
F14	26	1.13	12.52	81.62
F15	27	1.13	12.38	88.53
F16	26.12	1.12	14.56	84.49
F17	27.45	1.12	14.70	79.12
F18	27	1.12	14.85	82.31

5.4 In VitroBuoyancy Study

The in vitro buoyancy of Prazosin hcl floating microspheres were evaluated in HPLC water and presented in Table9. The percent buoyancies ranged from 73.45 to 90.21 % for all these microspheres. It was observed that the in vitro buoyancy of these microspheres was increased with the decreasing drug to polymer ratio[20,21]

5.5 In Vitro Drug Release Studies

In vitro release of drug from the various Prazosin hcl floating microspheres was presented in Table 10. It was observed that the drug release was dependent on the drug to polymer ratio[22,23].

Table10: In vitro drug release profile of Prazosin hcl floating Microspheres (F1-F18)

Formulations	TIME(hrs)									
	0	0.5	1	2	4	8	12	16	20	24
F1	0	15.38	27.09	59.87	72.97	89.04	99.23			
F2	0	17.64	25.04	59.54	78.54	98.23				
F3	0	12.14	26.38	67.05	73.13	86.40	99.21			
F4	0	15.96	24.38	58.42	83.77	98.44				
F5	0	14.50	20.38	55.36	76.08	87.21	95.36			
F6	0	24.32	45.02	63.46	88.06	99.57				

F7	**0**	**11.08**	**24.67**	**59.47**	**65.48**	**87.90**	**95.47**			
F8	**0**	**19.39**	**49.09**	**70.68**	**85.96**	**99.12**				
F9	**0**	**12.01**	**21.05**	**39.87**	**46.67**	**55.59**	**87.64**	**97.32**		
F10	**0**	**15.02**	**29.32**	**35.43**	**57.22**	**71.89**	**81.58**	**97.01**		
F11	**0**	**13.46**	**26.14**	**44.31**	**51.18**	**76.43**	**84.05**	**95.68**		
F12	**0**	**12.94**	**25.96**	**48.09**	**53.45**	**66.71**	**79.38**	**95.21**		
F13	**0**	**14.13**	**29.36**	**42.33**	**58.11**	**67.44**	**73.25**	**88.30**	**95.78**	
F14	**0**	**21.93**	**32.93**	**48.43**	**75.91**	**88.17**	**97.27**			
F15	**0**	**19.53**	**37.51**	**53.55**	**67.30**	**76.43**	**82.01**	**95.06**		
F16	**0**	**10.54**	**20.42**	**46.59**	**51.41**	**67.60**	**72.53**	**87.78**	**95.42**	
F17	**0**	**17.62**	**26.64**	**41.02**	**55.31**	**69.55**	**77.32**	**86.07**	**98.57**	
F18	**0**	**14.03**	**20.59**	**37.56**	**44.56**	**51.54**	**64.60**	**70.11**	**82.41**	**98.70**

5.6 Kinetic modeling of drug release

The kinetic drug release of all formulations was described in Table 11.The regression coefficient (R^2) values of the release data of all the formulations were obtained by the curve fitting method for the zero order, first order, Higuchi and the Korsemeyer-Peppas models. Most of the formulations followed the Korsemeyer and Higuchi models.

Table 11: Drug release kinetics of floating microspheres of Prazosin hcl (F1-F18)

Formulation code	**Zero order**	**First Order**	**Higuchi**	**Korsemeyer-Peppas**		**Best fitting model**
	R^2	**R^2**	**R^2**	**R^2**	**N**	
F1	0.7976	0.9601	0.9543	0.9197	0.580	**First order**
F2	0.8972	0.9911	0.9570	0.9544	0.725	**First order**
F3	0.7555	0.9284	0.8843	0.8664	0.628	**First order**
F4	0.7641	0.8578	0.9411	0.9140	0.703	**Higuchi**
F5	0.7843	0.9507	0.9443	0.9220	0.707	**First order**
F6	0.6650	0.7336	0.8887	0.8851	0.503	**Higuchi**
F7	0.8240	0.9635	0.9365	0.9033	0.651	**First order**
F8	0.6478	0.8087	0.8711	0.8115	0.551	**Higuchi**
F9	0.8944	0.9015	0.9553	0.9408	0.567	**Higuchi**
F10	0.8865	0.9187	0.9887	0.9832	0.529	**Higuchi**
F11	0.9077	0.9536	0.9920	0.9814	0.546	**Higuchi**
F12	0.9119	0.9776	0.9917	0.9742	0.537	**Higuchi**
F13	0.8347	0.8862	0.9658	0.9417	0.482	**Higuchi**
F14	0.8155	0.9743	0.9648	0.9722	0.479	**First order**
F15	0.7561	0.8816	0.9314	0.9194	0.425	**Higuchi**
F16	0.8374	0.8885	0.9611	0.9033	0.541	**Higuchi**
F17	0.7739	0.9467	0.9451	0.9594	0.420	**Korsemeyer-Peppas**
F18	0.8754	0.8588	0.9536	0.9218	0.451	**Higuchi**
Optimized formulation	0.9052	0.9673	0.9898	0.9746	0.478	**Higuchi**

5.7 Optimized Formulation

The optimized formulation containing1.5 to 2 D:P ratio(X1), 1.25 to 2.25 solvent ratio(X2),Speed=600 rpm(X3). Showed 99.87% drug release at the end of 24hours. Table12.

Table:12 cumulative drug release

Time (hr)	**% Cumulative drug release**
0	0
0.5	13.62
1	22.76
2	37.63
4	44.57
8	58.39
12	66.50
16	79.08
20	87.31
24	99.87

5.8 Drug - Excipient compatability studies

5.8.1 FT-IR spectroscopy:

FT-IR spectra of pure Prazosin hcl, Prazosin hcl floating microspheres, HPMC K100M and Ethyl cellulose, Eudragit were presented in Fig 5.The characteristic peaks 856.60 cm^{-1} due to ketone of the ring stretching, 3478.74 cm^{-1} due to C=0 stretching, 3127.16 cm^{-1} C-H stretch, C-C stretch at 885.38 cm^{-1} C-C In-

plane stretch at 1647.18 cm^{-1}. This phenomenon suggests that there was an absence of any chemical interaction between the drug and the excipients.

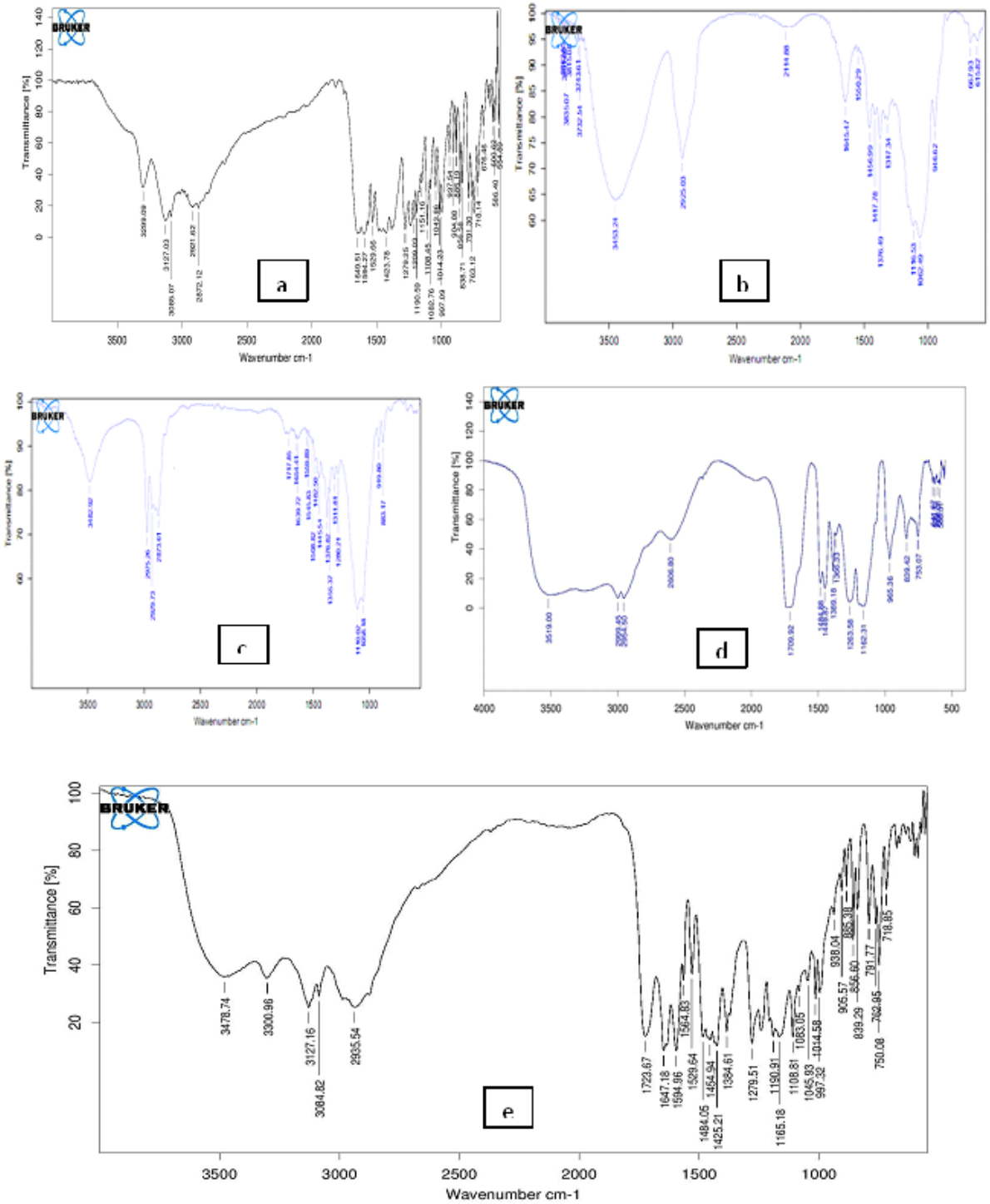


Fig 5: FTIR studies of a. prazosin hcl, b. HPMC K100M c.Ethyl cellulose d. Eudragit e.Optimized formulation

5.8.2 DSC studies

The DSC of pure prazosin hydrochloride showed an endothermic peak at 295.03°Cindicating the melting point of drug, the characteristic peak that appear in optimized formulation

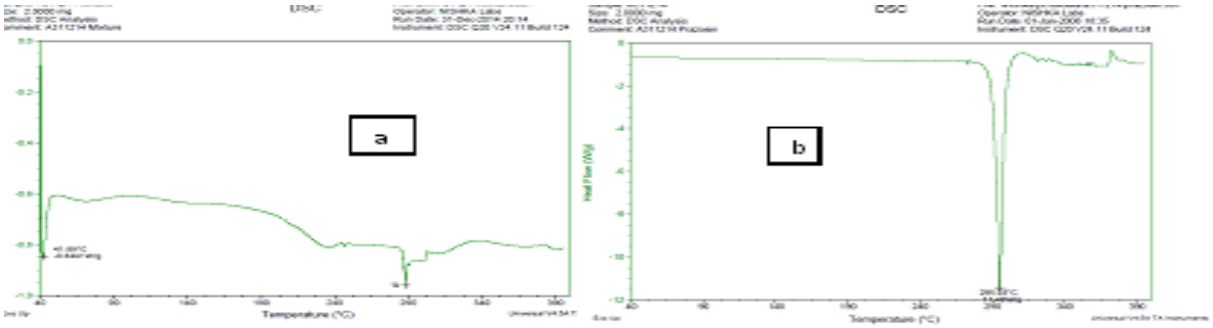


Fig6: DSC thermogram of a. optimized formulation b. prazosin hydrochloride

5.9 Accelerated stability studies

Optimized formulation showed 99.87% of drug release in initial month**.** Evidently, a slight increase in drug release at the end of 2 months was observed on comparing the freshmicrospheres to the stored microspheres. However, even with this increment, the stored microspheres compiled with the reported specifications of sustained-release products. This indicates that the optimized formulation was fairly stable at accelerated storage condition

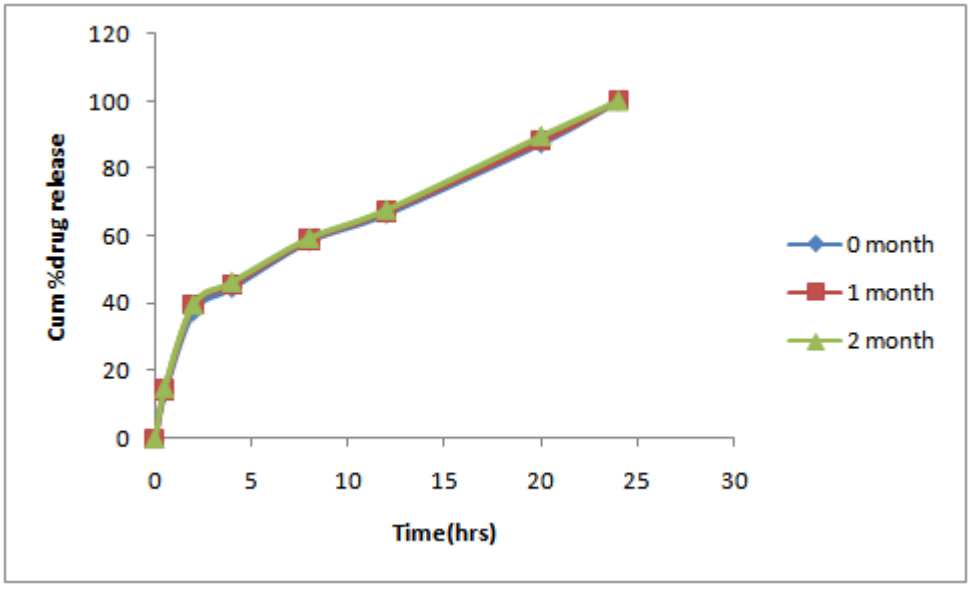


Fig7: Cumulative present drug release in 24 hours

VI. Discussion:

Central Composite Design was used to construct Quadratic process model which can be used for Robust Process Design.The Contour has resulted in Robust Process Design with the 97%, 98%, 99% , 100% of Drug release. The microspheres were prepared by solvent evaporation method. The increase in drug entrapment efficiency of these microspheres was observed with the increasing drug to polymer ratio. Since the higher the polymer content, higher the polymer surrounded by the drug, which acted as a barrier to prevent diffusion of drug molecules into the external phase. The mean particle size of these microspheres was increased with the decreasing of stirring speed.This phenomenon supports the principle that the high stirring speedcould provide the high shearing force needed to break down the drug-polymer droplets into smaller particles.The drug release was found delayed with the increasing drug to polymer ratio. The higher drug to polymer ratio of microspheres delayed the drug release. This may be due to the slower rate of drug diffusion from these microspheres into the dissolution media due to increased thickness of the polymeric-matrix.The R^2value of the optimized formulation was 0.991 and then value was 0.48, indicating Fickian release governed by drug diffusion. The FTIR and DSC analysis showed the absence of chemical interaction between drug and excipients.The results of the stability studies showed that all the examined parameters remained same at all the time intervals, indicating the good stability of Prazosinhcl microspheres

VII. Conclusion

A floating drug delivery system is a promising approach to reach an extended drug release using the synthetic polymer HPMCK100M, ethyl cellulose and Eudragit.A systematic study using Central Composite design revealed that, by taking a suitable composition of HPMCK100M, ethyl cellulose and Eudragit, the desired dissolution profile could be attained.

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