Research Article

FORMULATION *&IN VITRO* EVALUATION OF FLOATING MICROSPHERE OF PRAZOSIN HCl

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ABSTRACT

The Impetus of the current learning was to acquire the floating microspheres of Prazosin hydrochloride is an advanced drug delivery system and to go through the drug to get the better of the reactions as orthostatic hypotension. The devising was compel by solvent evaporation method. In this study, the microspheres were assessed for elementary framework as appearance, dimension, lightness percentage, and drug entrapment order. The accumulating % drug free of upgraded expression succeeding 24 hours was 91.4%. Prototype installing survey give away the free design kept to Peppas-Korsmeyer. The out turn signify a good connection between the forecasting and fact-finding worth, supporting the logic of the version. FTIR exhibited that there is not drug and polymer contraction. It was concluded under accelerated studied formulations was optimized.

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INTRODUCTION

Solitary majority of dominant for talk to reaching a extended drug administration in the GI tract is to travel in the gastric flat tempo by make using of gastro-retentive quantity forms (GRDFs). Gastro retentive floating drug delivery systems (GRFDDS) are having a volume solidity bottom than compared to gastric solution and so remainder floatable in the intestine in the absence of remaking in gastric empty charge for a long lasting phase of plan. It has particular edges on top of on the spot let out dosage forms as well as the decreased the variation in drug attentiveness in plasma and their locations of undertaking on top of draw outer periods of hours, reposing in optimized therapeutic planning and lower the side effect. Floating microspheres are showed to non-effervescent are gastro retentive drug delivery systems. The semicrospheres have to a size less than 200 μm, is present unoccupied flaccid talc and carry on floatable over gastric contentment and for a major draw came out spell. The drug is let go without hurrying from this floating system at the wanted rate, out-turn enlarged gastric retentive time and also have poor fluctuations in plasma drug concentration. Prazosin is a discriminate α-1-adrenergic receptor antagonist pre-owned for prevention of hypertension. Prazosin takes action by hold back the postsynaptic alpha-1-adrenoceptors on vascular smooth muscle. It obstructed the vasoconstrictor outcome of catecholamine (epinephrine and norepinephrine), derived in peripheral vasodilation. The mean plasma half -life of 2-3 hours in a time. Prazosin has a short half-life and bioavailability have been very lowest in the superior part of the GIT in consequence this is acceptable for gastro-retentive. [6, 7]

Floating microspheres

In floating categories the bulk density is shorter than the gastric fluid and so residue buoyant in stomach in the absence of influencing gastric emptying rate. The drug is freeing slowly at the desired rate, if the arrangement is floating on gastric gratified and enlarged gastric residence and extension fluctuation in plasma concentration. In addition this is to be very less chances of perceptible and amount of dumping. There is a different way to it creates longer for therapeutic out-turn and in consequence lower the amount rate of happening. The advantages of floating microspheres are**;** Microsphere remaking liquid to solid (powder as particles.) itself e.g., Clofibrate. As hoard them for a longer use of time, e.g., Mix of Aspirin and Chlorfilaramine. Microsphere safeguard materials from environment for examples by averting oxidization.eg; Vitamin A Palmitate Microsphere upgraded the fertile

life style. Microsphere hold on to a liquid on a flat surface by in out-turn, revamping it to a solid. Microsphere commands the releasing conditions. For example, we can control the timing of dissolving, volatilization, colouring, release of smell, mixing and reaction by remaking the size of the capsules, the ratio of core materials to shell materials, or the properties of the shell materials, such as strength and permeability or by adding supplementary materials to core or shell materials. It is changed the specific gravity and also be using a core materials easy to handle. Microspheres solidify tacky materials and increase its fluidity. E.g. thiamine HCl, riboflavin, etc. Some disadvantages of microsphere are; Drug entrapment is lowered since exiguous part of drug at only one-time in the dissipation vehicle. The industrial site lamella of microspheres formulation were manufacture is onerous because to keep going dimension of microspheres at industry amount is very difficult The mass producing of microspheres required for utilizes of solvents which make the operation expensive. As big comparison to the stick out release tablets and capsules, the assembling of microspheres is much more convoluted. Time pre-occupying activity as much time period for necessity for emulsification, vaporization of solvent, and rigidization of microspheres. [2, 3]

Criteria for preparation of microspheres [4]

1. The potential to incorporate kindly concentrations of the drug
2. Fastness of the composing in the wake of synthesis with a clinically sustainable shelf- life.
3. Manageable particle size and dispensability in aqueous vehicles for injection.
4. Liberation of active agent with good command over a broad time scale.
5. Biocompatibility with a handleable biodegradability.
6. Susceptibility to chemical tempering.

Challenges with earlier formulation of Prazosin and congeners

The key of restriction of the preliminary standard expression of Prazosin was a short half-life, fallowing in a very short duration of action. [1-3] This demand twice- or thrice-a-day dosing, to keep going effective sway. Obligation for monotonous dosing affects the patient's medication conformity, which may out-turn in inconsistent blood pressure control. Also, repetitive dosing, by itself, leads to fluctuating plasma concentrations of the drug at steady state. Plasma level fluctuations at steady state, may additionally lead to inconsistent blood pressure control. [19] The initial formulations of α blockers, including

Prazosin, doxazocin and terazosin, were correlated with first- order kinetics. This is identified by a speedy absorption of the drug, resulting in accomplishment of peak concentrations in the plasma. Fast exposure to higher drug concentrations, may be described the chances of more possibility of first-dose effect, observed commonly with this formulation. First-dose effect is a chief antecedent of the tolerability of α-blockers. The likelihood of hypotension and collapse were momentous have to do with, apart from other symptomatic adverse effects, which necessitated multiple-step dose titration of the drugs following rapid or fast absorption, a continual decline is remarked in the plasma levels, owing to drug metabolism. [1]

Technology limitation in preparing microsphere [8]

1. Surplus solvents firmness.
2. Non accessibility of disintegrated synthetic polymers.
3. Encapsulation planning.
4. Limitation of manufacturing process
5. Sterilization.

Applications

Assay - Coated microspheres provide measuring tool in biology and drug research ™

Buoyancy - Hollow microspheres are used to decrease material density in plastics (glass and polymer) ™

Ceramics - Used to create porous ceramics used for filters (microspheres melt out during firing, Polyethylene Microspheres) ™

Cosmetics - Opaque microspheres used to hide wrinkles and give colour, Clear microspheres provide "smooth ball bearing" texture during application (Polyethylene Microspheres) ™ Drug delivery - As miniature time release drug capsule made of, for example, polymers. A similar use is as outer shells of microbubble contrast agents used in contrast-enhanced ultrasound.

Electronics paper- Dual Functional microspheres used in Gyricon electronic paper. System FDDS can be divided into two systems. [10]

MATERIAL AND METHOD

Material

Prazosin was procured from Bangalore fine chemicals and Pharma Research Laboratories Pvt. Ltd. (Bangalore, India). HPMC and Ethyl cellulose polymer were obtained from Sigma-Aldrich Pvt. Ltd. (Mumbai, India) and solvents of Dichloromethane, Ethanol, & Chloroform were also obtained from Sigma-Aldrich Pvt. Ltd. (Mumbai, India). Heavy liquid paraffin and Tween-80 were obtained from

Loba Chemie Pvt. Ltd (Mumbai, India). All other materials and chemicals were of analytical grade.

Methods

Preformulation Studies

Pre-formulation link between drug discovery and drug delivery, pre-formulation assist in scanning lead candidates based on their physiochemical and biopharmaceutical properties of drug alone or in combination with other drug and with excipient to developed safe, stable, potent, bioavailable and efficacious dosage form. The drug Prazosin is tested for identification is term for melting point, solubility in various solvent UV absorption maxima and FTIR investigation, Calibration curve of drug were prepared by reported or by developed methods. [11]

Physical appearance

The sample of Prazosin was analysed for physical appearance. Melting point Melting point of Prazosin was determined by capillary method by using melting point apparatus BEA-54 (Biocraft science system Pvt. Ltd., New Agra). The melting point of Prazosin was found to be 277-280°C.

Solubility study

Solubility may be defined as the spontaneous interaction of two or more substance to form a homogenous molecular dispersion. The solubility of Prazosin was tested in various common solvent .A definite quantity (10 mg) of drug was dissolved in 10 ml of each investigated solvent at room temperature. The solubility was observed by visual inspection.

Melting point

Melting point of Prazosin was determined by capillary method by using melting point apparatus BEA- 54 (Biocraft science system Pvt. Ltd, New Agra). The melting point of Prazosin was found to be 277-280°C.

Determination of pH

The pH was determined by pH paper.

Determination of FT-IR Spectroscopy

FT-IR was transferred revealed to assess the interplayed in the middle of drug and excipients. One mg of material of solidify condition was ground with 100 mg of dry potassium bromide and inspected from 400-4000cm^{-1} make use of FT-IR spectrophotometer. [14]

Standard curve of Prazosin

1. Devising of stock solution Stock solution was composed by break down

of 10 mg of Prazosin in 10 mL of water.

2. Devising of quality level of solution 10 mL of stock solution was well blended with 100 mL of distilled water.
3. Various types of aliquots were make ready by proceeding different dilution of standard solution, volume was made up with distilled water.

Methods of preparation of microspheres

Solvent Evaporation Method:

These microsphere was to be performed by containing Prazosin hydrochloride as a key substance were make ready by Solvent Evaporation method is used. Drug and polymers (HPMC and ethyl cellulose) are well mixed in dichloromethane and chloroform at varied proportion. The slurry was obtuse to found into 90 mL of liquid paraffin restraining 1% of Tween-80 as emulsifying agent spell existence stirred at different rpm by a mechanical stirrer with accompanied by a three bladed propeller at room temperature. The solution was to be stirred for 2 hours for completely evaporation process of solvent and it was collected by filtration. The microspheres were after washing three times with n-hexane and three times with 180 ml petroleum ether to detached out of the remaining oily phase and then dried it overnight at particular room temperature for 24 hours in a day and subsequently may be stored in a desiccator. Make up volume of microspheres as per central composite design is given in Table 1 **[13]**

Table 1: Formulation of Floating microspheres of Prazosin HCL

Contents	F1	F2	F3	F4	F5	F6
Prazosin HCl (mg)	100	100	100	100	100	100
HPMC (mg)	100	100	100	100	100	100
EC (mg)	100	200	300	400	500	600
Heavy liquid paraffin (ml)	90	90	90	90	90	90
Dichloromethane (ml)	10	10	10	10	10	10
Ethanol (ml)	15	20	15	20	15	20
Tween 80 (%)	10	10	10	10	10	10
Petroleum ether (ml)	180	180	180	180	180	180

HPMC: EC were used in the ratio of 1:1, 1:2, 1:3, 1; 4, 1:5 and 1:6, respectively.

Ethanol: DCM were used in the ratio of 1:1

RESULT AND DISCUSSION

Preformulation studies

Physical appearance

The physical appearance of Prazosin was found to be white crystalline substance.

Melting point

Melting point of Prazosin was determined and observed to be 280 ºC.

Determination of pH

The pH of determination pH paper and found 7.4.

FT-IR Spectroscopy

This is showed the FT-IR spectra of pure foam of Prazosin HCl, Prazosin floating microspheres, HPMC K100M and Ethyl cellulose, were hand over in Fig. 1 and Tbale 2. The quality of peaks 856.60 cm^{-1} expected to ketone of the ring stretch, 3478.74 cm^{-1} and also expected to C=O stretching, 3127.16 cm^{-1} C-H stretch, C-C stretch at 885.38 cm^{-1} C-C In-.1.6 Resolution of FT-IR Spectroscopy plane was stretched at 1647.18 cm^{-1}. Occurrence advice that there was not present of any chemical to correlated linking the drug and the excipients. [15]

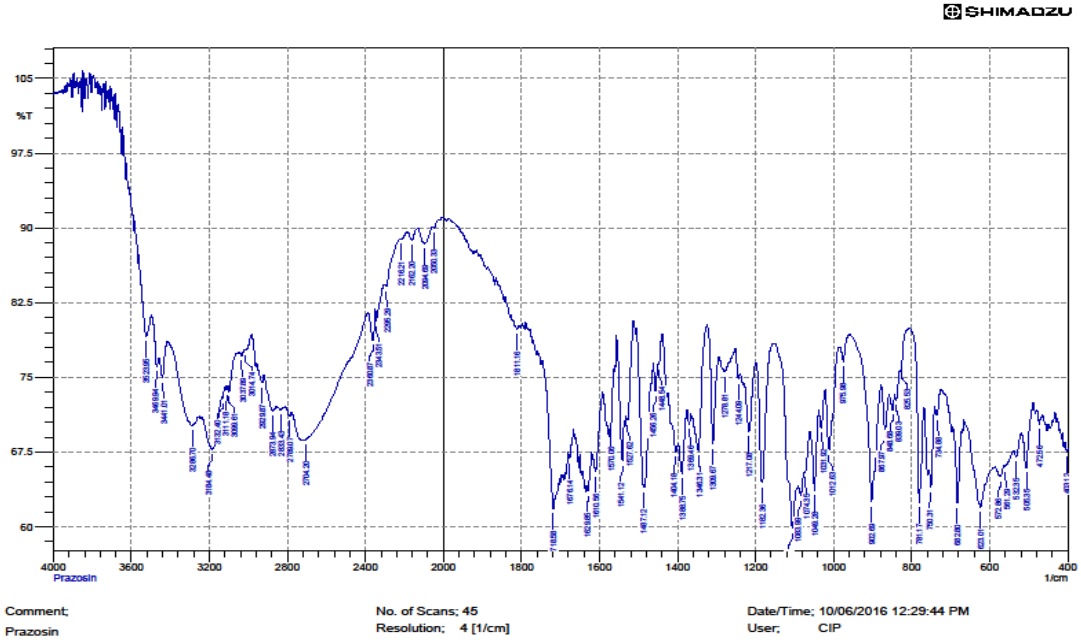

Figure 1: FTIR spectra of Prazosin HCl

Table 2: Interpretation of IR spectrum Prazosin

Sl. No.	Functional group	Peak (cm^{-1})	Peak (cm^{-1})
1	Mono sub C-H	1770	1752
2	C-C stretching	1680	1620
3	C-H stretching	3040	3010
4	C=O	1725	1705
5	C=N	1630	1625

Calibration curve of Prazosin drug

Standard calibration curve in Table.3 show absorbance of Prazosin at different concentration 2, 4, 6, 8, 10 µg/mL Fig. 2 the standard curve of Prazosin 254 nm the regression value was found to be (0.995)

Table 3: Determination of absorption maxima (ƛmax)

Sl. No	Concentration (µg/ml)	Absorbance
1	2	0.145
2	4	0.285
3	6	0.487
4	8	0.689
5	10	0.899

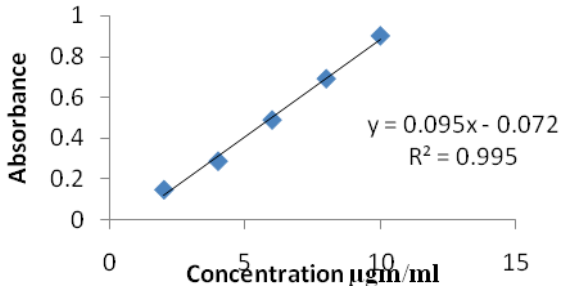

Figure 2: Standard calibration curve of Prazosin Determination of λ max for Prazosin HCl

The absorption spectrum of pure drug was scanned 200-400 nm. The λ max of pure drug was to be found 254 nm in 0.1 N HCl. [11, 15]

Characterization of Floating Microsphere of Prazosin HCl

The yield of microspheres were presented in Table 4.

Table 4: Percentage yield

Sl. No.	Formulation	% yield
1	F1	75.71%
2	F2	73.35%
3	F3	71.35%
4	F4	81.36%
5	F5	77.09%
6	F6	72.41%

Entrapment efficiency of Prazosin floating microsphere were presented in Fig. 3

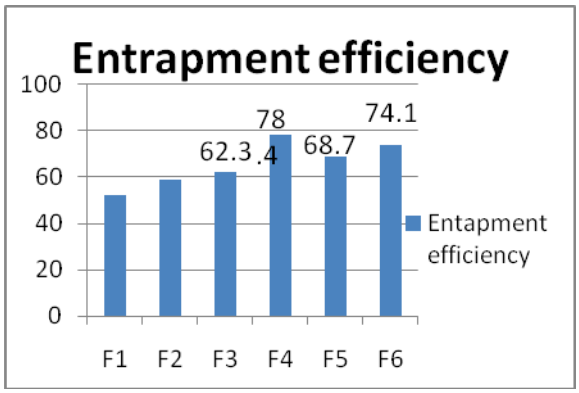

Figure 3: Drug Entrapment efficiency of all formulations

Buoyancy Study

The Floating microsphere prepared with EC and HPMC were more buoyant. EC being insoluble and remain floated whereas HPMC swells and erodes with time. Increase in concentration of HPMC increased in buoyancy. Floating behaviour of the formulation of EC and HPMC were shown in Table 5 and Fig. 4 [31]

Table 5: Percentage of Buoyancy of floating microsphere of Prazosin HCl

Formulation	Buoyancy Percent (%)
F1	74.61
F2	71.63
F3	80.43
F4	92.85
F5	78.64
F6	85.33

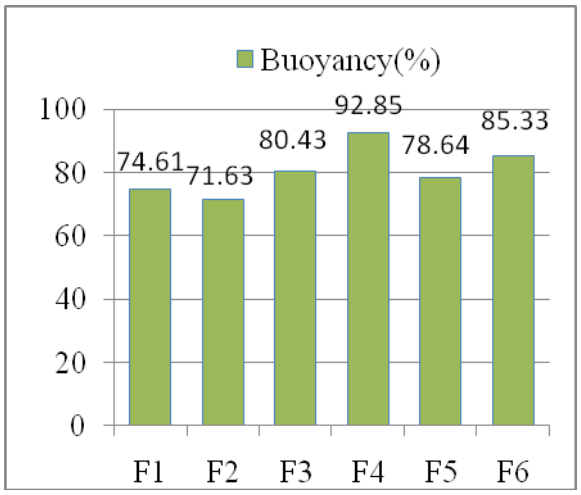

Figure 4: Buoyancy Percent of all formulations

Drug release from Floating microsphere decreased with increase in HPMC concentration due to its less permeability. It increases the Polymer matrix density leading to decrease in drug release from the Floating microsphere. The percentage drug release were presented in Table 6, Table 7 and Fig. 5

Table 6: *In vitro* Drug release profile of floating microsphere containing Prazosin HCl (F1)

Time (hr.)	% Drug Release
1.	12.54
2.	22.73
3.	35.41
4.	44.26
5.	53.42
6.	63.59
7.	72.15
8.	84.11
9.	87.54
10.	91.54

***In vitro* drug release study**

Table 7: *In vitro* Drug release profile of all formulation

Time (hr.)	F1 (%DR)	F2	F3	F4	F5	F6
1.	12.54	7.11	12.44	22.34	16.11	15.32
2.	22.73	12.11	18.33	33.21	17.33	24.11
3.	35.41	20.21	25.64	43.22	32.54	31.18
4.	44.42	26.31	34.86	50.22	50.30	42.19
5.	53.28	34.21	49.78	61.11	55.31	50.11
6.	63.59	41.58	54.28	69.22	63.29	63.25
7.	72.15	48.39	63.96	74.36	69.54	69.26

8.	84.11	57.54	74.22	85.22	74.87	74.56
9.	87.54	69.21	80.75	93.55	80.16	79.81
10.	91.54	78.33	84.32	98.22	86.17	83.17

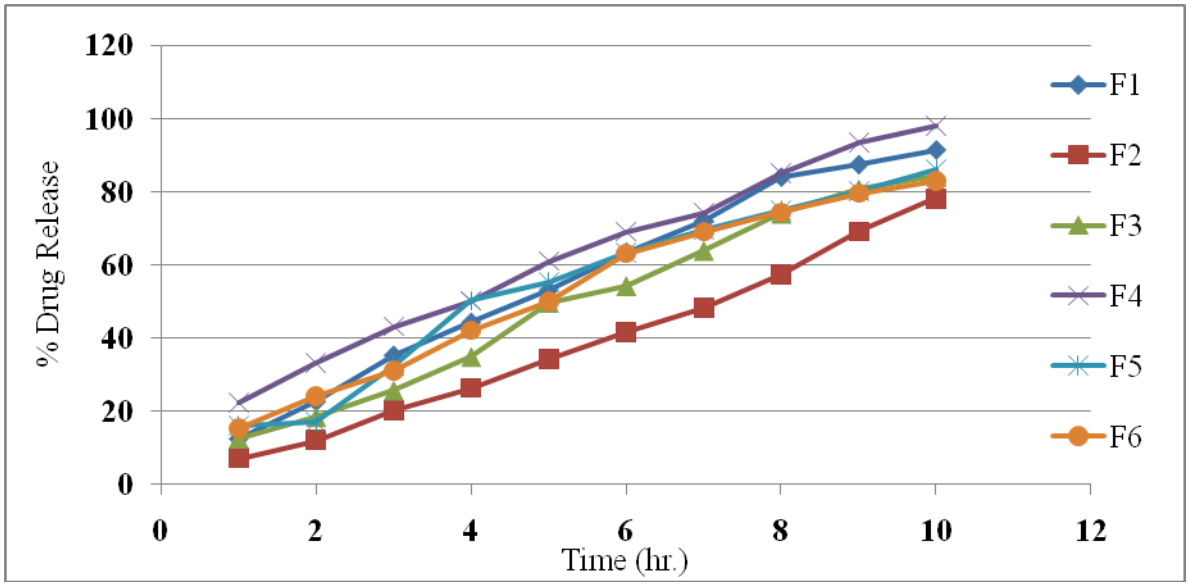

Figure 5: *In vitro* Drug release profile of all formulations.

Kinetic Treatment of Dissolution Data

Drug release data obtained with all formulations was analysed according to the following four kinetics models:

i. % DR vs. Time (Zero order rate kinetics)
ii. Log of % drug remaining to be release vs. Square root of time (First order rate kinetics)
iii. % DR vs. Square root of time (Higuchi model)
iv. Log % DR vs. Log time (Kosmeyer-Peppas model)

Calculated regression value for different formulations are shown in Table 8 these value were compared with each other for model fitting equation. The model giving a regression value close to unity was taken as order of release. [9]

Table 8: Best fit model for all Formulations

Formulation	Zero order (R^2)	First Order (R^2)	Higchi Model (R^2)	Korsmeyer-Peppas	Best Fit Model
F1	0.998	0.973	0.984	0.872	Zero Order
F2	0.990	0.836	0.918	0.968	Zero Order

F3	0.976	0.957	0.858	0.909	Zero Order
F4	0.990	0.994	0.907	0.902	First Order
F5	0.980	0.976	0.824	0.911	Zero Order
F6	0.989	0.934	0.913	0.836	Zero Order

DISCUSSION

Drugs having less half-life, when incorporated into floating delivery system may exhibits better release and improve bioavailability of the drug by maintaining good level of plasma drug concentration and thereby minimizes repeated drug administration and fluctuation and plasma concentration. Prazosin HCL is Freely Soluble in water and good protein binding so small quantity can be used in postural hypotension. It will enhance the penetration and provide prolonged release .the preformulation studies of floating microsphere of Prazosin was found to be determination of absorption maxima is 0.965. The physical appearance of Prazosin was to be found white crystalline powder. The melting point of Prazocin was found to be 277 to 280 ^{o}C and the pH is 7.4 and freely soluble in water, and slightly soluble in ethanol and water. Per formulation studied has been conducted to assess its purity ,Prazosin were identified by UV spectroscopy and FTIR method No major deviation in peaks were obtained in IR spectra ,hence this manifest that there was no fundamental interaction between drug and other ingredients . The above mentioned outcomes indicate that the drug are suitable to conduct further studies.

After that attempt to make to develop floating microsphere Prazosin with polymer HPMC and EC by using polymer combination HPMC and EC developed formulation were evaluated for the parameter such as Particle size determination, Entrapment efficiency, Buoyancy test Swelling index, Percentage yield, Drug release, and Kinetic release. [12]

The evaluation test was performed floating microspheres of Prazocin HCl. The best formulation of Prazocin HCl floating microspheres percentage yield was found to be 71.35% to 81.36% and entrapment efficiency was found to be 54.4% to 74.1% and buoyancy was found to be 70.36% to 90.85%. F4 formulation is the best among that all the formulation. The *in vitro* drug release study the formulation F2 formulation is the best among that all the formulation and All formulation follow the zero order kinetics except F4 formulation follow the zero order kinetics.

CONCLUSIONS

Microsphere was prepared successfully using solvent evaporation method .The release pattern was found to be zero order kinetics depend on combination of the polymer and the amount of the polymer used. The *in vitro* data for floating microsphere of Prazosin HCl showed good incorporation efficiency, good buoyancy and prolonged drug release. From the result it can be concluded that the drug release from the floating microsphere matrix was controlled by the polymer proportion. Prepared formulation showed best appropriate balance between buoyancy and drug release rate.

To achieve the extend drug delivery by using HPMC and ethylene cellulose, the desired dissolution profile is manufactured.

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