FORMULATION AND *INVITRO* EVALUATION OF PRAZOSIN HYDROCHLORIDE UNFOLDING TYPE GASTRO RETENTIVE FILM

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ABSTRACT

The present work is based on the formulation and In-vitro evaluation of a gastroretentive mucoadhesvie based drug delivery system containing prazosin hydrochloride for controlled release. It consists of a drug loaded polymeric film folded into a hard gelatin capsule. After administration film unfolds and its swelling and bioadhesion to the gastric mucosa. Prazosin hydrochloride, a histamine H2 receptor antagonist used for gastroesophageal reflux disease (GERD), duodenal ulcer and gastric ulcer. Prazosin hydrochloride absorbed only in the initial part of gastro intestinal tract (GIT) and has less bioavailability. Thus by retaining the drug in the gastric region improves its bioavailability. Films were prepared by solvent-casting method using HPMC K4M, and Carbopol 971P NF as polymers and PEG 400 as the plasticizer. The prepared film were evaluated for various parameters such as film thickness, folding endurance, uniformity of weight, surface pH, determination of drug content, moisture content, swelling index, In-vitro mucoadhesive study retention time, In-vitro unfolding behavior and In-vitro drug release studies and drug release kinetics. Differential scanning calorimetry revealed there were no polymorphic changes in drug as well as polymers during the formulation of polymeric film. Optimized formulation showed 99.02 % drug release at the end of 12 hrs and it follows the Korsmeyer-peppas kinetics model of drug release.

Keywords*: Gastroretentive mucoadhesive film, Solvent casting method, Prazosin hydrochloride.*

1. INTRODUCTION

Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutics advantages , such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have limited bioavailability because of short residence time thus drug release in stomach is often short. This problem can be overcome by prolonging the residence time of drug in the stomach. The most important approach for achieving a prolonged release of drug in GIT is to control the gastric residence time (GRT) by preventing its elimination from the GIT. Dosage forms with an increased gastric residence time (GRT) are known as gastroretentive dosage forms (GRDF), this will provide new and important therapeutics options. To extend the residence time of dosage form in stomach, a number of strategies have been developed, including (a) reducing density to promote floating in gastric content (b) increasing the density to promote retention in the lower part of stomach (c) introducing mucoadhesive properties and (d) producing a formulation that swell or unfold in the stomach to hinder its escape through the pyloric sphincter[1,2].

An alternative strategy is to combine mucoadhesion with the ability to expand by unfolding and swelling. Gastroretentive mucoadhesive drug delivery system prolong he drug release rate from formulation in stomach and upper part of small intestine until all the drug released for desired period of time. The aim of present work was to develop innovative gastroretentive mucoadhesive formulation based on drug loaded polymeric film folded in hard gelatin capsule. After ingestion the capsule dissolves and releases the film which then unfolds in

stomach and swells to a larger dimension resulting in its increased retention. Based on this hypothesis, the gasrroretentive mucoadhesive film was designed in such way that they should be retained in the stomach for a prolonged period of time, thus maximizing the exposure of the drug to its absorption site[3,4].

2. CHEMICAL USED:

Table 2.1 List of chemicals used

S.No	Name of the ingredient	Purpose	Supplier
1.	Prazosin hydrochloride	API	Gift sample from Hetero Drugs
2.	HPMC K100M	Synthetic Polymer	LOBA CHEMI
3.	Sodium alginate	Natural polymer	LOBA CHEMI
4.	Carbopol 934	Synthetic Polymer	LOBA CHEMI
5.	Glycerine	Plasticizer	LOBA CHEMI
6.	Methanol	Solvent	LOBA CHEMI

Laboratory grade chemicals and reagents was used for this study was

2.2 EQUIPMENTS USED:

Table 2.2 List of equipments used

S.No	Name f the Equipment used	Supplier
1.	Magnetic stirrer with Hot plate	REMI scentific
2.	Electronic weighing balance	Arson Scientific
3.	UV-Visible Spectrophoto meter	Systronic-128
4.	Dissolution test Apparatus	Lab India DS-800
5.	pH meter	Lab India
6.	Vernier Caliper	Calibra Scientific

2.3 Construction of standard calibration curve[5,6]

Preparation of 0.1 M hydrochloric acid (Stimulated gastric juice)

9 mL hydrochloric acid of analytical grade (36 %, 1N) was taken in 1 liter volumetric flask and the volume was made up to the mark with de-ionized water.

Preparation of standard curves of Prazosin Hydrochloride

Accurately weighed 10mg of drug was transferred into a 100mL volumetric flask and dissolved in small amount of methanol and made up the volume with 0.1N HCl solution to make the standard stock solution of 100□g/mL. Various aliquots of different concentration ranging from 5 to 50 □g/mL were prepared by transferring 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0 mL volume of stock solution (100 □g/mL) in 10 mL volumetric flasks and making up the volume to10 mL with distilled water. The absorbance of each solution was measured in systronic UV/visible Spectrophotometer at 246 nm.

2.4 Determination of physicochemical properties of Prazosin Hydrochloride[7].

i. **Colour**

Colour of the drug was identified in pure powder form.

ii. **Taste and odour**

Very less quantity of Prazosin Hydrochloride was used to get taste as well as smelled to get the odour.

iii. **Solubility**

The spontaneous interaction of two or more substances to form a homogeneous molecular dispersion is called as solubility. The solubility of drugs were studies in various polar and non-polar solvents. A definite quantity (10mg) of the drug was dissolved in 10mL of each investigated solvent at room temperature (30^{o}C), in tightly closed glass test tubes and shaken. The solubility was observed only by the visual inspection.

iv. **Melting point**

Melting point of drug was determined by using melting point apparatus. A pinch of powder was placed in a thin walled capillary tube 10-15 cm long, about 1 mm in inside diameter, and closed at one end. The capillary, which contains the sample, and a thermometer are then suspended so they can be heated slowly and evenly. The temperature range over which the sample is observed to melt is taken as the melting point.

2.5 Formulation of Gastro Retentive Films

Unfolding films are prepared by solvent casting method. Required quantity of drug needed for preparation of film was transferred into test tube containing 10 ml of solvent system, and drug was dissolved in the in solvent system. Required amount of polymers needed for film was taken into boiling tube and dissolved in 30 ml of solvent system, with slowly by Vortexing without formation of any polymer lumps. Boiling tube was kept a side for 5 hours to allow polymer to swell. Required quantity of plasticizer was added and mixed well. Prepared drug solution was added to the above a mixed well and kept a side for 2 hours. The above polymer drug mixture was casted in Petri plate and dried it at 40^{o}C for 6 hours in Vacuum oven. The formed films were collected, trimmed, cut into 2 cm X 2 cm size and subjected for different evaluation tests.

Table: 2.3 Formulation Table of Prazosin Hydrochloride polymeric films

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Prazosin Hydrochloride	20	20	20	20	20	20	20	20	20	20	20	20
Sodium Alginate	20	35	40	--	--	--	10	15	20	--	--	--
Carbopol 934P	--	--	--	20	35	40	--	--	--	10	15	20
HPMC K4M	--	--	--	--	--	--	10	10	10	10	10	10
PEG400 (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

2.6 Evaluation of gastroretentive polymeric films

2.6.1. Thickness[8.9]

For thickness uniformity of patches were measured by using vernier calipers. The measurements were performed on three different randomly selected patches from each batch and thickness measured at three different points in order to evaluate the statistical difference, if any. The homogeneity of film formulations in thickness is evaluated by these measurements. After measurements at six different points of ten randomly selected patches of the batch, the results were expressed in terms of mean ± standard deviations.

2.6.2. Uniformity of weight[10]

Three films of every formulation were selected randomly and individual weight of each 2 cm×2 cm film was noted on digital balance. The average weight was calculated.

2.6.3. Surface pH[11]

Surface pH of the patches was determined by the method described by Bottenberg *et al.* The patches were allowed to swell by keeping them in contact with 0.5ml of double distilled water for 1hr in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1min.

2.6.4. Folding endurance[12]

Three films of each formulation of 2 cm × 2 cm were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it break. The number of times, the film could be folded at the same place without breaking gives the value of folding endurance. The mean value of three readings was calculated.

2.6.5. Flatness[13]

Longitudinal strips from six randomly selected medicated films of each formulation were cut out from all batches. The length of each strip and variations in length due to non-uniformity

of flatness were measured. Flatness was calculated by measuring the constriction of the strips. 0% constriction was considered to be 100% flatness.

2.6.6. Moisture content[14]

The prepared films weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 hrs. The films were weighed again after a specified interval until they showed a constant weight. The percent moisture content was calculated by using following formula.

$$\% \text{ Moisture content} = \frac{[\text{Initial weight} - \text{Final weight}]}{\text{Final weight}} \text{X } 100$$

2.6.7. Percentage Swelling index[15,16]

Pieces of about 2.0 cm X 2.0 cm ($4cm^2$) were weighed (W_0) and immersed in 5.0ml of simulated gastric fluid buffer, pH 1.2 for 30min. After every five minutes time interval, the weight of swollen film was recorded for the experimental time period of 30min. After removal of excess water, the hydrated films were re-weighed (W_t). The procedure was repeated 6 times for each system. Results are obtained using below equation indicating the amount of swelling relative to the original weight

$$\text{Swelling index } (\%) = \frac{[W_2 - W_1]}{W_1} \text{X}100$$

2.6.8. Drug content[18,17]

The patch of 4cm2 area was dissolved in 100 mL of 0.1 N HCl and kept under mechanical shaker for 24hrs at 50rpm at room temperature. After 24hrs of shaking, the solution was suitably diluted, and was measured for UV absorbance at 246nm against 0.1 N HCl as blank. For each formulation three films were assayed individually. From each film batches, three films were selected randomly and assayed by UV spectroscopy method.

2.6.9. *In-vitro* unfolding behavior[19 ,20]

The capsules were taken for In-vitro unfolding behavior study in 900mL 0.1N HCl at 37 ± 0.5ºC using the USP Dissolution Apparatus1 basket (Electrolab) at 50 rpm. Baskets were removed after 5, 15,30,60,90,120,240,480 and 720 min and the films were examined for their unfolding behavior.

2.6.10. *In -vitro* drug release study[21,22]

The USP six station dissolution apparatus type -1 was used throughout the study. One film (2X2 cm size) of each formulation was fixed to the central shaft using an acrylate adhesive. The dissolution medium was consisted of 900 mL of 0.1 M HCl or simulated gastric fluid (SGF, pH 1.2).

The release study was carried out at 37±0.5ºC with a rotation speed of 50 rpm. The release study was performed for 12 h. After every1 h, 5 mL samples was withdrawn from each station and immediately it was replaced with fresh media. The withdrawn samples were filtered; the filtrate was diluted to 10 mL using 0.1N HCl. The samples were analyzed spectrophotometrically at 246nm,

2.6.11. *In vitro* release kinetics studies[23,24]

The release kinetics was examined according to different models such as zero-order kinetics, first-order kinetics, Higuchi kinetics, and Korsmeyer-Peppas models. The correlation coefficient was utilized to establish the best fitting model for the drug release.

Zero - Order kinetic model: Cumulative percent drug release Versus Time

First – Order kinetic model: Log cumulative percent drug remaining to be released versus Time

Higuchi Model: Cumulative percent drug release versus Square root of Time

Krosmeyer - Peppas model: Log cumulative percent drug release versus log time

Zero Order model

This describe the systems drug release rate is independent of the concentration of the dissolved species. The dissolution data are fitting into Zero order equation

$$A_t = A_0 - K_0 t$$

Where A_t = Amount of drug release at time (t)

A_0 = Initial Drug concentration

K_0 = Zero order rate constant (hr^{-1})

First order

The first order equation describes the release from the system where the dissolution rate is dependent upon the concentration of the dissolving species Release behaviour generally following first order equation

$$\log C = \log C_0 - \frac{Kt}{2.303}$$

Where, C = Amount of drug dissolved at time (t)

C_0 = Amount of drug dissolved at (t = o)

K = first order rate constant (hr^{-1})

Higuchi model

Drug released from the matrix derived by diffusion has been described by following Higuchi's classical diffusion equation

$$F_t = K_H * t_{1/2}$$

Where, F_t = Faction of drug released at time (t)

K_H = Higuchi's rate constant

The Higuchi's square root equation described the release from systems were the solid is dispersed in an insoluble matrix, and the rate of drug released is released to the rate of drug diffusion.

Krosmeyer – Peppas Model

To study the mechanism of drug release from the matrix tablet, the release data were also fitted to the well known exponential equation. Which is often used to describe the drug release behaviour from polymeric systems.

$$M_t/M_a = Kt^n$$

Where M_t/M_a = Fraction of drug released at time (t)

K = Constant incorporating the structural and geometrical characteristics of the drug/ Polymer system.

n= Diffusion exponent related to the mechanism of the release

Above equation can be simplified by applying log on both side, and we get

$$log\, {}^{M_t}/_{M_a} = logK + nlogt$$

Table: 3.4 Drug release mechanism based on "n" value

Table: 3.4 Drug release mechanism based on "n" value

S.No.	n value	Drug Release
1.	<0.45	Fickian release
2.	0.45 <n<1.0	Non Fickian release
3.	<1.0	Case II transport
4.	>1.0	Super case transport

3..RESULTS AND DISCUSSION

3.1 Physico Chemical properties of Prazosin Hydrochloride

Table 3.1 Preformulation studies for Prazosin Hydrochloride

S. NO	PARAMETER	OBSERVATION	COMMENT
1	Colour	White crystalline powder	Complies with I.P.
2	Taste and Odour	Pungent	Complies with I.P.
3	Solubility	Freely soluble in methanol	Complies with I.P.
4	pH	6.2	Complies with I.P.
5	Melting point	263^0C	Complies with I.P.

Discussion: All the parameters were complies with the I.P.limits; hence the drug was selected for further formulation development.

3.2 Construction of standard calibration curve

The calibration curve was taken in the range of 5-50 µg/mL for prazosin Hydrochloride at λ_{max} of 246nm. The prazosin was found to be linear within concentration range of 5–50 µg/mL with regression coefficient(R^2) of 0.993 by absorbance ratio method. There was an excellent correlation between absorbance and concentration.

Table 3.2 Calibration curve data of Prazosin Hydrochloride polymeric patches

S.No.	Concentration (µg/ml)	Absorbance
1.	5	0.2771
2.	10	0.3241
3.	15	0.3801
4.	20	0.4534
5.	25	0.5464
6.	30	0.5978
7.	35	0.6713
8.	40	0.7346
9.	45	0.8432
10.	50	0.9294

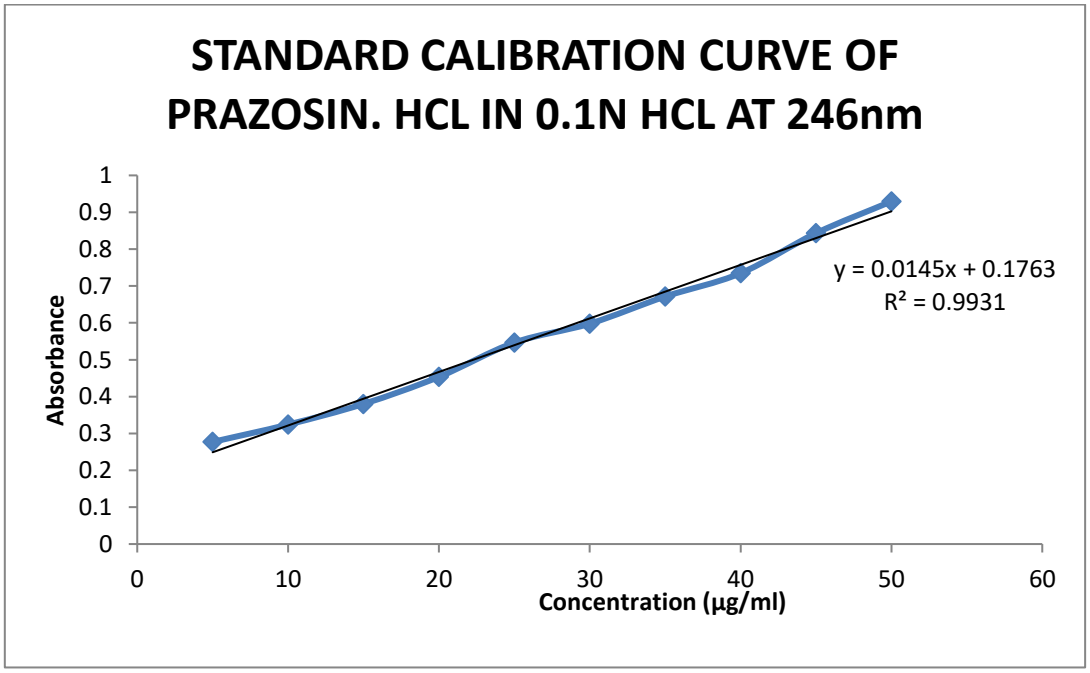

Fig. 3.1 Linearly Regressed Standard Curve of Prazosin Hydrochloride in SGF (pH 1.2) at λ_{max} 246 nm

3.3 THICKNESS UNIFORMITY

Table 3.3 Thickness of Prazosin Hydrochloride in formulation batch F1 to batch F12

Position	Sodium alginate			Carbopol 934P			HPMC : Sodium alginate			HPMC : Carbopol 934P		
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	0.24	0.28	0.29	0.18	0.21	0.26	0.31	0.32	0.32	0.24	0.31	0.32
2	0.28	0.28	0.30	0.20	0.20	0.24	0.30	0.30	0.34	0.26	0.32	0.32
3	0.26	0.30	0.30	0.24	0.22	0.28	0.30	0.31	0.35	0.29	0.30	0.34
Average	0.26 ± 0.02	0.29 ± 0.01	0.30 ± 0.01	0.21 ± 0.03	0.21 ± 0.01	0.26 ± 0.02	0.30 ± 0.01	0.31 ± 0.01	0.34 ± 0.02	0.26 ± 0.03	0.31 ± 0.01	0.33 ± 0.01

Discussion: The thickness of prepared film varied from 0.21±0.03 to 0.34±0.02. Maximum thickness was observed with F9 batch whereas the minimum thickness was of F5 batch which may be due increase in concentration of polymers. There was no significant difference found in thickness between the formulations.

4.4 Uniformity weight

Table 3.4 Weight variations of Prazosin Hydrochloride in formulations batch F1 to batch F12

Patch No.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	39	55	60	41	57	62	40	54	62	42	56	61
2	41	56	62	42	58	61	41	56	60	42	57	60
3	40	58	61	40	56	61	42	58	61	41	58	61
Average	40± 1.00	56± 1.53	61± 1.00	41± 1.00	57± 1.00	61± 0.58	41± 1.00	56± 2.00	61± 1.00	42± 0.58	57± .00	61± 0.58

Discussion: The results for weight uniformity in randomly selected 3 patches from each batch were determined and results are compiled. The weight variation shown with in the limit only.

3.4 Surface pH

Table 3.5 Surface pH of Prazosin Hydrochloride formulation batch F1 to batch F12 for 30minutes

S.No.	Formulation code	Surface pH
1.	F1	3.4 ± 0.2
2.	F2	4.1 ± 0.1
3.	F3	3.7 ± 0.3
4.	F4	3.5 ± 0.2
5.	F5	3.5 ± 0.3
6.	F6	4.0 ± 0.1
7.	F7	3.6 ± 0.1
8.	F8	4.1 ± 0.2
9.	F9	3.5 ± 0.1
10.	F10	4.0 ± 0.1
11.	F11	3.4 ± 0.4
12.	F12	3.5 ± 0.1

Discussion:

Surface pH of all formulation batches of F1 to F12 of films was found to range from pH 3.4 ± 0.4 to pH 4.1 ± 0.2 of acceptable limits. These results revealed that all formulations provided an acceptable pH in the range of stomach pH (2.0 to 3.5) and that they would not produce any local irritation to the mucosal surface. This study also suggested that the polymeric blend identified was suitable for GI application owing to the acceptable pH measurements.

3.4 Folding Endurance

Table 3.6 Folding Endurance of Prazosin Hydrochloride formulation batch F1 to batch F12 for 30minutes

S.No.	Formulation code	Folding Endurance
1.	F1	280± 10
2.	F2	260± 18

3.	F3	240± 11
4.	F4	260± 18
5.	F5	250± 16
6.	F6	290± 17
7.	F7	300± 12
8.	F8	301±22
9.	F9	265± 15
10.	F10	250± 27
11.	F11	310± 17
12.	F12	290± 8

The folding endurance values were found to increase with an optimum concentration of plasticizer. The folding endurance values of matrix films were found to be within 240–310 indicating good strength and elasticity, which is explained by the linear nature of the cellulose structure. The folding endurance measures the ability of patch to withstand rupture. It was found to be satisfactory. The result indicated that the patches would not break and would maintain their integrity when used.

4.7 Flatness

The flatness study results showed that none of the formulations had different strip lengths before and after longitudinal cut, indicating 100% flatness, and thus they could maintain a smooth surface when applied on to the target site.

3.5 Moisture content

Table 3.7 %Moisture content data of Prazosin Hydrochloride formulation batch F1 to batch F12 for 30minutes

S.No.	Formulation code	Moisture content (%) ± SD
1.	F1	2.58±0.049
2.	F2	1.63±0.044
3.	F3	1.17±0.028
4.	F4	2.74±0.012
5.	F5	3.36±0.044

6.	F6	1.38±0.041
7.	F7	2.28±0.024
8.	F8	3.08±0.033
9.	F9	3.46±0.041
10.	F10	2.44±0.012
11.	F11	3.86±0.041
12.	F12	3.17±0.028

All the formulations from batch F1 to batch F12 were evaluated for LOD and found to be in acceptable range of 1%-4%.

3.6 Percentage Swelling index

Table 3.8 Percentage Swelling index data of Prazosin Hydrochloride formulation batch F1 to batch F12 for 30minutes

Time in Min	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
10	0.94	1.50	6.65	3.23	4.31	5.80	2.46	4.25	6.95	3.21	3.55	6.38
20	6.78	9.68	11.86	9.61	12.34	13.66	8.33	9.28	11.86	9.92	12.01	14.49
30	9.66	12.52	11.86	13.02	14.28	14.47	12.77	14.24	14.58	13.26	14.46	14.49

Discussion

Results of the swelling property of the polymeric films against time indicated that the swelling ratio was dependent on the content of each polymer in films. More critical observation was seen in the polymer blend films like Sodium alginate: HPMC and Carbopol 934P: HPMC with the mixing percentage ratio of 2:1. This batch showed the lowest swelling ratio, possible because it had the highest hydrogen bondings among sodium alginate: HPMC and Carbopol:HPMC.

3.7 Drug content uniformity

Table 3.9 Percentage Drug content of Prazosin Hydrochloride formulation batch F1 to batch F12

S.No.	Formulation code	% Assay
13.	F1	98.94
14.	F2	99.95
15.	F3	99.15
16.	F4	98.89
17.	F5	98.45
18.	F6	100.98
19.	F7	99.66
20.	F8	101.12
21.	F9	98.38
22.	F10	98.47
23.	F11	98.56
24.	F12	99.89

Discussion

Polymeric films formulations from batch F1 to batch F12 showed the percent assay for drug content which ranged between 98.38% and 101.12% after 24hrs of study. This range was found to be acceptable for further studies of *in-vitro* evaluations.

4.11 Unfolding behaviour of the films

Films prepared by zigzag methods were evaluated for their *in vitro* unfolding behavior. The films of zigzag manner were unfolded within 15-30 min. Apart from folding pattern, for proper unfolding of a film, mechanical shape memory (resiliency to restore its original shape) is required. Such shape memory polymers may have the glass transition (Tg) at about room temperature. Film integrity of the formulations (F1- F12) primarily depends on the concentration of polymer. Formulations containing above 60% content of polymer, combination of total polymer content provided satisfactory film integrity over 24 hours.. As HPMC K 4M is water soluble polymer, film integrity does not depend on HPMC K 4M content. Polyethylene glycol 400 is the favourable plasticizer to impart elasticity of the polymeric film to allow unfolds satisfactory in the dissolution medium.

***In vitro* drug release study of formulated polymeric films**

Dissolution study was carried out according to the procedure given in 5.6.10.The results was shown in fig no 6.1(F1-F3), 6.2(F4-F6), 6.3(F7-F9) and 6.4(F10-F12). Data for F1-F12 formulations given in table no 6.10.

4. *In vitro* Drug release study

Table 4.1 *In vitro* drug release studies data of Prazosin Hydrochloride formulation batch F1 to batch F12

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	8.88 ± 0.06	7.63 ± 0.29	5.78 ± 0.38	8.62 ± 0.41	7.90 ± 0.51	8.86 ± 1.25	7.78 ± 0.74	8.27 ± 0.10	6.84 ± 0.54	9.22 ± 0.78	8.78 ± 0.82	6.78 ± 0.66
2	17.76± 1.38	15.25± 1.12	14.55± 0.94	17.24± 0.52	15.80± 0.46	17.72± 0.56	15.56± 0.92	16.55± 0.78	14.68± 0.82	18.44± 0.66	17.55± 0.14	14.15± 0.78
3	26.64± 1.89	22.88± 0.35	19.33± 0.76	25.86± 0.29	23.69± 0.42	26.57± 1.62	23.35± 0.08	24.82± 1.89	21.53± 0.66	27.66± 1.12	26.33± 0.14	18.33± 0.54
4	35.52± 0.07	30.50± 0.25	29.11± 1.02	34.48± 1.68	31.59± 1.78	35.43± 1.93	31.13± 0.84	33.10± 0.08	29.37± 2.15	36.89± 0.34	35.11± 1.54	30.11± 0.10
5	44.41± 1.98	38.13± 0.21	36.88± 1.88	43.09± 0.18	39.49± 0.24	44.29± 1.79	38.91± 1.56	41.37± 0.06	35.21± 1.12	46.11± 0.74	43.88± 1.98	38.88± 1.85
6	53.29± 0.36	45.75± 0.48	42.66± 1.56	51.71± 0.38	47.39± 0.11	53.15± 0.36	46.69± 1.12	44.65± 1.95	45.05± 0.54	55.33± 0.10	52.66± 0.54	50.66± 0.74
7	71.05±	61.01±	58.22±	68.95±	63.18±	60.86±	58.26±	52.20±	54.74±	63.77±	60.22±	58.48±

	1.22	1.34	0.66	0.09	1.46	0.56	1.54	0.10	1.27	0.66	1.12	0.34
8	88.81± 0.52	76.26± 0.52	67.77± 1.34	76.19± 1.42	78.98± 1.16	71.58± 0.46	67.82± 0.34	56.75± 0.48	64.42± 0.14	72.22± 0.82	67.77± 0.78	64.77± 0.82
12	95.70± 0.46	89.80± 0.48	72.40± 0.72	84.30± 1.21	81.20± 1.28	82.90± 1.39	76.70± 0.74	68.70± 0.13	71.30± 0.34	84.90± 0.10	81.70± 0.54	74.40± 1.12
16	99.89± 0.56	94.34± 0.88	85.32± 0.48	92.56± 1.26	89.22± 1.68	90.12± 1.08	82.48± 0.54	81.44± 0.42	80.26± 0.96	93.98± 0.78	89.68± 0.66	84.32± 0.66
20	--	99.12± 0.14	88.24± 0.37	98.32± 1.62	96.56± 0.68	94.12± 1.25	86.88± 1.12	93.24± 0.32	84.92± 0.66	95.22± 0.34	92.64± 0.82	89.24± 0.74
24	--	--	92.34± 1.54	--	--	93.36± 1.48	92.56± 0.10	98.56± 0.78	91.42± 0.74	97.64± 0.2	95.58± 0.14	93.34± 1.12

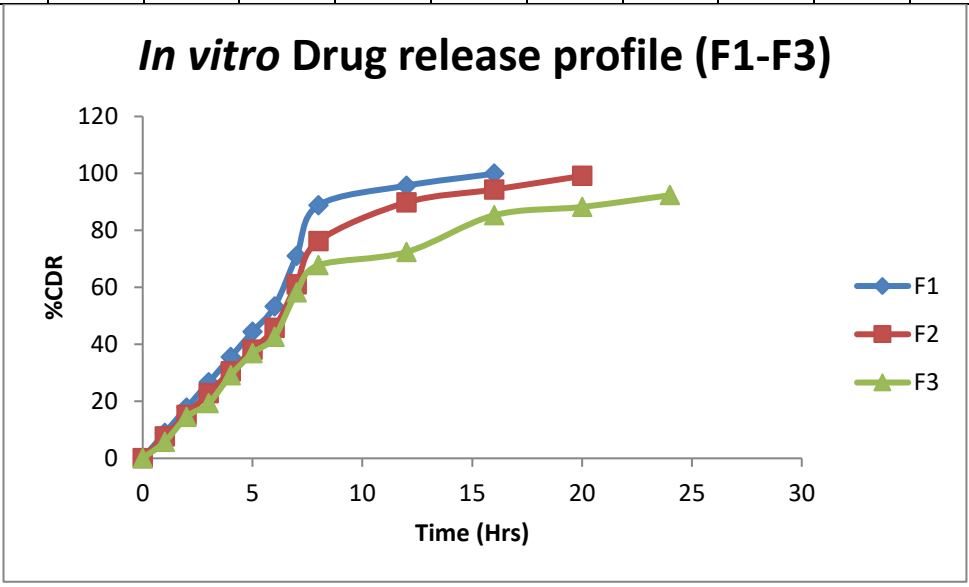

Fig. 4.1 *In vitro* drug release profile of formulation F1 – F3

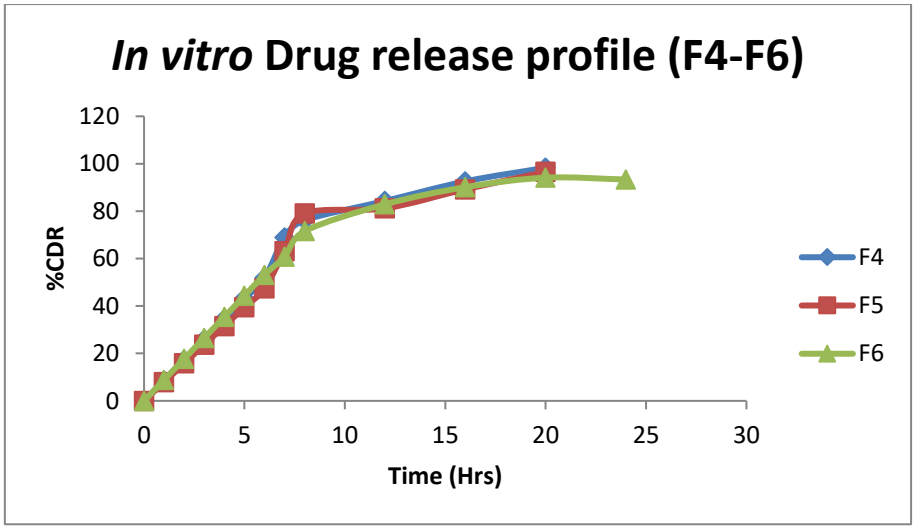

Fig. 4.2 *In vitro* drug release profile of formulation F4 – F6

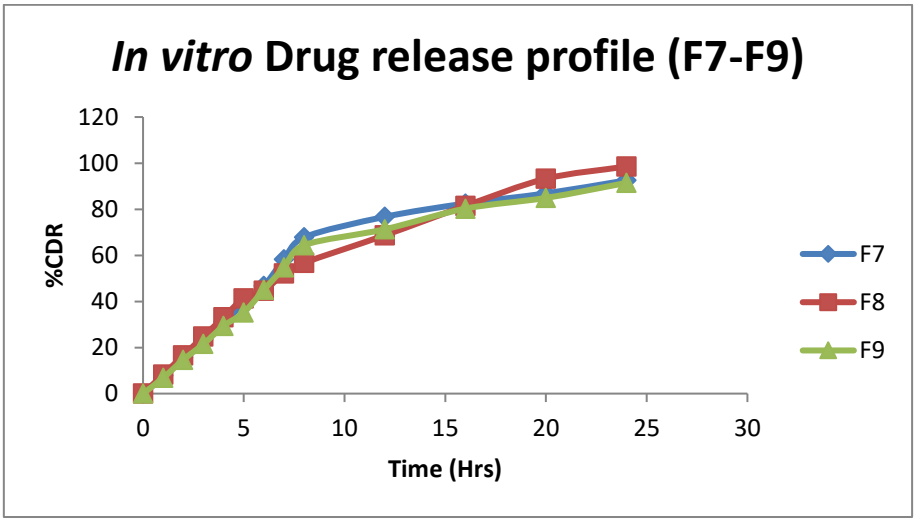

Fig 4.3 *In vitro* drug release profile of formulation F7 – F9

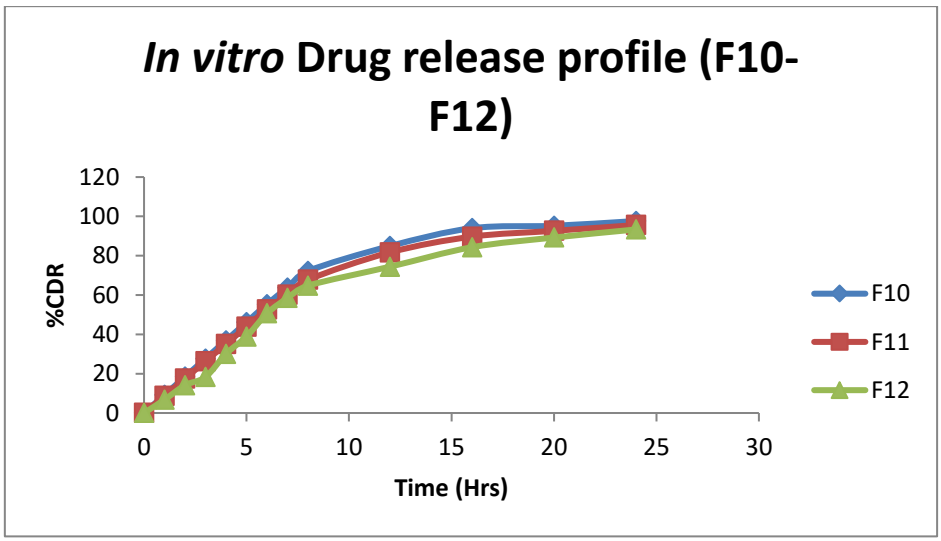

Fig 4.4 *In vitro* drug release profile of formulation F10 – F12

Discussion

The formulated polymeric films were then subjected to *In vitro* dissolution test for evaluating drug release from the formulation. The *In vitro* dissolution test was carried out in 900 ml of 0.1 N HCL in USP type-I basket type apparatus at 50 rpm and 37±0.5oC. The results of dissolution study was depends on polymer concentration. Formulation containing sodium alginate alone (F1,F2 & F3) released fastly compared to that of Carbopol 934P alone (F4,F5,F6) due to the less binding nature and controlled release property.

Formulation F1 to F3 contains sodium alginate alone, Formulation F4 to F6 contains carbopol 934P polymer only, Formulation F7-F9 contains combination of Sodium alginate and HPMC K4M with different ratios and Formulation F10-F12 contains combination of carbopol 934P and HPMC K4M with different ratios.

Formulation F1 released drug 99.89% in 16 hrs only, Formulation F2 released drug 99.12% in 20 hrs only, Formulation F3 released drug 92.34% in 24 hrs, Formulation F4 released drug 98.32% in 20 hrs only, Formulation F5 released drug 96.56% in 20 hrs only, Formulation F6 released drug 93.36% in 24 hrs, Formulation F7 released drug 92.56% in 24 hrs, Formulation F8 released drug 98.56% in 24 hrs, Formulation F9 released drug 91.42% in 24 hrs, Formulation F10 released drug 97.64% in 24 hrs, Formulation F11 released drug 95.58% in 24 hrs and Formulation F12 released drug 93.34% in 24 hrs.

Formulation F8 containing sodium alginate (5 mg) and HPMC k4M (3.75 mg) had given drug release 98.56% in 24 hrs. Then the formulations containing sodium alginate and HPMC K4M were given better release profiles when compared with formulations containing Carbopol and HPMC K4M.

4.2 Kinetic Studies of Prazosin Hydrochloride Films

Table 4.2 kinetic study of optimized formulation F8

Time (hrs)	Log Time	√Time	cumulative % drug release	Log cumulative % drug release	Log cumulative % drug remained
0	0.000	0.000	8.27	0	2.000
1	0.000	1.000	16.55	0.918	1.963
2	0.301	1.414	24.82	1.219	1.921
3	0.477	1.732	33.1	1.395	1.876
4	0.602	2.000	41.37	1.520	1.825
5	0.699	2.236	44.65	1.617	1.768

6	0.778	2.449	52.2	1.650	1.743
7	0.845	2.646	56.75	1.718	1.679
8	0.903	2.828	68.7	1.754	1.636
12	1.079	3.464	81.44	1.837	1.496
16	1.204	4.000	93.24	1.911	1.269
20	1.301	4.472	98.56	1.970	0.830
24	1.380	4.899	8.27	1.994	0.158

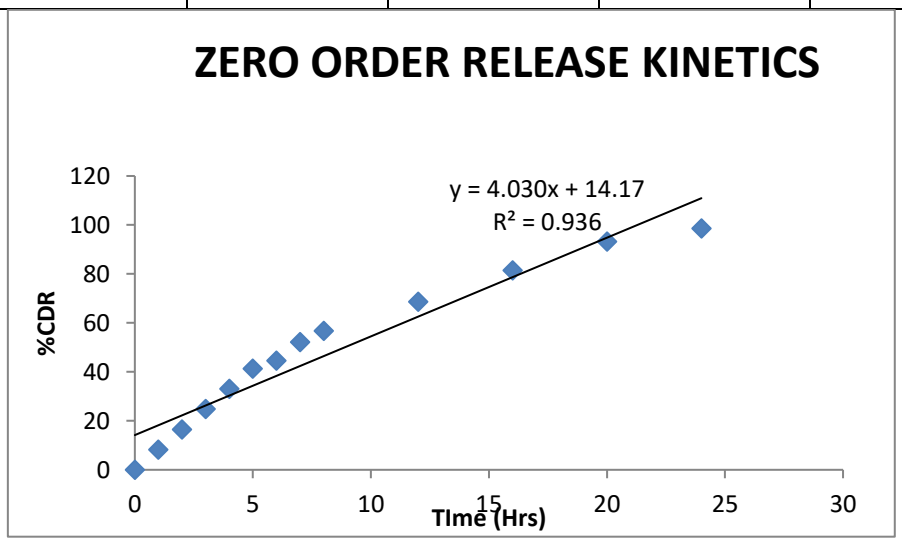

Fig. 4.5 zero order plot

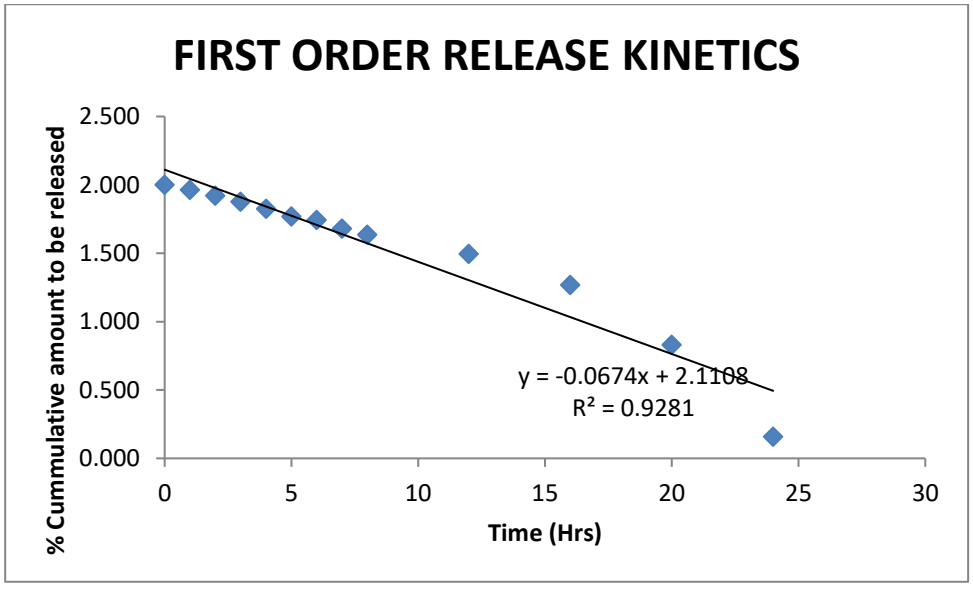

Fig. 4.6 First Order plot

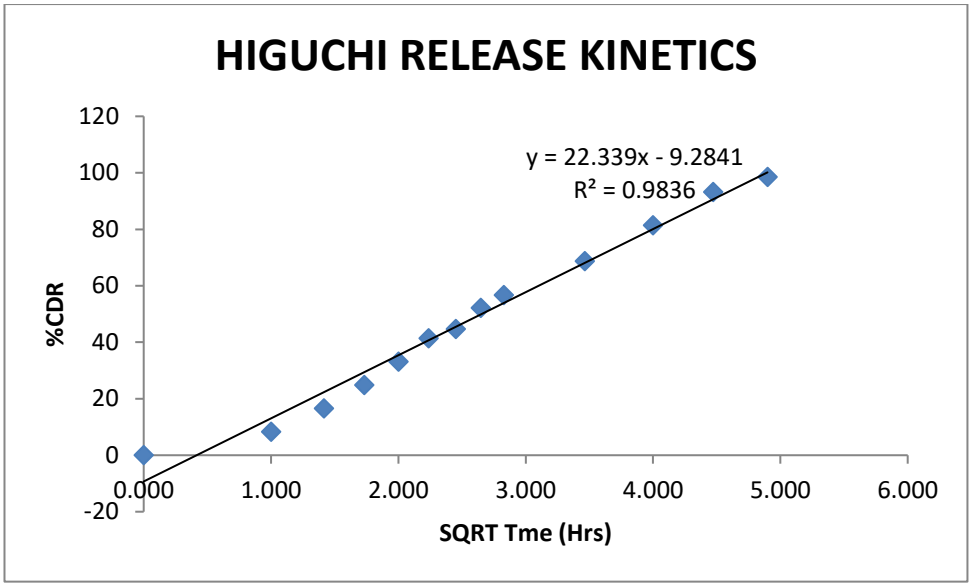

Fig. 4.7 Higuchi plot

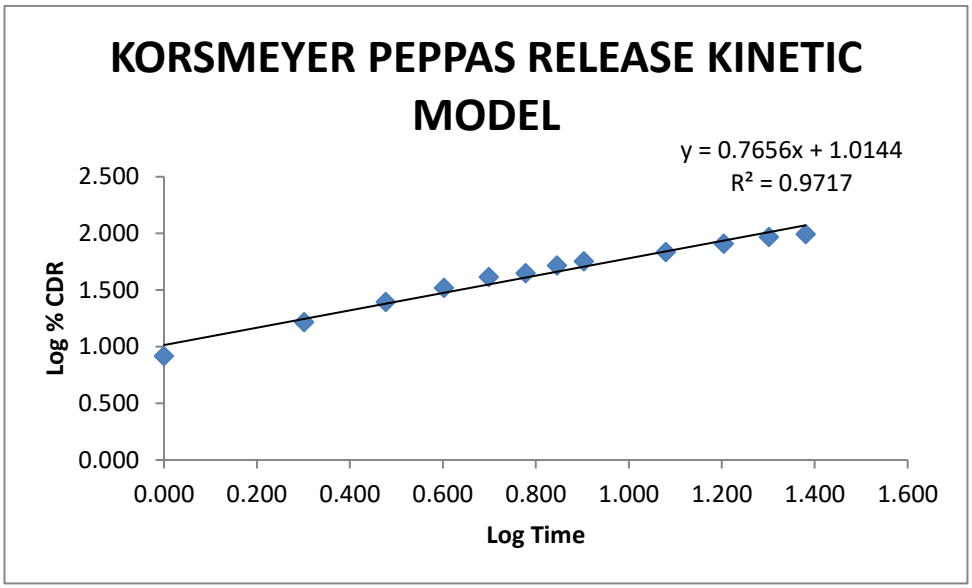

Fig. 4.8 Koresmeyer Peppas plot

Table 4.3Compression of r^2 values of different release kinetic profiles

Formulation	Correlation Coefficient values r^2				
	Zero Order	First Order	Higchi	Korsmeyer Peppas	Peppas 'n' value
F8	0.936	0.928	0.983	0.971	0.573

Discussion

In order to determine the mechanism of drug release form the formulations , the *In vitro* dissolution data was fitted to Zero order, First order, Higuchi plot and Korsemeyer-peppa's plot was drawn and interpretation of release exponent value (n) was calculated and results are shown in tables 24-25; figs 23-26. The results of r^2 for zero and first order were obtained as 0.936, 0.928. Based on that we confirmed that the optimized formulation followed zero order release. The drug release was diffusion controlled as the plot of optimized formulation F8 was found 0.983 as regression coefficient in Higuchi plot. From korsemeyer peppa's plot the release exponent value n was found as 0.573 and it was confirmed as the release of drug from the formulation was founded as anomalous non-fickian transport of diffusion. 'n' value between 0.45 to 0.89 it follows non fikain model.

5. SUMMARY AND CONCLUSION

Gastroretentive mucoadhesive film of Prazosin Hydrochloride has been developed using solvent casting method to provide a control release action to treat hypertension. All films prepared were smooth and elegant in appearance and showed no visible cracks. Thus gastroretentive dosage form (GRDF) for controlled release of Prazosin Hydrochloride has been developed and characterized for improved bioavailability. It consists of a drug loaded polymeric film, folded into a hard gelatin capsule. Thickness and Folding endurance of optimized formulation was 0.31±0.01 mm and 301±22 times; the folding endurance increased with an increase in HPMC K4M and presence of PEG400. Effect of HPMC K4M and PEG 400 on folding endurance was showed positive effect. Uniformity of weight, pH and drug content was obtained up to 56±2.00 mg;4.1±0.2 and 101.12% respectively moisture content was; mg;3.08±0.033% and swelling index was 14.24% after 30 minutes; the swelling index was directly proportional to the amount of polymers.

The complete unfolding action was obtained within 90 min and drug release was obtained up to 98.56 % in 24 hrs because increased amounts of HPMC K4M retard the drug release up to some extent but presence of sodium alginate might be extend drug release with R^2 =0.936 and showing non- Fickian transport diffusion mechanism (0.45 > n <0.89 i.e 0.573). The optimized film formulation batch F8 showed satisfactory controlled release in the development of GRDF were safe and proper combination of polymers will yield a novel expandable GRDF with good dissolution of the film. and 101.12% respectively. Moisture

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