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Formulation and evaluation of alfuzosin hydrochloride extended release tablets

Pradnya Zine
zine.pradnya@gmail.com
AISSMS College of Pharmacy, Pune, Maharashtra

Dr. Ashwini Madgulkar
armadgulkar@gmail.com
AISSMS College of Pharmacy, Pune, Maharashtra

Dr. Mangesh Bhalekar
mrbhalekar@gmail.com
AISSMS College of Pharmacy, Pune, Maharashtra

ABSTRACT

Purpose The aim of the study was to design extended release tablets capable of producing a 20 h extended release profile there by eliminating the use of immediate release tablets which require a frequent administration of three tablets containing 2.5 mg of alfuzosin hydrochloride of the daily dose. The present study deals with the formulation of Alfuzosin Hydrochloride extended release tablets. Benign prostatic hyperplasia is a noncancerous prostate problem in which the normal elements of the prostate gland grow in size and number, requires an alpha-adrenergic blocker which is having optimum therapeutic window concentration for a prolonged duration. With the above characteristics, Alfuzosin Hydrochloride was selected as an active therapeutic agent. Methods. Alfuzosin HCl extended release matrix tablets were prepared by direct compression method by employing hydrophilic polymer HPMC K 100 M and Crosslinked Xyloglucan (XG). The crosslinked XG was prepared by crosslinking of natural polysaccharide that is XG with crosslinking agent Sodium Trimetaphosphate (STMP). Simplex centroid design was applied for the optimization process. The prepared tablets were evaluated for various physicochemical parameters by official procedures. The in-vitro release study of matrix tablets was carried out in 0.01N HCl for 24 hours. Results. The tablets exhibited acceptable physicochemical characteristics and extended drug release pattern was observed for about 20h. Analysis of drug release data from the matrix system indicated that the drug release follows zero order kinetics by anomalous (non-fickian) diffusion. Conclusion. The crosslinked XG along with HPMC K 100M and DCP showed the potential for prolonged delivery of Alfuzosin over a 20 h period and therefore may be a suitable candidate for use in sustained release drug delivery system.

Keywords— *Immediate release, Alfuzosin, Crosslinked, Xyloglucan, Sodium trimetaphosphate*

1. INTRODUCTION

Hydrophilic gums have been used as matrix former in several sustain release delivery systems (Sumathi and Ray 2002). Xyloglucan (XG is natural polysaccharide obtained from seeds of Tamarindus indica, also known as tamarind seed polysaccharide. Crosslinking is the process of joining two or more molecules by covalent bond linkage through a chemical treatment. It reduces the hydrophilicity of the gums thereby decreasing the diffusion of the drug from the matrix rendering it to be used as a release retardant (Albhar et al 2012). Various cross linking agents have been reported in literature to reduce the drug release from tablets and microspheres (Sumathi and Ray 2002) The different crosslinkers such as glutaraldehyde have been reported but all these have toxicity, Sodium Tri Metaphosphate (STMP) is a biocompatible cross linker used widely in food and pharmaceuticals (Reddy et al 2012).

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Alfuzosin HCl is a selective antagonist of post-synaptic alpha -adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra. Alfuzosin is indicated for the treatment of benign prostatic hyperplasia.

(Beduschi et al 1998).The SR dose of Alfuzosin is 10 mg once daily. Formulation situations where the performance characteristics of formulations are dependent on the relative proportion of ingredients, Simplex centroid is used to optimize the proportion of ingredients which would give desired attributes to the formulations. This study attempts to formulate a matrix tablet of alfuzosin containing HPMC, Crosslinked Xyloglucan and Dicalcium Phosphate (DCP) whose proportions are optimized by simplex centroid design matrix to achieve once day release. This work includes the use of crosslinked XG, HPMC K100M and DCP to prepare the sustained release tablets and application of Simplex Centroid Mixture design to obtain the optimum formulation.

2. MATERIALS AND METHODS

Alfuzosin HCl was obtained from Cipla Ltd, Patalganga, India. XG was obtained as a gift sample from Encore polymer Pvt Ltd. Ahmadabad. STMP was purchased from Sigma Aldrich chemistry. All other chemicals used in the study were of analytical grade

3. PREPARATION AND EVALUATION OF ALFUZOSIN HCl ER TABLETS

The matrix tablets of Alfuzosin were prepared by direct compression by combining with HPMC K100M, crosslinked XG and DCP. A simplex centroid experimental design matrix was set up to find the optimum concentration of the above-mentioned ingredients (figure 1). Seven batches that is (S1 to S7) were prepared as a trial run to optimize the drug release at 2 h, 7th h and 20th h (Table I). The proportion of all other excipients such as lubricant, glidant was kept the invariant and the total weight of tablet was fixed at 200 mg. The tablets were compressed using 8mm concave punches on a Rimek Mini Press-II tablet compression machine. The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. The hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator by rotating at 25 rpm for 4 min. The thickness of the tablets was measured by vernier caliper. (Lachmann et al 1991 and IP 2007).

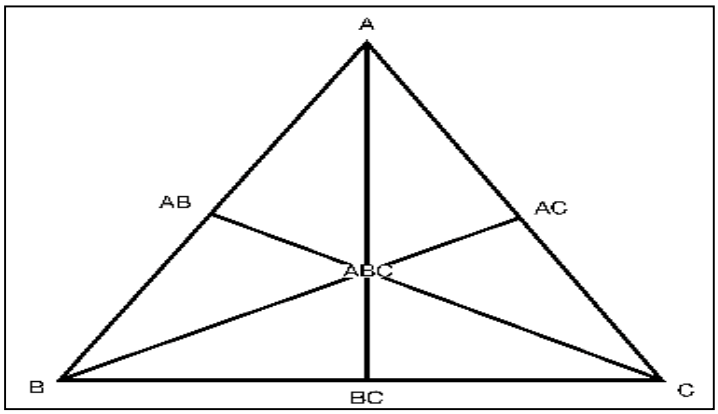

Fig. 1: Simplex lattice design for 3 components (A, B, C)

Table 1: Coded levels and their corresponding actual values of ingredients

Coded Level	Actual Values (mg)		
	Crosslinked XG (A)	HPMC K100M (B)	DCP (C)
0	0	0	0
0.33	61.66	61.66	61.66
0.5	92.5	92.5	92.5
1	185	185	185

Table 2: Composition of S1 to S7 formulations

Ingredients	Formulations						
	S1	S2	S3	S4	S5	S6	S7
Alfuzosin HCl	10	10	10	10	10	10	10
Crosslinked xyloglucan	0	185	0	92.5	0	92.5	61.66
HPMC K 100M	185	0	0	92.5	92.5	0	61.66
DCP	0	0	185	0	92.5	92.5	61.66
Talc	3	3	3	3	3	3	3
Magnesium Stearate	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200

All quantities in mg, qs= quantity sufficient, HPMC K100M = Hydroxypropyl methyl cellulose grade K100M, DCP = Dicalcium phosphate

3.1 In-vitro drug release study

(Chandana 2011, Nicholas and Karunakar 2011, Chin-Yang and Jun-Woo 2010, Roni et al 2009 and Satyanarayana et al 2011)**:** The samples were carried out using USP – type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml of 0.01N HCl, was placed into the dissolution flask maintaining the temperature at 37±0.5 ^{0}C and rpm at 100. The aliquots were collected at the hourly interval for 24 hours. The same quantity of fresh dissolution medium was replaced every time the sample was withdrawn. The Collected samples were filtered and analyzed at 245 nm using 0.01 N HCl as blank. The percent drug release was calculated using PCP Disso v3 software. The dissolution data obtained were subjected to kinetic analysis using PCP Disso V2.08 software (Poona College of Pharmacy, Pune).

3.2 Optimization of formulation

The data obtained from dissolution experiments were used to generate a polynomial equation for response drug release at 2h, drug release at 7 h and drug release at 20 h. The 3D response surface was generated using provisions of Design Expert 8. 0. 7.1

3.3 In vivo studies (Arkhel et al 2011, Patel.and Patel 2009)

The quantitative estimation of the drug in plasma was performed by HPTLC assay using Toluene methanol and triethylamine mixture in a ratio of 7:3:0.2 v/v as mobile phase. The optimized formulation and marketed tablet were subjected to *in vivo* studies using rabbits fasted for 12 h (weighing 2.8-3.2 kg). The tablets were administered orally using a hollow tube. The rabbits had free access to water throughout the study. The study was approved as per the CPCSEA guidelines for the care and use of laboratory animals (CPCSEA/IAEC/PT- 09/12-2K12**)**. The blood samples were collected from marginal ear vein, in EDTA tubes and were centrifuged at 5000 rpm for 10 minutes. The supernatant was collected and precipitated using acetonitrile in the ratio of 1:2 v/v and was further centrifuged at 5000 rpm for 10 minutes. The supernatant was collected, filtered and stored under deep freezer for further analysis.

4. RESULTS AND DISCUSSION

4.1 Preparation of crosslinked Xyloglucan

As XG does not contain any phosphate group in its structure, the typical stretching vibrations of P=O and P-O (at about 1200-1100/cm) were observed in the Crosslinked product and also bands assigned to hydroxyl stretching vibration (3400) in XG were decreased in intensity after the crosslinking reaction in the Crosslinked product.

The studies regarding the use of xyloglucan as release retardant matrix are reported [18] but it is observed that xyloglucan has to be combined with polymers like HPMC to sufficiently retard the release. Ray S et al reported the use of XG crosslinked with epichlorhydrin as release retardant. The use of STMP as a cross linker in pharmaceutical carriers has been widely reported in the literature, additionally, its biocompatibity makes it more suitable for use in pharmaceutical systems. The mechanism involved in the synthesis of crosslinked xyloglucan is a reaction between "OH" groups and metaphosphate groups in STMP leading to "O-P-O" linkages in between two xyloglucans moieties[15, 16]. Our studies reported as another publication concluded that crosslinked xyloglucan alone could retard the drug release up to 12 h. Since OD formulations offer better patient compliance it was decided to combine crosslinked XG with HPMC K100 M to achieve desired drug release attributes.

4.2 Preparation and evaluation of Alfuzosin HCl ER tablets

The tablets were prepared and evaluated for the parameters such as Hardness, friability, uniformity of weight, drug content and thickness. Prepared tablets had satisfactory tablet characteristics such as hardness between 4.5 to 6 kg/cm^{2,} friability was less than 1% and drug content between 95.23 to 101.30 % as shown in table 3.

Table 3: Evaluation of S1 to S7 Formulations

Batch code	Hardness (kg/cm^2)	Friability (%)	Uniformity of weight (mg)	Drug content (%)	Thickness (mm)
S1	6.1	0.34 ±0.22	201.2±1.6	95.23 ± 0.67	4.38±0.025
S2	4.5	0.31 ±0.12	200±0.98	99.30 ± 0.35	3.26±0.03
S3	4.5	0.28 ±0.31	200.5±1.1	101.30 ±0.35	2.41±0.01
S4	5.5	0.35 ±0.18	200.45±0.95	98.44 ± 0.83	3.84±0.05
S5	6	0.29± 0.27	201.7±1.15	97.34 ± 0.50	4.24±0.025
S6	4.5	0.28 ±0.52	201.3±2.23	99.65 ± 0.20	2.77±0.032
S7	5	0.33± 0.71	200±1	98.10 ± 0.18	3.13±0.015

4.3 In-vitro drug release study

The desired drug release at selected time points for the formulation was decided to be 13 to 33 % at 2h, 40 to 60% at 7h and >80% at 20h according to the patent [17]. The release at 2 h for all formulations was between 15.41 to 40.79 % and formulations S1, S2, S4, S5 and S7 showed the release within the desired range. S3 and S6 showed burst release which may be due to the absence of HPMC in these formulations. Release at 7th h was between 42.41to 84.23% the formulation S1, S2, S4 showed the desired drug release due to the presence of either HPMC or Crosslinked XG or both. The release at 20th h was between 93.66 to 100%, such release was exhibited by all formulations except S3 as it contained only DCP. It had shown the faster release of drug as compared to other formulations but the drug release was not properly controlled as 100% drug was released in about 9 h. The batches S2, S5, S6 and S7 showed about 100% release within 20 hs. Drug release was comparatively slower in batches S1 and S4 in comparison with the above batches. The S1 batch (containing only HPMC K100 M) and S4 batch (containing both crosslinked xyloglucan and HPMC K100 M) showed 95.89% and 93.66% release at 20th h. The rigid nature of HPMC, as well as crosslinked xyloglucan, could render it to sustain the drug release upto 20 h. The release of the drug depends not only on the nature of matrix but also upon the drug-polymer ratio, this is due to changes in the structural reorganization, tortuosity or gel strength of hydrophilic polymers. Failure to generate a uniform and coherent gel may cause rapid drug release. The drug release kinetics from formulation S2 belonged to Peppas model, S3 followed matrix model, S6 followed first order while formulations S1, S4, S5, S7displayed release kinetics described by Hixon Crowell equation. All the batches containing HPMC are known to follow Hixon Crowell model which indicates a change in surface area and diameter of tablets with the progressive dissolution of the matrix as a function of time (Shoaib et al 2006). These results indicate that the drug release kinetics from formulation containing crosslinked XG (S2) in higher proportion followed Peppas model, formulation containing a high proportion of DCP (S3) followed Matrix dissolution

model, formulation S6 containing crosslinked XG and DCP followed first order release kinetics while the formulations containing HPMC (S1, S4, S7, S5) followed Hixon Crowell model.

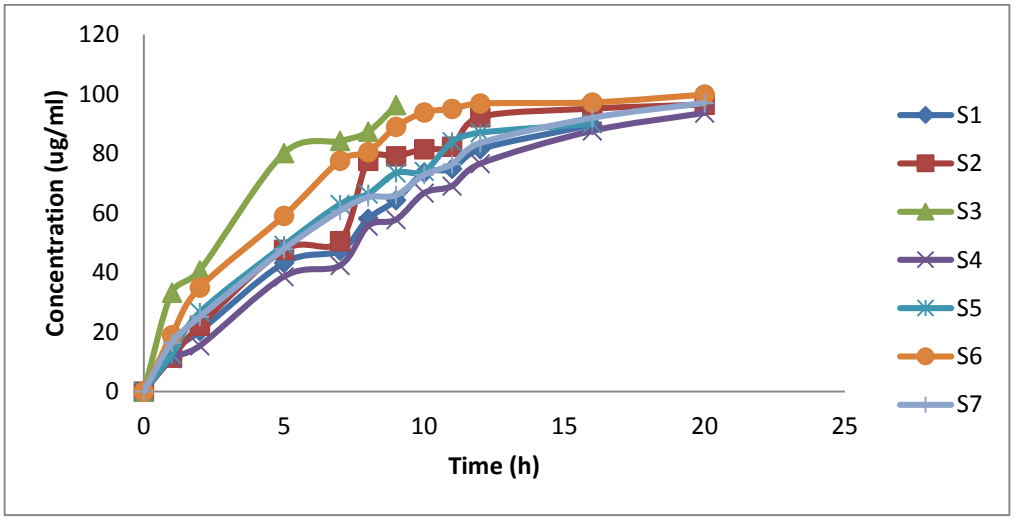

Fig. 2: Dissolution profile of batches S1 to S7

Table: 4 Kinetic values obtained from different plots of formulation S1 to S7

Formulation code	Release exponent (n)	Kinetic constant (k)	R	Best fit model
S1	0.6953	13.3854	0.9940	Hixon Crowell
S2	0.7563	13.0569	0.9782	Peppas
S3	0.4742	34.1669	0.9942	Matrix
S4	0.7713	10.4847	0.9956	Hixon Crowell
S5	0.6975	14.5862	0.9896	Hixon Crowell
S6	0.5792	22.4309	0.9855	First order
S7	0.6202	17.0840	0.9962	Hixon Crowell

4.4 Optimization of formulation

Simplex centroid mixture design is selected for optimization of excipients proportions when there are more than two variables. In this design, all the factors are studied in all the possible combinations, as it is considered to be most efficient in estimating the influence of individual variables (main effects) and their interactions, using minimum experimentation. The amounts of matrixing agent Crosslinked xyloglucan (A), gelling agent HPMC K100M (B) and dicalcium phosphate (DCP, C) were selected as independent variables. Percent release of drug at the second hour, seventh hour and twentieth hour were selected as dependent variables. To optimize the formulation the acceptance criteria set was as follows, percent drug release at two hours (rel 2 h) between 13 to 33%, percent drug release at 7 hours between 40 to 60% and percent release at 20th hour should be more than 85% according to the patent (M.Fischer et al 2006).

Statistical optimization was carried out in design expert software (version 8.0.7.1), In order to find out the contribution of each component and their interaction, Analysis of Variance (ANOVA) for Quadratic mixture model was carried. Table 6 shows the results of the ANOVA, which was used to generate mathematical models.

Table: 5 Values of Various Response Variables for Tablets

Formulation code	The concentration of HPMC K100 M (A)	The concentration of crosslinked polymer (B)	Concentration of DCP (C)	% release at 2nd h	% release at 7th h	% release at 20th h
S1	185	0	0	20.34	47.41	95.89
S2	0	185	0	22.21	50.56	96.45
S3	0	0	185	40.79	84.23	100
S4	92.5	92.5	0	15.41	42.17	93.66
S5	92.5	0	92.5	26.66	62.95	98.22
S6	0	92.5	92.5	34.97	77.64	99.82
S7	61.66	61.66	61.66	25.15	60.76	97

Table 6: ANOVA for selected statistical models

Response model	Rel_2 h	Rel_7 h	Rel_{20} h
Sum of Squares	457.11	1468.37	30.52
Degree of Freedom	5	5	5
Mean Square	91.42	293.67	6.10
Model F Value	5155.19	9691.23	378
P Value	0.0106	0.0077	0.0390
R Square	1	1	0.9995

4.5 Percent drug release at 2nd h (18)

The % drug release at 2nd h ranges from 15.41 to 40.79. Model adequacy was checked for percent drug release at the second hour (rel_2 h). The model which gave the highest order polynomial where the additional terms were significant was selected which suggested that polynomial equation derived to describe release at two hours followed a quadratic model with a p-value of 0.01, the model F-value of 5155.19 implied there is only a 1.06% chance that "Model F-value" this large could occur due to noise. Values of "Prob>F" less than 0.500 indicate model terms are significant.

The equation for percent drug release at the end second hour:

% release at 2nd h

$$Y1 = +0.11 * A + 0.12 * B + 0.22 * C - 6.78 * A * B - 4.50 * A * C + 4.12 * B *$$

Where A is HPMC K100 M, B is Crosslinked xyloglucan, C is DCP and Y1 is % release at 2nd h

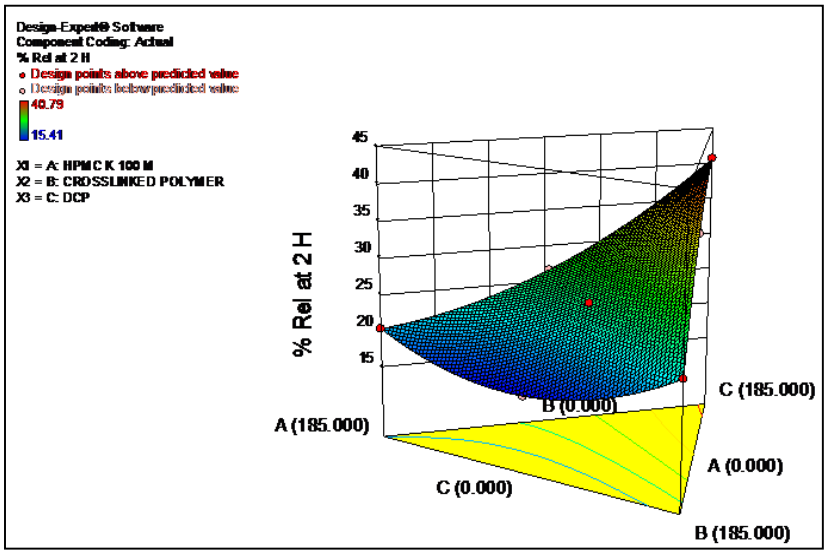

Fig. 3: 3-D response surface for % rel at 2nd h

4.6 Percent drug release at 7th h (18)

The % drug release at 7th h ranges from 42.17 to 84.23. Model adequacy was checked for percent drug release at seventh hour (rel_7 h). The model which gave highest order polynomial where the additional terms were significant was selected which suggested that polynomial equation derived to describe release at 7th h followed Quadratic model with a p-value of 0.0077, model F-value of 9691.23 implied the model was highly significant. There is only a 0.77% chance that "Model F-value" this large could occur due to noise. Values of "Prob>F" less than 0.500 indicate model terms are significant

The equation for percent drug release at the end seventh hour:

% rel at 7th h

$$Y2 = 47.42 * A + 50.60 * B + 84.24 * C - 27.56 * A * B - 11.78 * A * C + 40.67 * B * C$$

Where A is HPMC K100 M, B is Crosslinked xyloglucan, C is DCP and Y2 is % release at 7th h

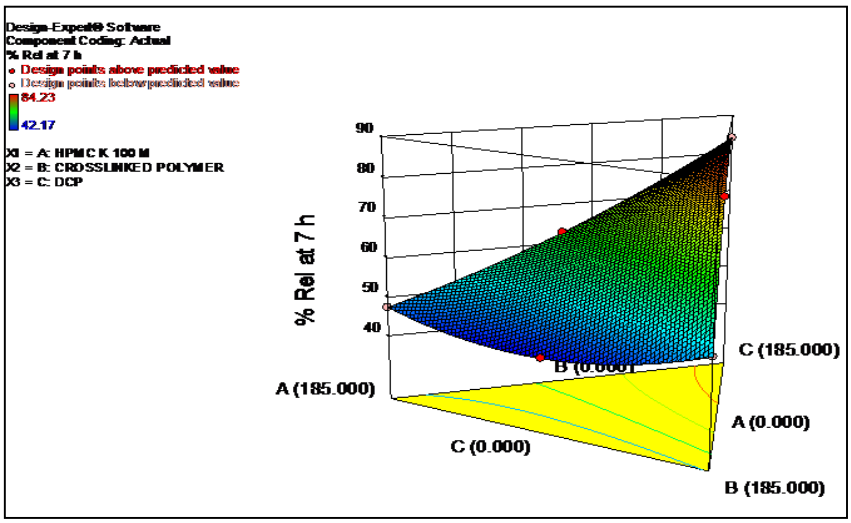

Fig. 4: 3-D response surface for % rel at 7th h

4.7 Percent drug release at 20th h (18)

The % drug release at 20th h ranges from 93.66 to 100. Model adequacy was checked for percent drug release at a twentieth hour (rel_{20} h). The model which gave highest order polynomial where the additional terms were significant was selected which suggested that polynomial equation derived to describe release at 20th h followed Quadratic model with a p-value of 0.0390, the

model F-value of 378.00 implied the model was highly significant. Value of p less than 0.05 indicates model terms were significant. There is only a 3.90% chance that "Model F-value" this large could occur due to noise. Values of "Prob>F" less than 0.500 indicate model terms are significant.

The equation for percent drug release at the end twentieth hour:
% rel at 20th h

$$Y3 = 95.90 * A + 96.46 * B + 100.01 * C - 10.26 * A * B + 0.88 * A * C + 6.16 * B$$

Where A is HPMC K100 M, B is Crosslinked xyloglucan, C is DCP and Y3 is % release at 20th h

The data clearly indicate that the values of drug release are strongly dependent on the selected independent variables. To demonstrate the effect of release-modifying polymers on the dissolution profile graphically, 3D response surface was generated. For % release at 2nd h as the concentration of crosslinked xyloglucan and HPMC K100 M increases the % drug release decreased signifying that the polymers have definite effect on drug release specially along the axis region of HPMC K100M and crosslinked XG the release was least at 1:1 ratio and increased slightly as the HPMC or Crosslinked XG concentration increased, while the DCP had effect of increasing the release in combination with any of other two polymers in all proportions (as shown in figure 3).

Almost similar results were observed with a 3D graph (as shown in figure 4) for rel$_7$ h. Here as the concentration of crosslinked xyloglucan and HPMC K100 M increased release retardation effect also increases due to increase in the diffusion path length and DCP is showing its effect at lower concentration but not in higher concentration.

For % release at 20th h (figure 5), the contribution of HPMC K100 M or Crosslinked XG towards release retardation is less promising than when both used in combination. They in combination tend to decrease the drug release whereas DCP does not show any prominent effect to retard the drug release.

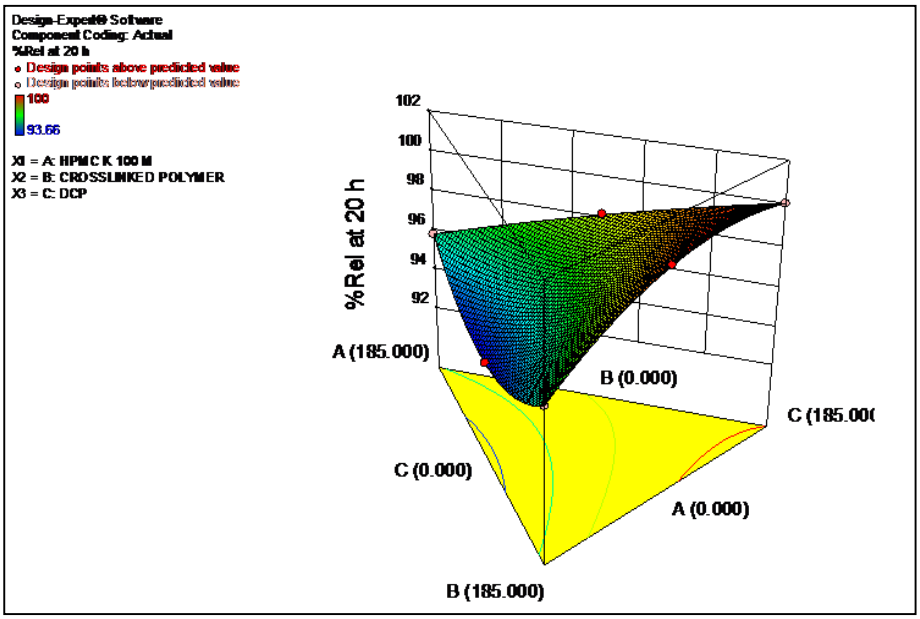

Fig. 5: 3-D response surface for % rel at 20th h

Based on acceptance criteria and desirability factor Design Expert suggested three optimum formulations, O1, O2, and O3. The value of desirability closest to 1 is considered most favorable. The value of desirability for three optimized formulation O1, O2, O3 were 0.938, 0.937 and 0.640 respectively. The optimum formulations were selected based on the criteria of attaining complete and sustained drug release.

Table 7: Composition of optimized batches

Batch Code	Composition			Response	Predicted Value	Experimental Value	% Error
	A	B	C				
O1	100.01	84.987	0.000	Y1 Y2 Y3	15.41 40.02 93.60	15.32 42 93.25	-0.09 1.98 -0.35
O2	92.500	92.500	0.000	Y1 Y2 Y3	15.42 42.10 93.61	15.39 41.28 93.64	-0.03 -0.82 0.03
O3	185.0	0.000	0.000	Y1 Y2 Y3	20.32 47.42 95.90	20.34 47.48 95.82	0.02 0.06 -0.08

Table 7 lists the compositions of the optimized formulations, the predicted and experimental values of all response variables, and the percentage error in prognosis.

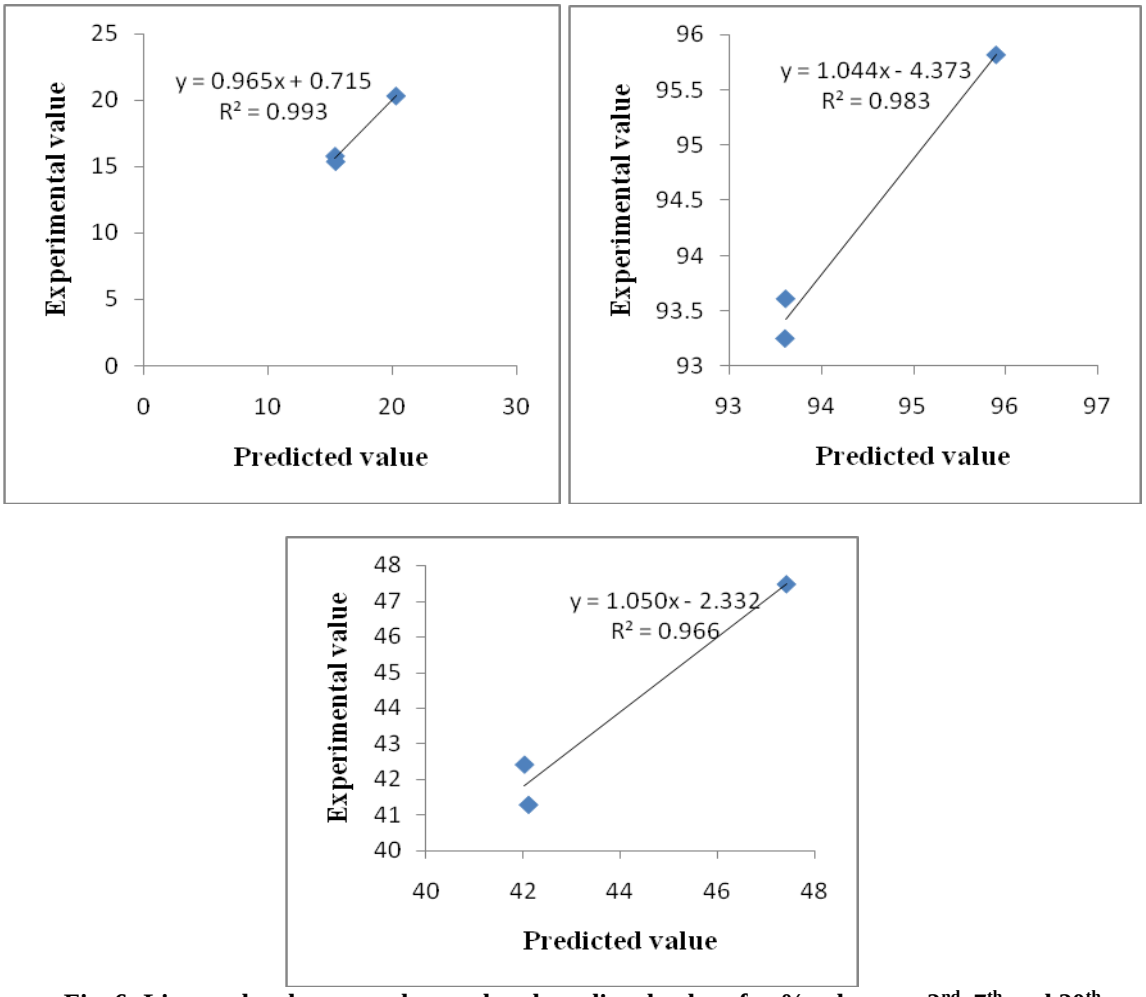

Fig. 6: Linear plots between observed and predicted values for % release at 2nd, 7th and 20th hr

The linear correlation plots drawn between the predicted and observed responses in figure 6 demonstrated higher values of R^2 (ranging between 0.993, 0.972 and 0.979) and equation for % release at 2nd h, 7th h and 20th h was found to be y = 0.965x + 0.715, y= 1.045x - 2.176 and y= 1.064x - 6.193 respectively indicating excellent fit of model (P<0.001). Upon comparison of the observed responses with that of the anticipated responses, the prediction error varied between -0.03 and + 1.98 %. Thus, the low magnitudes of error, as well as the significant values of R2 in the current study, indicated a high prognostic ability of Response Surface Methodology.

4.8 In vivo studies

T_{max} for test formulation was found to be 4 hours. The higher T_{max} of the test drug suggests slower absorption. This delayed absorption of test preparation is due to the sustained release of the drug. On the other hand, the C_{max} of the formulation was not significantly different from the reported one. The half-life of the reference preparation was low which indicates rapid removal of the drug from plasma. This was also supported by the high elimination rate constant value. On the other hand, the test formulation exhibited higher elimination half-life and low elimination rate constant value than the marketed formulation. However, the AUC value for the test formulation is higher as compared to marketed preparation which shows an increase in bioavailability and sustained release effect. (Table 8).

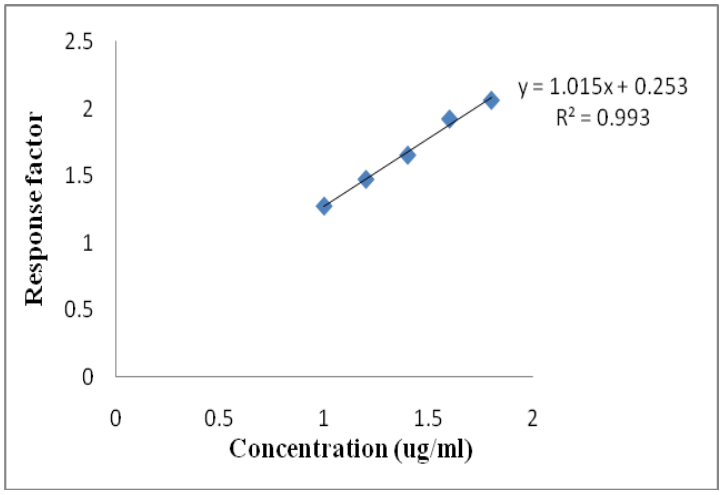

Fig. 7: Calibration curve of spiked plasma

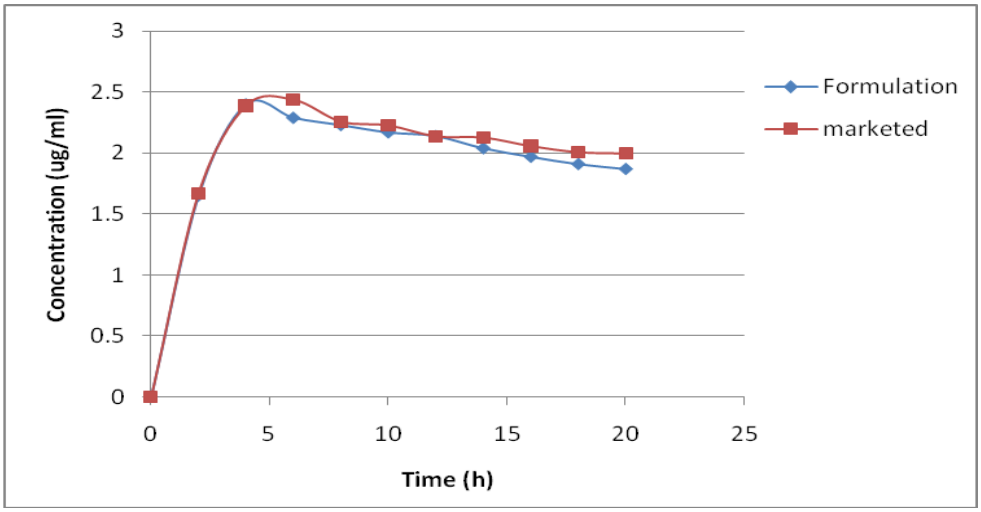

Fig. 8: Concentration-time curve for tablet and test formulation obtained from the rabbit plasma

Table: 8 Summary of pharmacokinetic parameters for marketed and test formulations

S no	Parameter	Test formulation	Marketed formulation
1	C_{max}	2.4ug/ml	2.44µg/ml
2	T_{max}	4 h	6 h
3	AUC $_{0\rightarrow t}$	40.66 µg h /ml	39.08µg h/ml
5	K_{el}	0.018 hr^{-1}	0.02hr^{-1}
6	Total AUC	144.54 µg h ml^{-1}	139.08 µg h ml^{-1}

5. CONCLUSION

The ER tablets of Alfuzosin HCL were prepared and evaluated for the various physicochemical parameters. The crosslinked Xyloglucan was used as a crosslinking agent which enhanced the Sustainability. Also, the Crosslinked Xyloglucan can be used as a novel excipient for Sustained Release Formulations.

6. ACKNOWLEDGEMENTS

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