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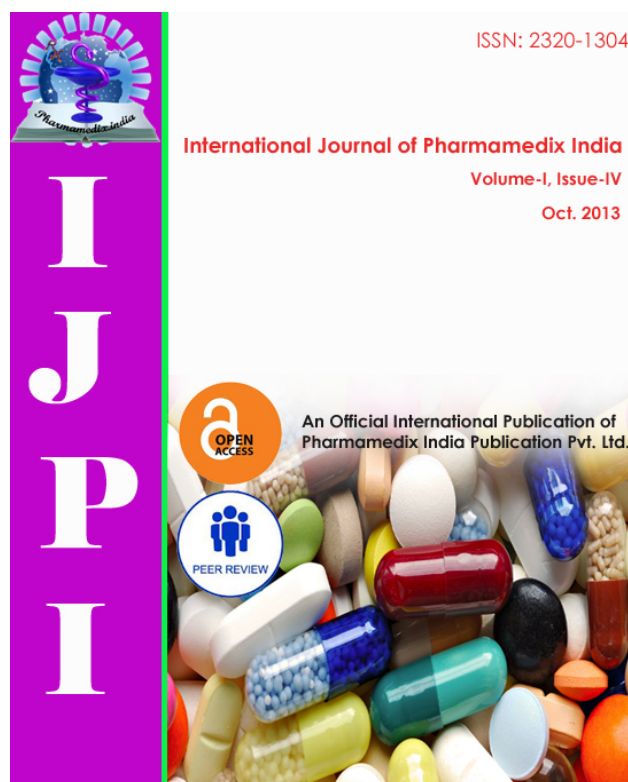
“Design and Development of Alfuzosin Hydrochloride Floating Tablet.”

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Abstract:

The purpose of present research was to develop and optimize prolong release floating tablet of alfuzosin hydrochloride which has narrow absorption window in proximal intestine to improve patient compliance and therapeutic efficiency in the treatment of benign prostatic hyperplasia. The system was designed to provide floating tablet by using hydroxyl propyl methyl cellulose. Different batches of tablets containing 10 mg of alfuzosin were prepared using by direct compression technique. Formulations were prepared using 3^2 factorial design and the type of polymer and diluents was taken as independent variables. The percentage drug release at 1,6,12 and 20 hours; floating lag time; diffusion exponent (n) and release rate constant were selected as dependent variable. Formulations were evaluated for their physical properties, drug content and in vitro drug release. All formulations had good physical integrity. Drug release from floating tablet was carried out for the 24 hour and showed that the release rate was highly significant to different grades of Methocel and type of diluents. Formulation batch F6 gave the continuous drug release for the 24 hours with Fickian diffusion type drug release mechanism and considered as optimum based on pre and post compression evaluations of the formulations. Study shows that floating drug delivery system is very useful system for prolong drug release control of highly soluble drugs.

Keyword: Alfuzosin Hydrochloride, HPMC, Floating Tablet, direct compression.

Introduction

Benign prostatic hyperplasia also known as benign prostatic hypertrophy is one of the most common non-malignant neoplasm affecting aging males. By 60 years of age, greater than 50% of men will have evidence of the disease and the prevalence may be as high as 80% by the age of 70.^[1] Lower urinary tract symptoms including urinary

frequency, nocturia, incomplete emptying, and urinary hesitancy are often associated with the benign prostatic hyperplasia. These symptoms can be caused by altered function of the smooth muscle tone that is regulated by the alpha1-adrenergic receptors in the prostate and its capsule, the bladder base and neck, and the prostatic urethra.^[2] Presumably alpha1-adrenergic receptor antagonist may be

implicated in the pathophysiology of benign prostatic hyperplasia and may cause relaxation of smooth muscles, improve in urine flow and reduction in lower urinary tract symptoms. American health care policy and research guidance recommended alpha-blockers as a first-line therapy for benign prostatic hyperplasia.

Alfuzosin hydrochloride is an alpha-adrenergic receptor blocker approved by FDA for the treatment of symptomatic prostatic hyperplasia. Alfuzosin hydrochloride relaxes the tone of the prostate smooth muscle, prostate capsule, bladder neck and proximal urethra. It competitively and selectively binds to the post synaptic α_1 -adrenergic receptors in the lower urinary tract. It also relaxes sympathetic nervous stimulation, reduces resting urethral pressure and inhibits urethral hypertonia induced sympathetic nervous stimulation. Alfuzosin hydrochloride exhibits narrow absorption window in the proximal part of the gastrointestinal tract and jejunum appear to be the main region for absorption. A controlled drug delivery system with prolonged residence time in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine. Bioavailability of a drug will be affected by factors that change gastrointestinal transit. In addition, they are difficult to formulate into extended release products because on arrival in the colon (or

even before), absorption will be low or non-existent.^[3,4]

Marketed alfuzosin formulation is three layered geomatrix tablet that requires special facilities, high cost, more time and complex operation than normal direct compression formulation. Therefore, a less complicated formulation is desired which can be prepared by conventional tools. So, aim is to develop prolong release tablet of alfuzosin hydrochloride by the direct compression method that deliver drug for longer time and thereby reduce the manufacturing cost and dosing frequency. Drug having high solubility and relatively shorter half- life suggests its suitability for a prolong release formulation.^[5,6]

Methods

Preparation of Alfuzosin HCl floating tablets

Tablets were prepared by direct compression process according to formula given in table 1. In all cases amount of active ingredient was 10 mg, ten percent sodium bicarbonate as gas generating agent, magnesium stearate (1 mg) added as lubricant and aerosil (1 mg) as glident. Tablettose 80 was used as the diluents for the all formulations.. For the formulation of different batches polymer type and quantity were selected as shown in the table. All ingredients were weighted accurately and passed through 40 mesh sieve. Drug was

mixed with the excipients in the geometric proportion for 10 min. Compression was done on a Rimek ten stations mini press using 6

mm (for first nine batches) and 8 mm (for last two batches) punch.

Table 1: Formulation of preliminary trial

Formulation	Formulation batch code										
Ingredients (mg)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Alfuzosin HCl	10	10	10	10	10	10	10	10	10	10	10
Nisso HPC H	25	50	75	-	-	-	-	-	-	-	-
Methocel K15M	-	-	-	25	50	75	-	-	-	-	-
Methocel K100M	-	-	-	-	-	-	25	50	75	100	125
NaHCO ₃	10	10	10	10	10	10	10	10	10	12	15
Tabletose 80	55	30	5	50	30	5	55	30	5	10	10
Mg stearate	1	1	1	1	1	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1	1	1	1	1	1
Total weight(mg)	102	102	102	102	102	102	102	102	102	134	162

Evaluation

Weight Variation Test ^[7]

Tablets were selected at random, weighed and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 10 %.

Friability ^[8]

For each formulation, pre weighed tablet sample were placed in the Roche friabilator (Electrolab, Mumbai, India) which was then operated for 100 revolutions. The tablets were deducted and reweighed. Conventional compressed tablets that loose < 0.5 to 1% of

their weight were considered acceptable. For sintered tablets the friability was almost negligible.

Content uniformity ^[9]

Tablets were weighed and finely powdered. Transfer an accurately weighed portion of the powder, equivalent to about 40 mg of alfuzosin hydrochloride to a 500-ml volumetric flask and add 50 ml of 0.1N hydrochloric acid, and sonicated to dissolve it. Shake by mechanical means for 10 minutes, dilute with 0.1N hydrochloric acid to volume, mix, and pass through a filter having a 0.5µm or finer porosity. Drug content was

determined by using UV Visible Spectrophotometer at 244nm.^[3]

In vitro buoyancy studies^[10]

Tablet's Buoyancy lag time test was performed by placing each of the tablets in a 250 ml beaker containing 200 ml 0.1 N HCl with Tween 20 (0.02%w/v), pH 1.2, maintained at 37±0.5°C in a water bath. Their physical state was observed for 24 h. The time between introduction of the dosage form and its buoyancy on the 0.1 N HCl (lag time) and the time during which the dosage form remains buoyant (total buoyancy time) were determined visually. Three replicates of each formula were performed.

In vitro dissolution studies^[10]

The in vitro study was performed by using a USP XXII paddle apparatus at a rotational speed of 50 rpm. Exactly 900 ml of 0.1 N HCL was used as a dissolution medium and was maintained at 37±0.5°C. Then 5 ml of the dissolution medium was withdrawn at specified time interval until 24 hr. Exact 5 ml of fresh medium was replaced to the dissolution vessel after each withdrawal to

maintain a constant volume. The sample withdrawn were analyzed by using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan) at 244 nm.^[3] Cumulative percentage drug release was calculated using an equation obtained from a calibration curve which was developed in the range of 1-7 µg/ml with 0.1 N HCl (Triplicate).

Drug Excipient Compatibility Study^[11]

For the drug excipient compatibility study, fourier transform infrared spectroscopy had been used to identify the physical and chemical interactions between drug and the excipients. Fourier transform infrared (FTIR) spectra of alfuzosin hydrochloride (alone) and formulation (containing Methocel) were recorded using KBr mixing method on FTIR instrument in a scanning range 400-4000 cm⁻¹ as shown in US patent no. US 2007/0100143 A1.

Optimization of variables using full factorial design^[12]

The composition of factorial design batches (F1-F9) is shown in Table 2.

Table 2: Composition of Factorial Batches

Ingredients (mg)	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Alfuzosin Hydrochloride	10	10	10	10	10	10	10	10	10
Methocel K4M	125	-	-	125	-	-	125	-	-
Methocel K15M	-	125	-	-	125	-	-	125	-

Methocel K100M	-	-	125	-	-	125	-	-	125
DCP	10	10	10	-	-	-	-	-	-
Tablettose 80	-	-	-	10	10	10	-	-	-
MCC	-	-	-	-	-	-	10	10	10
NaHCO ₃	15	15	15	15	15	15	15	15	15
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1	1	1	1
Total weight	162	162	162	162	162	162	162	162	162
<i>All ingredients are in mg.</i>									

Comparison of drug release profile for optimization of formulation batch ^[13]

The statistical methods assess the difference between the means of two drug release data sets in single time point dissolution or in multiple time point dissolution.

The similarity factor (f₂)

The similarity factor (f₂) is a logarithmic transformation of the sum-squared error of differences between the test T_t and reference products R_t over all time points. The release profile of products were compared using a f₂ which is calculated from following formula,

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^n w_t (R_t - T_t)^2 \right]^{-0.5} \right\} \times 100$$

Where, n is the release time and R_t and T_t are the reference (theoretical and test value of alfuzosin hydrochloride) at time t. w_t is the optional weight factor. The similarity factor

fits the result between 0 and 100. It is 100 when the test and reference profiles are identical and tends to 0 as the dissimilarity increases. The release profiles are considered to be similar when f₂ is between 50 and 100. This method is more adequate to dissolution profile comparisons when more than three or four dissolution time points are available.

Dissimilarity factor (f₁)

The dissimilarity factor calculates the present difference between the two curves at each time point and is a measurement of the relative error between the two curves. The percent error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles.

$$f_1 = \left[\sum_{t=1}^n w_t (R_t - T_t) / \sum_{t=1}^n R_t \right] \times 100$$

Accelerated stability study of optimized batch

For the determination of the changes in the physical properties and in-vitro release profile on storage, optimized batch tablets were stored at $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity. Samples were evaluated at 21 days (3 weeks) time for in vitro release.

Result & Discussion

Preformulation study

Physical Characteristics

Alfuzosin hydrochloride is a white crystalline powder

Melting point

Melting point of the alfuzosin hydrochloride was found in the range of 225°C to 230°C which is near by the reference of alfuzosin hydrochloride given in monograph of British Pharmacopoeia.

Solubility

After performing the solubility study it was found that alfuzosin hydrochloride is freely soluble in both 0.1 N HCl and water whereas insoluble in methylene chloride.

Drug Excipient Compatibility Study

In formulations drug-excipients interactions make important effect in the release of drug from formulation. Fourier transform infrared spectroscopy has been used for the study, physical and chemical interactions between drug and the excipients used in the formulation. Alfuzosin Hydrochloride exhibits peak due to carbonyl (3373.61) and hydroxyle (1600.97) group. It was observed that there were no changes in these main peaks in the FTIR spectra of a mixture of drug and polymers (Figure 1 and 2). Hence, it was concluded that no physical or chemical interactions of alfuzosin hydrochloride with Methocel

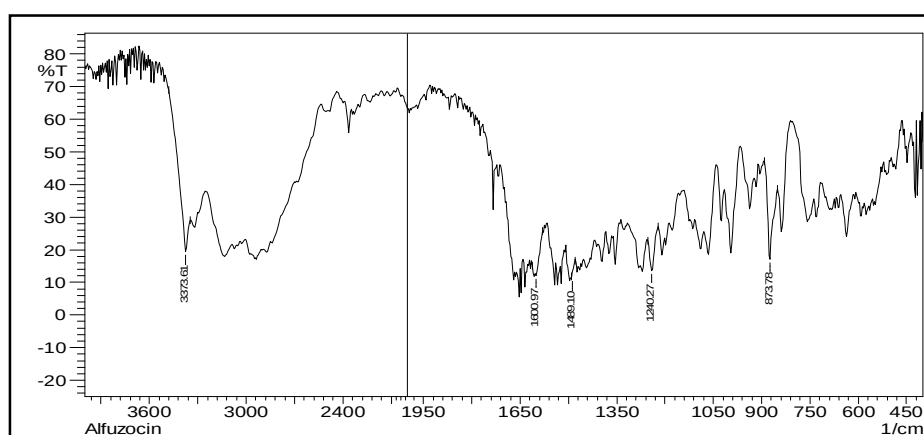


Figure 1: FTIR spectrum of alfuzosin hydrochloride

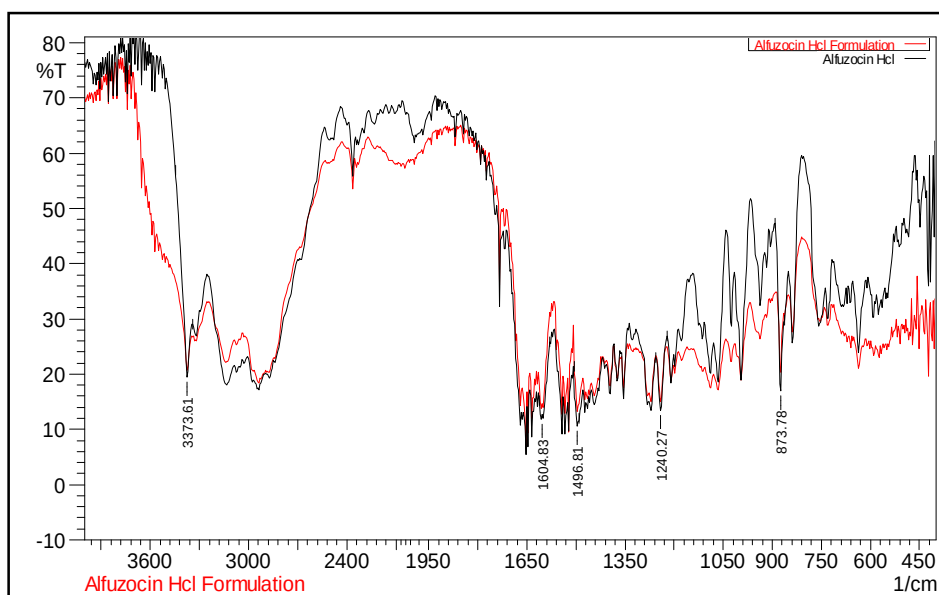


Figure 2: FTIR spectrum of alfuzosin hydrochloride formulation

Preliminary work

Selection of polymer concentration

In preliminary study, different batches were prepared as per the composition given in Table 2 of experimental work. All the batches were evaluated for precompression and post compression parameters.

All powder blends showed good flow property and compressibility index. Value of

compressibility index ranged from 12.1 to 14.8 whereas Angle of repose ranged from 23.4 to 31.5, and Hausner's ratio ranged from 1.13 to 1.17 respectively. The results of angle of repose indicates good flow property of the powder and the value of compressibility index further showed support for the flow property. So all the formulations passed the standard protocol value of the pre compression parameters and subjected to evaluated for post compression parameters.

Table 3: Evaluation parameters of P1 to P11 for preliminary screening

Batch code	Assay (%)	Avg. weight(mg)	Hardness (Kg/cm ²)	Thickness (mm)	Friability (%)	Buoyancy	
						FLT	TFT
P1	97.5±1.67	101±1.3	5.4±0.2	3.16±0.04	0.79	57	>24
P2	98.4±0.93	103±2.4	5.8±0.3	3.34±0.07	0.74	73	>24
P3	101.12±0.88	100±1.7	5.1±0.2	3.38±0.04	0.69	69	>24
P4	96.1±1.04	101±2.6	5.9±0.4	3.11±0.02	0.72	48	>24
P5	99.5±0.76	102±2.1	6.3±0.3	3.16±0.05	0.77	71	>24
P6	98.6±1.47	99±3.2	6.1±0.3	3.41±0.03	0.64	92	>24

P7	100.2±0.89	100±1.3	6.5±0.2	3.06±0.05	0.76	81	>24
P8	102.5±1.87	104±1.7	6.0±0.4	3.21±0.09	0.68	156	>24
P9	98.3±0.95	101±1.8	5.2±0.3	3.18±0.03	0.57	162	>24
P10	99.26±1.28	133±2.5	5.6±0.2	3.02±0.07	0.69	112	>24
P11	97.68±0.84	161±1.3	5.7±0.4	3.36±0.04	0.54	146	>24

The low value of the standard deviation in the result indicates uniform drug content in the tablets prepared and all formulations are within the prescribed official limits (Table 3). The thickness values were near to range. All the prepared floating tablets were evaluated for weight variation and results are given in above table. The percentage deviation from the average weight was found to be within the prescribed official range. Hardness of the prepared tablets was found to be in the range of 5.2 to 6.3 kg/cm³ and friability of all the tablets was in the range of 0.54 to 0.79 as given in table of result. The value of hardness and friability shows that Tablets of batch P1 had lowest floating lag time and batch P8 showed highest floating lag time as compare to other batches. Tablets of all formulations remain float for more than 24 hours.

In vitro drug release

Floating tablets of Alfuzosin hydrochloride were prepared by direct compression method using different type of polymers in various proportions. The results of in vitro drug release study are depicted in Table 4. From the dissolution profile it was observed that there was a significant outcome of polymer

grades and polymer load on drug release. All batches exhibit initial burst release of drug due to rapid dissolution of drug from tablet surface. Formulations containing higher viscosity grades and higher amount of polymer have slower drug release rates when compared to formulations with lower viscosity grades of polymer and low amount i.e. formulations P1, P2 and P3 shows the faster drug release and formulations P9, P10 and P11 shows slowest drug release. From the figure 5.4, it was observed that as the concentration of HPC-H increased drug release rate was gradually decreased. But drug was completely released within 6 hr, 12 hr and 13 hr in that order. It was observed that formulations with increased load of Methocel K15M shows decreased drug release rate. Batch P4, P5 and P6 shows drug retention for the duration of the 11 hr, 12 hr and 15 hr correspondingly. Batch P7, P8 and P9 shows the drug release for the 15 hr, 16 hr and 18 hr respectively. Batch P10 and P11 shows drug release for the 20 hr and 24 hr. Results revealed that the drug release rate was decreased as polymer weight and viscosity increases.

Table 4: Cumulative percentage drug release (CPR) of preliminary batches

Time (hr)	Cumulative Percentage Release										
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	50.6	24.3	29.9	22.3	19.8	18.6	23.9	21.8	20.9	25.8	27.7
2	72.6	31.4	35.5	33.6	30.3	26.4	34.0	28.3	27.0	32.4	31.4
4	90.6	46.5	47.5	57.2	47.7	42.7	49.7	42.0	40.3	42.1	37.7
6	97.5	63.3	60.5	79.0	60.7	56.7	59.5	56.0	51.8	54.3	45.4
8		76.1	69.8	84.3	78.0	67.2	67.6	67.6	63.1	64.8	52.3
10		91.9	80.1	96.9	87.3	76.5	76.8	76.9	73.5	74.4	60.1
12		101.3	88.9		99.5	86.8	86.9	83.9	78.8	81.2	67.8
16								101.1	91.6	93.0	81.6
20										99.2	91.2
24											98.7

Among all the batches, P11 gives better result as compare to other formulations. From this preliminary batches polymer concentration (125 mg) selected for the preparation of the final batches.

Full factorial design

Pre-compression parameters of design batches

From result it was found that the powder blend prepared for Factorial batches had angle of repose (24.5 ± 0.2 to 38.5 ± 0.3), Carr's index (11.72 ± 0.04 to 15.11 ± 0.05) and Hausner's ratio (1.12 ± 0.02 to 1.18 ± 0.04).

The result of angle of repose and carr's index indicated that the flowability of blend is significantly good. So the flow of the mass from the hopper was able to fill the mass in the die for the tablet compression.

Post compression parameters for design batches

Table 5: Result of post-compression parameters of designed tablet batches

Batch code	Assay (%)	Avg. weight (mg)	Hardness (Kg/cm ²)	Thickness (mm)	Friability (%)	Buoyancy	
						FLT	TFT
F1	95.62 $\pm$ 0.87	158 $\pm$ 2.3	6.2 $\pm$ 0.35	3.37 $\pm$ 0.05	0.65	104	>24
F2	99.34 $\pm$ 0.97	164 $\pm$ 1.4	5.4 $\pm$ 0.22	3.15 $\pm$ 0.09	0.76	122	>24

F3	98.96±0.78	162±2.7	5.9±0.46	3.26±0.07	0.59	136	>24
F4	94.92±1.19	155±1.6	6.3±0.34	3.04±0.02	0.78	96	>24
F5	99.52±0.83	152±3.1	5.6±0.32	3.27±0.09	0.62	108	>24
F6	98.28±1.32	166±2.8	6.1±0.26	3.15±0.02	0.69	126	>24
F7	101.2±0.92	157±2.3	5.5±0.29	3.38±0.05	0.56	102	>24
F8	99.47±1.63	169±1.2	5.8±0.45	3.24±0.07	0.64	116	>24
F9	97.03±1.01	153±1.5	6.2±0.33	3.19±0.04	0.71	129	>24

The data of physical parameters like weight variation, hardness, friability, drug content and buoyancy characteristics were evaluated for factorial batches (Table 5).

Weight variation test:

The weight of the tablet was 162 mg for all the batches. The variation in weight was within the range of 10% complying with pharmacopoeial specification (IP), indicating uniformity of weight.

Hardness and Friability:

The hardness of the formulations was in range of 5.4±0.22 to 6.3±0.34 and friability in range of 0.56 to 0.78. These results indicate good mechanical resistance of the tablets.

Assay:

In the content uniformity test, the drug content of all batches was found to be within the Limit, shown in table 5. Hence, all formulation passed the content of uniformity according to IP.

In vitro buoyancy study

All formulations had floating lag time below 3 minute, formulations containing the higher viscous grade of polymer shows higher floating lag time compare to other formulation. In case of less viscous polymer medium enter in the tablet core easily and react faster with sodium bicarbonate to generate carbon dioxide. Generated carbon dioxide entrapped in the polymer matrix which lowers the density of the tablet below 1 g/cm³, made tablet able to float on the medium. The total floating time was found to be more than 24 hours for all the formulations.

In vitro dissolution study

In vitro dissolution study was performed for all the 9 batches and compared with that of the drug release pattern of theoretical drug release pattern. From the all batches batch no. F6 found to be better correlated with the desired property.

Table 6: Cumulative percentage drug release from tablets of factorial design batch (n = 3)

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	TP
1	27.33	25.35	22.18	29.39	27.33	27.13	28.65	26.5	24.87	18.6
2	32.27	29.29	25.54	34.1	31.78	30.44	33.27	30.37	27.79	22.1
4	41.9	37.73	30.92	42.92	40.66	36.89	42.41	39.23	33.74	29.1
6	50.72	46.26	36.69	52.42	49.54	43.72	51.16	48.36	40.26	36.1
8	57.41	56.2	42.62	62.26	59.69	49.94	60.24	57.5	45.85	43.1
10	65.4	63.68	48.38	69.47	67.63	56.85	70.41	67.56	51.94	50.1
12	72.4	71.49	54.27	77.91	75.97	63.39	77.12	75.64	58.78	57.1
16	90.61	85.34	65.81	96.48	89.43	76.58	92.25	88.41	70.67	71.1
20		95.89	77.36		97.73	90.12			83.01	85.1
24			86.41			101.5			92.37	99.1

Standard deviation values of all batches are within the limit of ± 5 (n=3).

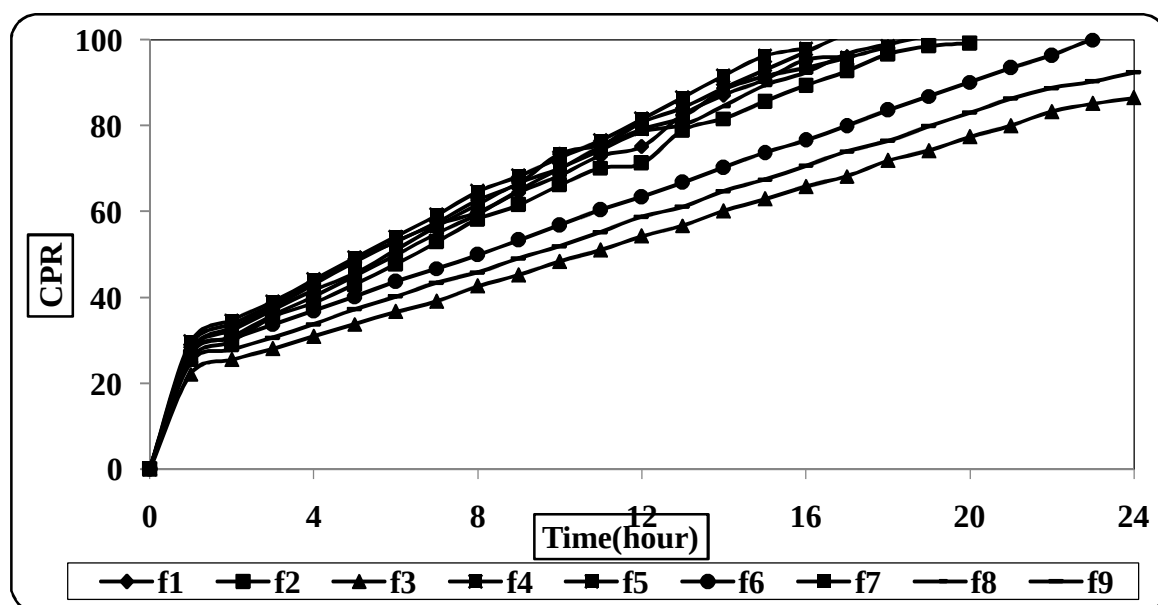


Figure 3: cumulative percentage release from tablets for factorial batches

Statistical analysis of factorial batches

Table 7: Formulation and evaluation of batches in 3^2 factorial design

Batch Code	Percentage drug release				Floating lag time (sec)	n	K
	Q ₁	Q ₆	Q ₁₂	Q ₂₀			

F1	27.63	52.99	75.12	96.03	104	0.4715	0.2381
F2	25.6	47.76	71.24	99.17	122	0.5049	0.2108
F3	22.62	42.98	67.73	91.81	136	0.5244	0.1829
F4	29.69	54.22	81.51	97.84	96	0.4661	0.2515
F5	27.58	51.04	79.12	98.35	108	0.4883	0.2308
F6	25.43	45.35	70.14	94.88	126	0.4851	0.2107
F7	28.95	52.96	80.72	101.5	102	0.4749	0.2439
F8	26.75	49.86	78.64	100.9	116	0.4806	0.2197
F9	25.02	47.89	68.65	95.52	129	0.4894	0.1994

R^2 value for Q_1 , Q_6 , Q_{12} , Q_{20} , floating lag time, diffusion exponent (n), and release rate constant (K) are 0.9907, 0.9839, 0.9682, 0.9257, 0.9941, 0.9458 and 0.9926 respectively indicating good correlation between dependent and independent variables. The low R^2 value, 0.9257 for Q_{20} indicates poor correlation between dependent and independent variables showing drug release at 20 hr is less dependent on selected variables.

The reduced models were developed for response variables by omitting the insignificant terms with $P > 0.050$. The terms with $P < 0.050$ were considered statistically significance and retained in the reduced model. The significance levels of the coefficients in the diffusion exponent (n) were found to be insignificant at $P > 0.05$ hence do not contribute significance information to the prediction of diffusion exponent (n).

Full and Reduced Model for Q_1

The significance levels of the coefficients b_{12} and b_{22} were found to be $P = 0.190$ and 0.526 respectively, so they were omitted from the full model to generate a reduced model. The results of statistical analysis are shown in Table 5.10. The coefficients b_0 , b_1 , b_2 and b_{11} were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{12} and b_{22} contribute significance information to the prediction of Q_1 . The critical value of F for $\alpha = 0.05$ is equal to 9.552 (df=2,3). Since the calculated value ($F = 1.676$) is less than critical value ($F = 9.552$), it may be concluded that the interaction term b_{12} and b_{22} do not contribute significantly to the prediction of Q_1 and can be omitted from the full model to generate the reduced model.

Poly nominal equation for Q_1 is:

$$\text{Full model: } Y = 27.68 + 2.21X_1 + 0.891X_2 + 0.295X_1X_2 - 1.55X_1^2 - 0.176X_2^2$$

Reduced Model: $Y = 27.56 - 2.21X_1 + 0.89X_2 - 1.55X_1^2$

From the surface plot of Q_1 (drug release at 1 hour), it can be concluded that as viscosity of Methocel (X_1) increases drug release rate was decreases whereas in case of variable X_2 , drug release was highest from Tablettose containing formulation, intermediate from MCC containing formulation and lowest from DCP containing formulation.

Full and Reduced Model for Q_6

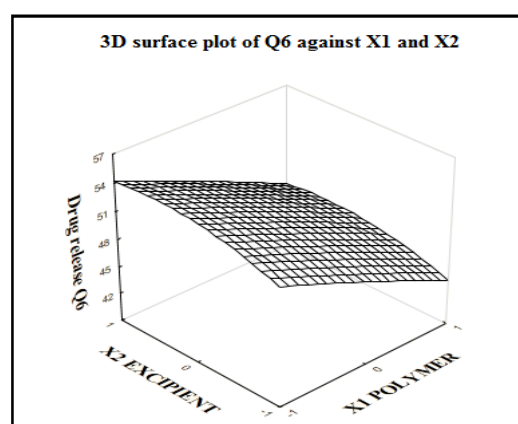
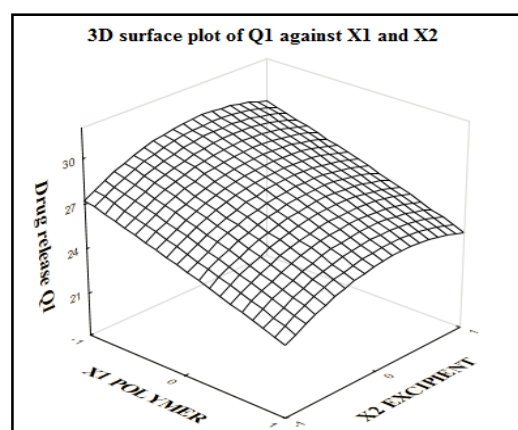
The significance levels of the coefficients b_{11} , b_{22} , and b_{12} were found to be $P=0.1338$, 0.797 and 0.051 respectively, so they were omitted from the full model to generate a reduced model. The coefficients b_{11} , b_{22} , b_{12} were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{11} , b_{12} and b_{22} contribute significance information to the prediction of Q_6 . The results of model testing are shown in Table 5.9. The critical value of F for $\alpha = 0.05$ is equal to 9.276 ($df=3,3$). Since the calculated value ($F = 4.73$) is less than critical value ($F=9.276$), it may be concluded that the interaction term b_{11} , b_{12} and b_{22} do not contribute significantly to the prediction of Q_6 and can be omitted from the full model to generate the reduced model.

Poly nominal equation for Q_6 is:

Full model: $Y = 50.30 - 3.99X_1 + 1.16X_2 + 1.235X_1X_2 - 1.13X_1^2 - 0.155X_2^2$

Reduced Model: $Y = 49.45 - 3.99X_1 + 1.16X_2$

From the surface plot of Q_6 (drug release at 6 hour), it can be concluded that as viscosity of Methocel (X_1) increases drug release rate was decreases whereas in case of variable X_2 the drug release rate was highest from Tablettose containing formulation, intermediate from MCC containing formulation and lowest from DCP containing formulation.



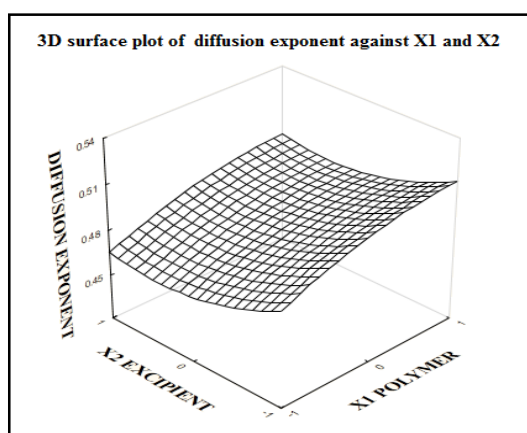
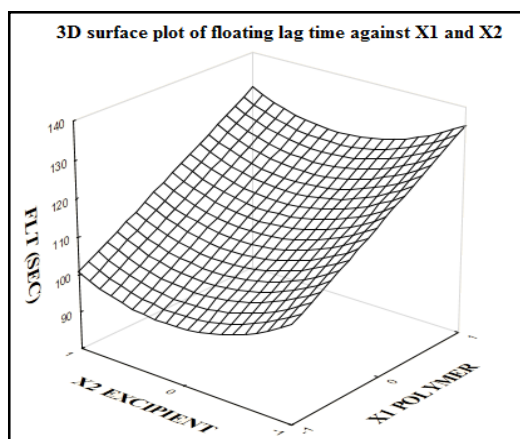
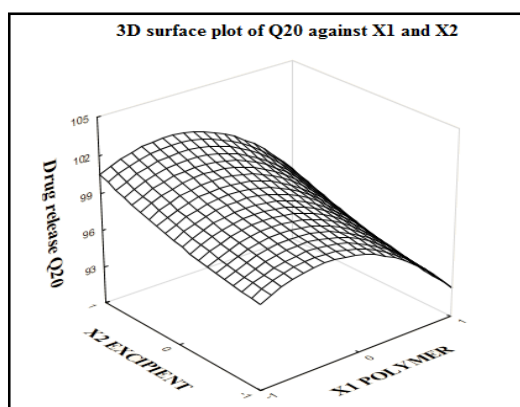
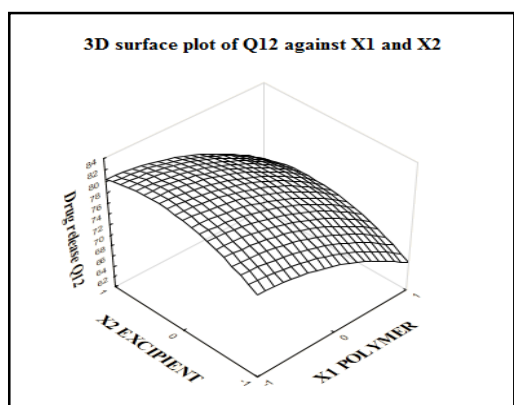


Figure 4: response surface plot for Q_1 , Q_6 , Q_{12} , Q_{20} , FLT, diffusion exponent

Full and Reduced Model for Q_{12}

The significance levels of the coefficients b_{11} , b_{22} , and b_{12} were found to be $P = 0.0625$, 0.125 , 0.235 respectively, so they were omitted from the full model to generate a reduced model. The results of statistical analysis are shown in Table 5.10. The coefficients b_{11} , b_{12} , b_{22} were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{11} , b_{12} and b_{22} contribute significance information to the prediction of Q_{12} . The critical value of F for $\alpha = 0.05$ is equal to 9.276 ($df=3,3$). Since the calculated value ($F = 5.01$) is less than critical value ($F = 9.276$), it may be concluded that the interaction term b_{11} , b_{12} and b_{22} do not contribute significantly to the prediction of Q_{12} and can be omitted from the full model to generate the reduced model.

Poly nominal equation for Q_{12} is:

$$\text{Full model: } Y = 78.49 - 5.13X_1 + 2.32X_2 - 1.17X_1X_2 - 3.24X_1^2 - 2.35X_2^2$$

$$\text{Reduced Model: } Y = 74.76 - 5.13X_1 + 2.32X_2$$

From the surface plot of Q_{12} (drug release at 12 hour), it can be concluded that as viscosity of Methocel increases (X_1) the release rate decreases whereas in case of variable X_2 the drug release was highest from Tablettose containing formulation, intermediate from

MCC containing formulation and lowest from DCP containing formulation.

Full and Reduced Model for Q_{20} :

The significance levels of the coefficients b_{11} and b_{12} were found to be $P= 0.656, 0.562$ respectively (Table 5.8), so they were omitted from the full model to generate a reduced model. The coefficients b_{12} and b_{11} were found to be significant at $P< 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{11} and b_{12} contribute significance information to the prediction of Q_{20} . The results of model testing are shown in Table 5.9. The critical value of F for $\alpha =0.05$ is equal to 9.28 ($df=2,3$). Since the calculated value ($F= 0.331$) is less than critical value ($F=9.55$), it may be concluded that the interaction term b_0, b_1, b_2 and b_{21} do not contribute significantly to the prediction of Q_{20} and can be omitted from the full model to generate the reduced model.

Poly nominal equation for Q_{20} is:

$$\text{Full model: } Y= 99.17 - 2.19X_1 + 1.83X_2 - 0.44X_1X_2 + 0.48X_1^2 - 3.22X_2^2$$

$$\text{Reduced Model: } Y= 99.49 - 2.19X_1 + 1.83X_2 - 3.25X_2^2$$

From the surface plot of Q_{20} (drug release at 20 hour), it can be concluded that as viscosity of Methocel increases (X_1) the release rate decreases whereas in case of variable X_2 the

drug release was highest from Tablettose containing formulation, intermediate from MCC containing formulation and lowest from DCP containing formulation.

Full and Reduced Model for floating lag time

The significance levels of the coefficients b_{12} and b_{22} were found to be $P= 0.24, 0.89$, respectively, so they were omitted from the full model to generate a reduced model. The coefficients b_{12} and b_{22} were found to be significant at $P< 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{12} and b_{22} contribute significance information to the prediction of floating lag time. The results of model testing are shown in Table 5.10. The critical value of F for $\alpha =0.05$ is equal to 9.55 ($df=2,3$). Since the calculated value ($F= 1.06$) is less than critical value ($F=9.552$), it may be concluded that the interaction term b_{12} and b_{22} do not contribute significantly to the prediction of floating lag time and can be omitted from the full model to generate the reduced model.

Poly nominal equation for floating lag time is:

$$\text{Full model: } Y= 109.88 + 14.8X_1 - 2.5X_2 - 1.25X_1X_2 + 8.16X_1^2 + 0.16X_2^2$$

$$\text{Reduced Model: } Y= 110 + 14.83X_1 - 2.5X_2 + 8.16X_1^2$$

From the surface plot of floating lag time, it can be concluded that as Methocel viscosity (X_1) increases the floating lag time increases whereas in case of variable X_2 the drug floating lag time was lowest for Tablettose containing formulation, intermediate for MCC containing formulation and highest for DCP containing formulation.

Full and Reduced Model for diffusion exponent (n)

The significance levels of the coefficients b_{11} , b_{22} , and b_{12} were found to be $P = 0.105$, 0.301 and 0.067 respectively (Table 5.8), so they were omitted from the full model to generate a reduced model. The coefficients b_0 , b_1 and b_2 were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{11} , b_{12} and b_{22} contribute significance information to the prediction of diffusion exponent (n). The critical value of F for $\alpha = 0.05$ is equal to 9.27 (df=3,3). Since the calculated value ($F = 4.89$) is less than critical value ($F = 9.27$), it may be concluded that the interaction term b_{11} , b_{12} and b_{22} do not contribute significantly to the prediction of diffusion exponent (n) and can be omitted

from the full model to generate the reduced model.

Poly nominal equation for diffusion exponent is:

$$\text{Full model: } Y = 0.48 + 0.01X_1 - 0.099X_2 - 0.099X_1X_2 + 0.011X_1^2 - 0.003X_2^2$$

$$\text{Reduced Model: } Y = 0.48 + 0.014X_1 - 0.009X_2$$

From the surface plot of diffusion exponent, it can be concluded that as viscosity of Methocel (X_1) increases the diffusion exponent increases whereas in case of variable X_2 the diffusion exponent was highest for Tablettose containing formulation, intermediate for MCC containing formulation and lowest for DCP containing formulation.

Kinetic modeling of dissolution data

The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Krossmayer-Peppas model as evident from regression coefficients. In case of the controlled release or sustained release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms.

Table 8: Kinetic treatment of dissolution data

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order									
B	4.3313	11.066	4.040	4.6512	4.3247	3.6601	4.5283	4.2734	3.588
A	25.247	5.5484	23.72	25.818	25.2347	24.249	25.570	24.332	23.630
R²	0.9981	0.9942	0.9966	0.9991	0.9959	0.9974	0.9991	0.9965	0.9951
First order									
B	0.0319	0.1143	0.0296	0.0335	0.0314	0.0273	0.0323	0.0309	0.9620
A	1.4926	1.1219	1.476	1.5036	1.4934	1.4778	1.5094	1.4855	0.0265
R²	0.9777	0.9262	0.9711	0.9823	0.9725	0.9724	0.9802	0.9712	0.9620
Higuchi									
B	23.112	41.753	23.271	24.120	23.7845	21.549	24.144	24.069	22.103
A	-1.834	-27.65	-5.608	-1.685	-3.4942	-3.469	-2.686	-5.388	-6.090
R²	0.9903	0.9899	0.9921	0.9897	0.9927	0.9927	0.9905	0.9928	0.9948
Hixon Crowell									
B	-1.443	-3.688	-1.119	-1.550	-1.4415	-1.220	-1.509	-1.424	-1.1961
A	-5.082	-4.573	-4.575	-5.272	-5.0782	-4.749	-5.190	-4.777	-4.5433
R²	0.9981	-0.994	-0.999	-0.999	-0.9959	-0.997	-0.999	-0.996	0.9958
Korsemeyer and Peppas									
A	-0.623	-0.676	-0.737	-0.599	-0.636	-0.676	-0.612	-0.658	-0.7136
n	0.4715	0.5049	0.5244	0.4661	0.4883	0.4851	0.4749	0.5036	0.5166
R²	0.9868	0.9864	0.9892	0.9828	0.9857	0.9856	0.9841	0.9858	0.9908
B = slope, A= intercept, R²= Square of correlation coefficient, n= diffusion exponent									

Formulation containing swelling polymers show swelling as well as diffusion mechanism because the kinetic of swelling include relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from a glassy to rubbery state. The value of diffusion exponent (n) for all factorial formulations except batches F1 and F2 were below 0.5 indicating fickian diffusion

type drug release whereas batches F2 and F3 have value between 0.5 to 0.85 indicating anomalous type drug releases from the formulations.

Kinetic Model Higuchi indicating that R² value of F1 to F9 was between 0.9897 to 0.9948, Shown that drug release type was diffusion type from gel network and extends

drug release for longer period of time. Kinetic model of zero order indicating that R^2 value of F1 to F9 was between 0.9951 to 0.9991 that near about 1.000 clearly mentioned that drug release from stiff gel networking was zero order drug release that not depends on concentration of drug. Kinetic model first order indicating that R^2 value of F1 to F9 was between 0.9262 to 0.9823 that having less than Zero order release R^2 value, mentioned that drug release type was not first order release from gel network.

Comparison of dissolution profiles for selection of optimum batch

The values of similarity factor (f_2) for the batch F6 shown maximum f_2 value 74.65. The values of dissimilarity factor (f_1) for the batch F6 shown minimum f_1 value 5.31. Hence, formulation batch F6 was considered as optimum batch.

Results of accelerated stability study

In order to determine the change *in vitro* release profile on storage, stability study of formulation F6 was carried out at 40°C in a humidity jar having 75 % RH. Samples evaluated after 21 days (3 weeks) showed no change *in vitro* drug release pattern. The value of similarity factor was 92.8545 and value of dissimilarity was 1.4243 indicating good similarity of dissolution profiles before and after stability studies.

Conclusion

It was observed that in all the cases that increase in amount of polymer lead to increased floating lag time. Increase in amount and grade of Methocel from K4M to K100M increased floating lag time. Use of different excipients has significant effect on drug release, because DCP retarded the release due to hydrophobic nature and due to non swelling and insoluble nature, on the contrary MCC increased drug release for its swelling property and causing burst release compare to DCP, and Tablettose moderately affected drug release due to channeling action and hence causing drug release at desired rate and amount.

In-vitro studies demonstrated that optimized batch (F6) showed 101.5 % drug release in 24 hour and best fitted in korsmeyer's peppas model showing diffusion type of release. The results of the present study demonstrated that Methocel K 100 could be successful hydrophilic polymer for the formulation of prolong release tablets of alfuzosin hydrochloride. In vitro dissolution studies indicated a sustain release pattern throughout the 24 h study period which was compatible with the theoretical release profile. Hence Methocel K100M, based floating tables seem to have a desirable sustained pattern of drug release, in order to reduce the dosing frequency.

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