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FORMULATION AND *IN- VITRO* EVALUATION OF ALFUZOSIN HCL FLOATING TABLET

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ABSTRACT

The purpose of this Research work was to prepare and optimized floating tablet of Alfuzosin HCl. Alfuzosin HCl is an alpha-1 adrenergic receptor blocker for the treatment of benign prostatic hyperplasia. Alfuzosin HCl exhibits narrow absorption window in the proximal part of the gastrointestinal tract & jejunum appear to be the main region for absorption. Alfuzosin HCl has a short biological half life (3-5 hours). The dose may range from 2.5 mg thrice a day to a maximum of 10 mg once a day which results into inconveniency to the patients. By preparing sustained release floating tablet of Alfuzosin HCl that deliver drug for longer time, reduce dosage frequency & better patient compliance. The present Research work describes the influence of the concentration of Xanthan Gum and Sodium bicarbonate on Alfuzosin HCl floating tablet using Central Composite Design. The Xanthan Gum (X1) and Sodium bicarbonate (X2) were selected as independent variables, while time required for 50% drug release (t_{50}), time required for 90% drug release (t_{90}), drug release at 12 hr (Q_{12}), floating lag time, diffusion exponent (n), release rate constant (k) were selected as a dependent variables. Tablets were prepared by direct compression technique & evaluated for pre-compression and post-compression parameters. Dissolution data were fitted to various models to ascertain kinetic of drug release. Regression analysis and analysis of variance were performed for dependent variables. All the batches were evaluated for the pre-compression and post-compression parameters and results were within the limits. All the batches exhibited appropriate floating lag time & showed total floating time of more than 24 hrs. It was observed that concentration of Xanthan Gum and Sodium bicarbonate had significant influence on t_{50}, t_{90}, Q_{12}, floating lag time, n, and k. Optimized formulation (H10) showed

99.52% drug release at the end of 24 hrs and maximum similarity factor (f_2=83.15) and minimum dissimilarity factor (f_1=2.80) with Theoritical release profile of Alfuzosin HCl. Optimized formulation followed by anomalous non Fickian release mechanism and found to be stable after 23 days at accelerated condition.

KEYWORDS: Alfuzosin hydrochloride, direct compression, Floating tablet, Xanthan Gum, Guar Gum, Central Composite design.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common benign condition affecting men and symptoms can start as early as age 30. Benign prostatic hyperplasia also known as Benign enlargement of the prostate (BPE), Adenofibromyomatous hyperplasia and Benign prostatic hypertrophy. Benign prostatic hyperplasia is a progressive condition characterized by prostate enlargement accompanied by lower urinary tract symptoms. Benign prostatic hyperplasia involves hyperplasia of prostatic stromal and epithelial cells resulting in the formation of large, fairly discrete nodules in the periurethral region of the prostate. Benign prostatic hyperplasia can result in the prostatic urethra is compressed which restricts the flow of urine from the bladder, this interference with urine flow may cause uncomfortable symptoms such as frequency, urgency, nocturia, intermittency, decreased stream and hesistancy. Benign prostatic hyperplasia can leads to the risk of urinary tract infection, urinary retention and kidney blockage. Benign prostatic hyperplasia does not lead to the risk of cancer. Intially management for benign prostatic hyperplasia includes lifestyle modification, used alpha blockers and 5-alpha reductase inhibitors. The alpha blockers work to relax the smooth muscle at the prostate and bladder neck by blocking alpha1 receptor. By relaxing the smooth muscle at the prostate neck, the urinary channel is opened which allows a less constricted urinary flow. Alfuzosin HCl is an alpha-1 adrenergic receptor blocker for the treatment of benign prostatic hyperplasia (BPH).Alfuzosin HCl exhibits narrow absorption window in the proximal part of the gastrointestinal tract & jejunum appear to be the main region for absorption. Alfuzosin HCl has a short biological half life (3-5 hours). The dose may range from 2.5 mg thrice a day to a maximum of 10 mg once a day, if it is formulated as conventional tablets it will required multiple daily administration (2-3 times daily) which results into inconveniency to the patients. So Alfuzosin HCl is an ideal candidate for controlled release in the proximal upper parts of the gastrointestinal tract. Thus formulation of floating drug delivery satisfied these conditions. Gastroretentive drug delivery system can

be retained in stomach for prolonged time & assist in increasing controlled delivery of drug that have narrow absorption window.

MATERIALS

Alfuzosin HCl was obtained as gift sample from Sun Pharmaceutical. Xanthan Gum was kindly gifted from Megh Pharmaceutical, Modasa. Guar Gum was gifted from Alembic Pharmaceutical Ltd, Vadodara. Sodium bicarbonate and Microcrystalline cellulose was obtained as gift sample from Finer Chemicals Ltd, Ahmedabad. Magnesium stearate was gifted from Acme Chemicals, Mumbai and Talc was obtained as gift sample from Lesar Chemicals Ltd, Vadodara.

METHOD

Preparation of Alfuzosin HCl Floating Tablets

Tablets were prepared by direct compression technique. All the ingredients were accurately weighed and passed through sieve no. 60 before using into formulation. All the ingredients mixed except magnesium stearate and talc geometrically. Required quantity of polymer and sodium bicarbonate as gas generating agent were mixed then Alfuzosin HCl is added and mixed properly then diluent is added to make up the weight. The blend obtained was then lubricated by adding magnesium stearate and talc and manually compressed on 10 station rotary tablet machine using flat-faced die punches of 6.0 mm diameter. The tablets were compressed to obtain hardness in a range of 6-7 Kg/cm^2.

Evaluation of Powder Blend and Tablets [7-12]

Drug-Excipients Compatibility study

Drug-excipients play important role in the release of drug from the dosage forms. Fourier transform infrared spectroscopy has been used to study the physical and chemical interaction between drug and the excipients used. Fourier transform infrared (FTIR) spectra of Alfuzosin hydrochloride, Xanthan Gum were recorded using KBr mixing method.

Loose Bulk Density

Weigh accurately 5 gm of powder blend, and transferred in 100 ml graduated cylinder. Carefully level the powder blend without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula:

Bulk Density = Mass/ apparent volume

Tapped Bulk Density

Weigh accurately 5 gm of powder blend, and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V_2) to the nearest graduated units, if the difference between the two volumes is less than 2% then final the volume (V_2). Calculate the tapped bulk density in gm/ml by the following formula:

Tapped Density = Mass/ tapped volume.

Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the Bulk Density and Tapped Density of a powder blend and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index = Tapped Density-Bulk Density×100/ Tapped Density.

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder blend material. Hausner's Ratio = Tapped Density/Bulk Density.

Angle of Repose

The angle of repose of powder blend powder was determined by the funnel method. The powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder blend cone was measured and angle of repose was calculated using the following Equ.

Angle of Repose **(Ø)** = $\tan^{-1}h/r$

Where, h = Height of the powder blend cone

r = Radius of the powder blend cone.

Weight Variation Test

The 20 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

For each formulation, pre weighed tablet sample (10 tablets) were placed in the Roche friabilator which is then operated for 100 revolutions. The tablets were deducted and reweighed. Conventional compressed tablets that loose < 0.5 to 1% of their weight are considered acceptable.

Hardness

Hardness of tablet was determined using Monsanto hardness tester.

Content Uniformity

The 20 tablets were crushed and the powder equivalent of 100 mg of drug was transferred to 100 ml of 0.1 N HC1 in volumetric flask. The solution was analyzed at 244 nm using double beam UV-Vis spectrophotometer after suitable dilution. The content of drug was calculated from calibration curve.

***In vitro* buoyancy study**

The *In vitro* buoyancy was characterized by floating lag time (FLT) and total floating time (TFT). The test was performed using USP 24 type II paddle apparatus using 900 ml of 0.1 N HC1 at 50 rpm at 37 ± 0.5°C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium were noted as FLT and TFT, respectively.

***In vitro* drug release study**

The *In vitro* drug release was performed using USP 24 type II paddle apparatus in 900 ml of 0.1N HC1 at 50 rpm at 37 ± 0.5°C. The samples were withdrawn at predetermined time intervals for period of 24 hr and replaced with the fresh medium. The samples were filtered through 0.45 µm membrane filter, suitably diluted and analyzed at 244 nm using double beam UV-Vis spectrophotometer. The content of drug was calculated using calibration curve.

kinetic model for release data [13-16]

The drug released data of all batches were fitted with desired kinetic model such as Zero order kinetic, First order kinetic, Higuchi model and Korsemeyer peppas model to ascertain the drug release. The Zero order and First order drug release. The Zero order and First order drug release explain the drug release depend on drug concentration or not. The Korsemeyer

peppas model described the method of drug release and Higuchi model described the diffusional drug release.

Zero order = $Q_1 = Q_0 + K_0 t$

First order = $Q_t = Q_{0e}^{-K1t}$

Higuchi model = $m = (100-q) \times t^{1/2}$

Hixon Crowell Model = $W_0^{1/3} - W_t^{1/3} = kt$

Korsemeyer peppas model = $Mt/M\alpha = K \times t^{n}$

Where Q_1 is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution, Q_t is the amount of drug dissolved in time t, W_0 is initial amount of drug in dosage form, W_t is remaining amount of drug in dosage form at time t, Mt/Mα is the fraction of drug release at time t and n is diffusion exponent. K_0, K_1, and k refer to the rate constant.

Statistical Analysis (17-18)

The statistical analysis of the factorial design batches was performed by multiple regression analysis using Microsoft Excel. Data obtained from all formulations were analyzed using statistica software and used to generate the study design and the response surface plots. Polynomial models were generated for all the response variables using Microsoft Excel. In addition analysis of variance (ANOVA) was used to identify significant effects of factors on response regression coefficients. The F value and p values were also calculated using Microsoft Excel. The relationship between the dependent and independent variables was further elucidated using response surface plots.

Similarity factor (f_2)

To evaluate and comparison of dissolution profiles, the dissolution profiles were analyzed using similarity factor f_2 The equation for calculating f_2 is given below.

Similarity factor f_2

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

Where, n is numbers of dissolution time point, W_t is optional weight factor, R_t is reference dissolution point at time t and T_t is test dissolution point at time t. The f_2 value between 50 and 100 suggests that the dissolution profiles are similar. The f_2 value of 100 suggests that the dissolution profiles are similar. The f_2 value of 100 suggests that the test and reference

profiles are identical and as the value becomes smaller, the dissimilarity between releases profile increases.

Dissimilarity factor (f_1)

The dissimilarity factor (f_1) calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \left\{ \left[\sum_{t=1}^{n} n \mid Rt - Tt \mid \right] / \left[\sum_{t=1}^{n} n\ Rt \right] \right\} \times 100$$

Where n is the number of time points, Rt is the dissolution value of the theoretical dissolution profile at time t and Tt is the dissolution value of the formulation at time t. The values should lie between 0-15. For curves to be considered similar f_1 values should be close to 0.

Accelerated stability study

The purpose of stability testing is to provide evidence on how the quality of drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test for the drug substance or a shelf life for the drug product and recommended storage condition. The storage condition used for stability studies were accelerated condition (40^0C ± 2^0C / 75 % ± 5% RH). Stability study was carried out for the optimized formulations. Tablets of optimized formulation were striped packed and kept in humidity chamber on above mention temperature.

RESULT AND DISCUSSION

Drug Excipient Compatibility Study

Fourier transform infrared spectroscopy has been used to study the physical and chemical interactions between drug and the excipients used. Fourier transform infrared (FTIR) spectra of Alfuzosin hydrochloride, Xanthan Gum were recorded using KBr mixing method. FTIR study showed that there was no interaction between drug and polymer that are shown in figure 1. So, the drug and polymer were compatible with each other.

Results of Pre-Compression evaluation parameter of trial batches

The powder mixture used for tablet preparation were evaluated for pre-compression parameter like bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose, results are shown in table 2. The bulk density was varied in the range of 0.512 gm/ml to 0.625 gm/ml, tapped density range between 0.571 gm/ml to 0.689 gm/ml, Hausner's ratio

in the range of 1.11 to 1.16, Carr's index was varied in the range of 10.52 % to 13.95 % and angle of repose was varied in the range of 25.19° to 30.46°. This all parameters show good flow property and direct compressibility.

Results of Pre-Compression parameters of CCD batches

The tablet blend of all the batches were evaluated for different derived properties viz.- Bulk density (between 0.28-0.32 gm/ml), Tapped density (between 0.33-0.37 gm/ml), Hausner's ratio (between 1.12-1.18), Carr's index (between 11.20-15.63), and Angle of repose (between 27.21-30.25). The results of Angle of repose and compressibility indicated that the Flowability of blend is significantly good. So the flow of the prepared mass from the hopper was able to fill the die completely for compression. After the lubrication the blend ready for compression had good flow property and excellent compressibility. The results are shown in the table 7.

Results of Post-Compression evaluation parameter of trial batches

All the prepared tablets showed acceptable pharmaceutical properties. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness were shown in the range of 6.2-6.4 kg/cm^2 in all the formulations which indicated good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations, the friability value was less than 1% and meets the official limit. The percentage drug content of all the tablets was found to be between 96.1%-101.0% of Alfuzosin HCl which was within acceptable limit. The results are shown in the table 3.

Results of Post-Compression parameters of CCD batches

All the prepared tablets showed acceptable pharmaceutical properties. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness were shown in the range of 6.0-7.0 kg/cm^2 in all the formulations which indicated good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations, the friability value was less than 1% and meets the official limit. All the batches exhibited appropriate floating lag time and showed total floating time of more than 24 hrs. The percentage drug content of all the tablets was found to be between 98.05%-101.5% of Alfuzosin HCl which was within acceptable limit. The results are shown in the table 8.

Result of *In-Vitro* drug release of trial batches

The results of *in vitro* drug release study are depicted in figure 2. Floating tablets of Alfuzosin HCl 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 10 and figure 5. From the dissolution profile it was observed that there was significant outcome of different polymers 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 viscous polymer and higher amount of polymer have slower drug release rates when compared to formulations with lower viscous polymer and lower amount and low amount of polymer. Formulation F1 contain 20 mg Xanthan Gum shows release 97.00% in 10 hr. F2 contain 40 mg Xanthan Gum shows release 100.39% in 13 hr. F3 contain 60 mg Xanthan Gum shows release 105.72% in 19 hr. F4 contain 80 mg Xanthan Gum shows release 83.10% in 24 hr. F5 contain 20 mg Guar Gum shows release 94.13% in 3 hr. F6 contain 40 mg Guar Gum shows release 98.14% in 5 hr. F7 contain 60 mg Guar Gum shows release 104.22% in 9 hr. F8 contain 80 mg Guar Gum shows release 103.00 % in 13 hr. Results revealed that the drug release rate was decreased as polymer weight and viscosity increases. All the formulations were floated.F3 formulation shows release up to 19 hr and F4 formulation shows release greater than 24 hr which contain 60 mg and 80 mg Xanthan Gum respectively So finally, it was concluded that the concentration of Xanthan gum can be required between 1:6 and 1:8 of drug to polymer ratio which can be used as release retarding polymer in the formulation of Alfuzosin HCl floating drug delivery system.

Table 1: Composition of Preliminary Batches

Formulation Ingredients (mg)	Formulation Batch Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Alfuzosin HCl	10	10	10	10	10	10	10	10
Xanthan Gum	20	40	60	80	-	-	-	-
Guar Gum	-	-	-	-	20	40	60	80
$NaHCO_3$	10	10	10	10	10	10	10	10
MCC	58	38	18	10	58	38	18	10
Magnesium stearate	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
Total weight (mg)	100	100	100	112	100	100	100	112

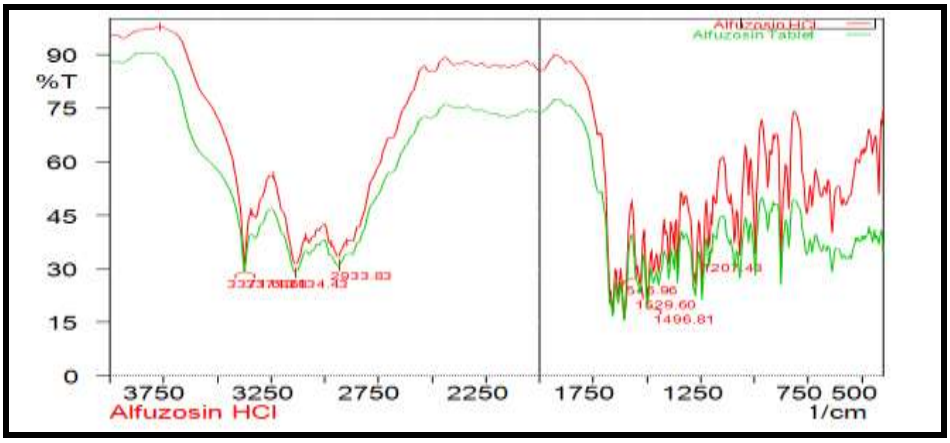

Figure 1: FTIR spectrum of Alfuzosin HCl formulation

Table 2: Pre-Compression evaluation parameter of trial batches

Batch	Bulk density (gm/ml)	Tap density (gm/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose
F1	0.571	0.645	11.47	1.12	27.89
F2	0.555	0.645	13.95	1.16	30.46
F3	0.526	0.588	10.52	1.11	29.35
F4	0.625	0.714	12.46	1.14	28.07
F5	0.512	0.571	10.25	1.11	29.05
F6	0.526	0.606	13.15	1.15	25.19
F7	0.540	0.625	13.52	1.15	28.29
F8	0.606	0.689	12.12	1.13	26.56

Table 3: Post compression evaluation parameter of trial batches

Batch	Weight variation (mg) n= 20	Hardness (Kg/cm^2)*	Friability (%)	Content uniformity (%)*	Floating Lag Time (sec)
F1	103±0.82	6.3±0.12	0.69	97.8±0.17	135
F2	98±1.36	6.2±0.20	0.68	99.3±0.21	169
F3	101±1.05	6.2±0.17	0.64	96.1±0.15	182
F4	110±1.54	6.4±0.10	0.57	99.6±0.12	203
F5	102±1.10	6.3±0.21	0.71	101±0.10	147
F6	99±1.23	6.2±0.13	0.76	97.04±0.23	172
F7	100±1.18	6.3±0.11	0.66	98.30±0.13	190
F8	114±0.94	6.3±0.14	0.63	96.75±0.15	216

Table 4: List of Independent Variables and Dependent Variables

Independent Variables:	
Xanthan Gum (X1)	Sodium bicarbonate (X2)
Dependent Variables:	
Time required for 50% drug release (t_{50})	Floating lag time (sec)
Time required for 90% drug release (t_{90})	Diffusion coefficient (n)
% drug release after 12 hrs (Q_{12})	Release rate constant (k)

Table 5: Design layout of Coded value and Actual value

Formulation Code	Coded value		Actual value	
	X1	X2	Xanthan Gum (X1)	Sodium bicarbonate(X2)
H1	-1	-1	70	5%
H2	-1	+1	70	15%
H3	+1	-1	80	5%
H4	+1	+1	80	15%
H5	-1.414	0	67.93	10%
H6	+1.414	0	82.07	10%
H7	0	-1.414	75	2.93%
H8	0	+1.414	75	17.07%
H9	0	0	75	10%
H10	0	0	75	10%

Table 6: Formulation of Alfuzosin HCl CCD Batches

Formulation Code		H1	H2	H3	H4	H5	H6	H7	H8	H9	H10
Ingredients (mg)	Alfuzosin HCl	10	10	10	10	10	10	10	10	10	10
	Xanthan Gum	70	70	80	80	67.93	82.07	75	75	75	75
	$NaHCO_3$	6	18	6	18	12	12	3.51	20.48	12	12
	MCC	32	20	22	10	28.07	13.93	29.49	12.52	21	21
	Mg. Stearate	1	1	1	1	1	1	1	1	1	1
	Talc	1	1	1	1	1	1	1	1	1	1
Total Weight (mg)		120	120	120	120	120	120	120	120	120	120

Table 7: Pre-Compression parameters of CCD batches

Batch Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's Ratio	Carr's Index (%)	Angle of repose (Ɵ)
H1	0.3214	0.3750	1.16	14.29	30.25
H2	0.2812	0.3333	1.18	15.63	29.74
H3	0.2960	0.3488	1.17	15.13	29.93
H4	0.3000	0.3488	1.16	13.99	30.06
H5	0.3040	0.3543	1.16	14.19	29.74
H6	0.3040	0.3488	1.14	12.84	29.05
H7	0.3146	0.3543	1.12	11.20	29.16
H8	0.3214	0.3781	1.17	14.99	28.49
H9	0.3146	0.3668	1.17	14.69	27.82
H10	0.3169	0.3750	1.18	15.49	27.21

Table 8: Post-Compression parameters of CCD batches

Batch Code	Weight variation (mg) n=20	Hardness (Kg/cm^2)*	Friability (%)	Content uniformity (%)*	Floating Lag Time (sec)	Total Floating Time (hr)
H1	111±1.24	6.40±0.15	0.61	99.89±0.15	220	>24
H2	115±1.05	6.30±0.10	0.69	98.05±0.19	75	>24
H3	109±0.85	6.20±0.11	0.54	100.9±0.41	233	>24
H4	114±1.18	6.40±0.20	0.56	98.25±0.13	88	>24
H5	123±1.13	6.20±0.12	0.66	101.5±0.19	190	>24
H6	118±1.49	6.30±0.15	0.51	98.88±0.20	207	>24
H7	121±1.32	6.30±0.19	0.58	100.07±0.31	311	>24
H8	116±1.20	6.50±0.15	0.59	99.81±0.13	50	>24
H9	119±1.39	6.70±0.10	0.57	98.80±0.34	201	>24
H10	115±1.27	6.50±0.22	0.58	99.57±0.26	194	>24

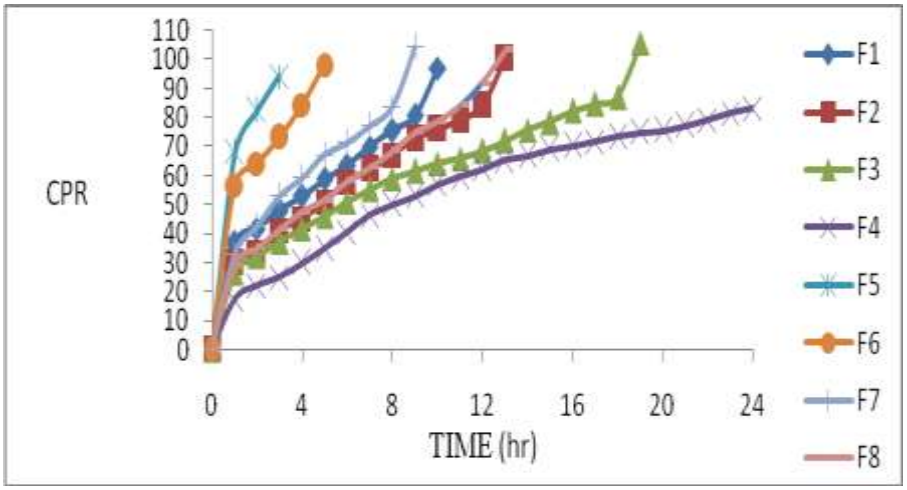

Figure 2: In-vitro Drug release studies of Trial batches of F1-F8

Result of *In-Vitro* drug release of CCD batches

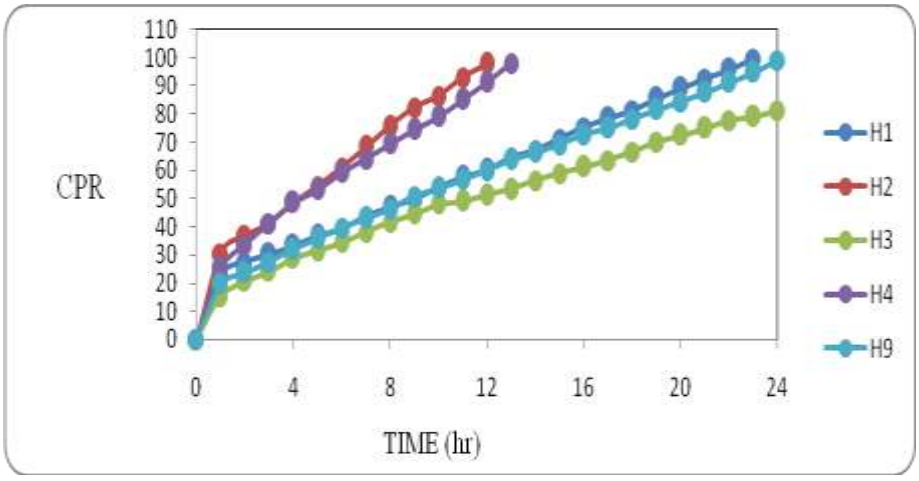

Figure 3: In-vitro Drug release studies of CCD batches of H1-H4 and H9

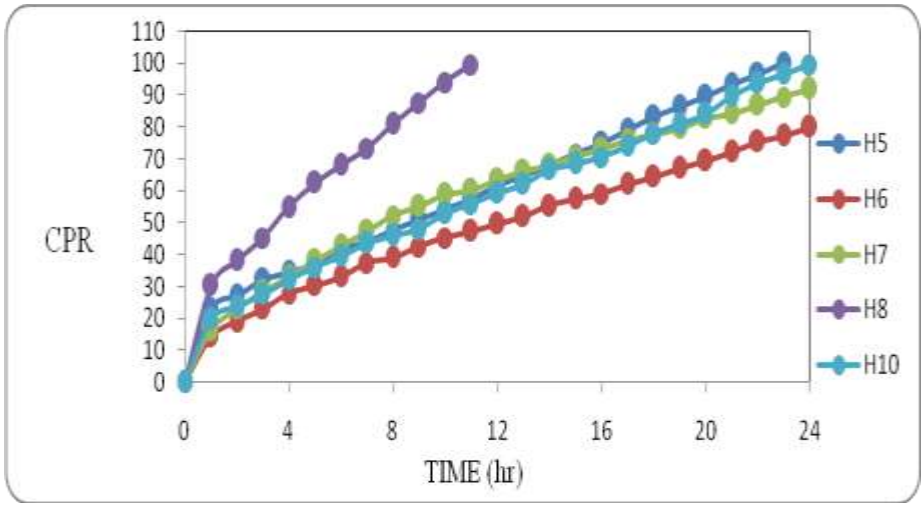

Figure 4: In-vitro Drug release studies of CCD batches of H5-H8 and H10

The results of *In vitro* drug release study are depicted in Figure 3&4. All batches exhibits burst release of drug at the initial stage due to rapid dissolution of drug from tablet surface. The formulation batches H1 & H3 contain 70 mg & 80mg Xanthan gum respectively and 5% sodium bicarbonate. Formulation batches H1 shows 99.59% drug release at the end of 23 hrs and H3 shows 81.33% drug release at the end of 24 hrs due to the higher concentration of polymer. Formulation batches H2 & H4 contain 70 mg & 80mg Xanthan gum respectively and 15% sodium bicarbonate. Formulation batches H2 Shows 97.87% drug release at the end of 12 hrs and H4 shows 98.07% drug release at the end of 13 hrs.

Formulation batches H2 and H4 contain higher concentration of Sodium bicarbonate that causes the pore in tablet and ultimately shows faster drug release. Formulation batches H5 & H6 contain 67.93 mg and 82.07 mg Xanthan Gum respectively and both contain 10% Sodium bicarbonate. H5 shows 99.89% drug release at the end of 23 hrs and H6 shows 79.92% drug release at the end of 24 hrs due to the higher amount of Xanthan Gum. Formulation batches H7 to H10 contain 75 mg Xanthan Gum and 2.93%, 17.07%, 10% & 10% Sodium bicarbonate respectively. H7 Shows 91.85% drug release at the end of 24 hrs. H8 shows 99.57% drug release at the end of 11 hrs due to the extremely high amount of Sodium bicarbonate and H9 & H10 shows 99.05% and 99.52% drug release at the end of 24 hrs respectively.

Result of statistical analysis of CCD batches

Table 9: Result of dependent variables

Batch code	Variable levels		t_{50}	t_{90}	Q_{12}	Floating lag time (Sec)	N	K
	X1	X2						
H1	-1	-1	8.84	20.36	60.96	220	0.5100	0.1788
H2	-1	+1	4.18	10.51	99.42	75	0.5016	0.2628
H3	+1	-1	11.85	26.36	50.39	233	0.5438	0.1373
H4	+1	+1	4.69	11.65	92.01	88	0.5293	0.2357
H5	-1.414	0	8.65	20.19	61.60	190	0.5056	0.1828
H6	+1.414	0	12.50	27.29	48.64	207	0.5578	0.1279
H7	0	-1.414	8.89	22.01	59.46	311	0.5514	0.1592
H8	0	+1.414	3.57	9.36	108.97	50	0.5130	0.2772
H9	0	0	9.36	21.35	58.80	201	0.5476	0.1583
H10	0	0	9.42	21.29	58.67	194	0.5431	0.1597

Full and reduced model for t_{50} (hr)

Full Model Y1= 9.39 + 1.120 (X_1) – 2.417 (X_2) + 0.339 (X_1X_1) – 1.833 (X_2X_2) - 0.625 (X_1X_2) ,

Reduced Model Y1'=9.77 +1.120(X_1) -2.41(X_2) – 1.978 (X_2X_2)

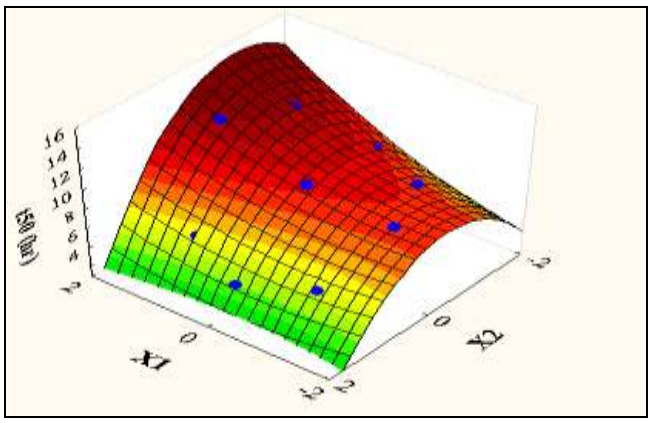

Figure 5: Response surface plot of t_{50}

Response surface plot shows that X1 as concentration of drug to polymer ratio increase from level -1.41 to 1.41 the stiff gel is formed due to increase in the gel strength so time required to release 50% of drug increases and X2 concentration of sodium bicarbonate increase from level -1.41 to 1.41 the more acid is penetrated in matrix so time required to release 50% of drug decreases. The calculated value (F= 0.870) is less than the critical value (F= 6.944), It may be concluded that the omitted terms do not contribute significantly to the prediction of t_{50} (hr).

Full and reduced model for t_{90} (hr)

Full Model Y1= 21.32 + 2.146 (X_1) – 5.305 (X_2) + 0.586 (X_1X_1) – 3.438(X_2X_2) – 1.214 (X_1X_2),

Reduced Model Y1'=21.99 +2.146(X_1) -5.305(X_2) – 3.689 (X_2X_2)

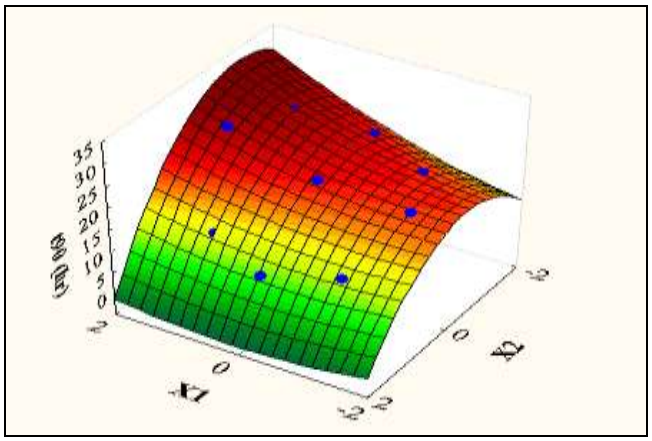

Figure 6: Response surface plot of t_{90}

Response surface plot shows that X1 as concentration of drug to polymer ratio increase from level -1.41 to 1.41 the stiff gel is formed due to increase in the gel strength so time required to release 90% of drug increases and X2 concentration of sodium bicarbonate increase from level -1.41 to 1.41 the more acid is penetrated in matrix so time required to release 90% of drug decreases. The calculated value (F= 0.783) is less than the critical value (F= 6.944), It may be concluded that the omitted terms do not contribute significantly to the prediction of t_{90} (hr).

Full and reduced model for Q_{12} (%)

Full Model Y1= 58.73 – 4.53 (X_1) + 18.76 (X_2) – 0.300 (X_1X_1) + 14.24 (X_2X_2) + 0.79 (X_1X_2)

Reduced Model Y1'= 58.39 - 4.53 (X_1) + 18.76 (X_2) + 14.37 (X_2X_2)

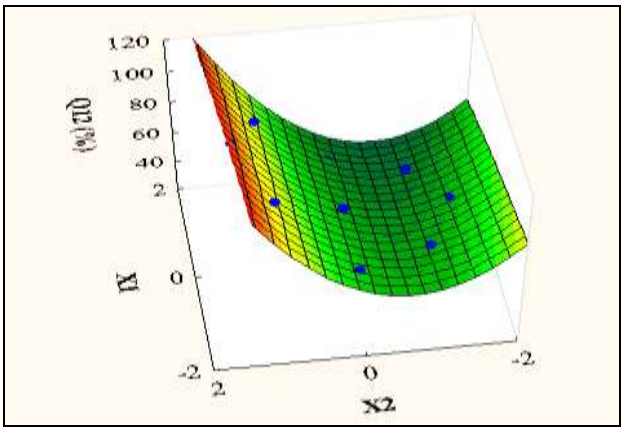

Figure 7: Response surface plot of Q_{12} (%)

Response surface plot shows that X1 as concentration of drug to polymer ratio increase from level -1.41 to 1.41 the stiff gel is formed due to increase in the gel strength so release rate of the drug (% drug release at 12^{th} hr) is decrease and X2 concentration of sodium bicarbonate increase from level -1.41 to 1.41 the more acid is penetrated in matrix so release rate of the drug (% drug release at 12^{th} hr) is increased. The calculated value (F= 0.0681) is less than the critical value (F= 6.944), It may be concluded that the omitted terms do not contribute significantly to the prediction of Q_{12} (%).

Full and reduced model for Floating lag time (sec)

Full Model Y1= 197.50 + 6.25 (X_1) – 82.38 (X_2) -8.37 (X_1X_1) – 17.37 (X_2X_2) –+5.33E-15 (X_1X_2),

Reduced Model Y1'=176.9 - 82.38 (X_2)

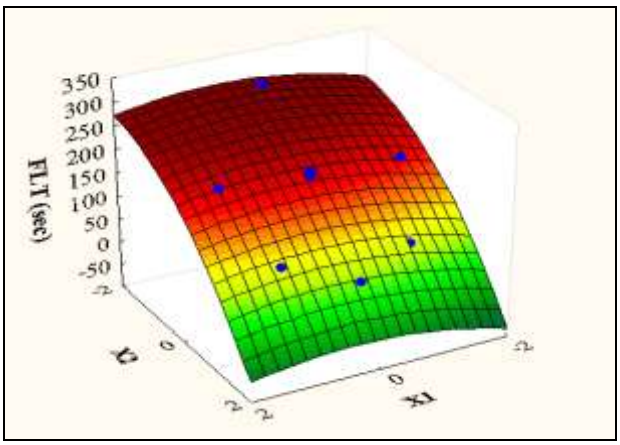

Figure 8: Response surface plot of FLT (sec)

Response surface plot shows that X1 as concentration of drug to polymer ratio increase from level -1.41 to 1.41 the stiff gel is formed due to increase in the gel strength so floating lag time is increase and X2 concentration of sodium bicarbonate increase from level -1.41 to 1.41 the more acid is penetrated in matrix so floating lag time is decreased. The calculated value (F= 0.510) is less than the critical value (F= 6.388), It may be concluded that the omitted terms do not contribute significantly to the prediction of floating lag time (sec).

Full and reduced model for Diffusion exponent (n)

Full Model Y1= 0.545 + 0.0169 (X_1) – 0.0096 (X_2) - 0.0095 (X_1X_1) -0.0092 (X_2X_2) – 0.00153 (X_1X_2)

Reduced Model Y1'=0.530+ 0.0169 (X_1) – 0.0096 (X_2)

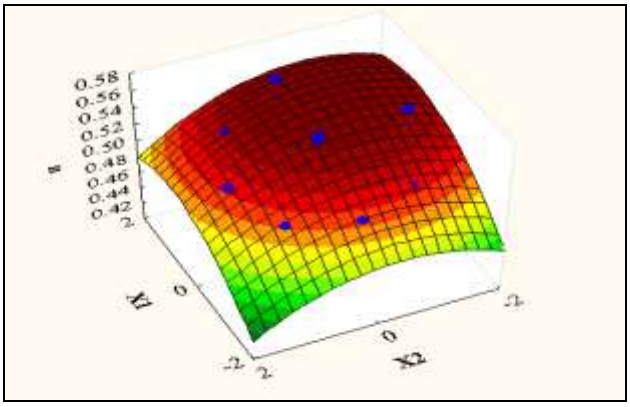

Figure 9: Response surface plot of diffusion exponent (n).

Response surface plot shows that X1 as concentration of drug to polymer ratio increase from level -1.41 to 1.41 the stiff gel is formed due to increase in the gel strength so diffusion exponent is increase and X2 concentration of sodium bicarbonate increase from level -1.41 to 1.41 the more acid is penetrated in matrix so is diffusion exponent decreased. The calculated value (F= 1.990) is less than the critical value (F= 6.5913), It may be concluded that the omitted terms do not contribute significantly to the prediction of diffusion exponent (n).

Full and reduced model for Release rate constant (k)

Full Model Y1= 0.159- 0.0182 (X_1) + 0.0436 (X_2) + 0.0023 (X_1X_1) + 0.0338 (X_2X_2) + 0.0036 (X_1X_2)

Reduced Model Y1'=0.161- 0.0182 (X_1) + 0.0436 (X_2) + 0.0327 (X_2X_2)

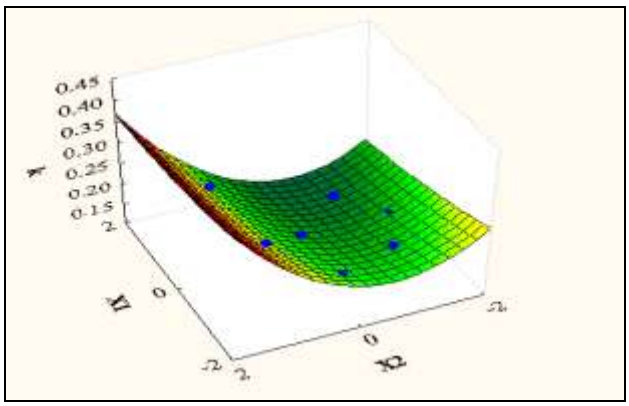

Figure 10: Response surface plot of release rate constant (k)

Response surface plot shows that X1 as concentration of drug to polymer ratio increase from level -1.41 to 1.41 the stiff gel is formed due to increase in the gel strength so release rate constant is decrease and X2 concentration of sodium bicarbonate increase from level -1.41 to 1.41 the more acid is penetrated in matrix so is release rate constant increased. The calculated

value (F= 0.254) is less than the critical value (F= 6.944), It may be concluded that the omitted terms do not contribute significantly to the prediction of release rate constant (k).

Result of kinetic treatment of dissolution data

The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Korsmeyer-Peppas model as evident from regression coefficients (Table 10).

Table 10: Kinetic treatment of dissolution data

	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10
	Zero order									
S	3.472	6.325	2.758	5.751	3.466	2.705	3.049	6.902	3.336	3.371
I	19.304	23.524	17.300	23.000	20.015	16.186	22.881	25.331	18.775	18.224
R^2	0.999	0.999	0.996	0.997	0.999	0.996	0.984	0.998	0.998	0.998
	First order									
S	0.0271	0.0459	0.0265	0.0438	0.0268	0.0271	0.0259	0.0492	0.0272	0.0272
I	1.423	1.484	1.344	1.464	1.432	1.320	1.424	1.502	1.401	1.400
R^2	0.983	0.986	0.954	0.967	0.982	0.951	0.920	0.976	0.966	0.972
	Higuchi									
S	21.052	28.867	17.315	27.397	21.026	16.982	19.464	30.592	20.827	20.940
I	-8.342	-5.723	-6.387	-5.980	-7.627	-7.047	-4.395	-4.965	-9.490	-9.990
R^2	0.982	0.987	0.994	0.994	0.983	0.994	0.999	0.994	0.991	0.986
	Hixon Crowell									
S	-1.157	-2.108	-0.919	-1.917	-1.155	-0.901	-1.016	-2.300	-1.112	-1.123
I	26.898	25.491	27.566	25.666	26.661	27.937	25.706	24.889	27.074	27.258
R^2	-0.999	-0.998	-0.996	-0.997	-0.999	-0.996	-0.984	-0.998	-0.998	-0.998
	Korsmeyer and Peppas									
N	0.5100	0.5016	0.5438	0.5293	0.5056	0.5578	0.5514	0.5130	0.5476	0.5431
I	-0.747	-0.580	-0.862	-0.627	-0.737	-0.892	-0.797	-0.557	-0.800	-0.796
R^2	0.976	0.981	0.995	0.996	0.979	0.996	0.999	0.992	0.990	0.987
	S= slope, I= intercept, R^2= square of correlation coefficient, n= diffusion exponent									

Comparison of dissolution profiles for selection of optimum batch

The values of Dissimilarity factor (f_1) for batches H1, H3, H5, H7, H9, and H10 were less than 15 compared with theoretical dissolution profile indicating good similarity in dissolution (Table 11). The batch H10 showed minimum value of f_1 (2.80). The values of similarity factor (f_2) for batches H1, H3, H5, H7, H9, and H10 were greater than 50 compared with theoretical dissolution profile indicating good similarity in dissolution. The batch H10 showed maximum value of f_2 (83.44).

Table 11: Similarity Factor *(f_2)* and Dissimilarity factor *(f_1)* for B1-B9

Batch	Similarity factor *(f_2)*	Dissimilarity factor *(f_1)*
H1	71.76	6.17
H2	28.23	70.03
H3	51.95	12.51
H4	30.92	59.02
H5	68.45	7.27
H6	48.42	15.51
H7	63.64	7.95
H8	25.44	84.12
H9	81.15	3.25
H10	83.44	2.80

Result of accelerated stability study

Parameter	Initial	After 23 day
Hardness (kg/cm^2)	6.5	6.6
Friability (%)	0.58	0.60
Floating lag time (sec)	194	203
Total floating time (hr)	>24	>24
Drug content (%)	99.57	99.44
similarity factor (f_2)	83.44	84.17
Dissimilarity factor (f_1)	2.80	2.69

CONCLUSION

In the present Research work, attempt has been made to develop Alfuzosin HCl floating tablets based on Natural Polymers as matrix forming material utilizing effervescent approach. FTIR spectroscopy revealed that there was no chemical interaction between drug and polymer. The drug content was uniform in all the formulation of the tablets prepared.

It was concluded that Xanthan Gum retards the drug release more as compared to Guar Gum. The polymer concentration was found to influence the release of drug from the formulation. As the polymer level was increased, the release rates were found to be decrease. Amount of sodium bicarbonate has influence on floating lag time. It was found that increases in the concentration of sodium bicarbonate decrease the floating lag time and increase the drug release rate. It was found that 10% sodium bicarbonate is required to attain buoyancy.

The influence of different concentration of Xanthan Gum and Sodium bicarbonate on kinetics of Alfuzosin HCl was studied and successfully optimized by using Central Composite Design. From the Central Composite Design and different graphical representation, it was

finalized that batch H10 was found to be optimized batch having drug release upto 24 hr. More ever, the dissolution profile of optimized batch H10 was found to be similar with theoretical drug release profile having similarity factor more than 50 (*f2*= 83.44) and dissimilarity factor less than 15 (*f1*=2.80) which reflects the feasibility of the optimization procedure in successful development of floating matrix tablet containing Alfuzosin HCl by using Xanthan Gum.

The *In vitro* data is fitted in to different kinetic models and the best fit was achieved with zero order model and Higuchi model. The optimized formulation followed by anomalous non Fickian release mechanism and found to be stable after 23 days at accelerated condition.

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