Development, Optimization and Evaluation of Controlled Release Matrix Tablets of Alfuzosin HCL

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Abstract:
Extended release formulation of alfuzosin, an α-antagonist used for prostatic hypertrophy, is available in market. It is convenient for older patients to take only one tablet a day. 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. The aim of the present study was the determination of formulation factors and the in vitro evaluation of an extended release dosage form of a freely soluble weakly basic drug (alfuzosin hydrochloride). Binary mixer of PEO and Guar Gum were used in tablets prepared by direct compression. The amounts of both polymers were taken as independent variables for the Box-Behnken design. The % Rel at 2 hr, $t_{50\%}$ and Release exponent were selected as responses. The main effect and interaction terms were quantitatively evaluated using mathematical model. Dissolution data were fitted to zero order, Korsmeyer Peppas and Higuchi's release kinetics to evaluate kinetic data. Both the diffusion and erosion mechanisms were responsible for drug release as shown by the power law.

Keywords: *Alfuzosin HCL, Box-Behnken, Release kinetic, benign prostatic hypertrophy*

1. Introduction

Alfuzosin hydrochloride, a selective alpha adrenergic antagonist is used against benign prostatic hypertrophy (BPH) [1-3] in elderly males. The prostate gland of the patients enlarges in BPH and prevents urine flow from bladder which results in urinary retention. The treatments available are surgical removal of excess tissue or drug therapy [4]. Two classes of drugs are used, 5-alpha reductase inhibitors and alpha adrenergic antagonists. The second class includes terazosin, doxazosin, tamsulosin and alfuzosin. Alfuzosin is freely soluble in water [5-6], and thus readily absorbed after administration. The oral absorption is significantly aided by the presence of food. The dose of immediate release alfuzosin tablet is 2.5 mg thrice daily [7-9]. Recently 10 mg once daily extended release formulation has become available in the market [10] which is more convenient for older patients [11]. Marketed alfuzosin formulation is a three layered Geomatrix tablet that requires special facilities, high cost, more time and complex operation than

conventional formulations [12]. An easier directly compressible formulation was reported by Nair *et al.* [13] which is also followed in the current experiment. The aim of this work was to prepare and evaluate the Alfuzosin Hydrochloride once daily extended release tablets and to compare them with reference product. The most commonly used method for fabricating drugs in a controlled release formulation is by incorporating them into a matrix containing a hydrophilic rate controlling polymer [14] .Matrix systems are widely used in oral controlled drug delivery because of their flexibility, cost effectiveness and broad regulatory acceptance. Cellulose ethers like Hydroxypropylmethyl Cellulose (HPMC), copolymers of acrylic-methacrylic acid (Eudragits) like Eudragit RL and RS and some natural gums like guar gum are widely used hydrophilic polymers as release retardants [15-16].

2. Materials and Methods

2.1 Materials

Guar gum grades Supercol U (Guar U) and Supercol K-1 (Guar K), HPMC K4M and PEO 301 were provided by Colorcon Inc (WestPoint, PA).

2.2 Methods

Selection of polymers

Preparation of matrix tablets

A constant amount of polymer (600mg) was compressed on a hydraulic using a matching flat round 11 mm pre-lubricated punch and die set. For HPMC and PEO a force of 1 ton was maintained for approximately 10 seconds. For Guar gum a force of 1.5 tons was needed to form coherent tablets.

3. Mass Loss and Dissolution Medium Studies

The erosion and water uptake of the polymer tablets were measured with the aid of a standard USP 23 paddle apparatus. To avoid adhesion of the sticky hydrating tablets to the bottom of the dissolution vessel the tablets were placed on the circular wire mesh discs that where placed at the bottom of the dissolution flask. A stirring speed of 50 rpm was used to agitate the dissolution and swelling medium which was kept at 37^{o}C throughout and consisted of 1000 ml of pH 1.5 or pH 6.4 USP recommended buffer.

The dissolution medium uptake and mass loss were determined gravimetrically following the procedure of akbari et al. (1998)[17] and was calculated according to the following equations:

$$\% \text{ Medium Uptake} = \frac{100 \cdot (\text{Wet Weight} - \text{Remaining Dry Weight})}{\text{Remaining Dry Weight}} \quad (1)$$

$$\% \text{ Mass Loss} = \frac{100 \cdot \text{Remaining Dry Weight}}{\text{Original Dry Weight}} \quad (2)$$

Three tablets were used per time point per batch. At the predetermined times the circular mesh supporting the partially hydrated tablets were carefully removed and the tablets were lightly patted with tissue paper to remove excess surface water. The tablets were then carefully transferred to a petared glassine weighing paper. After determining the wet weight, the tablets were dried at 70^{o}C for 10 days before reweighing to determine the remaining dry weight.

4. Preparation of Controlled Release Matrix Tablet

Tablets were fabricated by direct compression according to the formula. The amount of active ingredient and tablet weight was held constant. All ingredients except lubricant were sieved through # 40 mesh and mixed manually for 10 min. Magnesium stearate (1%) was then added after passing through # 60 mesh and the powder mixture was blended for 2 min. The resultant mixture was compressed manually in rotary tablet by using 6 mm concave round punch with 1.5 ton compression force.

5. Optimization Using Box-Behnken Design

5.1 Experimental design

Box–Behnken designs are experimental designs for response surface methodology, devised by George E. P. Box and Donald Behnken in 1960. Box-Behnken design, as illustrated in Table 1 is mainly used after screening.

The statistical significance of the differences among the various values of kinetic parameters obtained from dissolution and floating profiles were compared by ANOVA test at the P = 0.05 level and Design expert was used for all the data analysis.

A Box-Behnken statistical design with 3 factors, 3 levels, and 15 runs was selected for the optimization study[18]. The experimental design consists of a set of points lying at the midpoint of each edge and the replicated center point of a multidimensional cube. Independent and dependent variables are listed in Table 1.This design generally involves a dependent variable Y. and several independent or controlled variables, X_1, X_2,…., X_k. The response surface can be expressed as

$$Y = f(X_1, X_2, \ldots, X_k)$$

The three independent formulation variables selected for this particular study are:

X_1, PEO loading level; X_2, Guar Gum loading level; X_3: Maltodextrin loading level;

All other formulation and processing parameters, such as the level of active ingredient, blend and filling conditions and other process variables were kept invariant throughout the study. The response variables include the following:

Y_1, Release exponent (*n*), Y_2, Time for 50% of alfuzosin HCL released (t_{50}%),
Y_3, Percentage of alfuzosin HCL release at 2 hr (Rel).

Table 1: Composition of formulations used in Box-Behnken design

Formulation Code	Alfuzosin HCL (mg)	Formulation variables		
		PEO (mg)	Guar Gum (mg)	Maltodextrin (mg)
H1	10	80	75	80
H2	10	55	75	60
H3	10	30	50	60
H4	10	30	100	60
H5	10	55	75	60

Formulation Code	Alfuzosin HCL (mg)	Formulation variables	Formulation Code	Alfuzosin HCL (mg)
H6	10	80	50	60
H7	10	55	75	60
H8	10	55	75	60
H9	10	80	100	60
H10	10	30	75	80
H11	10	80	75	40
H12	10	30	75	40
H13	10	55	50	80
H14	10	55	75	60
H15	10	55	100	80
H16	10	55	50	40
H17	10	55	100	40

6. Regression Analysis

The polynomial equation generated by this experimental design is as follows:

$Yi = b0 + b1X1 + b2X2 + b3X3 + b12X1X2 + b13X1X3 + b23X2X3 + b11X12 + b22X22 + b33X32$ **(3)** Where Yi is the dependent variable, $b0$ is the intercept, $b1$ to $b33$ are the regression coefficients, and $X1$, $X2$ and $X3$ are the independent variables selected from preliminary experiments.

7. Evaluation of Controlled Release Matrix Tablets

All the prepared floating hydrophilic matrix tablets were evaluated for following official parameters.

7.1 Hardness

The hardness of ten tablets was measured using Monsanto Hardness tester. Mean and standard deviation were computed and reported. It is expressed in kg/cm^2.

7.2 Friability

The friability of the tablets was determined using Roche friabilator. It is expressed in percentage (%). 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again. The % friability was then calculated using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100 \quad \textbf{(3.4)}$$

7.3 Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in Table 2 and none deviate by more than twice the percentage shown.

Table 2: The weight variation tolerance for uncoated tablets

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

7.4 In vitro drug release study

Dissolution studies were carried out for controlled release Alfuzosin HCLformulations using 0.01N HCl as dissolution medium. The amount of drug dissolved in the medium was determined by UV spectrophotometer (Shimadzu, Japan) at 244 nm wavelength. Dissolution studies were conducted by USP method 2 at 100 rpm and the temperature was maintained at 37±0.5 ^{o}. This operation was continued for 24 h while samples of 5 ml were withdrawn at regular interval from the dissolution medium and replaced with fresh dissolution medium to maintain the volume constant. The samples were filtered and suitably diluted. Drug dissolved at specified time periods was plotted as mean percent release versus time (h) curve. This drug release profile was fitted into several mathematical models to get an insight of the release mechanism of the drug from the dosage form. The results are shown in Tables 4 to 7 and Figures 5 and 8.

8. Data Analysis

The response surface methodology is a collection of mathematical and statistical techniques used for modeling and analysis of problems in which a response of interest is influenced by several variable and the objectives is to optimize this response.

The run or formulation, which are designed based on Box-Behnken design are evaluated for the response. The response values are subjected to multiple regression analysis to find out the relationship between the factor used and the response value obtained. The response values subjected for this analysis are:

1. % Rel 2 hr
2. $t_{50\%}$
3. Release Exponent *(n)*

The Release Exponent *(n)* obtained after fitting the release rate to Korsmeyer and Peppas model. The multiple regression analysis was done using DESIGN EXPERT 6.0.11 (STAT-EASE) demo version software, which specially meant for this optimization process.

Analysis of data was carried out using ANOVA and the individual parameter was evaluated with F-test. Using the regression coefficient of factor, the polynomial equation for the each response is generated. The results are shown in Tables 9 to 12.

9. Response Surface Methodology (RSM)

Many sets of experiments may be performed in order to develop an optimal MRDDS formula for in vivo testing. The use of response surface methodology (RSM), first developed by Box and Behnken, has been proven to be an useful technique in the development of the solid dosage form.

Some attractive features of response surface methodology are (a) RSM is suitable for simulating the curvature feature of the real life design space; (b) readily understood geometric terms could be used to represent the experimental problem; and (c) RSM is applicable for any number of variables; (d) pure error can be evaluated by experimental center point, which is an integral part of the design, and therefore enable one to check lack of fit of the model. The basic procedure of response surface methodology include experimental design, regression analysis, optimization algorithms and validation. The specifics of the technique were well described by Box and Behnken.

Graph presentation of the data can help one better understand the mechanism underlying the observed phenomena. It gives similar information as that of the model equation obtained from statistical analysis. The response surface graphs were presented in Figures 9 and 10 as an example. The plot covered the entire variable range of the design.

10. Optimization

The optimized formulation obtained by applying constrains is shown in Table 13 and was prepared and evaluated for % Rel 2 hr,, $t_{50\%}$, Release Exponent*(n)*. In this study, optimization was undertaken using both simplex technique incorporated in design expert software package. Optimized formula is shown in Table 14. Dissolution data of optimized formulation are shown in Table 15 and dissolution profile of optimized formulation is shown in Figure 11.

11. Stability Studies

In order to determine the change in performance of dosage form on storage, stability study of optimized batch was carried out at 40°C in a humidity jar having 75 % RH according to ICH. Samples were withdrawn after regular interval and evaluated for change in buoyancy characteristics and drug release pattern. The similarity (f_2) and dissimilarity (f_1) factor was applied to study the effect of storage on the optimized batch. The results are shown in Table 18 and Figure 12.

12. Results AND Discussion

12.1 Evaluation of controlled release matrix tablet

All the prepared controlled release hydrophilic matrix tablets were evaluated for following official parameters.

12.2 Hardness

The hardness (kg/cm^2) of tablets of different batch was found to be in range of 3 to 4 kg/cm^2**.**

12.3 Friability

The percentage friability of different batches of tablets was found to less than 1 %. All the batches of tablets were found to pass the friability test.

12.4 Weight Variation

All the prepared batches comply with the IP standards.

12.5 Selection of Polymers

In contrast to Guar K, Guar U (Five time greater solution viscosity) appears to be considerably less erodible. Although up to ~10 hours water uptake and mass loss are relatively similar to the

Guar K, Guar U appears to undergo only limited swelling and erosion thereafter. The difference is primarily due to the higher molecular weight of Guar U.
A noticeable trend is that for both types of guar gum the matrix erosion and water uptake is somewhat pH dependent with greater water uptake and correspondingly greater erosion in pH 6.4 buffer. The maximal hydration rate for guar has been reported to occur in the region of pH 7.5 – 9, while a minimum in hydration rate occurs at acidic pH. It is possible that the observed differences are therefore hydration rate dependent. It is noteworthy that the HPMC K4M matrices showed almost no variability in terms of pH.

The faster rate and greater extent of hydration observed for PEO and guar as opposed to HPMC K4M may be related to structural similarities and differences between the various polymer types. PEO by virtue of the numerous oxygen atoms in the polyether chain is capable of extensive hydrogen bonding. PEO therefore readily interacts with water molecules which replace the relatively weaker interchain associative bonds by hydrogen bonding. This result in rapid swelling and in shorter, low molecular weight chains relatively rapid disentanglement and dissolution occurs.

Similar to PEO, guar is a linear hydrophilic molecule with no cross links or hydrophobic substituent that may result in strong hydrophobic associations between polymer chains. By virtue of the high degree of galactose substitution on the mannose backbone and the presense of cis-hydroxyl groups on every galactose and mannose subunit, guar is also capable of extensive hydrogen bonding. Furthermore the regular short galactose side branches discourage close association between adjacent chains, thus conferring high swelling and at low molecular weight, relatively good solubility.

In contrast, HPMC hydration and solubility is in part related to the ratio of hydroxyproply to methoxyl substituent. The hydroxypropyl substituent readily interact with water, however this is counteracted by the presence of hydrophobic methoxyl moieties. Associative bonding of neighboring molecules through hydrophobic interaction of methoxy groups is possible. The restraining force of these bonds can only be slowly overcome by penetrating water thus limiting the extent of polymer chain relaxation and dissolution.

The swelling and erosion behavior of guar gum is somewhat analogous to that of polyethylene oxides of various molecular weights. Guar shows rapid hydration and good erodibility, both of which are essential in controlling early rapid diffusion in high drug load matrices and yet achieving complete and non-fickian drug release. Furthermore water uptake in guar appears to be non-fickian (combination of diffusion and relaxation controlled). This increases the possibility of a avoiding fickian diffusion dominated drug release. The results were shown in figures 3.1 to 3.4.

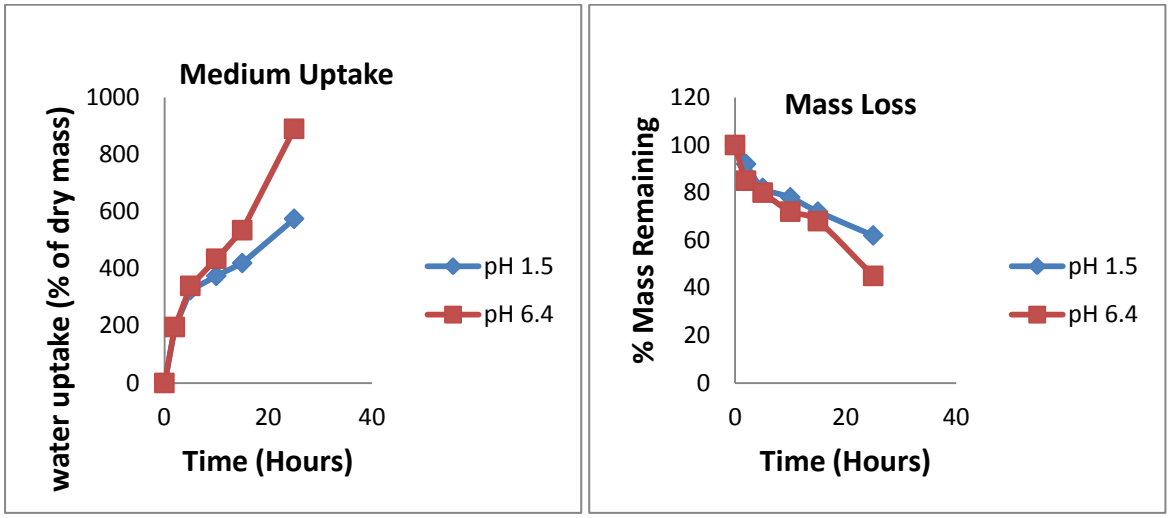

Figure 1 Dissolution medium uptake and mass loss for Guar U matrices

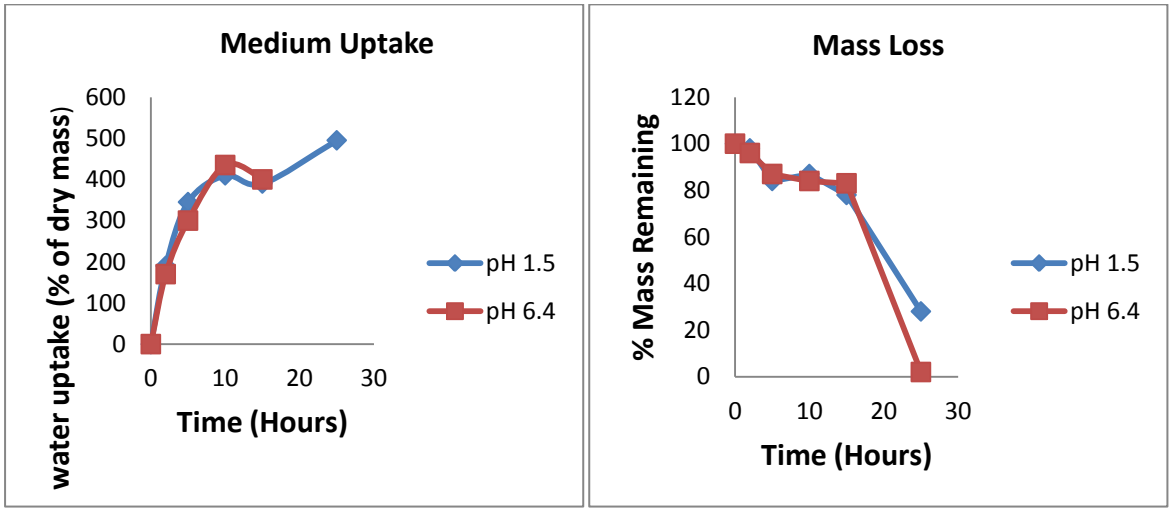

Figure 2 Dissolution medium uptake and mass loss for Guar K

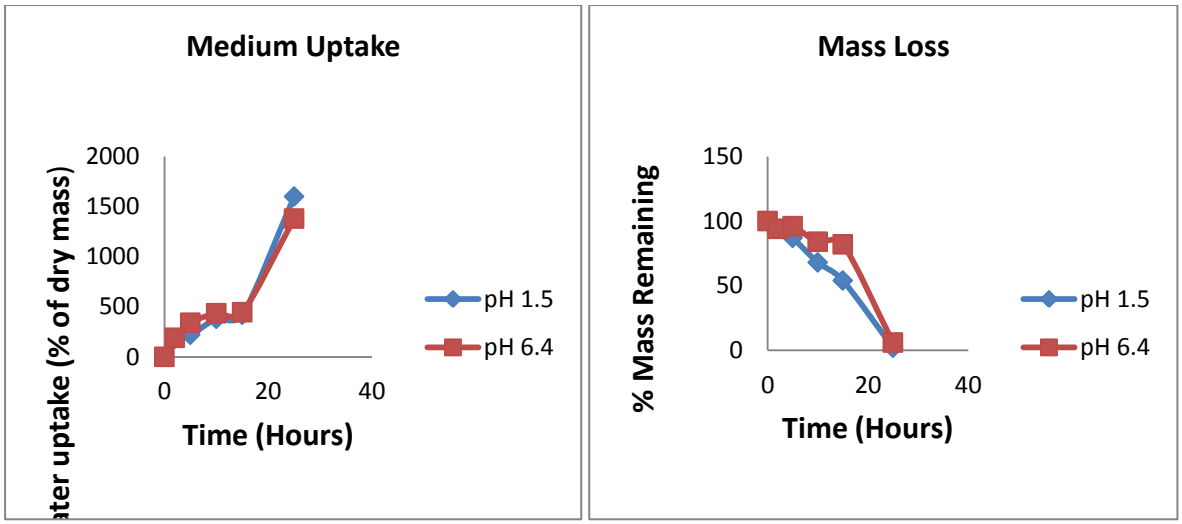

Figure 3 Dissolution medium uptake and mass loss for PEO 301

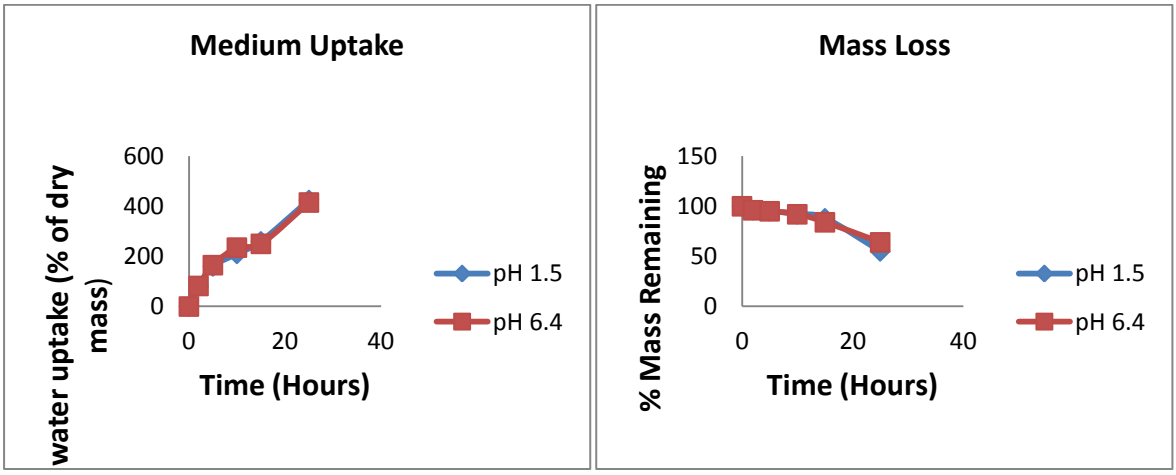

Figure 4 Dissolution medium uptake and mass loss for HPMC K4M

13. Summary of Screening Study

From the various water uptake and mass loss profile it can be seen that in all cases the mass loss closely follows the pattern and extent of water uptake. However, the various polymers show vastly different behavior. PEO 301 and 2 types of guar matrices show markedly faster and greater hydration and erodibility than HPMC K4M. The PEO 301 and Guar K matrices archive almost complete dissolution and relatively linear dissolution over 24 hours. It is remarkable that at 24 hours the water content of the swollen PEO 301 matrices (1600%) is approximately 4 fold that of HPMC K4M (~400%).

14. Optimization Using Box- Behnken Design

14.1 Formulation Development Studies

Based on the conclusions from the screening study, a further evaluation of the formulation variables was performed using a full factorial design to narrow down the range of the formulation variables. In this set of studies, the effect of Guar Gum (Guar U) and the effect of addition of PEO were evaluated.

14.2 Formulation Optimization

The objective of this set of study is to develop an optimized alfuzosin HCL MRDDS formulation and to examine the effects of several formulation variables, including: PEO loading, Guar Gum loading and Maltodextrin loading and on the release properties of the mixed polymeric MRDDS. The optimal range of these formulation variables were chosen based on our screening and formulation development studies. Specifically, seventeen formulations based on a central composite, rotatable, Box-Behnken design were tested. Their release properties were fitted to a quadratic model and obtain the major release responses - release exponent *(n)* and time for half of drug release (t_{50}%). The release exponent was used as the major optimization response. The settings for the optimized formulation were calculated based on the quadratic model obtained from Box-Behnken design.

15. Drug Content

The various batches of active drug have been prepared and it was analyzed for drug contents according to IP standards. The results have been shown in Table 3. The data indicates that all the bathes pass the official criteria of IP.

Table 3: Drug content of different batch

Batch	Drug content	
	Average	SD*
H1	10.14	0.15
H2	9.67	0.22
H3	9.78	0.36
H4	9.43	0.46
H5	9.65	0.22
H6	9.18	0.33
H7	10.32	0.33
H8	10.44	0.35
Batch	**Drug content**	
	Average	**SD***
H9	10.39	0.64
H10	10.17	0.30
H11	9.36	0.28
H12	9.58	0.45
H13	9.27	0.51
H14	9.34	0.14
H15 - H17	9.11	0.37
*mean±SD, n=3		

***15.1 In vitro* drug release study**

Release profiles from the 17 formulations conceived from Box-Behnken design are shown in Table 4 to 7. From Figure 5, it is clear that except for formulation H3 the rest of the formulations show a linear fashion of release in their initial phase, indicating the appropriate choice of the range of the formulation variables. Formulation H3, however, bears a common property, i.e., low PEO (Table 1). Figure 7 illustrated the drug release profile, once again, formulation H10 and H12, which bear the lowest loading of PEO are the worst in terms of controlled release of drug.

Table 4 Dissolution data of tablets of batch H1 to batch H4

Time (hr)	Batch							
	H1		H2		H3		H4	
	%CR	SD*	%CR	SD*	%CR	SD*	%CR	SD*
0	0	0	0	0	0	0	0	0
1	15.26	3.26	18.54	0.3	21.28	2.59	14.58	0.24

Time (hr)	Batch	Time (hr)	Batch	Time (hr)	Batch	Time (hr)	Batch	Time (hr)
2	18.36	2.86	19.45	0.9	34.25	3.88	16.95	0.68
3	21.45	3.69	24.58	0.32	40.48	1.47	20.59	0.7
4	25.36	2.27	26.98	0.3	56.27	1.3	23.48	0.6
5	29.35	2.72	34.65	0.78	70.15	0.83	27.89	0.64
6	35.14	2.96	39.47	2.3	82.47	0.62	33.56	0.44
7	41.59	3.95	48.26	2.28	89.24	0.31	41.58	0.71
8	48.57	2.58	57.48	3.08	94.36	0.32	47.95	0.69
9	59.48	0.94	72.45	1.6	95.48	0.15	58.48	0.16
10	71.54	0.43	86.35	2.82	96.27	0.07	70.48	0.49
11	84.56	0.15	91.24	0.62	96.84	1.51	85.96	1.97
12	88.15	0.42	92.54	1.3	96.47	0.7	94.58	1.71
*mean±SD, n=3								

Table 5: Dissolution data of tablets of batch H5 to batch H8

Time (hr)	Batch							
	H5		H6		H7		H8	
	%CR	SD*	%CR	SD*	%CR	SD*	%CR	SD*
0	0	0	0	0	0	0	0	0
1	17.85	0.4	18.59	0.24	17.24	4.41	18.23	0.17
2	21.85	0.66	21.58	0	20.55	1.71	21.22	0.26
3	25.5	0.23	24.59	1.15	25.2	1.2	24.14	0.93
4	28.2	0.78	29.48	1.13	28.18	1.63	29.18	0.3
5	35.15	0.58	32.58	0.48	33.69	2.09	34.65	1.85
6	38.47	1.22	38.59	0.86	41.27	1.99	38.97	3.3
7	51.76	1.94	46.78	1.58	49.66	1.79	49.21	4.13
8	56.69	3.24	51.48	1.41	58.14	2.71	58.67	6.06
9	72.45	1.72	62.58	1.87	71.89	1.54	71.67	5.42
10	85.25	1.19	71.54	3.39	84.15	2.09	84.85	5.25
11	90.21	1.75	84.56	1.08	90.23	1.16	90.1	1.35
12	93.39	1.21	88.15	1.13	93.14	1.2	93.44	0.3
*mean±SD, n=3								

Table 6: Dissolution data of tablets of batch H9 to batch H12

Time (hr)	Batch							
	H9		H10		H11		H12	
	%CR	SD*	%CR	SD*	%CR	SD*	%CR	SD*
0	0	0	0	0	0	0	0	0
1	12.48	0.46	20.58	0.09	16.66	3.22	21.53	8.02
2	15.68	1.37	32.96	0.38	20.34	3.01	32.12	4.75
3	18.48	0.69	38.48	1.6	23.66	3.17	39.14	2.95
4	22.48	1.06	54.25	1.45	27.12	3.21	53.67	3.1
5	26.48	1.14	68.95	1.43	31.75	3.53	67.25	1.92

Time (hr)	Batch	Time (hr)	Batch	Time (hr)	Batch	Time (hr)	Batch	Time (hr)
6	31.96	1.54	80.45	1.7	35.45	1.97	78.35	1.4
7	37.65	1.51	87.69	3.3	41.59	2.48	85.28	0.83
8	44.81	1.89	92.65	2.88	47.23	1.82	92.65	0.75
9	52.84	2.41	96.58	3.64	58.78	3.13	95.52	1.3
10	67.28	2.47	96.45	3.89	72.45	1.18	96.45	0.65
11	79.48	1.26	96.58	1.28	83.86	0.47	97.34	0.32
12	86.59	1.06	97.21	1.45	88.15	1.97	97.21	3.25
*mean±SD, n=3								

Table 7: Dissolution data of tablets of batch H13 to batch H17

Time (hr)	Batch									
	H13		H14		H15		H16		H17	
	%CR	SD*	%CR	SD*	%CR	SD*	%CR	SD*		
0	0	0	0	0	0	0	0	0	0	0
1	22.36	0.31	18.54	0.93	15.25	1.18	20.36	0.31	17.52	0.93
2	30.65	1.07	21.09	1.07	20.65	1.16	27.15	1.07	21.14	1.07
3	36.45	1.08	25.9	1.17	23.59	1.82	34.13	1.08	24.29	1.17
4	41.56	1.49	28.12	1.1	24.58	3.15	39.26	1.49	25.11	1.1
5	48.65	2.27	34.65	1.35	31.84	3.11	48.65	2.27	31.84	1.35
6	55.69	0.79	41.34	1.89	36.59	2.41	57.24	0.79	37.18	1.89
7	62.95	1.97	47.51	0.83	39.84	2.8	61.92	1.97	39.24	0.83
8	74.65	1.52	57.34	3.65	45.89	2.47	75.22	1.52	43.52	3.65
9	85.95	1.66	71.42	3.15	55.39	2.39	86.12	1.66	54.39	3.15
10	92.38	1.47	84.33	3.8	69.48	3.1	92.38	1.47	68.23	3.8
11	94.58	0.31	90.24	0.78	81.97	0.94	93.51	0.31	79.25	0.78
12	95.28	0.79	92.51	0.73	91.58	0.71	94.25	0.79	89.24	0.73
*mean±SD, n=3										

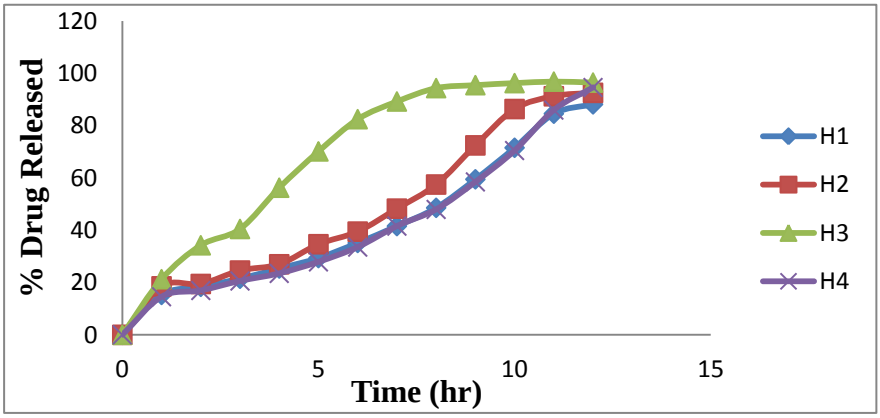

Figure 5 Drug release profile of batch H1 to H4

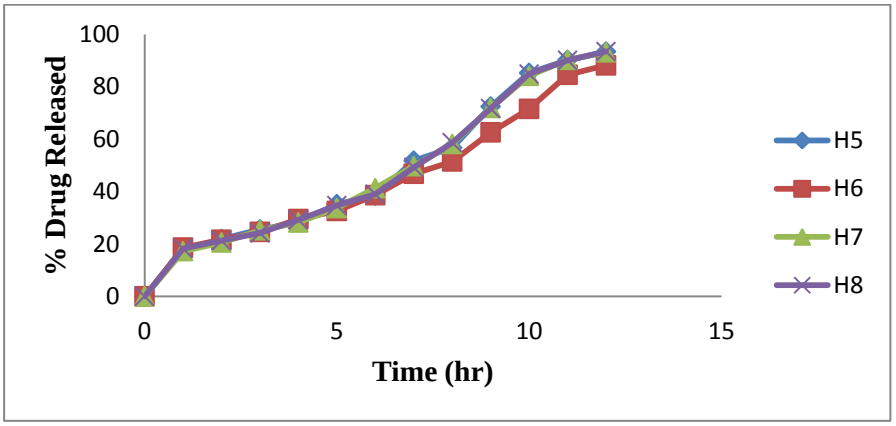

Figure 6 Drug release profile of batch H5 to H8

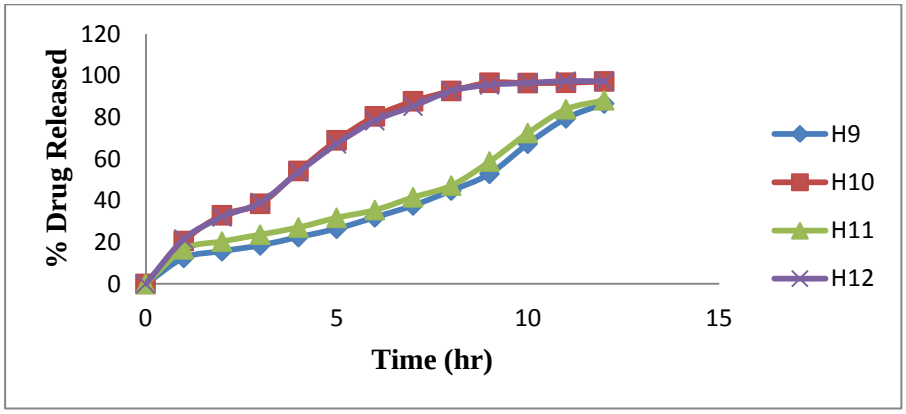

Figure 7 Drug release profile of batch H9 to H12

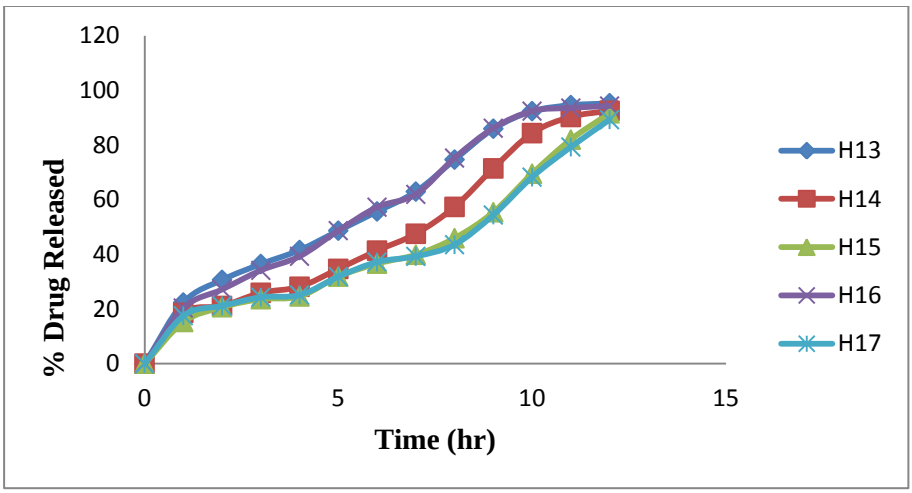

Figure 8 Drug release profile of batch H13 to H17

16. Characterize Release Profiles

Following the procedure described in the method section, drug dissolution data were fitted to power law. Most of the fittings give high r^2 values close to 1.0 (Table 8). Release exponents *(n)*

thus obtained ranged from 0.459 to 0.607. Three formulations (H3, H10 and H12) which do not show a linear fashion in its initial release profile (Figure 5 and 7) bear very low n values, 0.459, 0.471 and 0.465 respectively. The low PEO settings for these formulations are at least partially responsible for the incapability of the controlled release of drug from MRDDS. Other formulations give decent n values, such as formulation H4 and H9 bear a value around 0.60. T_{50}% values of different formulations were obtained and results were summarized in Table 3.9. Formulations (formulation 3, 10 and 12) correspond to a low t_{50}% values. Several formulations have their t_{50}% values around the desired range, i.e. from 6 to 8 hr. Some of the formulations, such as: formulation H1,H2,H4,H5,H7,H8,H9,H10,H14 and H15 have a n value close or greater than 0.55, the $t_{50\%}$ value of these formulations are also within a reasonable range (i.e. between 6 to 8 hr). ANOVA table for the release properties of the formulations has demonstrated that the two main effectsPEO and Guar Gum are all significant to the release exponent n (Y_1). In the same vein, these main effects and their interactions are also important in terms of t_{50}% (Y_2), % rel 2 hr (Y_3).

Table 3.8: Dissolution data treatments of tablets of batch H1 to batch H17

Batch	Zero order		Higuchi		Korsmeyer Peppas		
	K_0	r^2	K_H	r^2	n	r^2	Km
H1	15.777	0.9916	7.749	0.9926	0.562	0.9935	28.07
H2	19.585	0.9675	6.893	0.9829	0.552	0.9858	26.80
H3	48.568	0.7746	22.457	0.9798	0.459	0.989	17.14
H4	13.367	0.9978	11.481	0.9887	0.592	0.9911	28.87
H5	20.122	0.9693	6.393	0.9865	0.554	0.9891	26.62
H6	19.716	0.9936	3.795	0.9945	0.508	0.9934	26.86
H7	19.850	0.9719	6.568	0.9894	0.560	0.9928	26.71
H8	19.526	0.9720	6.942	0.9872	0.562	0.9875	26.82
H9	12.365	0.9963	10.764	0.9902	0.607	0.9950	29.21
H10	46.571	0.7918	20.328	0.8918	0.471	0.9245	17.80
H11	17.449	0.9916	5.306	0.9902	0.525	0.9904	27.51
H12	45.977	0.8095	19.428	0.9061	0.465	0.9363	18.00
H13	33.260	0.9304	7.582	0.9775	0.464	0.9886	22.24
H14	20.338	0.9720	5.465	0.9865	0.538	0.9890	26.55

H15	15.869	0.9959	7.150	0.9871	0.545	0.9897	28.04
H16	32.057	0.9221	5.690	0.9738	0.493	0.9862	22.64
H17	17.109	0.9965	4.636	0.9851	0.502	0.9846	27.63

All the tablets showed good fit for Higuchi (r^2 =0.97-0.99) and Korsmeyer (r^2 =0.98-0.99) kinetic models (Table 3.8). From Higuchi model it is evident that alfuzosin is released by diffusion process from the matrices. The diffusion exponent (n) of Korsmeyer model ranged from 0.45-0.60 indicating anomalous or non-Fickian transport.

17. Data Analysis

The responses were recorded and analysis of data was carried out using ANOVA in (STAT-EASE). The individual parameter was evaluated using F-test and a polynomial equation for each response was generated using MLRA. The design and response summary data are represented in Table 9

Table 9: The design and response summary data

Std.	Factors			Response		
	A: Amt of PEO	B: Amt of Guar Gum	C: Amt of Maltodextrin	% Rel 2 hr	$t_{50\%}$ (hr)	Release exponent (n)
1	80	75	80	21.45	11	0.9922
2	55	75	60	24.58	9	0.9778
3	30	50	60	40.58	3	0.9876
4	30	100	60	20.59	11	0.9918
5	55	75	60	25.5	8	0.9884
6	80	50	60	24.59	10	0.9980
7	55	75	60	25.2	8	0.9898
8	55	75	60	25.14	8	0.9933
9	80	100	60	18.48	11	0.9963
10	30	75	80	38.48	3	0.9889
11	80	75	40	23.66	11	0.9912
12	30	75	40	39.14	3	0.9846
13	55	50	80	36.45	5	0.9712
14	55	75	60	25.90	9	0.9712
15	55	100	80	25.59	11	0.9602
16	55	50	40	34.13	5	0.9914
17	55	100	40	24.29	11	0.9857

Response: % Rel 2 hr

Table 10: ANOVA for response surface quadratic model (% Rel 2 hr)

Source	SS	DF	MS	F value	Prob > F
Model	739.15	9	82.13	15.95	0.0007
A	318.91	1	318.91	61.94	0.0001
B	272.61	1	272.61	52.95	0.0002
C	0.070	1	0.070	0.014	0.9103
A^2	1.89	1	1.89	0.37	0.5641
B^2	0.044	1	0.044	8.466E-003	0.9293
C^2	94.97	1	94.97	18.45	0.0036
AB	47.47	1	47.47	9.22	0.0189
AC	0.60	1	0.60	0.12	0.7427
BC	0.26	1	0.26	0.051	0.8286
Residual	36.04	7	5.15	--	--
Lack of fit	35.09	3	11.70	49.38	0.013
Pure error	0.95	4	0.24	--	--
Cor total	775.19	16	--	--	--

The Model F-value of 15.95 implies the model is significant. There is only a 0.07% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B, AB, C^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.The "Lack of Fit F-value" of 49.38 implies the Lack of Fit is significant. There is only a 0.13% chance that a "Lack of Fit F-value" this large could occur due to noise.

Response: $t_{50\%}$

Table 11: ANOVA for response surface quadratic model ($t_{50\%}$)

Source	SS	DF	MS	F value	Prob > F
Model	132.50	3	44.17	16.59	0.0001
A	72.00	1	72.00	27.04	0.0002
B	60.50	1	60.50	22.72	0.0004
C	2.842	1	2.842	1.067	1.0000
A^2	1.72	1	1.72	0.33	0.5238
B^2	0.058	1	0.058	7.32	0.0310
C^2	94.97	1	94.97	18.45	0.0068
AB	46.42	1	46.42	8.25	0.0172
AC	0.60	1	0.60	0.14	0.6845
BC	0.26	1	0.26	0.048	0.8835
Residual	34.62	13	2.66	--	--
Lack of fit	32.82	9	3.65	8.10	0.0296
Pure error	1.80	4	0.45	--	--
Cor total	167.12	16	--	--	--

The Model F-value of 16.59 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms.Values greater than 0.1000 indicate the model terms are not significant.The "Lack of Fit F-value" of 8.10 implies the Lack of Fit is significant. There is only a 2.96% chance that a "Lack of Fit F-value" this large could occur due to noise.

Response: Release exponent *(n)*

Table 12: ANOVA for response surface quadratic model (Release Exponent)

Source	SS	DF	MS	F value	Prob > F
Model	3.01	9	0.33	18.91	0.0004
A	1.03	1	1.03	57.94	0.0001
B	5.35E-003	1	5.35E-003	0.30	0.5993
C	0.89	1	0.89	50.16	0.0002
Source	**SS**	**DF**	**MS**	**F value**	**Prob > F**
A^2	0.024	1	0.024	1.34	0.2856
B^2	0.11	1	0.11	6.45	0.0386
C^2	0.077	1	0.077	4.36	0.0753
AB	0.095	1	0.095	5.34	0.0541
AC	0.45	1	0.45	25.33	0.0015
BC	0.34	1	0.34	19.47	0.0031
Residual	0.12	7	0.018	--	--
Lack of fit	0.091	3	0.030	3.64	0.0122
Pure error	0.033	4	8.31E-003	--	--
Cor total	3.14	16	--	--	--

The Model F-value of 18.91 implies the model is significant. There is only a 0.04% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, C, B^2, AC, BC are significant model terms.

Figure 9 illustrates that more amount of PEO is better in order to decrese the % Rel at 2 hr. there is a decrease of % Rel at 2 hr as PEO loading goes from a lower to upper level, while for Guar Gum, it seems no effect. Figure 10 illustrates that more amount of Guar Gum is better in order to increase the $t_{50\%}$, while for PEO, it seem less effect.

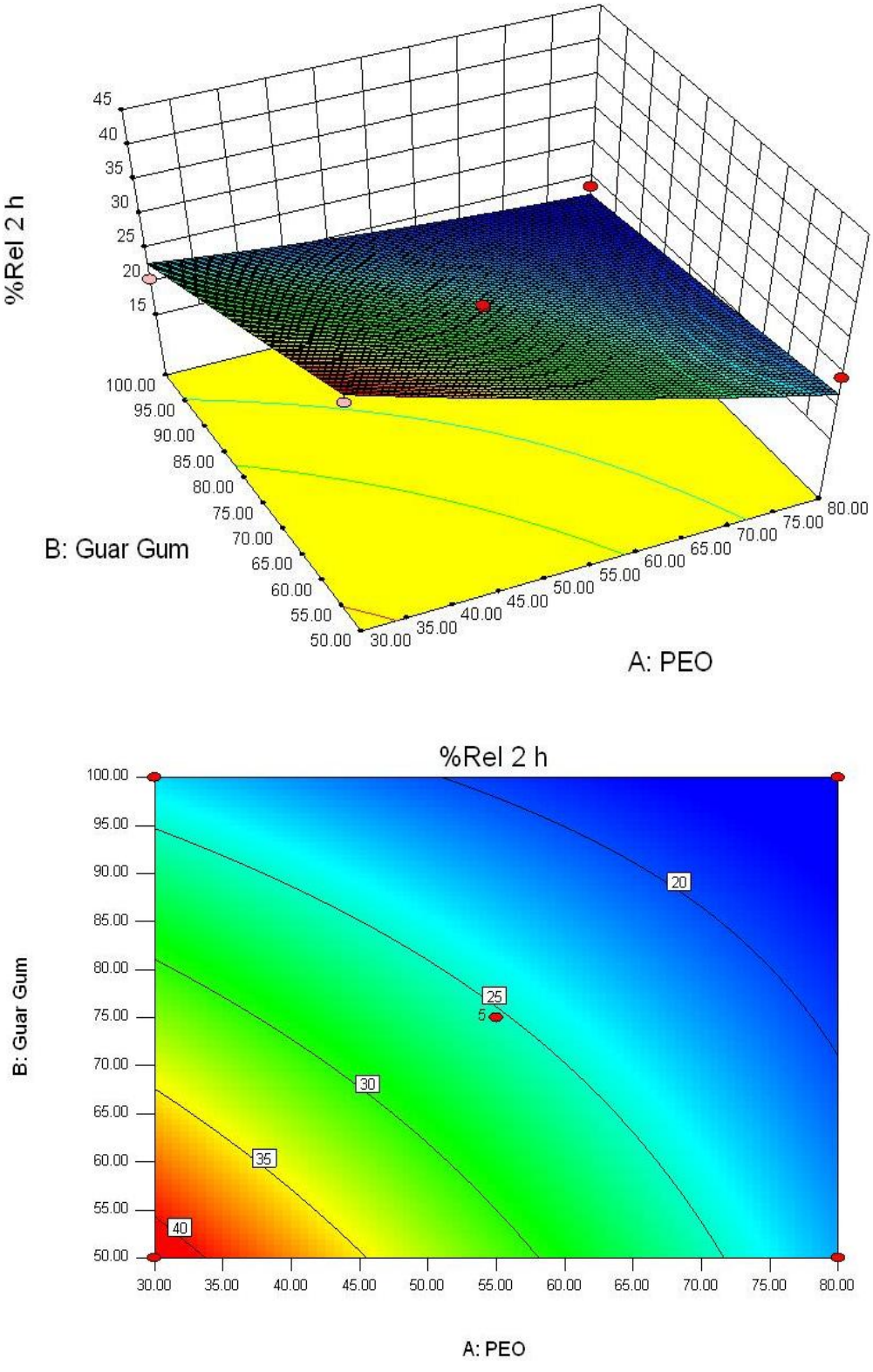

Figure 9 Response surface graph and counter plot showing the effect of Guar Gum and PEO on % Rel 2hr

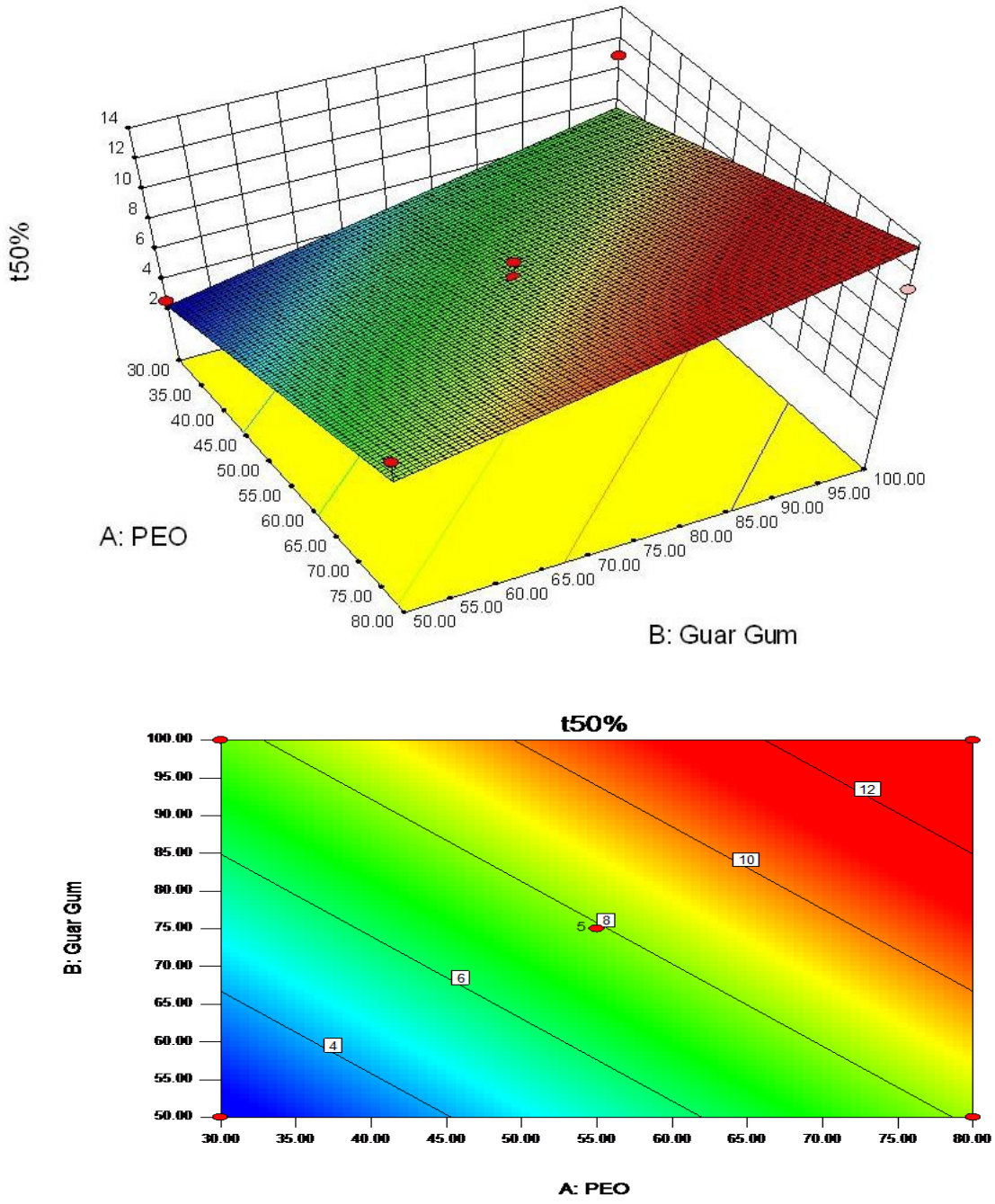

Figure 10 Response surface graph and counter plot showing the effect of Guar Gum and PEO on $t_{50\%}$

Optimization

The optimized formulation obtained by applying constrains is shown in Table 13 and was prepared and evaluated for % Rel 2 hr, $t_{50\%}$ and Release Exponent *(n)*. In this study, optimization was undertaken using both simplex technique incorporated in design expert software package. Maximization of the release exponent would be favorable indicating a more uniform release rate

(i.e., approach zero order release) from the polymeric system. In the mean while, certain constraint was applied on $t_{50\%}$, % Rel 2 hr and Release Exponent.

Table 13: Constrains for optimization

Name	Goal	Lower Limit	Upper Limit
Amt of PEO	Is in range	30	80
Amt of Guar Gum	Is in range	50	100
Amt of Maltodextrin	Is in range	40	80
% Rel 2 hr	Is target = 25	18.48	40.48
$t_{50\%}$	Is target = 8	2.5	11
Release Exponent *(n)*	Is target = 0.9898	0.9602	0.9980

Table 14: Optimized formulation

Ingredients	Quantity (mg)
Drug	10
PEO	70.00
Guar Gum	60.00
Maltodextrin	68.00
Mg. Stearate	2.00

Dissolution data of optimized formulation are shown in Table 15 and dissolution profile of optimized formulation is shown in Figure 11.

Table 15: Dissolution data of optimized formulation

Time (hr)	% CR ± SD*
0	0.0 ± 0.0
1	10.02 ± 0.17
2	19.98 ± 0.25
3	29.26 ± 0.68
4	38.03 ± 1.16

5	46.53 ± 1.50
6	54.78 ± 0.21
7	62.67 ± 0.68
8	70.62 ± 0.75
9	77.84 ± 1.71
10	83.26 ± 1.77
11	89.46 ± 0.79
12	96.96 ± 0.95
*mean± SD, n=3	

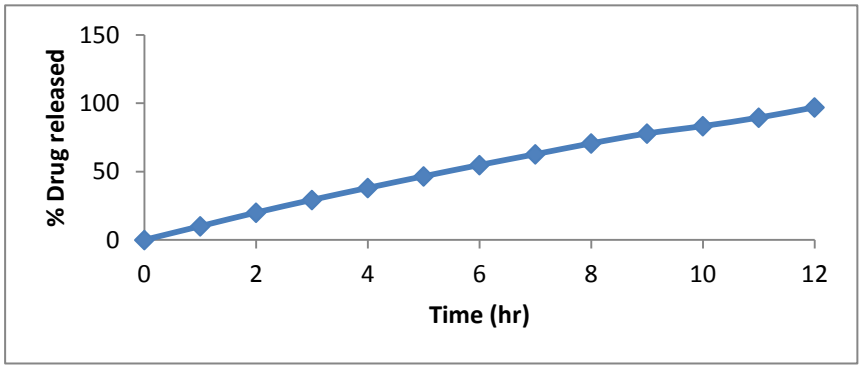

Figure 11 Dissolution profile of optimized formulation

17. Treatment of Dissolution Data

The data obtained after dissolution was subjected to zero order kinetic equation, Higuchi equation and Korsmeyer and Peppas equation. The results obtained are shown in Table 16.

Table 3.16: Treatment to dissolution data of optimized formulation

Zero order		Higuchi		Korsmeyer- Peppas		
K_0	R^2	K_H	r^2	n	r^2	Km
6.46	0.9825	26.62	0.9943	0.792	0.9961	31.17

The dissolution data of optimized formulation showed good fit for Higuchi (r^2 =0.9943) and Korsmeyer (r^2 =0.9961) kinetic models (Table 16). From Higuchi model it is evident that alfuzosin is released by diffusion process from the matrices. The diffusion exponent (n) of Korsmeyer model is 0.792 indicating anomalous or non-Fickian transport.

% error of optimized formulation for $t_{50\%}$ was found to be more. However other responses exhibit negligible values of % Error. The predicted and observed values with % error of optimized formulation for the responses % Rel 2 hr, $t_{50\%}$ and Release Exponent (n) are displayed in Table 17.

Table 17: Comparison between observed values and predicted values of optimized formulation

Response	Observed	Predicted	% error
% Rel 2 hr	23.98	25	4.08
$t_{50\%}$	7.6	8	5.00
Release exponent (n)	0.9998	1	1.00

17.1 Stability studies of the optimized batch

Stability study for optimized formulation was performed for 3 months. The condition maintained was 40°C / 75% RH. After 3 months, optimized formulation was evaluated for hardness, drug content and dissolution study. Comparison of hardness, drug content and dissolution study is shown in Table 18 and release profile in figure 12. The formulation was stable in terms of morphology, drug content and drug release.

Table 18: Evaluated data of fresh sample and after 3 months

Parameter	Fresh Sample	After 3 months
Hardness	4 kg/cm^2	4 kg/cm^2
Drug content	9.92 ± 0.35 mg	9.58 ± 0.36 mg
% CDR (12hr)	94.25	93.89

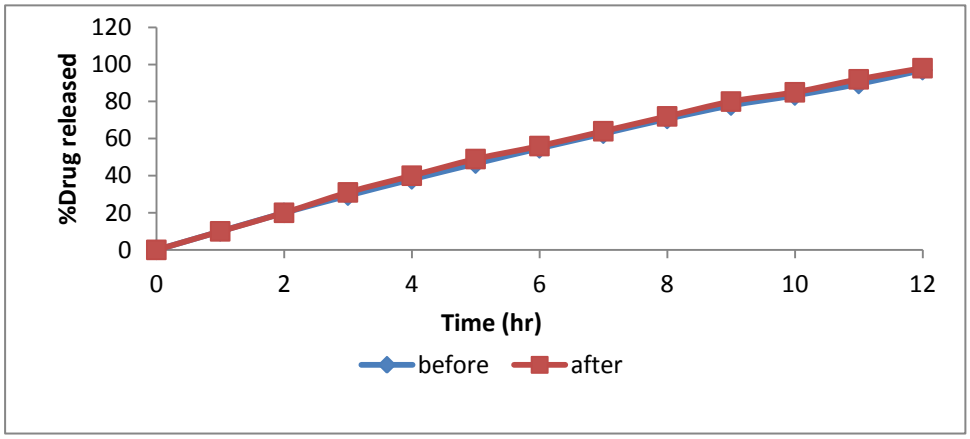

Figure 12 Dissolution profile of optimized formulation at 0 and 3 months

18. Conclusion

The *in vitro* developmental work consists of two major parts, including screening the formulation variables and optimizing the formulation using central composite, Box-Behnken design. The polymer used in the final formulation (PEO and Guar Gum) were found to be in good correlation with each other. The effect of various factors on response Release exponent, $t_{50\%}$, % Rel 2 hr were evaluated using DESIGN EXPERT 8.0.6.1 (STATEASE) demo version software. Each response was analyzed using ANOVA and the individual parameter was evaluated using F-test.

The optimized formulation was obtained by applying constraints on responses. The optimized formulation was evaluated and observed value of response is compared with predicted values.

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