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Original Article

# *In Vitro* Studies of Controlled Release Alfuzosin Matrix Tablets Prepared with Ethylcellulose and Hydroxypropyl Methylcellulose

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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 study was the development and *in vitro* evaluation of a controlled release dosage form of a freely soluble weakly basic drug (alfuzosin hydrochloride). Binary mixer of one hydrophilic polymer (hydroxypropyl methylcellulose) and one hydrophobic polymer (ethyl cellulose) was used in tablets prepared by direct compression, $3^2$ factorial design was chosen and the amount of two polymers were taken as independent variables. The percent drug released at 1, 6, 12, and 20 h were selected as response. The main effect and interaction terms were quantitatively evaluated using mathematical model. Dissolution data were fitted to zero order, first order, and Higuchi's release kinetics to evaluate kinetic data. According to Korsmeyer's equation drug release followed both diffusion and erosion mechanism in all cases. Drug release was different from three fillers (microcrystalline cellulose, lactose and dibasic calcium phosphate).

*Keywords:* Alfuzosin; Ethyl cellulose; Hydroxypropyl methylcellulose; Release kinetics.

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## 1. Introduction

Alfuzosin hydrochloride is a selective α-adrenergic antagonist used against benign prostatic hypertrophy (BPH) [1-3]. It is freely soluble in water [4] and readily absorbed after oral administration. The $pK_a$ of the drug is 8.1 and elimination half life of immediate release tablet is 3-5 h [5]. The usual dose of alfuzosin is 2.5 mg thrice daily [6-8]. Recently 10 mg once daily extended release formulation has become available in market [5]. It is convenient for older patients to take only one tablet a day [9]. Marketed alfuzosin formulation is three layered geomatrix tablet

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that requires special facilities, high cost, more time and complex operation than normal direct compression formulation [10]. Therefore, a less complicated formulation is desired which can be prepared by conventional tools. In this experiment, matrix tablets were prepared by direct compression method to simplify the process. The matrix system is both economic and easy to scale up [11-12].

As alfuzosin is freely soluble in water, it is difficult to sustain release for 24 h. Therefore, a polymer combination (hydroxypropyl methylcellulose (HPMC) and ethylcellulose (EC) was tried to reduce drug release. Combination of HPMC and EC was used in sustained release coating formulations [13, 14] as well as in matrix tablets [15-17], previously. HPMC is widely used in matrix formulations as a release retardant polymer [18-20]. It can control drug release by quickly forming a gel barrier. When a drug is formulated with gel forming hydrocolloids such as HPMC, it swells in the gastric fluid affording a prolonged gastric residence time. Its muco-adhesive nature was also reported [21]. EC has been used in different dosage forms as a coating polymer [22, 23], as a tablet binder for microcapsules [24] and also as a matrix forming material for sustained release dosage forms [25, 26].

Because alfuzosin is a new drug molecule, reports on its formulation aspects are very limited. Very recently different HPMC grades were used to control release of alfuzosin [27, 28]. There is no report on alfuzosin matrix tablet prepared by both HPMC and EC in direct compression method.

## 2. Materials and Methods

### *2.1. Materials*

The following materials were used in the experiment: Alfuzosin HCl BP (Standard Chem. & Pharma. Co. Ltd, Taiwan), micro-crystalline cellulose PH 101 (MCC; Ming Tai Chemical Co. Ltd., Taiwan), HPMC (Methocel® K15M CR, The Dow Chemical Company, USA), EC (Ethocel® 20 cps, The Dow Chemical Company, USA), EC aqueous dispersion (Surelease®,Colorcon, USA), magnesium stearate (Paul Lohman, Germany), polyvinyl pyrollidone (Kollidon 30, BASF, Germany), lactose (Flowlac® , Meggle GmbH, Germany) and dibasic calcium phosphate (Interpharm Ltd., UK). Other chemicals used were reagent grade.

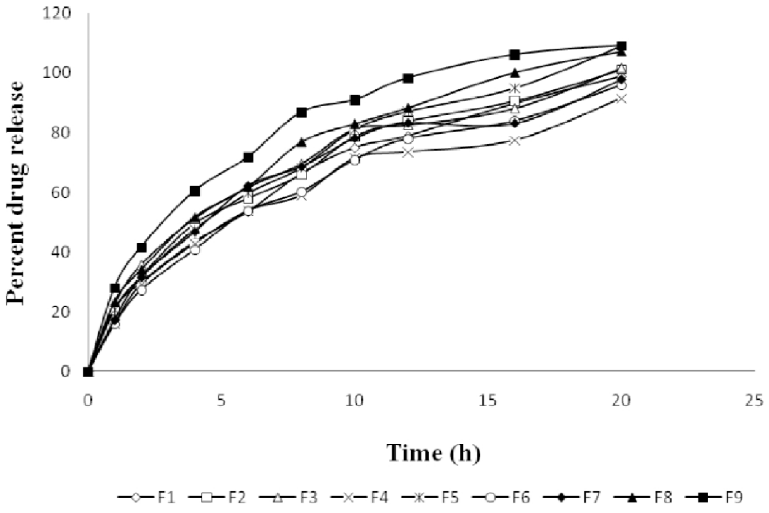


**Figure 1.** Zero order release profile of alfuzosin HCl formulations. [Ratio of HPMC and EC is10:1(F1), 2:1(F2), 3:1(F3), 5:1(F4), 8:3(F5), 10:3(F6), 8:5(F7), 4:1(F8) and 6:1(F9)]. The mean of 3 runs. Error bars omitted for the sake of clarity.

**Table 1.** Composition of tablet formulations.

| Formulation code | Weight (mg)/ Tablet | | | | | | |
|---|---|---|---|---|---|---|---|
| | Alfuzosin HCl | HPMC (Methocel® K15M CR) | EC | Magnesium stearate | Kollidon 30 | MCC 101 | Total |
| F1 | 10 | 150 | 15 | 3 | 9 | 113 | 300 |
| F2 | 10 | 90 | 45 | 3 | 9 | 143 | 300 |
| F3 | 10 | 90 | 30 | 3 | 9 | 158 | 300 |
| F4 | 10 | 150 | 30 | 3 | 9 | 98 | 300 |
| F5 | 10 | 120 | 45 | 3 | 9 | 113 | 300 |
| F6 | 10 | 150 | 45 | 3 | 9 | 83 | 300 |
| F7 | 10 | 120 | 15 | 3 | 9 | 143 | 300 |
| F8 | 10 | 120 | 30 | 3 | 9 | 128 | 300 |
| F9 | 10 | 90 | 15 | 3 | 9 | 173 | 300 |

*2.2. Experimental design*

A $3^2$ full factorial design was adopted for the experiment. Two variables ($X_1$, $X_2$) are the amount of two release controlling polymers as shown in Table 1. The selected responses for all possible 9 formulations were the percentage of drug released at 1, 6,12 and 20 h. HPMC was evaluated at 30%, 40% and 50% while EC was evaluated at 5%, 10% and 15%.

*2.3. Preparation of matrix tablets*

Tablets were prepared by direct compression process according to the formula given in Table 1. In all cases the amount of active ingredient was 10 mg and the total weight of the tablet was 300 mg. The ingredients were sieved through 40 mesh and mixed manually for 10 min. Magnesium stearate (1%) was then added after sieving through 60 mesh and blended for 2 min. The tablets were compressed with B type 16 station rotary compression machine (Manesty, UK) using 10 mm diameter punches with 1.5 ton compression force.

In case of aqueous dispersion of EC containing formula wet granulation was chosen. All the ingredients except magnesium stearate were sieved through 40 mesh and Surelease® alone or diluted with water was added as granulating solution. They produced sticky mass which may be due to the presence of water which induce gel formation and swelling of HPMC. After the granules were dried in a tray oven at 60 °C for one h, rock solid granules were obtained which could not be compressed into tablet. Therefore, Surelease® containing formula could not be studied.

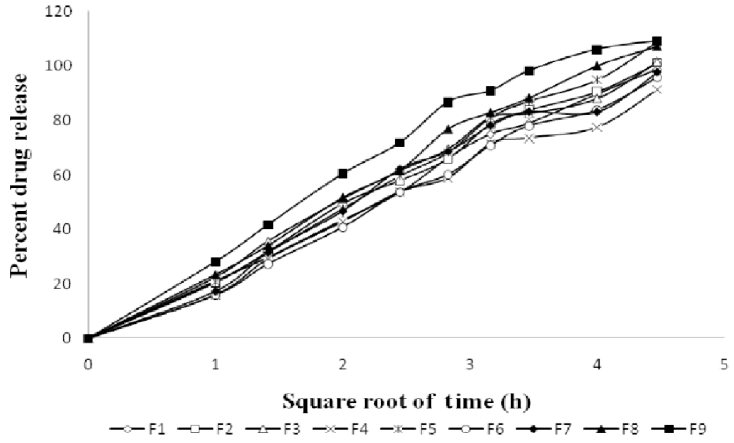


**Figure 2.** Higuchi release profile of alfuzosin HCl formulations. [Ratio of HPMC and EC is10:1(F1), 2:1(F2), 3:1(F3), 5:1(F4), 8:3(F5), 10:3(F6), 8:5(F7), 4:1(F8) and 6:1(F9)].

**Table 2.** Physical characteristics of alfuzosin matrix tablets (mean values).

| Formulation Code | Weight variation % | Hardness ($Kg/cm^2$) | Friability (%) | Bulk density (loose) $g/cm^2$ | Bulk density (tapped) $g/cm^2$ | Carr's index | Hausner ratio |
|---|---|---|---|---|---|---|---|
| F1 | 1.20 | 2.00 | 0.03 | 0.40 | 0.58 | 31.03 | 1.45 |
| F2 | 1.31 | 2.50 | 0.01 | 0.41 | 0.58 | 29.31 | 1.41 |
| F3 | 0.80 | 0.50 | 0.01 | 0.40 | 0.57 | 29.82 | 1.43 |
| F4 | 1.50 | 2.00 | 0.01 | 0.42 | 0.59 | 28.81 | 1.40 |
| F5 | 0.50 | 2.00 | 0.01 | 0.41 | 0.58 | 29.31 | 1.41 |
| F6 | 1.76 | 2.50 | 0.01 | 0.40 | 0.58 | 31.03 | 1.45 |
| F7 | 2.14 | 2.50 | 0.01 | 0.43 | 0.59 | 27.12 | 1.37 |
| F8 | 0.65 | 2.50 | 0.01 | 0.42 | 0.60 | 30.00 | 1.43 |
| F9 | 0.67 | 3.00 | 0.01 | 0.41 | 0.58 | 29.31 | 1.41 |

*2.4. Physical evaluation of tablets*

The weight variation was evaluated with 10 tablets using an electronic balance (Sartorius, Germany) and hardness was determined using a Monsanto hardness tester. Friability was determined according to British Pharmacopoeia with Roche friabilator (Erweka, Germany). Bulk density and tapped density of the powder blend was determined with graduated cylinders according to USP guidelines. Flow property and compressibility of the powder blend were determined from Hausner ratio and Carr's index [29].

*2.5. In vitro dissolution studies*

All dissolution studies were carried out for extended release alfuzosin formulations using 0.01 N HCl as dissolution medium [30]. The amount of drug dissolved in the medium was determined by UV spectrophotometer (Shimadzu, Japan) at 244 nm. Dissolution studies were conducted in paddle method with USP dissolution tester (Erweka, Germany) at a speed of 100 rpm [30] and the temperature was maintained at 37 °C±0.5 °C. As the tablets have floating tendency, metallic sinker was used to keep tablets immersed into the medium. This operation was continued for 24 h. At 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 h intervals samples of 5 ml were withdrawn 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

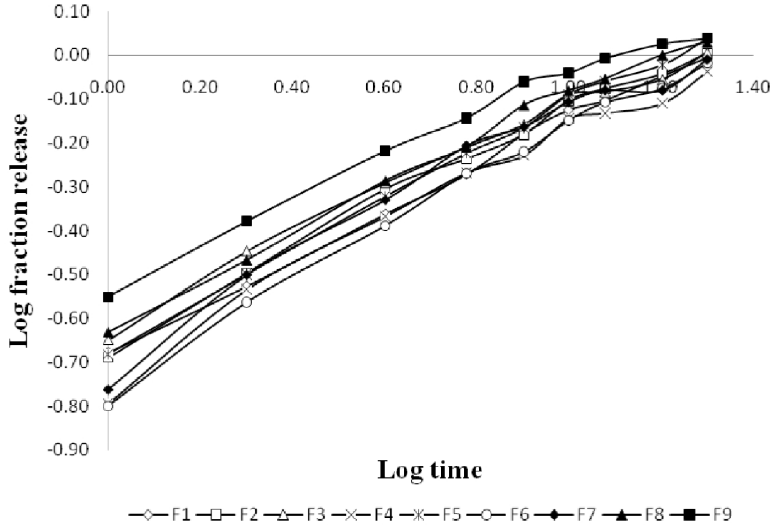


**Figure 3.** Korsmeyer release profile of alfuzosin HCl formulations [ratio of HPMC and EC is10:1(F1), 2:1(F2), 3:1(F3), 5:1(F4), 8:3(F5), 10:3(F6), 8:5(F7), 4:1(F8) and 6:1(F9)].

**Table 3.** Release kinetics of alfuzosin from matrix tablets.

| | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| **Zero order** | | | | | | | | | |
| $r^2$ | 0.89 | 0.86 | 0.85 | 0.86 | 0.89 | 0.88 | 0.84 | 0.85 | 0.77 |
| $K_0$ | 3.97 | 3.92 | 3.85 | 3.56 | 4.31 | 3.84 | 3.82 | 4.21 | 4.03 |
| **First order** | | | | | | | | | |
| $r^2$ | 0.94 | 0.91 | 0.89 | 0.98 | 0.96 | 0.97 | 0.94 | 0.90 | 0.96 |
| $K_1$ | 0.08 | 0.09 | 0.08 | 0.05 | 0.09 | 0.06 | 0.08 | 0.11 | 0.13 |
| **Higuchi** | | | | | | | | | |
| $r^2$ | 0.99 | 0.98 | 0.98 | 0.98 | 0.99 | 0.99 | 0.97 | 0.98 | 0.95 |
| $K_H$ | 22.07 | 22.08 | 21.83 | 20.00 | 23.95 | 21.38 | 21.67 | 23.76 | 23.55 |
| **Korsmeyer** | | | | | | | | | |
| $r^2$ | 0.99 | 0.98 | 0.98 | 0.97 | 0.99 | 0.98 | 0.96 | 0.98 | 0.96 |
| n | 0.52 | 0.51 | 0.47 | 0.54 | 0.54 | 0.57 | 0.54 | 0.50 | 0.44 |
| K | 0.21 | 0.22 | 0.25 | 0.19 | 0.22 | 0.18 | 0.21 | 0.25 | 0.31 |
| MDT | 6.69 | 6.35 | 6.10 | 7.74 | 5.79 | 7.50 | 6.31 | 5.29 | 4.38 |
| $t_{25\%}$ | 1.40 | 1.28 | 1.00 | 1.66 | 1.27 | 1.78 | 1.38 | 1.00 | 0.61 |
| $t_{50\%}$ | 5.30 | 5.00 | 4.37 | 6.00 | 4.57 | 6.00 | 4.99 | 4.00 | 2.96 |
| $t_{75\%}$ | 11.57 | 11.08 | 10.36 | 12.71 | 9.69 | 12.23 | 10.56 | 9.00 | 7.45 |
| $t_{90\%}$ | 16.42 | 15.84 | 15.26 | 17.82 | 13.58 | 16.84 | 14.81 | 12.96 | 11.27 |

Note : $K_0$,$K_1$,$K_H$ and K are the rate constants for zero order, first order, Higuchi and Korsmeyer, respectively. n is the diffusion exponent.

(Figure 1). 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.

*2.6. Drug release kinetics*

The rate of drug release from the preparation may follow zero order kinetics, first order kinetics or Higuchi's model. To evaluate the mechanism of drug release from the preparation, data of drug release may be plotted in Korsmeyer *et al*. (Equation 1) [31] which is often used to describe the drug release behavior from polymeric systems.

$$\text{Log}\left(\frac{M_t}{M_f}\right) = \text{Log } k + n\text{Log } t$$

Where $M_t$ is the amount of drug release at time t, $M_f$ is the amount of drug release after

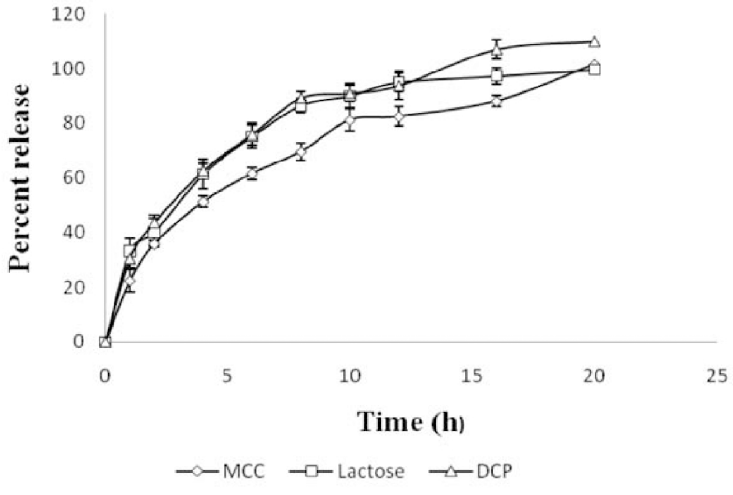


**Figure 4.** Effect of filler on alfuzosin matrix tablets prepared according to formula 2 (Table 1). Microcrystalline cellulose (MCC) was replaced by lactose and dibasic calcium phosphate (DCP). (mean±SD, n=3)

**Table 3.** Release kinetics of alfuzosin from matrix tablets.

| | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| **Zero order** | | | | | | | | | |
| $r^2$ | 0.89 | 0.86 | 0.85 | 0.86 | 0.89 | 0.88 | 0.84 | 0.85 | 0.77 |
| $K_0$ | 3.97 | 3.92 | 3.85 | 3.56 | 4.31 | 3.84 | 3.82 | 4.21 | 4.03 |
| **First order** | | | | | | | | | |
| $r^2$ | 0.94 | 0.91 | 0.89 | 0.98 | 0.96 | 0.97 | 0.94 | 0.90 | 0.96 |
| $K_1$ | 0.08 | 0.09 | 0.08 | 0.05 | 0.09 | 0.06 | 0.08 | 0.11 | 0.13 |
| **Higuchi** | | | | | | | | | |
| $r^2$ | 0.99 | 0.98 | 0.98 | 0.98 | 0.99 | 0.99 | 0.97 | 0.98 | 0.95 |
| $K_H$ | 22.07 | 22.08 | 21.83 | 20.00 | 23.95 | 21.38 | 21.67 | 23.76 | 23.55 |
| **Korsmeyer** | | | | | | | | | |
| $r^2$ | 0.99 | 0.98 | 0.98 | 0.97 | 0.99 | 0.98 | 0.96 | 0.98 | 0.96 |
| n | 0.52 | 0.51 | 0.47 | 0.54 | 0.54 | 0.57 | 0.54 | 0.50 | 0.44 |
| K | 0.21 | 0.22 | 0.25 | 0.19 | 0.22 | 0.18 | 0.21 | 0.25 | 0.31 |
| MDT | 6.69 | 6.35 | 6.10 | 7.74 | 5.79 | 7.50 | 6.31 | 5.29 | 4.38 |
| $t_{25\%}$ | 1.40 | 1.28 | 1.00 | 1.66 | 1.27 | 1.78 | 1.38 | 1.00 | 0.61 |
| $t_{50\%}$ | 5.30 | 5.00 | 4.37 | 6.00 | 4.57 | 6.00 | 4.99 | 4.00 | 2.96 |
| $t_{75\%}$ | 11.57 | 11.08 | 10.36 | 12.71 | 9.69 | 12.23 | 10.56 | 9.00 | 7.45 |
| $t_{90\%}$ | 16.42 | 15.84 | 15.26 | 17.82 | 13.58 | 16.84 | 14.81 | 12.96 | 11.27 |

Note: $K_0$, $K_1$, $K_H$ and K are the rate constants for zero order, first order, Higuchi and Korsmeyer, respectively. n is the diffusion exponent.

infinite time; k is a release rate constant incorporating structural and geometric characteristics of the dosage form, n is the diffusional exponent indicative of the mechanism of drug release [32].

The log value of the percentage of drug dissolved is plotted against log time for each formulation according to the equation. For a cylinder shaped matrix the value of $n \leq 0.45$ indicates Fickian (case I) release; >0.45 but <0.89 for non-Fickian (anomalous) release; and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release [33].

Mean dissolution time (MDT) can be calculated from dissolution data according to Mockel and Lippold (1993) equation [34]

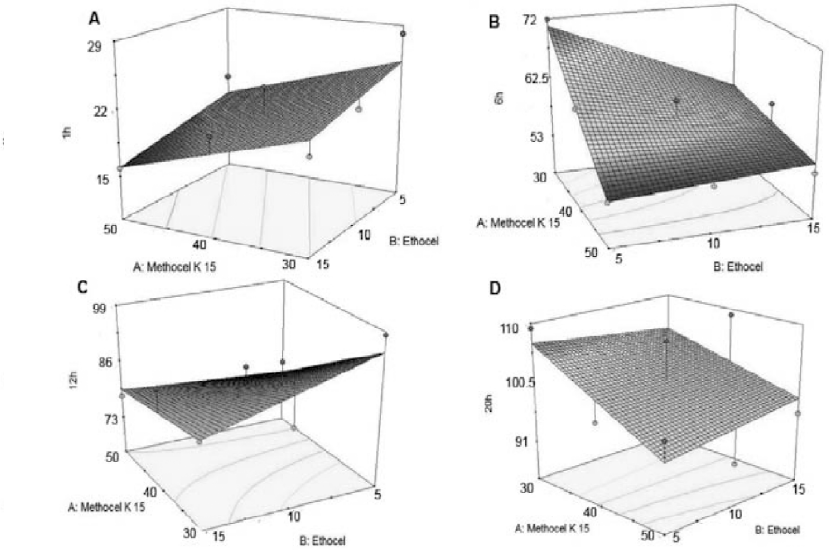


**Figure 5.** Response surface plots showing effect of polymer content on drug release at 1 h (A), 6 h (B), 12 h (C) and 20 h (D).

**Table 4.** The casual factor and responses of model formulations.

| Formulation code | $X_1$ | $X_2$ | $Y_1$ | $Y_2$ | $Y_3$ | $Y_4$ |
|---|---|---|---|---|---|---|
| F1 | -1 | 1 | 21.00 | 53.54 | 78.97 | 98.80 |
| F2 | 1 | -1 | 20.46 | 58.03 | 83.84 | 101.01 |
| F3 | 0 | -1 | 22.41 | 61.57 | 82.48 | 101.53 |
| F4 | 0 | 1 | 16.07 | 53.86 | 73.60 | 91.43 |
| F5 | 1 | 0 | 20.82 | 59.68 | 87.10 | 109.00 |
| F6 | 1 | 1 | 15.86 | 53.80 | 78.06 | 95.89 |
| F7 | -1 | 0 | 17.30 | 62.19 | 83.20 | 97.75 |
| F8 | 0 | 0 | 23.39 | 61.87 | 88.35 | 107.30 |
| F9 | -1 | -1 | 28.13 | 71.86 | 98.33 | 109.20 |
| Coded level | | -1 | | 0 | | 1 |
| $X_1$ (EC) | | 5% | | 10% | | 15% |
| $X_2$ (HPMC) | | 30% | | 40% | | 50% |

characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. MDT value can be calculated from dissolution data using Equation 2, where n is the release exponent and k is release rate constant.

$$MDT = \left( \frac{n}{n+1} \right) k^{-1/n}$$

A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa.

*2.7. Statistical analysis*

The response surface graphs and multiple regression analysis were carried out by Design Expert version 7.0 (Stat-Ease Inc., Minneapolis, Minnesota) software at 5% significance level.

## 3. Results and discussion

*3.1. Physical parameters*

The weight of the tablets from all batches varied between 0.5-2.1% (1.17±0.56%), thickness between 4.0-4.5 mm (4.23±0.19 mm) and hardness 0.5-3.0 kg/cm$^2$ (2.17±0.71 kg/cm$^2$) as shown in Table 2. All of the tablets showed friability below 1% and similar diameters (10.07 mm). The weight variation and friability of the batches complied with British Pharmacopoeia. The particle size of the blend was on an average of 420 µm, and flow property was determined by Hausner ratio (1.37-1.45) and Carr's Index (27.12-31.03%). The data showed that the flow properties of all blends were satisfactory [29]. Thus all of the physical parameters of different batches were within the control range.

*3.2. Effect of polymers on drug release*

About 25% of the drug was released within first hour ($t_{25\%}$= 1.26 h±0.36 h) of *in vitro* dissolution. It took 3-6 h to release about 50% of the drug ($t_{50\%}$ = 4.80±0.97 h) and 75% of the drug was released within 10 h ($t_{75\%}$ =10.51±1.64 h) from all formulations (Table 3). The highest release retardant formulations were 150/30 mg and 150/45 mg HPMC/EC ratio as determined by their MDT values. The gradual increase of HPMC quantity in the matrix, while keeping the amount of EC constant, decreased drug release as expected. It may be due to increased gel barrier strength which retards drug release. For instance, in HPMC/EC 90/15, 120/15 and 150/15 mg (w/w) ratios the drug release after 12 h was 98.33%, 83.20% and 78.97%, respectively. Similarly, by increasing EC levels, drug release was reduced as predicted. For example, in HPMC/EC 90/15, 90/30 and 90/45 mg ratios (w/w) the average drug release after 10 h was 91%, 81.14% and 78.7%, respectively.

*3.3. Release kinetics*

All of 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;

**Table 5.** Regression equation for each response variable determined by multiple regression analysis.

| Regression coefficient | Independent variables | $Y_1$ | $Y_2$ | $Y_3$ | $Y_4$ |
|---|---|---|---|---|---|
| $b_0$ | - | 20.604 | 59.600 | 83.770 | - |
| $b_1$ | $X_1$ | - | -2.680 | - | - |
| $b_2$ | $X_2$ | -3.011 | -5.043 | -5.670 | - |
| $b_{12}$ | $X_1X_2$ | - | 3.522 | - | - |

Insignificant values ($p$>0.05) are not shown on regression equation.

Figures 2 and 3). From Higuchi model, it is evident that alfuzosin is released by diffusion process. HPMC control the release of soluble drugs by diffusion process and poorly soluble drugs by both diffusion and erosion mechanism [35-37]. This diffusion is probably due to the presence of gel barrier of HPMC. From Korsmeyer model the diffusion exponent (n) ranges from 0.44-0.57 indicating anomalous or non-Fickian transport. Therefore, both diffusion and erosion mechanisms play a role in alfuzosin release from HPMC-EC matrix. The presence of erosion mechanism maybe due to the insolubility of EC.

*3.4. Multiple regression analysis*

The drug release percentages at 1, 6, 12 and 20 h were selected as response variable (Table 4). These time periods were selected to detect any initial burst effect, time for 50% and 90% drug release. The equations of all responses (Table 5) represent the quantitative effect of independent variables upon the responses. A positive sign indicates a synergistic effect while a negative sign indicates antagonistic effect upon the responses [38]. As shown in Table 5, $b_0$ is the arithmetic mean response of the 9 runs and $b_i$ is the estimated coefficient for $X_i$ (Table 5). It was found that HPMC ($X_2$) was responsible for reducing drug release, significantly ($p$<0.05) at 1,6 and 12 h. EC did not initially control drug release, but at 6 h its effect was found to be significant. There was positive interaction between HPMC and EC during the 6$^{th}$ h (Table 5). Response surfaces depicting the effect of the casual factors on each response variable are presented in Figure 5.

*3.5. Effect of fillers*

The tablets in the experiment were prepared with MCC as the filler. The effect of other fillers on release of alfuzosin hydrochloride was also investigated. Directly compressible lactose and dibasic calcium phosphate dihydrate (DCP) were used for this purpose. Lactose was selected due to its water solubility and DCP was selected for its insolubility. Equal amounts of lactose or DCP replaced microcrystalline cellulose in those formulations.

From Figure 4, it is evident that MCC can slow down drug release from matrix tablets. As MCC is swellable and insoluble, it retarded drug release along with HPMC. Lactose containing tablets released alfuzosin faster than MCC. Lactose dissolved in dissolution media and formed channels for drug release. Tablets containing DCP showed similar drug release pattern as lactose containing ones up to 12 h, but after that, drug release increased in the next 8 h. It may be due to the fact that DCP slowly dissolves in acidic media, therefore, after 12 h, they were dissolved and formed channels to facilitate drug release.

## 4. Conclusion

Alfuzosin extended release tablets were successfully prepared with hydrophilic (HPMC) and hydrophobic (EC) polymers by direct compression method. The experiments revealed that HPMC was more efficient than EC in retarding drug release when used together. The fine powder of EC is more appropriate than its aqueous dispersion for the formulations containing HPMC. Alfuzosin was released from the matrix tablets by diffusion and erosion mechanisms in all of the formulations.

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