# Formulation and evaluation of gastroretentive controlled release tablets of alfuzosin hydrochloride

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**Abstract**: Alfuzosin hydrochloride is a novel drug used in the treatment of urinary incontinency. The purpose of this research was to develop controlled release floating matrix formulations of Alfuzosin HCl. Floating matrix tablets of Alfuzosin HCl were prepared using hydroxypropyl methylcellulose (HPMC), Polyethylene oxide (PEO), Carbopol 971P NF polymer (Direct compressible) and Blend of Polyvinyl Acetate and Povidone 30 (80:19:1(0.8% sodium laury sulfate and 0.2% silica)). Combination of citric acid and sodium bicarbonate were also used as gas forming agent. Matrix formulations were prepared by direct compression method and evaluated for floating, *in vitro* drug release profile and swelling characteristics. The mechanism of drug release was found to follow non-Fickian or anomalous type. The data obtained from the *invitro* release studies demonstrated that the floating matrix tablets containing HPMC 100K CR (controlled-release) and carbopol along with sodium CMC were found to sustain the release of drug over a period of 12 hours. Formulations containing 25% PEO 303WSR was also capable of sustaining delivery the release of Alfuzosin HCl.

**Keywords**: Floating gastroretentive drug delivery system; alfuzosin hydrochloride; HPMC; PEO; blend of polyvinyl acetate and povidone, carbopol; sodium bicarbonate and citric acid.

## INTRODUCTION

The gastroretentive drug delivery system was found to be an efficient technique for increasing bioavailability of various drugs. Controlled release dosage forms have many pharmacokinetic and Pharmacodynamic benefits over conventional formulations which include constant therapeutic drug level over an extended period of time with reduced plasma drug fluctuations, reduced dosing frequency and improved patient compliance. Gastric floating drug delivery systems are useful for the drug that are mainly absorbed in proximal small intestine, controlled release of such drugs in the stomach will enhance their bioavailability (Sanford Boltan *et al.*1989*)*.

The gastric retention of the dosage form depends upon several factors like size and shape of the tablets, density, fasting and fed state, age, body mass index, gender, posture, and diseased states (Samyuktha Rani *et al.,* 2010). The presence of food, gastric emptying time and motility of stomach will contribute for retention of dosage form in stomach (Klausner *et al., 2003*; O'Reilly *et al.,* 1987; Sangekar *et al.,* 1987; Khosla *et al.,* 1989; Abrahamsson *et al.,* 1993). To retain the drug in stomach various approaches were developed which includes floating, swellable and mucoadhesive formulations. Among the various technique to increase gastric retention low density floating was found to be more useful because of ease of fabrication (Baumgartner *et al*., 2000; Li *et al*., 2003). These floating drug delivery system remains buoyant in the gastric content without affecting the gastric emptying time and are protected from peristaltic movement (Brahma and Kwon., 2000; Rouge *et al.,* 1996).

Alfuzosin is a quinazolin derivative for oral administration (in the form of the hydrochloride) that selectively blocks postsynaptic alpha-1-receptors. Alfuzosin hydrochloride is white, water-soluble crystalline powder, with melting point of 240°C, with relatively short half-life (3-5hrs) and is more intensly observed at deodenum-jejanum (Maggi *et al.,* 2000). Thearpy with immediate release Alfuzosin tablets typically require a daily dose of 3 tablets containg 2.5mg of Alfuzosin HCl. Hence for these reasons alfuzosin is a good candidate for the preparation for the controlled relese in the proximal upper part of the GI tract that can be achieved by making it into a swellable controlled release gastro retentive system with continous delivery of drug from stomach to the intestine.

The aim of this research work was to develop formulations for the controlled release of Alfuzosin HCl. In the present work matrix formulations were prepared using HPMC, Polyethylene oxide, carbopol and mixture of poly vinyl acteate with povidone. Prepared tablets were evaluated for physical properties, swelling, floating and drug release profiles.

## MATERIALS AND METHODS

### *Materials*

Alfuzosin hydrochloride received as gift sample by zydus cadila, Microcrystalline Cellulose (MCC) (Direct compressible grade), Lactose monohydrate (Direct compressible grade), Magnesium stearate, HPMC K100M

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CR, HPMC K4M, PEO, Blend of Polyvinyl Acetate (PVA) and Povidone (Povidone 30); Carbopol 971P NF polymer (Direct compressible), Sodium bicarbonate and Citric acid.

***Compatability study***

Active pharmaceutical ingredient (Alfuzosin hydrochloride) and excipients compatibility studies were carried out using all excipients used in tablets preparation. The physical mixture in a ratio of 1:1 (drug and excipients) (table 1) was made and stored at 60°C for 15 days in open condition. Incompatability was checked using physically and FTIR.

***Formulations***

Matrix formulations containg various polymess like Hydroxypropyl methylcellulose (HPMC), Polyethylene oxide (PEO), Sodium carboxymethyl cellulose (NaCMC), Carbopol, blend of polyvinyl Acetate and povidone and other excipients were prepared as per composition as given in table 2. Matrix tablets of Alfuzosin hydrochloride with other excipients were prepared by direct compression. The weight of Alfuzosin hydrochloride was kept constant in all the prepared tablets by varying polymer propotions. Direct compressible grade of Lactose monohydrate and Microcrystalline cellulose were used as diluent in these formulations. Sodium bicarbonate was incorporated as an effervescent substance to aid buoyancy to the dosage form. Citric acid was used as acid source. Magnesium stearate was employed as a lubricant.

To make powder mixtures for direct compression, the drug, polymer and excipients were thoroughly mixed for 8 min. This powder mixture was then lubricated with magnesium stearate for 2 min by mixing. Blend flow property was found satisfactory and compressed into tablets using 14.8x6.4mm oblong shaped punches. The force of compression was adjusted so that hardness of all the prepared tablets ranges from 6-7kg/cm2.

***Floating study***

The time taken for tablet to float on the surface of the medium is known as floating lag time (FLT) or buoyancy lag time (BLT) and duration of time the dosage form float on the surface of the medium is called the total floating time (TFT). The floating behaviour of the prepared matrix tablets was studied in USP type II dissolution apparatus, 100rpm at 37±0.5°C in 900 mL of 0.01N HCl. The time of duration of floatation was observed visually. The measurements were carried out for each series of matrix formulations (n =6).

***Water uptake study***

The swelling behavour of the polymers can be measured by their ability to absorb water and swell. The water uptake study of prepared tablets was done using USP dissolution appartus II with 900ml of distilled water as medium at 50rpm at 37±0.5°C. During the study the tablets were withdrawn after selected time interval, bloated and weighed. Swelling charcteristics of the prepared tablets were expressed interms of water uptake (Gerogiannis *et al*., 1993).

Water uptake (wu)%=(Wt-Wo)/Wo*100

Where,

Wt = Weight of tablet at time t

Wo = Initial weight of the tablet.

***In vitro drug release study***

The release of Alfuzosin hydrochloride from the prepared matrix tablets was studied using USP dissolution apparatus II. The dissolution medium was 900ml of 0.01 N HCl. The temperature was maintained at 37±0.5ºC. The rotation speed was 100rpm. The samples were withdrawn at predetermined time intervals. Each time aliquot of 5ml samples were withdrawn, filter through what man filter paper 1 and diluted suitably and the absorbance was measured at 244nm using Shimadzu, UV/Visible spectrophotometer.

***Release kinetics***

Results obtained from *invitro* dissolution studies were evaluated using different mathematical models to describe the kinetics of the drug release from tablets. Release kinetics was evaluted using zero order, Higuchi and Korsmeyer-peppas models (Higuchi, 1963; Korsmeyer, 1983; Peppas, 1985; Harland *et al.,* 1988).

The dissolution data obtained were plotted as percent cumulative drug released verses time for zero order, percent cumulative drug released verses square root of time as per Higuchi's equation,

$Q = Kt^{½}$

Log cumulative percent drug released verses log time as per Korsmeyer and Peppas equation to determine the value of release exponent, n; the value of n is indicative of mechanism of drug release

$Mt/M\alpha = Kt^n$

Where Mt is the drug release at time t

Mα is the total amount of drug released (Dose)

K is the constant incorporating structural and geometric characteristics of the controlled release device

The goodness fit was evaluated using the correlation coefficient values. The release kinetics data of all the formulations were summerised in table 4.

## RESULTS

***Preformulation***

The pre-formulation studies were performed for the active pharmaceutical ingredient (API) to assess its formulation compatibility. Drug-excipent interaction plays a vital role with respect to formulation stability there by-product performance. This was done by mixing in a ratio of 1:1 (drug and excipients) and stored at 60°C for 15 days in

open condition. The physical observations were noted and the details are given in table I. Physical properties (Colour and odour) at 60°Cfor 15 days samples were checked against initial samples at room temperature and no significant changes were observed.

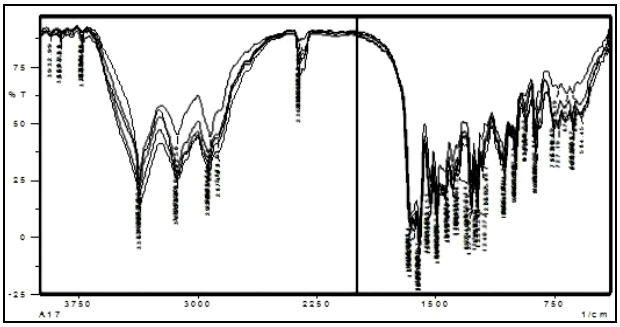

**Fig. 1**: FTIR spectra of Alfuzosin HCl, HPMC, PEO, Carbopol with sodium CMC and Blend of Polyvinyl Acetate and Povidone with Carbopol.

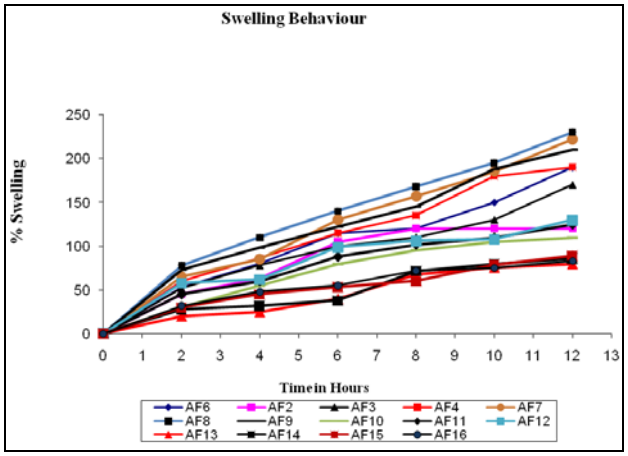


**Fig. 2**: Swelling Behavior

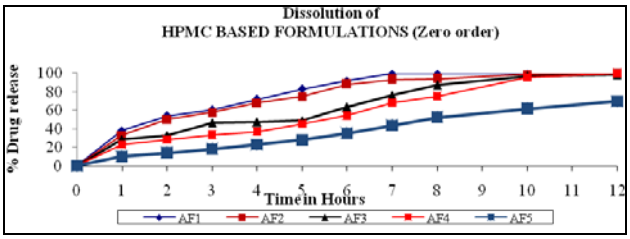


**Fig. 3**: *In vitro* drug release profiles HPMC formulations

Above samples were also subjected for FTIR studies to check physical and chemical interaction between drug and excipients and shown in fig. 1. FTIR studies indicated that drug and the polymer with excipients in the formulations do not exhibit significant chemical interaction and compatible with each other.

***Floating study***

Rapid system floatation is highly desirable for gastro retentive dosage form and can be potentially prolong gastric residence. The concentration of gas generating agent that is sodium bicarbonate was assessed by varying its proportion in formulations from 30 to 100mg. The tablets were evaluated for tablet floating lag time and floating time. The tablets prepared with lower concentration of sodium carbonate gave higher floating lag time (>10 minutes). The mixture of citric acid and sodium bicarbonate provides desired floating and therefore this combination was selected for the formulation of the controlled release floating tablets. The floating lag time for the tablets prepared with 65mg of sodium bicarbonate and 13mg of citric acid was found to be less than 1 minute. All the prepared formulations had desired buoyancy lag time (<1 minute) (table 3).

***Water uptake study***

The swelling of polymers is measured by water uptake of the tablets. The percent swelling of the tablets at various time intervals was determined by the method described in water uptake study. The percent swelling of HPMC as well as PEO were found to be higher than that of carbopol and Blend of Polyvinyl Acetate and Povidone formulations. The percent swelling of various formulations with respect to matrix excipients were in the order of HPMC>PEO>Carbopol> blend of Polyvinyl Acetate and Povidone. Drug diffusion mainly depends on the presence of amount in the tablet. This water content of matrix system will affect the diffusion of drug by increasing the mobility of polymer chains. As the amount of water present in the system increases there is a relaxation of polymer chains with expansion of volume resulting increased swelling of the system. Effect of different concentrations of polymers on swelling behavior is shown in fig. 2.

***In vitro dissolution studies***

Effect of different concentrations of HPMC 100K CR on *in vitro* release of Alfuzosin HCl was as shown in fig. 3 as the concentration of HPMC increased from 15% to 40% per tablet, initial drug release as well as drug release in the later hours was reduced. In these formulations water soluble and hydrophilic diluent lactose was used, lactose by its water soluble and hydrophilic nature provides greater matrix hydration and facilitates gel formation. The time taken to release 25% of drug (t25%) was found to be in the range of 0.5-4.2hrs for HPMC formulations and it was observed that t75% was in the range of 4.8 to 8 hrs except AF5, which could release only 69.97% of drug in 12 hrs. The higher initial drug release at lower concentrations of polymer was observed and when the concentrations of HPMC increased from 15% to 40% the burst drug release was decreased this might be due to the increased polymer concentration could have increased the path length of the drug which might have retarded the drug release from the formulations. It is observed that the release of water-soluble drug from HPMC matrices was controlled by diffusion gel layer and by erosion of the outer polymer chain for drugs with poor water solubility (Mitchell *et al.*, 1993).

**Table 1**: Physical stability study of drugs and excipients mixture at 60°C for 15 days

| S. No | Drug | Excipients | Physical mixture ratio | Observations | | |
|---|---|---|---|---|---|---|
| | | | | Colors | Odor | Remarks |
| 1 | Alfuzosin HCl | HPMC K100CR | 1:1 | White | Odorless | Stable |
| 2 | Alfuzosin HCl | PEO 303 | 1:1 | White | Odorless | Stable |
| 3 | Alfuzosin HCl | Sodium bicarbonate | 1:1 | White | Odorless | Stable |
| 4 | Alfuzosin HCl | Citric acid | 1:1 | White | Odorless | Stable |
| 5 | Alfuzosin HCl | Magnesium stearate | 1:1 | White | Odorless | Stable |
| 6 | Alfuzosin HCl | Lactose monohydrate (Direct compressible) | 1:1 | White | Odorless | Stable |
| 7 | Alfuzosin HCl | MCC (Direct compressible) | 1:1 | White | Odorless | Stable |
| 8 | Alfuzosin HCl | HPMC + Sod.bicarbonate +citric acid +magnesium stearate | 1:1:1:1:1 | White | Odorless | Stable |
| 9 | Alfuzosin HCl | PEO + Sod.bicarbonate +citric acid +magnesium stearate | 1:1:1:1:1 | White | Odorless | Stable |
| 10 | Alfuzosin HCl | Carbopol 971P + Sod.bicarbonate +citric acid +magnesium stearate | 1:1:1:1:1 | White | Odorless | Stable |
| 11 | Alfuzosin HCl | Blend of Polyvinyl Acetate and Povidone + Carbopol 971P +Sod.bicarbonate +citric acid +magnesium stearate | 1:1:1:1:1:1 | White to off white | Odorless | Stable |

**Table 2**:Composition of matrix formulations of Alfuzosin HCl

| S. No. | Ingredients (mg/tablet) | Formulation code | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | AF1 | AF2 | AF3 | AF4 | AF5 | AF6 | AF7 | AF8 | AF9 | AF10 | AF11 | AF12 | AF13 | AF14 | AF15 | AF16 |
| 1. | Alfuzosin HCl | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 2. | HPMC 100K CR | 67.5 | 90 | 112.5 | 135 | 180 | - | - | - | - | - | - | - | - | - | - | - |
| 3. | PEO 303 | - | - | - | - | - | 67.5 | 90 | 112.5 | 135 | - | - | - | - | - | - | - |
| 4. | Sodium bicarbonate | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 |
| 5. | Citric acid | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 |
| 6. | Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 7. | Lactose monohydrate (Direct compressible) | 292.5 | 270 | 247.5 | 225 | 180 | - | - | - | - | 270 | 225 | 202.5 | 270 | 247.5 | 225 | 225 |
| 8. | MCC (Direct compressible) | - | - | - | - | - | 292.5 | 270 | 247.5 | 241 | - | - | - | - | - | - | - |
| 9. | Blend of Polyvinyl Acetate and Povidone | - | - | - | - | - | - | - | - | - | - | - | - | 45 | 67.5 | 90 | 90 |
| 10. | Carbopol 971P | - | - | - | - | - | - | - | - | - | 67.5 | 90 | 112.5 | 45 | 45 | 45 | - |
| 11. | Sodium CMC | - | - | - | - | - | - | - | - | - | 22.5 | 45 | 45 | - | - | - | 45 |
| | Total (mg) | 450 | 450 | 450 | 450 | 450 | 450 | 450 | 450 | 466 | 450 | 450 | 450 | 450 | 450 | 450 | 450 |

**Table 3**: *In vitro* floating and swelling characterisation

| Parameters | AF1 | AF2 | AF3 | AF4 | AF5 | AF6 | AF7 | AF8 | AF9 | AF10 | AF11 | AF12 | AF13 | AF14 | AF15 | AF16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Buoyancy lag time (BLT) | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 |
| Total floating time (TFT) (in Hours) | 10 | >12 | >12 | >12 | >12 | 10 | >12 | >12 | >12 | >12 | >12 | >12 | 10 | 10 | >12 | 8 |

Alfuzosin HCl is a water-soluble drug, which is released through HPMC hydrogels by diffusion process. This fact is supported by the regression coefficient values of Higuchi's plot, which was found to be in the range of 0.980 to 0.990. Fickian diffusion is described for drugs which are released mainly by the diffusion process through polymeric matrix and non-Fickian or anomalous diffusion is mainly used to describe the drugs which are released by other process in addition to diffusion. When log cumulative % drug released verses time was plotted for the Korsmeyer-Peppas equation indicated a good linearity with r = 0.97 to 0.99. The release exponent 'n' was found to be in between 0.48 to 0.83 in formulations AF1 to AF5 prepared with HPMC K 100CR, which indicates that the release of drug from these HPMC formulations was controlled by diffusion and erosion mechanisms, predicted as anomalous diffusion and release is controlled by more than one process.

Another hydrophilic polymer PEO was selected because of low weight variation, high breaking force and low friability values at compression force of 15 and 20 KN. PEO has been considered as an alternative rate retarding polymer to HPMC in controlled release formulations (Yang *et al.,* 1993; Kim, 1995). Microcrystalline Cellulose is selected as diluent along with PEO

formulation because of its high compactability and produces more compact tablets. MCC being fibrous and hydrophilic in nature can facilitate water uptake and improve matrix integrity and provide for modulation of matrix erosion rate. The release profiles of PEO based formulations are shown in fig. 4. The rate of drug release was decreased with increase in the polymer concentration. The time taken to release 25% of drug (t25%) was found to be in the range of 0.8-1.8 hrs for PEO based formulations and it was observed that t75% was in the range of 4.5 to 9 hrs. The Formulation AF8 showed the optimum drug release of 75% drug release at 7.2hrs and the release was linear with a regression 'r' value of 0.97. In order to understand the mechanism and kinetics of drug release, the drug release data of the *in vitro* dissolution studies were analyzed with various kinetic model like Zero order, Higuchi model and Peppas model equation (table 4), the slope value in Peppas model was to be in the range of 0.539 to 0.675 indicating drug release mechanism was found to be non Fickian type.

**Table 4**: Linear regression analysis data

| Formulation code | Zero order (r) | Higuchi Model (r) | Korsmeyer-Peppas model (Slope (n) |
|---|---|---|---|
| AF1 | 0.9960 | 0.9960 | 0.483 |
| AF2 | 0.9821 | 0.9821 | 0.512 |
| AF3 | 0.9710 | 0.9794 | 0.547 |
| AF4 | 0.9884 | 0.9804 | 0.642 |
| AF5 | 0.9941 | 0.9882 | 0.834 |
| AF6 | 0.9375 | 0.9375 | 0.539 |
| AF7 | 0.9631 | 0.9631 | 0.662 |
| AF8 | 0.9678 | 0.9882 | 0.588 |
| AF9 | 0.9731 | 0.9951 | 0.675 |
| AF10 | 0.9604 | 0.9867 | 0.466 |
| AF11 | 0.9781 | 0.9751 | 0.639 |
| AF12 | 0.9833 | 0.9856 | 0.772 |
| AF13 | 0.9697 | 0.9697 | 0.663 |
| AF14 | 0.9836 | 0.9836 | 0.698 |
| AF15 | 0.9916 | 0.9916 | 0.692 |
| AF16 | 0.9943 | 0.9943 | 0.482 |

In another approach carbopol was used to control the release of Alfuzosin HCl matrix tablets, it is a free-flowing granular form of Carbopol 971P NF polymer used in direct compression formulations especially controlled release performance in tablet. During the dissolution process a general trend observed in all the formulations, the polymer swelled; as concentration of polymer was increased the rate swelling was found to increase and resulted in the drug release rate.

The release profiles of carbopol-based formulations are shown in 5. The time taken to release 25% of drug (t25%) was found to be in the range of 0.8-1.7 hrs and t75% was in the range of 6.2 to 8.4 hrs. The Formulation AF12 showed the optimum drug release of 75% drug release at 8.4hrs and the release was linear with a regression 'r' value of 0.98.

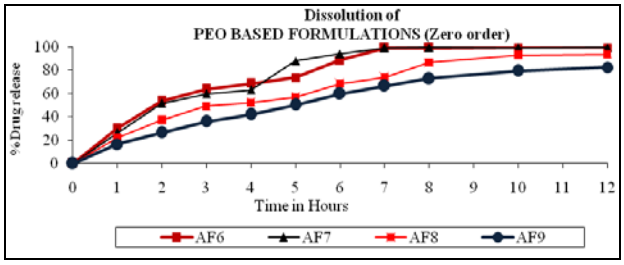


**Fig. 4**: *In vitro* drug release profiles PEO formulations

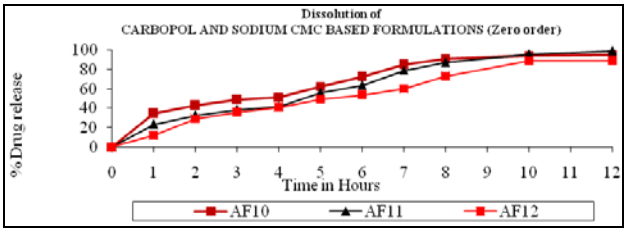


**Fig. 5**: *In vitro* drug release profiles Carbopol and sodium CMC formulations

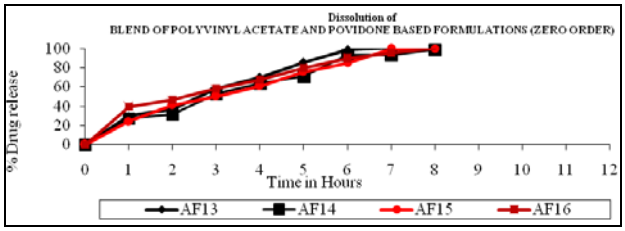


**Fig. 6**: *In vitro* drug release profiles Blend of Polyvinyl acetate and povidone

In another approach Blend of Polyvinyl Acetate and Povidone is used as matrix forming material, which has excellent compressibility and endows tablets with enormous hardness and low friability. When tablets formulated with this product are introduced into gastric or intestinal fluid, the water-soluble povidone is leached out to form pores through which the active ingredient slowly diffuses out resulting in sustained action. Blend of Polyvinyl Acetate and Povidone was used along with carbopol and Sodium CMC in the present work. The release profiles of blend of Polyvinyl Acetate and Povidone based formulations are shown in fig. 6. The time taken to release 25% of drug (t25%) was found to be in the range of 0.7-1.1 hrs and t75% was in the range of 4.3 to 5.3 hrs.

## DISCUSSION

In the current study, the formulation of gastro retentive controlled release tablets used to treat benign prostatic hyperplasia were prepared using the matrix forming polymer HPMC, PEO and Carbopol with the aid of gas generating agent in different ratios by direct compression technique. Floating gastro retentive tablets developed

using direct compression without any time-consuming granulation processes. The prepared floating controlled release tablets exhibited satisfactory physicochemical characteristics. General appearance and FTIR during compatibility study did not change significantly. All the optimized formulation had desired buoyancy with controlled release. Data fitting to zero-order kinetics, Korsmeyer-Peppas model and Higuchi Model indicated that the mechanism of drug release could be non-Fickian diffusion mechanism.

## CONCLUSION

In the present study we developed gastro retentive floating oral drug delivery systems by using direct compression without any time consuming granulation processes. From the data obtained, it can be concluded that gastro retentive controlled release tablets of Alfuzosin hydrochloride can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability. The derivatives of swellable polymer HPMC, PEO and Carbopol showed better control over the drug release. Formulated tablets gave satisfactory results for floating lag time, total floating time, content uniformity and *in vitro* drug release. Formulations AF5 (containing Alfuzosin HCl, HPMC 100K CR, sodium bicarbonate, citric acid, magnesium stearate and Lactose monohydrate) AF8 (containing Alfuzosin HCl, PEO 303, sodium bicarbonate, citric acid, magnesium stearate and MCC) and AF12 (containing Alfuzosin HCl, Carbopol 971P, Sodium CMC, sodium bicarbonate, citric acid, magnesium stearate and MCC) gave better-sustained drug release in comparison to other formulations. These formulations best fitted to zero-order kinetics, Korsmeyer-Peppas model and Higuchi Model and drug release was found to be by non-Fickian diffusion mechanism.

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