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NOVEL SUSTAINED RELEASE DRUG DELIVERY SYSTEM OF ALFUZOSIN HYDROCHLORIDE WITH IMPROVED BIOAVAILABILITY: INVESTIGATION OF DRUG RELEASE KINETICS

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ABSTRACT
Present study outlines a systematic approach for design and development of Alfuzosin hydrochloride floating-mucoadhesive tablets to enhance the bioavailability and therapeutic efficacy of the drug. Alfuzosin hydrochloride, an α- adrenergic receptor blocker used for the treatment of symptomatic prostatic hyperplasia is primarily dissolved and absorbed from the upper gastro intestinal tract. Different formulations of Alfuzosin HCl were prepared by wet granulation technique using HPMC K4M, HPMC K15M, Na CMC, Carbopol 934 and Chitosan as polymers along with other standard excipients. The formulations were evaluated for their physicochemical properties, floating capacity, swelling index, percent erosion and *in-vitro* drug release. Optimized formulation FM2 containing HPMC K4M, HPMC K15M and Na CMC showed floating lag time of 34 sec and total floating time of 12 h. *In-vitro* drug release mechanism was evaluated by linear regression analysis. The r^2 value for zero order plot was found to be 0.995 and 'n' value for Korsmeyer-Peppas was found to be 0.83 indicating that the drug release mechanism was non- fickian diffusion. Therefore, it can be concluded that formulation containing combination of high and low viscosity HPMC along with sodium CMC shows good mucoadhesive properties and is capable of sustaining release of Alfuzosin HCl up to 12 hrs in upper gastrointestinal tract.

Keywords: *Alfuzosin HCl; gastro-retentive system; high and low viscosity HPMC; floating-mucoadhesive; Zero-order drug delivery.*

INTRODUCTION

During the last decade, many studies have been performed concerning the sustained release dosage forms of drugs, which have been aimed at the prolongation of gastric emptying time (GET). The GET has been reported to range from 2 to 6 hrs in humans in the fed state[1] Retention of drug delivery systems in the stomach prolongs the overall gastrointestinal transit time, thereby resulting in improved bioavailability. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are basically subjected to two complications, that is short gastric residence time and unpredictable gastric emptying rate[2]. Depending on the mechanism of buoyancy and mucoadhesion, effervescent systems have been used in the development of floating-mucoadhesive drug delivery systems[3].

Alfuzosin HCl is an alpha-adrenergic receptor blocker approved by FDA for the treatment of symptomatic prostatic hyperplasia (BPH). Lower urinary tract symptoms (LUTS) including urinary frequency, nocturia, incomplete emptying, and urinary hesitancy are often associated with the benign prostatic hyperplasia. These symptoms can be caused by altered function of the smooth muscle tone that is regulated by the á$_1$-adrenergic receptors in the prostate and its capsule, the bladder base and neck, and the prostatic urethra [4].

Alfuzosin shows linear kinetics when administrated at doses up to 30 mg daily. The absolute bioavailability of Alfuzosin is about 49% under fed condition, while the corresponding value under fasting condition is around 25%. Absorption of Alfuzosin after oral administration preferentially takes place from the proximal part of the gastrointestinal tract and, in particular, jejunum appear to be the main region for absorption [5].

Therefore, a drug delivery system which allows drug to get absorbed from upper GIT as well as prolonging gastric residence time for continuous delivery of drug is required for improved bioavailability of Alfuzosin HCl. Extended release tablet of Alfuzosin HCl is available in the market under the brand name Uroxatral® -10 mg.

Literature reports design and characterization of triple layer composite matrices of Alfuzosin HCl for zero order drug delivery via gastro-retentive system[6]. The only reported gastroretentive formulation is a complex system i.e. three layerd geomatrix composite which is complicated from manufacturing aspect as well as cost

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effectiveness for commercial purpose. Extended release matrix tablet formulation using combination of HPMC K-15 and Eudragit (RS-PO) is also reported in the literature[7-8]. These extended release systems are not meant for gastric retention; hence once the tablet formulation crosses proximal part of the GIT, bioavailability of the drug will be hampered as jejunum appear to be the main region for absorption.

As there are very few formulations of Alfuzosin HCl in the market there is a need to design and formulate cost effective controlled release gastro-retentive formulation giving zero order release. Therefore, present research work focuses on formulation of simple gastroretentive floating mucoadhesive matrix tablet of Alfuzosin HCl using combination of high and low viscosity grades of HPMC for controlling drug release. Since bioadhesion on soft tissues of certain natural or synthetic polymers has been exploited to control as well as to prolong the gastric retention of the delivery systems, gelling agents like sodium CMC, Carbopol 934 and chitosan were used for mucoadhesion of the formulation in the present work. The objective of the study was to know the dynamics of swelling and erosion in relation to drug release kinetics. The polymers incorporated in the systems promote swelling to a size required for preventing their passage through pyloric sphincter resulting in prolonged GRT. The mucoadhesive systems are intended to extend the GRT by adhering them to the gastric mucous membrane[9]

Literature reports HPMC K4M as a good polymer for floating dosage forms[10]. HPMC is used in controlling drug delivery because it gives flexibility to obtain desirable drug release profile, easy compressibility as well as economy and safety.

Materials and Methods

Materials

Alfuzosin HCl was obtained as a gift sample from Zim Laboratories Pvt. Ltd, Nagpur. Hydroxy propylmethyl-cellulose (HPMC) K15M, Microcrystallinecellulose (MCC), Aerosil as gift samples from Zim Laboratories Pvt. Ltd, Nagpur. Hydroxypropylmethylcellulose (HPMC) K4M, Lactose, Sodium bicarbonate, Citric acid, and Magnesium stearate were procured from SD Fine Chemicals, Mumbai. Carbopol 934, Chitosan, Sodium carboxymethylcellulose (NaCMC), Polyvinylpyrollidone (PVP-K30) were procured from Hi-Media. All other chemicals used were of analytical reagent grade.

Preparation of floating-mucoadhesive tablets

Wet granulation technique

Alfuzosin HCl floating-mucoadhesive tablets were prepared by using wet granulation technique. In all the formulations amount of drug added was kept constant (10 mg) and the total weight of the tablet was 100 mg. All the excipients and drug were passed through # 60 mesh, mixed and granulated with 7.5% solution of PVP K 30 in isopropyl alcohol (Table 1). The wet mass was passed through #16 mesh and dried at 45°C for 30 minutes. Dried granules were evaluated for pre-compression parameters i.e. angle of repose, compressibility index and Hausner's ratio. Granules passing all the evaluation tests were passed through #24 mesh and mixed with magnesium stearate and Aerosil. Granules were compressed into tablets using 12 station tablet compression machine (CEMACH, Ahmadabad, India) using 6mm concave punches with 5 ton compression force.

Table 1: Composition of Alfuzosin HCl floating-mucoadhesive tablets

Ingredients*	Formulation code					
	FM1	FM2	FM3	FM4	FM5	FM6
Drug	10	10	10	10	10	10
HPMC K4M	20	20	20	20	20	20
HPMC K15	20	15	20	15	20	15
Na CMC	10	15	---	---	---	---
Carbopol 934	---	---	10	15	---	---
Chitosan	---	---	---	---	10	15
MCC	14	14	14	14	14	14
Lactose	10	10	10	10	10	10
$NaHCO_3$	6.5	6.5	6.5	6.5	6.5	6.5
Citric acid	6.5	6.5	6.5	6.5	6.5	6.5
Aerosil	1	1	1	1	1	1
Mg. Stearate	2	2	2	2	2	2
PVP K30 (7.5%)	q.s	q.s	q.s	q.s	q.s	q.s
Tablet Weight	100	100	100	100	100	100

**All the quantities are in mg.*

Drug content and physical characterization

Five tablets were powdered in a glass mortar and about 100 mg of powder was placed in a 100 ml stoppered conical flask. The drug was extracted using 0.1N HC1 with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 5 hrs and filtered into 100 ml volumetric flask through cotton wool and filtrate was made up to the mark by passing more 0.1N HCl through filter, further appropriate dilutions were made and absorbance was measured at 245 nm against blank using UV spectrophotometer (model No.- UV 1800 PC)[11]. Tablets were also evaluated for post-compression parameters like weight variation, tablet hardness, friability and thickness[12-13].

Buoyancy test

The buoyancy test (floating property) of the tablets was carried out using USP type II dissolution apparatus. The buoyancy test was performed using 900 ml of 0.1N HCl dissolution medium at 37±2°C at a rotational speed

of 50 rpm. The time taken for tablet to emerge on surface of the medium and the duration of time by which the tablet constantly remain on surface of medium was noted [14].

Swelling study

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen tablet was weighed at predefined time intervals over the period of 12 h. The swelling index (SI), expressed as a percentage[15]**.** The % weight gain by the tablet was calculated by the formula,

$$\text{Swelling Index (SI)} = \{(W_t\text{-Wo})/Wo\} \times 100$$

Erosion study

Erosion studies were carried out to determine tablet weight loss in 0.1N HCl. The USP dissolution test apparatus type II at 75 rpm and 37±2°C was used. Single tablet was placed in thoroughly cleaned 900 ml beaker. At 60 minutes time interval, beaker containing the remnants of tablet were removed and dried to a constant weight in hot air oven at 60 °C for 24 hours. After cooling in desiccators at room temperature these baskets were weighed accurately and the percent weight loss (% erosion) was calculated [16].

$$\text{Erosion (\%)} = \frac{\text{Initial Weight of Tablet - Final Weight of Tablet X 100}}{\text{Initial Weight of Tablet}}$$

Mucoadhesive force measurement

Two-arm balance method was used to measure the bioadhesion of floating mucoadhesive tablets (Fig. 1). Goat gastric mucosa was used for the study and 0.1 N HCl was used as a moistening fluid. Gastric mucosa section (2-mm thick, 2×2 cm) was fixed on the bottom of small beaker attached to a big beaker. Krebs solution was added to the beaker up to the upper surface of gastric mucosa. A tablet was attached to the upper clamp and the platform was slowly raised until the tablet surface came in contact with mucosa. After a preload time of 5 minutes, water was added to the polypropylene bottle until the tablet gets detached from the gastric mucosa. The water collected in the bottle was measured and expressed as weight (g) required for the detachment [17-18]. The maximum force required for detachment of the tablet was measured in terms of dyne/cm^2.

The Mucoadhesive Strength [19]was then calculated as:

i) Mucoadhesive Strength (in dynes/cm^2):

$$\frac{\text{Mucoadhesive strength (in gm) x 980}}{\text{3.14 X (radius of tablet)}^2}$$

ii) Force of Mucoadhesion(in newton) :

$$\frac{\text{Mucoadhesive strength (in gm) x 9.81}}{100}$$

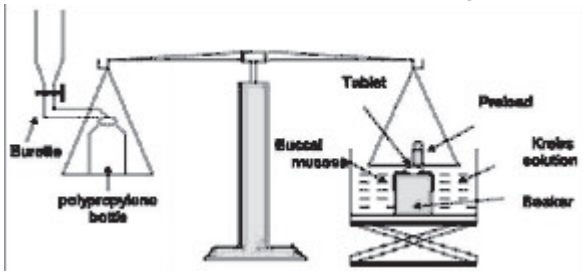

Fig. 1: *Modified physical balance to measure mucoadhesive force*

***In- vitro* dissolution studies**

The release of drug from the floating-mucoadhesive tablets was determined using the USP type II dissolution test apparatus. The dissolution test was performed using 900ml of 0.1N HCl dissolution medium pH 1.2 at 37±2°C and rotational speed of 50 rpm. Aliquots (5ml) were withdrawn at an interval of 1hr till 12 hrs. The samples were replaced by their equivalent volume of fresh dissolution medium. The samples were analyzed at 245 nm by UV spectrophotometer. The % cumulative drug release was calculated using the equation generated from standard curve [20].

Drug release mechanism

To describe the kinetics of drug release from the formulations, mathematical models zero-order, first order, Higuchi, Hixon-crowell, Korsmeyer-Peppas were used. The criterion for selecting the best fit model was chosen on the basis of the goodness fit test [21].

Stability studies

Stability studies were carried out for optimized formulation. The tablets were wrapped in aluminum foil of thickness 0.04 mm and stored in stability chamber (Programmable Environmental Chamber, Remi, India.) at temperature 40 $\pm$ 2°C and 75 $\pm$ 5% relative humidity for 3 months. At an interval of one month, samples were evaluated for physical appearance, drug content and % cumulative drug release [22].

Fourier Transform infra-red analysis (FTIR) of optimized formulation

IR has been the method of choice to probe the nature and extent of interactions in polymer blends. The FTIR spectra of pure Alfuzosin HCl and optimized formulation was recorded in the range of 4000 to 500 cm^{-1} on FTIR(Model No.84005 Shimadzu Asia Pacific Pvt Ltd, Singapore)[23]. The samples were prepared on KBR press.

Results and Discussion

Gastroretentive mucoadhesive floating formulations were successfully prepared by wet granulation technique using various ratios of HPMC K4 and HPMC K15 along with gas generating agents and mucoadhesive polymers (Table 1). Precompression as

well as Post compression parameters of these formulations were evaluated further.

Precompression parameters-

Formulations FM1–FM6 were found to possess angle of repose in the range between 28.54° - 28.73° indicating excellent flow property. It was also observed that % compressibility values for all the formulations were ranging from 14.63-13.14 as well as Hausner's ratio values in the range 1.16- 1.15. Therefore granules of all the compositions FM1-FM6 were compressed in to tablets.

Post compression parameters

The hardness of the prepared Alfuzosin HCl floating-mucoadhesive tablets was found to be in the range of 5.2 to 5.6 kg/cm^2 and the friability of all the formulations was found to be less than 1% *i.e.* in the range 0.34% to 0.62%. The percentage deviation from the average weight was found to be within the prescribed official limits. The drug content in all the formulations was found to be in the range 96.85%–99.13% (Table 2).

Table 2: *Physicochemical properties of formulations FM1 to FM6*

Sr. No.	Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug Content (%)
1.	FM1	5.42±0.08	3.65±0.06	102.51±0.04	0.34±0.015	98.30±0.38
2.	FM2	5.35±0.14	3.84±0.05	101.62±0.02	0.48±0.023	97.82±0.49
3.	FM3	5.53±0.22	3.67±0.02	101.71±0.03	0.52±0.018	96.85±0.42
4.	FM4	5.28±0.15	3.42±0.07	102.43±0.07	0.58±0.023	98.12±0.73
5.	FM5	5.61±0.31	3.56±0.13	103.10±0.08	0.62±0.012	99.13±0.35
6.	FM6	5.48±0.27	3.27±0.09	101.62±0.03	0.53±0.041	97.98±0.29

**All the values are expressed as mean ±S.D. ,n=3*

Buoyancy test

All the formulations containing low density polymers i.e. Na CMC and Carbopol 934 showed very less floating lag time (FLT) i.e. 35-40 sec. and remained buoyant for about 12 hrs (Fig. 2.) It can be observed that formulations FM1 and FM2 which contains Na CMC and optimum concentration of HPMC showed satisfactory FLT i.e. 40 sec and 34 sec respectively. This may be due to the presence of low density polymer (Na CMC) in the formulation. It was observed that total floating time of the system increases with increasing polymer concentration, because it swells on the surface of the tablet when comes in contact with 0.1N HCl which results in an increase in bulk volume and also due to the presence of internal voids in the center of the tablet. Sodium bicarbonate acts as a gas generating agent. It generates gas when comes in contact with an acidic environment of the stomach. This gas formation into the matrix of water soluble polymers makes tablet float in an acidic environment of the stomach. The air trapped by the swollen polymer also confirms buoyancy to the tablet [24].

Swelling studies

The floating ability as well as an increased dimension offers the system gastoretentive property. These properties are imparted by the swelling of the

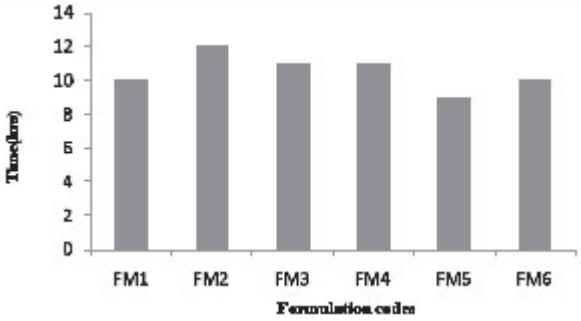

Fig. 2: *Total floating time of formulations FM1 to FM6*

formulation due to the presence of hydrophilic polymers and a gas generating agent. As the tablet comes in contact with the GI fluid, CO_2 is liberated and gets entrapped in swollen hydrocolloid which provides buoyancy to the dosage form. Swelling behavior of the formulation is important with regard to prolonged drug release through swollen matrices by diffusion. Water sorption increases with increase in the concentration of the polymers. HPMC and NaCMC are the highly hydrophilic polymers while Chitosan and Carbopol are hydrogels. Uptake of water results in relaxation of the originally stretched entangled or twisted polymer chains, resulting in exposure of all polymer bioadhesive sites for bonding to occur. The faster the swelling of the polymer, faster is initiation of diffusion and formation of adhesive bonds resulting in faster initiation of bioadhesion[25].

As seen from Fig.3. percent water uptake of the formulations (FM1-FM6) after 12 hrs ranges from 122.18 to 252 %. The formulation FM2 (248.62%) containing Na CMC showed significant increase in swelling index as compared to FM1 (186.45%) as a result of increase in amount of Na CMC in the formulation. The formulation FM2 containing 20 mg of HPMC K4M showed optimum swelling index and maintained tablet integrity at a ratio of 4:3 of HPMC and Na CMC.

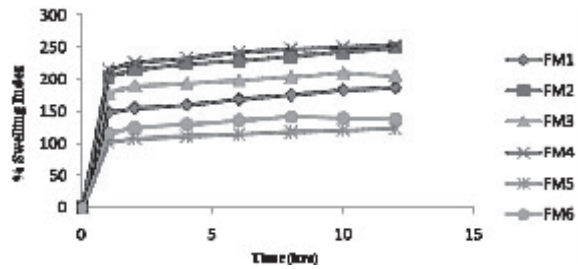

Fig. 3. *Swelling studies of formulations FM1 to FM6*

Non-ionic polymer HPMC and anionic polymer- Na CMC produces synergistic increase in viscosity, this may be due to strong hydrogen bonding between the carboxylic groups and the hydroxyl group of the HPMC leading to stronger cross- linking between the two polymers [26].

The formulation containing higher amount of Carbopol 934 (15%w/w) exhibited the highest swelling index, i.e., 254.64% for formulation FM4 as compared to 205.12% for formulation FM3 which contains 10% w/w Carbopol 934. The percent water uptake was found to increase on increasing the concentration of HPMC K4M in all the formulations. Formulations FM5 (122.18%) and FM6 (137.85%) containing Chitosan showed low swelling index as compared to Carbopol 934.

Erosion study

It is observed that buoyancy of the tablet is governed by both the swelling of the hydrocolloids as well as the presence of internal voids in the tablet i.e. porosity[27]. Swelling and erosion of the material occur simultaneously resulting in moving boundary conditions which continuously modifies the effective diffusivity of the drug. Erosion increases the dissolution rate. The floating lag period could be explained on the basis of swelling and erosion rate. Lactose is an erosion promoter. Gas generating agent is also required in combination with lactose. These are used for disentanglement of HPMC matrices.

It can be observed from Fig. 3 and Fig. 4 that formulation FM2 exhibits highest % swelling index as well as % erosion index respectively. It was also observed that formulation FM2 has lowest floating lag time and remain buoyant for about 12 hours. The high erosion index in FM2 might be due to high concentration of hydrophilic polymer i.e. sodium CMC which made the formulation to erode rapidly.

Formulations FM3 and FM4 containing Carbopol 934 shows lowest values for % Erosion Index 20.51% and 22.84% respectively. This might be due to highly crosslinked nature and high swelling indices of Carbopol 934. Formulations FM5 (25.68%) and FM6 (29.42%) containing Chitosan showed considerable % Erosion Index.

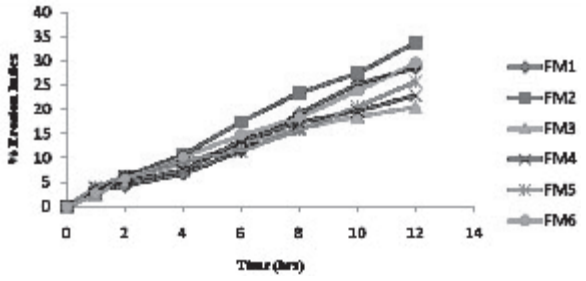

Fig. 4: *% Erosion indices of formulations FM1 to FM6*

Measurement of mucoadhesive force

Various hydrogels like Na CMC, Carbopol 934 and Chitosan are used in the present gastroretentive formulation to impart mucoadhesive strength to the tablet. Mucoadhesive property of the tablet supports sustained drug delivery from the formulation.

The hydrogels are known to swell readily, when they come in contact with hydrated mucous membrane[28]. Water sorption reduces the glass transition temperature below ambient conditions and hydrogels become progressively rubbery due to uncoiling of polymer chains and subsequent increased mobility of the polymer chains. This glass-rubbery transition provides hydrogel plasticization resulting in a large adhesive surface for maximum contact with mucin and flexibility to the polymer chains for interpenetration with mucin[29]. Increasing the polymer amount may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting consequently in the augmentation of bioadhesive strength.

There are various kinds of adhesive force, *e.g.* hydrogen bonding between the adherent polymer and the substrate, *i.e.* mucus, which are involved in muco-adhesion at the molecular level[30]. Therefore as the concentration of polymer increases, the mucoadhesive force also increases.

As seen from Table 3, formulation FM4 containing high concentration of Carbopol has highest mucoadhesive strength as compared to formulations containing Na CMC and Chitosan. Formulations FM1 (121.82 dynes/cm^2) and FM2 (143.37 dynes/cm^2) containing combination of HPMC and Na CMC showed satisfactory mucoadhesion (Table 3).

Table 3: *Evaluation of Mucoadhesive strength of formulations FM1 to FM6*

Formulation Code	Mucoadhesive Strength (gm)	Mucoadhesive Strength (dynes/cm2)	Force of Mucoadhesion (Newton)
FM1	5.20±0.06	121.82±0.12	0.510±0.02
FM2	6.12±0.021	143.37±0.022	0.600±0.02
FM3	6.5±0.11	152.27±0.014	0.637±0.01
FM4	7.5±0.08	175.70±0.011	0.735±0.02
FM5	4.04±0.09	94.64±0.013	0.392±0.018
FM6	5.12±0.13	119.94±0.020	0.502±0.021

*All the values are expressed as mean±S.D, n=3

Combination of HPMC and Na CMC showed mucoadhesion on account of their hydrogen bonding properties. This property of both the polymers is closely associated with mucoadhesion because polymers swell readily when it comes in contact with hydrated mucus membrane, which in turn increases diffusion and interpenetration of polymer. It was also observed that formulations (FM3 and FM4) containing Carbopol 934 as a mucoadhesive polymer has highest mucoadhesive strength (Fig.5) This may be because of formation of secondary mucoadhesive bonds with mucin due to rapid swelling and interpenetration of the polymer chains in the interfacial region.

In-vitro **drug release studies**

The dissolution profiles of all the developed floating formulations at pH 1.2 at 50 rpm are illustrated in Fig.6 and Fig.7. The study was carried out for 12 hrs. All the tablet formulations retained their integrity throughout the study. As Alfuzosin HCl is a highly water soluble drug, penetration of water in the matrix is the rate limiting factor for its dissolution.

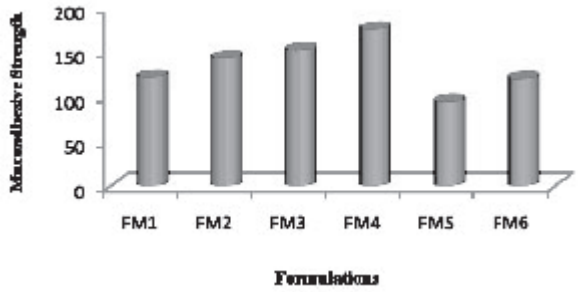

Fig. 5. *Mucoadhesive strength of formulations FM1 to FM6*

From Fig. 6 and Fig. 7 it can be observed that formulation FM2 containing HPMC K15 and NaCMC in 1:1 ratio released almost all the drug i.e. 98.21% within 12 hrs whereas formulation FM1 containing HPMC K15 and Na CMC in 2:1 ratio released only 93.15% drug within 12 hrs, it may be because of higher amount of HPMC which led to more swelling of tablet leading to prolonged drug release. The concentration of HPMC K4M might be the key factor governing the drug release.

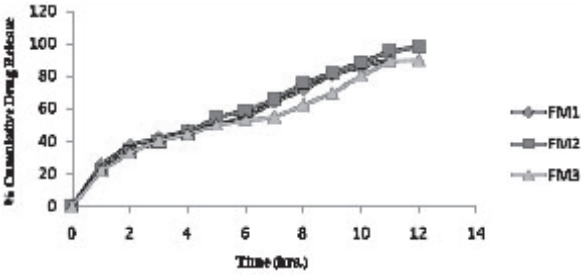

Fig. 6. *Dissolution profiles of formulations FM1 to FM3*

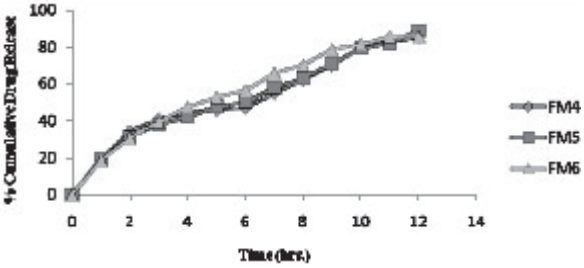

Fig. 7: *Dissolution profiles of formulations FM4 to FM6*

Formulations FM3 and FM4 containing Carbopol 934P showed 89.71% and 85.84% drug release at 12th hr respectively. This might be due to higher swelling leading to an increase in the dimension of the tablet with an increase in the diffusional length and thus reduction in dissolution rate. Formulations FM5 and FM6 containing Chitosan released 89.08% and 85.97% of drug within 12 hrs. From these observations formulation FM2 found to posses desirable Floating lag time, Total floating time, swelling index and dissolution profile to be an effective gastro retentive floating drug delivery system.

Kinetic modeling of the drug release

The data obtained from dissolution studies of formulation FM2 was subjected to kinetic analysis using Korsemeyer –Peppas equation – $\mathbf{mt/má = k\ t^n}$ Where, mt/má is fraction of drug released, k is kinetic constant, t is release time and n is the diffusional exponent for drug release. The value of 'n' gives an indication of the release mechanism; when n = 1, the release rate is independent of time (zero-order) (case II transport), n = 0.5 for Fickian diffusion and when 0.5 < n <1.0, diffusion and non-Fickian transport are implicated. Lastly, when n > 1.0 super case II transport is apparent.

The 'n' value for optimized formulation FM2 from Korsmeyer- Peppas equation was found to be 0.83 (Table 4) indicating that the release mechanism was Non-Fickian (0.5 < n < 1.0), i.e. the release was dependent on drug diffusion and erosion process. R^2 value for Zero order plot was found to be maximum i.e. 0.995. Therefore release kinetics fits Zero Order plot.

Table 4: *Kinetic treatment of dissolution study data for optimized formulation FM2*

Variables	Zero Order	First Order	Hixson Crowell	Korsmeyer and Peppas	Higuchi Plot
R^2 Value	0.995	0.849	0.889	0.970	0.977
Slope	6.953	-0.121	0.508	0.590	28.70
Intercept	18.12	2.163	-2.634	1.326	-6.538

Stability studies

Stability study was carried out for optimized formulation FM2 to assess the stability with respect to its physical appearance, drug content, in-vitro floating ability as well as drug release profile. As per ICH guidelines samples were kept in stability chamber at 40 $\pm$ 2^{0}C and 75 $\pm$ 5% relative humidity for 3 months. The samples were analyzed each month for various parameters stated above. It was observed from the results that formulation FM2 remained stable for the period of 3 months at 40±2^{0}C and 75±5% RH, there was no considerable changes in physical appearance as well as in dissolution behavior of the formulation (Fig. 8).

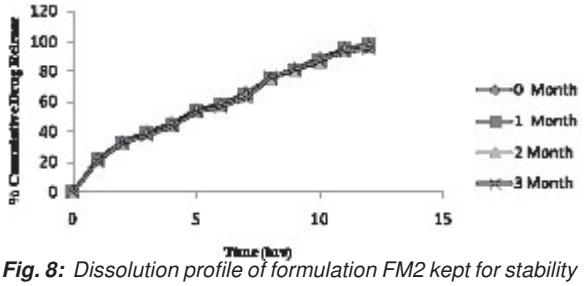

Fig. 8: *Dissolution profile of formulation FM2 kept for stability study*

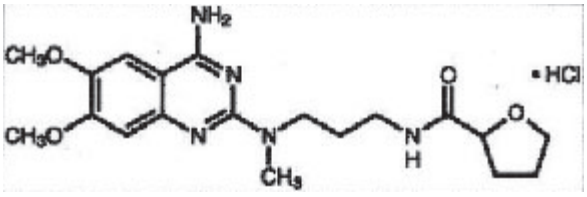

Fig.9: *Structure of Alfuzosin Hydrochloride*

Fourier Transform infra-red analysis (FTIR)-

FTIR spectrum of pure Alfuzosin HCl (Fig.10) showed principle characteristic peaks at 3371cm^{-1} (primary N-H stretching) and 3324 cm^{-1} (secondary N-H stretching), 1631 cm^{-1} (C=O stretch), 1087 cm^{-1} of ether, 3134 cm^{1} (aromatic C-H stretch), 2936 cm^{-1} (aliphatic C-H stretch. In FITR spectra of formulation FM2 (Fig.11) peak of aromatic C-H stretch 3134 cm^{-1} slightly shifted to 3132 cm^{-1} and peak 2936 cm^{-1} (aliphatic C-H stretch) slightly shifted to 2933 cm^{-1}. Therefore it can be concluded that little interaction between drug and excipients was observed which is insignificant. Retention of characteristic peaks indicates compatibility.

N-[3-[(4-amino-6,7-dimethoxy-quinazolin-2-yl)-methyl-amino]propyl] tetrahydrofuran- 2-carboxamide

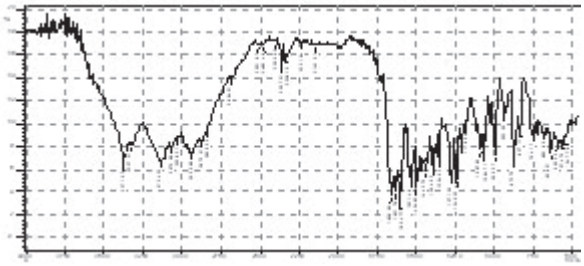

Fig.10 : *FITR spectra of Alfuzosin HCl*

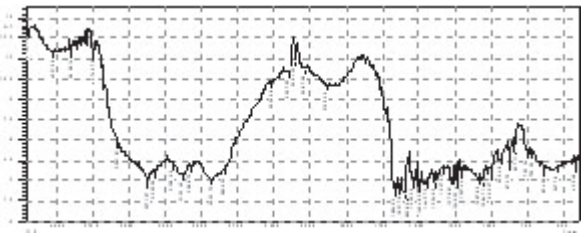

Fig.11: *FTIR spectra of Optimized formulation FM2 (Alfuzosin HCl, HPMC K4M, HPMC K15 and Na CMC)*

Conclusion

Alfuzosin HCl floating-mucoadhesive tablets were successfully prepared using hydrophilic polymers by wet granulation technique. The studies revealed that combination of HPMC K4M, HPMC K15M and sodium carboxymethyl cellulose was most efficient in sustaining the drug release at pH 1.2 for 12 hrs. Rapid initial swelling and optimum erosion of the tablet was observed due to the presence of proper proportion of highly swellable polymers. Incorporation of gas generation agents in the formulation supported rapid swelling and flotation upto 12 hrs in the optimized Alfuzosin HCl tablet formulation. Developed gastroretentive formulation also showed satisfactory mucoadhesive strength required for retention in upper gastrointestinal region for improved bioavailability. The swelling and floating ability were dependent on the composition of the polymers in the tablets. Therefore the developed simple matrix system seems to be suitable for sustaining the release of highly water soluble drug like Alfuzosin HCl which possess narrow window of absorption.

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