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Formulation and evaluation of Alfuzosin hydrochloride floating tablets

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ABSTRACT

Floating matrix tablets of Alfuzosin hydrochloride were developed to prolong gastric residence time. Alfuzosin hydrochloride was chosen as a model drug because it is poorly absorbed from the lower gastrointestinal tract. The tablets were prepared by direct compression and melt granulation technique, using polymers such as hydroxy propyl methyl cellulose K15M, sodium carboxy methyl cellulose, compritol 888 ATO and either alone or in combination, and other standard excipients. Tablets were evaluated for physical characteristics hardness, % friability, floating capacity, weight variation, content uniformity, in-vitro release characteristics for 12 hours and in-vivo gastic retention time. In-vitro release mechanism was evaluated by linear regression analysis. The calculated regression coefficients value of higuchi and koresemayer (0.998, n value 0.520) for optimized formulation F2 and the drug release mechanism was found to be non-ficikian diffusion. No drug-polymer interaction was observed by Fourier Transform Infrared Spectra Analysis. In-vivo studies showed that the tablets retained in stomach for 6hours. It was concluded that, HPMC K15M alone retarded the drug release for highly water soluble drug (Alfuzosin hydrochloride) for a period of 12 hours.

Keywords: Alfuzosin hydrochloride, Floating, X-ray radiographic studies, HPMC, compritol 888ATO.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a chronic disease often associated with the Lower urinary tract symptoms (LUTS) including urinary frequency, nocturia, incomplete emptying, and urinary hesitancy and requires a steady-state concentration throughout the treatment [1]. These symptoms can be caused by altered function of the smooth muscle tone that is regulated by the alpha1-adrenergic receptors in the prostate and its capsule, the bladder base and neck, and the prostatic urethra [2]. Selective antagonist of post synaptic alpha-1 adrenoreceptor drug Alfuzosin hydrochloride is used to treat the BPH through the oral route. This drug can cause relaxation of smooth muscle, improve urine flow and reduces the LUT symptoms [3]. The absolute bioavailability of Alfuzosin is about 49%, Alfuzosin is preferentially absorbed in the proximal

part of the gastrointestinal tract and, in particular, jejunum appear to be the main region for absorption [4] and having short biological half-life (3.8hr). Based on this, an attempt was made through this investigation to formulate floating matrix tablets of Alfuzosin using different polymers and their combinations.

Gastro-retentive dosage forms have been the topic of interest 6in recent years as a practical approach in drug deliveries to the upper GI tract or for release prolongation and absorption [5, 6 & 7]. These dosage forms are particularly suitable for drugs that have local effects on the gastric mucosa in the stomach, such as delivery of drugs used for *Helicobacter pylori* treatment [8]. Other candidates include drugs that are mainly absorbed in the stomach or upper small intestine, or drugs that are unstable in basic environment of distal intestine and colon or those with low solubility at elevated pH conditions [9]. Approaches to increase the gastro-retention time (GRT) include, bioadhesive systems, which adhere to mucosal surfaces [10], Floating has been achieved with the preparation of low-density dry solid systems (e.g. inclusion of sponges, highly porous systems) [11,12] density- controlled systems, which either float or sink in gastric fluids[13], systems ,which decrease in density upon contact with gastric fluids based on the expansion of swelling agents or carbon dioxide generation [14].

MATERIALS AND METHODS

Materials

Alfuzosin hydrochloride (AI) a gift sample from Dr. Reddys laboratory Pvt. Ltd, Hyderabad, Hydroxy propyl methyl cellulose K15M(HPMC K15M) gift sample from Dr. Reddys laboratory, Pvt. Ltd, Hyderabad, Sodium carboxy methyl cellulose(Sodium CMC), Microcrystalline cellulose (MCC, Avicel pH 101) sodium bicarbonate S.D fine chemicals Pvt Ltd. Mumbai Compritol 888 ATO gift sample from Shashan pharmaceutical Pvt. Ltd, Pondichery. All other chemicals were analytical reagent grade

Methods

AI floating tablets formulation F1 to F9 were prepared by direct compression technique. The respective ingredients were passed through a sieve no. 60(250 µm) and blended. All batches were compressed on 16 station rotary tablet punching machine (Cadmach, Ahmadabad, India) with 6mm flat round punches. Individual tablet weight 100mg. the composition of floating tablets of AI given in [Table 1].

Table1. Composition (in mg/tablet) of Alfuzosin hydrochloride floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Alfuzosin hydrochloride	10	10	10	10	10	10	10	10	10	10	10
HPMC K15M	20	30	-	-	20	30	-	-	-	-	-
Sodium CMC	-	-	20	30	20	30	-	20	30	20	30
Compritol 888 ATO	-	-	-	-	-	-	20	20	30	20	30
MCC	56	46	56	46	36	26	56	36	26	56	46
Sodium Bicarbonate	10	10	10	10	10	10	10	10	10	10	10
Magnesium Sterate	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2

HPMC K15M: Hydroxypropylmethylcellulose; Sodium CMC: Sodium Carboxy methylcellulose; MCC: Microcrystalline cellulose; Compritol 888 ATO: Glyceryl behenate

Formulations F10, F11 but they were prepared by melt granulation technique. Lipid polymer Compritol 888 ATO was melted at 50^{o}C and drug, sodium CMC, sodium bicarbonate; MCC was added to this melted lipid with proper mixing and cooled to room temperature. The mass was

passed through a 510- µm sieve to obtain uniform sized granules, which were then lubricated with magnesium stearate and talc and compressed in to tablets [15].

Evaluation of Prepared Granules and Prepared Floating Tablets

Prepared floating granules were evaluated for Angle of repose, Carr's Index and Hausners Ratio and the floating tablets were characterized for weight variation (n=20), hardness (n=6, Monsanto hardness tester), thickness(n=20) using a screw-gauge micrometer (Campbell Electronics, Mumbai, India) and % friability (n=6, Roche friabilator, Electrolab, Mumbai, India).

Assay of Tablets

The assay of tablets was determined by randomly choosing 3 tablets of each batch, which were powdered by mortar and pestle. Powder equivalent to 100mg of AI floating tablets was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in 0.1 N HCl. The prepared solution was kept on rotary shaker for 24 h. Five milliliters of the resulting solution was diluted with 0.1 N HCl. A portion of the sample was filtered through wattman filter paper and absorbance of the solution was measured at 242nm using a double-beam spectrophotometer (Systronics PC based, 2202, Ahmadabad, India).

In-vitro Buoyancy Study

The *in vitro* buoyancy was determined by floating lag times as per the method described by [16]. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The time for which the tablets remained float was taken as total floating time. The tablets that showed the best floating behavior was taken for in-vitro release studies.

***In vitro* Dissolution Studies**

The release rate of AI floating tablets was determined using USP dissolution Testing Apparatus Type II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at 37±0.5° and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus time intervals 0,0.5,1,2,3,4,6,8,10,12 hours and the samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 244nm using a double-beam spectrophotometer (Systronics PC based, 2202, Ahmadabad, India).

Kinetics of Drug Release

The in-vitro release data of the floating tablets were evaluated kinetically by zero-order, first-order, higuchi, korsmeyer-peppas, and the ideal kinetic models were estimated for drug release [17].

Zero- order kinetics:

A linear relationship between the fraction of drug released versus time

$Q = K_O t$

Q is the fraction of drug release at time t & K_O is the zero order release rate constant.

A plot of fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First-order kinetics: The equation that describes first order kinetics is

$\ln (1-Q) = -k_1 t$

Q is the fraction of drug release at time t & K_1 is the first order release rate constant. Thus, a plot of logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi Model

$$Q_t = K_H t^{1/2}$$

Where Q_t = the amount of drug released at time t and
K_H = the Higuchi release rate constant.

Koresemayer Peppas Model
A simple semi empirical model relating exponentially the drug release to the elapsed time (t).

$$Q_t/Q_\alpha = K_k t^n$$

K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism.

Fourier Transform Infra-Red Analysis (FT-IR)
FT-IR measurements of drug, optimized polymer and physical mixture were obtained JASCO FTIR, Japan. The spectra were scanned over the wave numbers range of 3600-400 cm^{-1} at ambient temperature.

In-vivo Studies
In-vivo floating ability was carried by X-ray radiographic studies in healthy human volunteers (n=3) of aged 24-30 years and having 55 to 65 kg weight. The volunteers were asked to swallow the tablets containing radio labeled barium sulphate along with 100ml water after taking a light break-fast. Images were taken at 30 minutes, 2 hours, 4 hours, 6 hours and 8 hours. Volunteers were in supine position during imaging.

RESULTS AND DISCUSSION

The Flow properties of formulations F1 to F9 were within the official limits but the formulations F10, F11 showed poor flow properties because of the lipid nature of polymer. The evaluation properties of prepared tablets, such as weight variation, hardness, friability, hardness, thickness, and assay were determined by using standard protocols and all tablets were within the range of official limits. The results were recorded in [Table 2] and [Table 3].

Table 2. Physical properties of alfuzosin hydrochloride floating tablets

Formulation Code	Angle of Repose	Carr's Index	Hausner's Ratio
F1	27.31±1.66	12.06	1.17
F2	29.24±0.95	14.67	1.18
F3	29.37±1.54	15.54	1.17
F4	32.96±0.87	12.46	1.16
F5	28.38±1.76	14.42	1.15
F6	26.61±1.55	12.24	1.12
F7	30.76±2.09	13.67	1.14
F8	27.51±0.98	12.45	1.13
F9	28.66±1.09	14.54	1.14
F10	39.06±1.34	19.96	1.14
F11	38.66±1.43	17.09	1.17

**Values are the means ± SD (n=3)*

Table 3. Evaluation parameters of prepared floating tablets of alfuzosin hydrochloride.

Formulation code	Hardness (kg/cm2)[*a]	Weight variation (W/W)[*b]	Friability (%)[*c]	Thickness (mm)[*d]	Assay (%)[*e]
F1	5.70±0.76	98.88±1.01	0.30±1.09	2.65±0.56	98.33±0.15
F2	6.01±1.63	98.55±1.09	0.29±0.87	3.05±0..48	97.40±0.54
F3	5.27±1.08	99.08±1.03	0.41±0.35	2.75±0.78	97.90±1.09
F4	5.37±0.58	99.55±1.25	0.23±1.05	2.55±0.65	97.25±0.87
F5	5.51±0.98	97.88±0.19	0.15±1.54	2.79±0.76	100.00±1.15
F6	5.45 ±0.78	98.75±1.91	0.12±0.65	2.86±0.57	96.91±1.07
F7	6.10±1.43	99.08±0.87	0.24±1.34	2.99±0.56	99.81±1.54
F8	6.50±0.54	99.95±1.75	0.20±1.14	2.53±0.86	99.95±1.22
F9	5.61±1.12	98.98±1.07	0.17±1.06	2.75±0.77	98.31±0.76
F10	6.11±1.12	98.98±1.01	0.17±0.98	2.75±0.17	98.31±0.46
F11	5.75±1.12	97.98±1.02	0.17±0.67	2.75±0.57	98.31±0.76

**a.Values are the means ±SD (n=6) ;*
**b.Values are the means ±SD (n=20)*
**c.Values are the means ±SD (n=6);*
**d.Values are the means ±SD (n=20) & *e. Values are the means ±SD (n=3)*

The floating lag time of formulations F1-F6 was less than 1 min. The rapid system floatation associated with the developed formulations can be attributed to rapid water up take and overall system swelling which is highly desirable for the gastro- retentive dosage forms to increase the gastric retention time and improves the bioavailability of drug substances with narrow window of absorption. Presence of sodium bicarbonate in the developed matrix formulation generally resulted in generation of carbon dioxide gas within the hydrating matrix thus complementing the swelling rate of the dosage form. Floating properties were not observed in formulation F7 and floating lag time was less than 4 min in formulation F8 and F9. Formulation F7 prepared with lipophilic polymer compritol 888 ATO does not swell when it contact with water so the floatation was not observed. F8, F9 formulations prepared in combination of compritol 888 ATO and sodium CMC, floating lag time was less than 4 min because sodium CMC is a gel forming polymer. The formulation F10, F11 prepared with compritol 888 ATO and sodium CMC using melt granulation technique also floated within 4 min. therefore there was no difference observed in floating lag time in the formulations prepared with different preparation techniques.

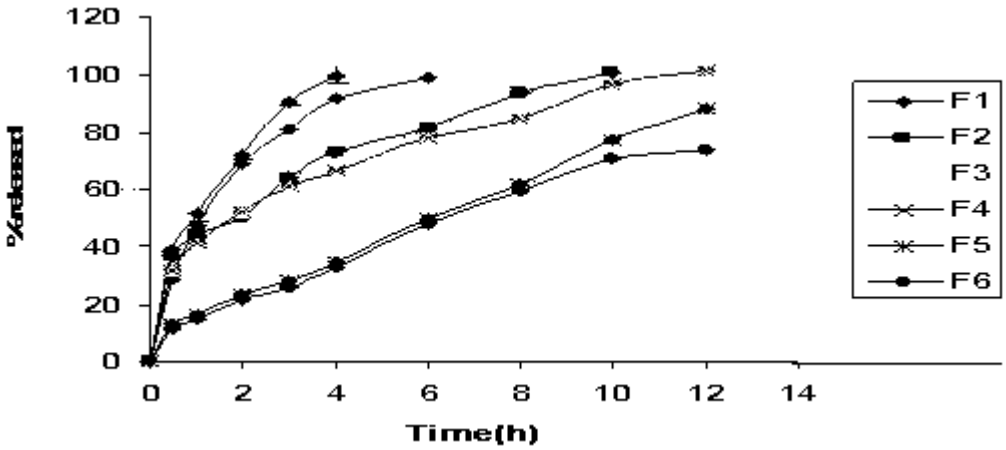

Figure1. In-vitro release profiles showing the effect of HPMC K15 M,(F1 20%,F2 30%)sodium CMC(F3 20%.F430%) and combination of HPMC K15M, sodium CMC(F5 and F6)on drug release on alfuzosin hydrochloride.

In-vitro dissolution of prepared tablets with HPMC K15M (F1, F2) retarded the drug release up to 12 hours. Formulation F1 contains 20 % HPMC K15 M the drug release was controlled up to

12hours and formula F2 (30% HPMC K15M) drug release was desirable and 98% drug was released in 12 hour. Because of high solubility of AI in water and low viscosity (1000cpc) of sodium CMC a hydrophilic polymer, the water penetrates into the polymer and the drug release was not retarded and the tablets were shrinked after 6 hours. 98 % 0f drug releases was observed in formulation F3 prepared with 20% of sodium CMC, and 99% of drug release was observed in formulation F4 prepared with 30% of sodium CMC in 6 hours was shown in [Figure 1].

Formulations F5 and F6 prepared with the combination of HPMC and sodium CMC, the drug release was 88 % and 74% in 12 hours, drug release mechanism was non fickian. The drug release was retarded in combination of HPMC and sodium CMC due to the Sodium (CMC) having the synergistic hydrogen-bonding interactions with HPMC,s these polymers showed a synergistic increase in viscosity, which allowed erosion to occur at a rate equating to the movement of the front between the glassy and the rubbery polymer[18,19,20].

The lipophilic polymer Compritol 888 ATO, having low-density, was tried for floating controlled release. For formulation F7 the in-vitro dissolution profile was not performed because the buoyancy properties were not observed. To overcome this the compritol 888 ATO and low-density hydrophilic polymer sodium CMC was used in combination(F8,F9,F10,F11) .In formulation F8 drug release in first 4 hours was retarded, after that the release was high and 80 % of drug release was observed in 12 hours.

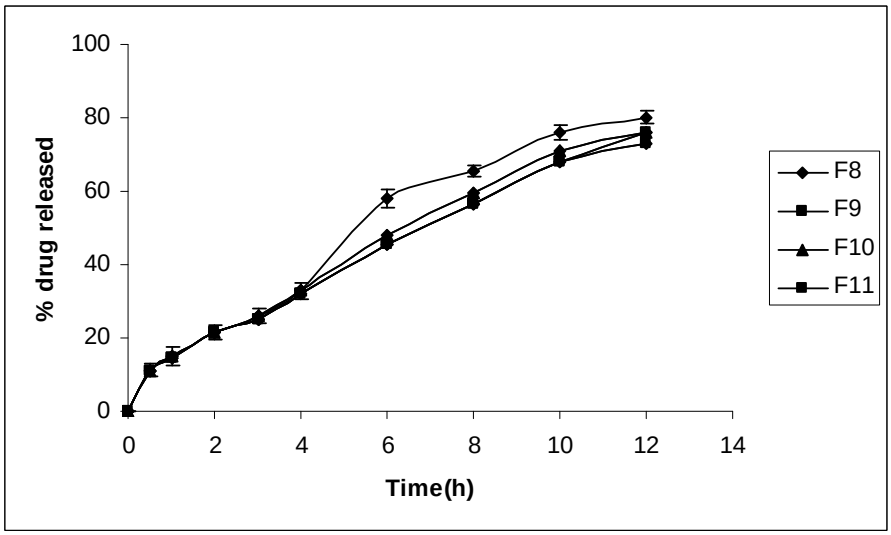

Figure2. In-vitro release profile showing the effect of Compritol 888 ATO and sodium CMC prepared by direct compression method(F8,F9) and Compritol 888 ATO, sodium CMC prepared by melt granulation(F10,F11).

The drug release of F9 was controlled and the % release was 72% in 12 hours, the controlled release of drug mainly depends on the concentration of the polymer if the concentration of polymer increased the drug release was decreased. Formulation F10 had the same composition as that of F8, and formula F11 had the same composition as that of F9 but these were prepared by melt granulation method in order to see the effect of melt granulation on the drug release. But the release profile did not show any significant difference in the release profile [Figure 2].

Kinetic models were calculated for all formulations. Formulation F2 has the higher regression coefficient value of korsmeyer–peppas 0.998 and the n value was 0.520, the release profile was non-fickian.

The FTIR spectra reveal that characteristic peaks of the optimized formulation followed the same trajectory as that of the drug alone with minor differences. The peak at 3359.64 cm^{-1} is characteristic peak of the 1^0 aromatic amine N-H stretching, 3134 is characteristic peak of the aromatic C-H stretching ,2947.33 cm^{-1} is characteristic peak of aromatic C-H stretching and 1604 cm^{-1} aromatic ring stretch (C=C-C) Thus there was no drug-excipient interactions.

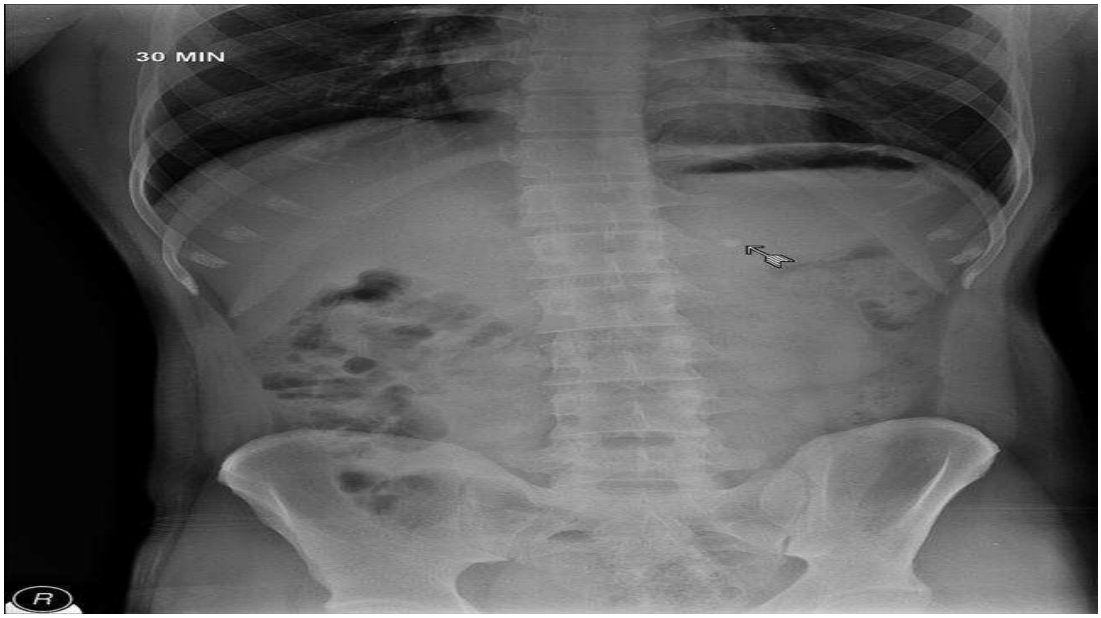

Figure 3.a. Intragastric behaviour of the $BaSO_4$ loaded floating tablets represented by typical radiographic images after definite time intervals (the tablet is pointed by an arrow) 30min.

The X-Ray photographs of the AI floating at different time intervals in human volunteers. Images at different time intervals were taken to find the location of the tablet. The presence of the tablet in the stomach was observed for 6 h and the tablet was not cited at 8 h, the change in the location of tablet at different time points suggest that tablet did not adhered to the gastric mucosa and the gastric retention time was 6 hours. [Figure 3 a, b, c & d]

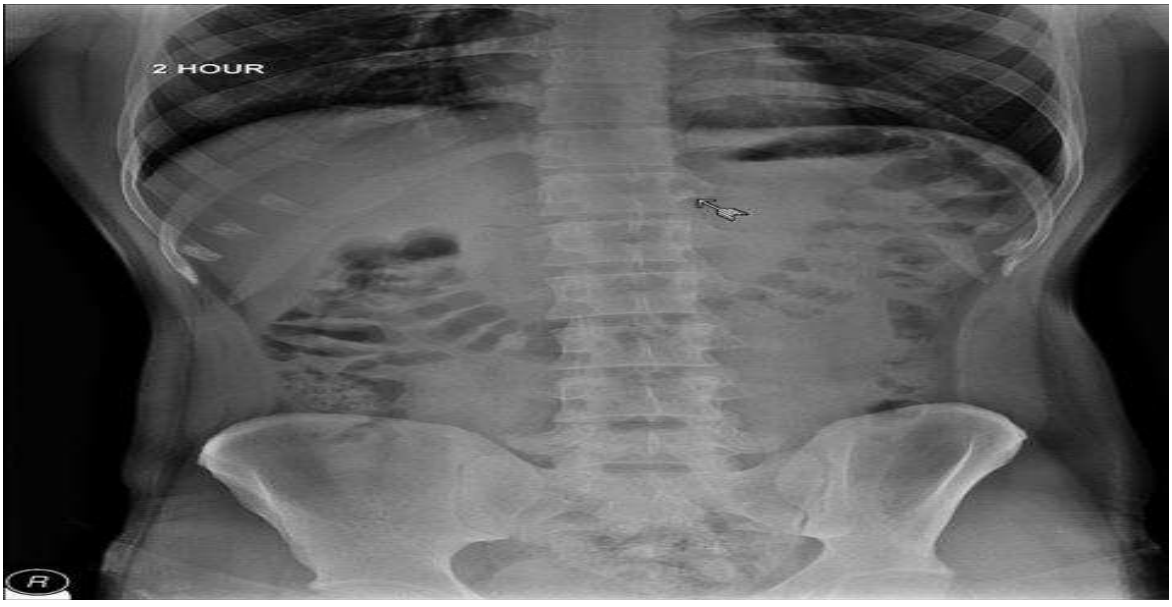

Figure 3.b. Intragastric behavior of the $BaSO_4$ loaded floating tablets represented by typical radiographic images after definite time intervals (the tablet is pointed by an arrow) 2 h.

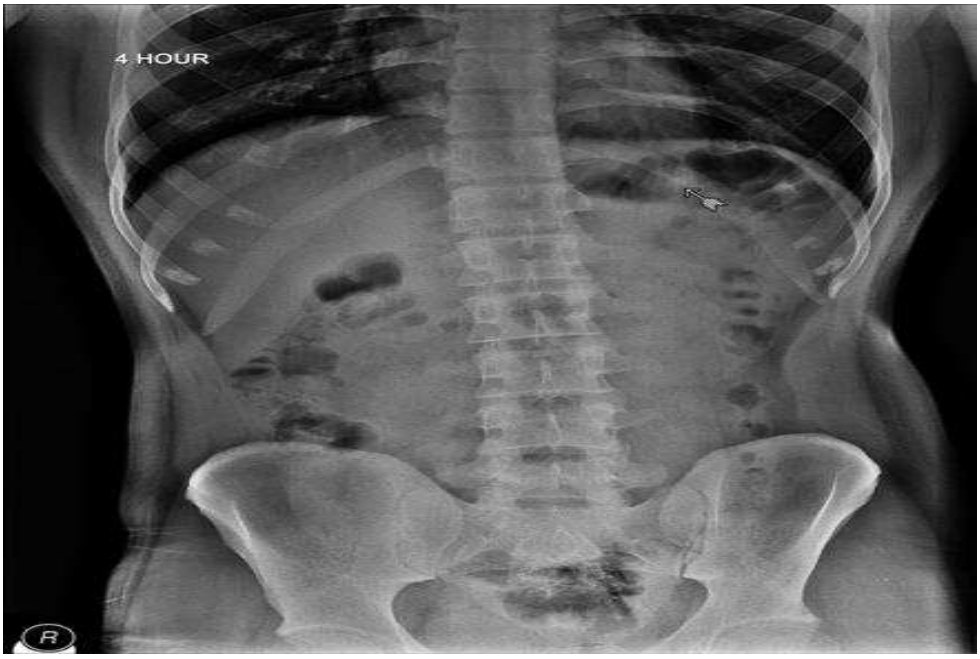

Figure 3.c. Intragastric behavior of the $BaSO_4$ loaded floating tablets represented by typical radiographic images after definite time intervals (the tablet is pointed by an arrow) 4h.

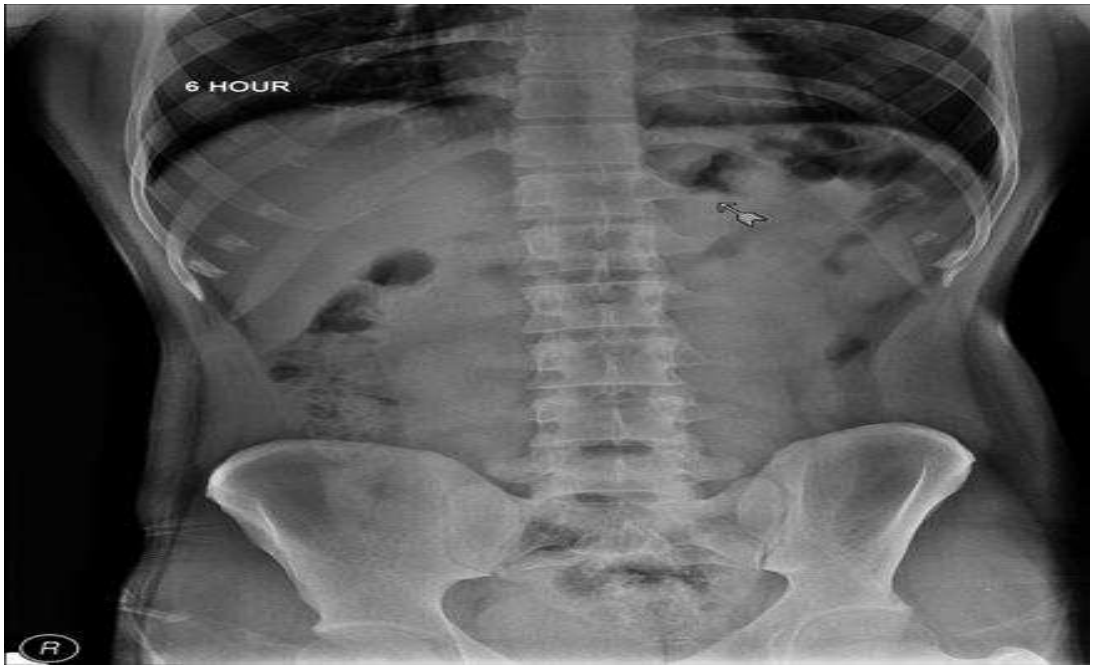

Figure 3.d. Intragastric behavior of the $BaSO_4$ loaded floating tablets represented by typical radiographic images after definite time intervals (the tablet is pointed by an arrow) 6h.

CONCLUSION

It was concluded that the combination of two hydrophilic polymers and combination of hydrophilic, hydrophobic polymers has not shown any significant difference in drug release but difference was observed in floating lag time and floating duration time. The calculated regression coefficient value was high for the formulation F2 (30% HPMC K15M) and it alone retarded the drug release for highly water soluble drug (Alfuzosin hydrochloride) for a period of 12 hours and

the drug release mechanism was non-fickian diffusion. In-vivo studies supported that the tablet was retained in stomach for 6 hours.

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