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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF GA-STRORETENTIVE DRUG DELIVERY SYSTEM OF AL-FUZOSIN HYDROCHLO-RIDE

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Abstract

Gastro-retentive drug delivery systems are an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper GIT for local or systemic effect. Gastro-retentive drug delivery systems formulations greatly improves the pharmacotherapy of stomach by releasing the drug locally and thus results into high concentration of drug at the gastric mucosa which can be sustained over a longer duration of time Gastro-retentive drug delivery system formulated by direct compression method using (i) Alfuzosin HCL an antihypertensive drug (ii) Polyethylene oxide WSR301 , Hydroxy propyl methyl cellulose K4M and Xanthan gum as polymers (iii) Sodium bicarbonate used as gas generating base . The effect of these polymers concentration was evaluated with respect to Floating Lag Time, Total Floating Time, Matrix integrity, swelling study and In-*vitro* release behaviors and release kinetics with model fitting. Infrared spectroscopic study confirmed the absence of any drug-polymer interaction. Differential scanning colorometry confirmed melting point, purity of drug and polymers. Incorporation of sodium bicarbonate in the Gastro-retentive drug delivery system proved to be an effective method to achieve desired buoyancy. The designed system, combining excellent buoyant ability and suitable drug release pattern, from the study it was concluded that, controlled release Alfuzosin HCL floating tablets can be achieved with success using direct compression technique.

Keywords: Gastroretention , Alfuzosin HCl, Hydroxy Propyl Methyl Cellulose, Polyox WSR301 , Xanthan gum, *In- vitro* floating,

Introduction

Oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has several physiological problems. Including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (80-12h), and the existence of an absorption window in the upper small intestine for several drugs.[1] One novel approach in this area is GRDDSs (gastro retentive drug delivery system). Dosage forms that can be retained in the stomach are called GRDDs. GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site[2]. Benign prostatic hyperplasia (BPH) is the most common benign condition affecting men and symptoms can start as early as age 30. Benign prostatic hyperplasia also known as Benign enlargement of the prostate (BPE), Adenofibromyomatous hyperplasia and Benign prostatic hypertrophy. Benign prostatic hyperplasia is a progressive condition characterized by prostate enlargement accompanied by lower urinary tract symptoms. Benign prostatic hyperplasia involves hyperplasia of prostatic stromal and epithelial cells resulting in the formation of large, fairly discrete nodules in the periurethral region of the prostate Benign prostatic hyperplasia can result in the prostatic urethra is compressed which restricts the flow of urine from the bladder, this interference with urine flow may cause uncomfortable symptoms such as frequency, urgency, nocturia, intermittency, decreased stream and hesitancy. Benign prostatic hyperplasia can leads to the risk of urinary tract infection, urinary retention and kidney blockage. Benign prostatic hyperplasia does not lead to the risk of cancer. Initially management for benign prostatic hyperplasia includes lifestyle modification, used alpha blockers and 5-alpha reductase inhibitors. The alpha blockers work to relax the smooth muscle at the prostate and bladder neck by blocking alpha1 receptor. By relaxing the smooth muscle at the prostate neck, the urinary channel is opened which allows a less constricted urinary flow. Alfuzosin HCl is an alpha-1 adrenergic receptor blocker for the treatment of benign prostatic hyperplasia (BPH).Alfuzosin HCl exhibits narrow absorption window in the proximal part of the gastrointestinal tract & jejunum appear to be the main region for absorption. Alfuzosin HCl has a short biological half life (3-5 hours). The dose may range from 2.5 mg thrice a day to a maximum of 10 mg once a day, if it is formulated as conventional tablets it will required multiple daily administration (2-3 times daily) which results into inconveniency to the patients. So Alfuzosin HCl is an ideal candidate for controlled release in the proximal upper parts of the ga-

strointestinal tract. Thus formulation of floating drug delivery satisfied these conditions. Gastroretentive drug delivery system can be retained in stomach for prolonged time & assist in increasing controlled delivery of drug that have narrow absorption window .[3]

Materials

Alfuzosin hydrochloride (DOW chemical, Mumbai), Polyox WSR301 (DOW chemical Industry, Mumbai), HPMC K4M, Xanthan gum, Magnesium strearate, Sodium bicarbonate, Microcrystalline cellulose, Talc (Fine Chemical, Mumbai).

Methods

Direct Compression method

Preparation of Alfuzosin Hydrochloride tablet by direct compression

Tablets were prepared by direct compression technique. All the ingredients were accurately weighed and passed through sieve no. 60 before using into formulation. All the ingredients mixed except magnesium stearate and talc geometrically. Required quantity of polymer and sodium bicarbonate as gas generating agent were mixed then Alfuzosin HCl is added and mixed properly then diluents is added to make up the weight. The blend obtained was then lubricated by adding magnesium stearate and talc and manually compressed on 10 station rotary tablet machine using flat-faced die punches of 6.0 mm diameter. The tablets were compressed to obtain hardness in a range of 6-7 Kg/cm2

Table No. 1 Composition of Alfuzosin Tablet

Ingredients	Batch Codes	
	F1	F2
Alfuzosin HCl	10	10
Polyoxwsr301	20	25
HPMCK4M	20	25
Xanthan Gum	20	25
MCC102	18	18
$NaHco_3$	10	10
Talc	1	1
Magnecium streate	1	1
Total weight(mg)	100 (Mg)	115 (Mg)

Results of Pre and post compression Parameters Of Alfuzosin HCl

The powder mixture used for tablet preparation were evaluated for pre-compression parameter like bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose, results are shown in table 3. The bulk density was varied in the range of 0.332±0.2 gm/ml to 0.582±0.04 gm/ ml, tapped density range between 0.420±0.6 gm/ ml to 0.643±0.02 gm/ml. Hausner's ratio in the range of 1.42±0.2 to 1.11±0.05, Carr's index was varied in the range of 21.42±0.03 % to 14.32±0.04 % and angle of repose was varied in the range of 30.81±0.05^0 to 32.02±0.02 ^{0}. This all parameters show good flow property and direct compressibility.

All the prepared tablets showed acceptable pharmaceutical properties. The hardness of all core tablets was between 6.4±0.4 to6.4±0.7 kg/cm2 in all formulations which indicated good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In the present study, the loss in total weight in friability test was in the range of to 0.74±0.4 to 0.74±0.1% that indicates the percentage friability for all the formulation was found below 1% indicating that friability (%) is within the acceptable limits. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets weighing more than 250 mg is ±5%. The average percentage deviation of all tablet formulations was found to be within limit, and hence all formulations passed the test for uniformity of weight as per official requirements.

Swelling index

The Swelling studies were carried out for F1 formulations containing Polyox wsr 301, Hpmc K4M, xanthan gum as polymer, F1 formulation was hydrated only 12 hours after which their was no further increase in tablet weight due to water uptake. Swelling indices of these formulations F1 were archived 3.08 at12 hr throught the study there was gradual increase in the swelling indices with increase in polymer ratio. The maximum swelling indices of these formulations F2 were achieved 3.18 at 12 hr throught the study there was gradual increase in the swelling indices with increase in polymer ratio. This may be related to high viscosity grades of polymer.

Floating properties

Floating lag time of all formulations was in between 80 to 89 secs and floating duration 20 and > 20.

***In-vitro* drug release of formulation batches**

The dissolution of F1 formulation was carried out with Combination of polymers preparation. The dissolution profile of F1 batch prepared with 1: 2, 1:2, 1:2 ratio of drug : Polyox wsr-301, HPMC K4M, Xanthan gum showed controlled drug release 73.02% which was sustained up to 24 hrs. The dissolution of F2 formulation was carried out with Combination of polymers preparation. The dissolution profile of F2 batch prepared with 1:2, 1:2, and 1:2 ratio of drug: Polyox wsr-301, HPMC K4M, Xanthan gum showed controlled drug release 93.78% which was sustained up to 24 hrs. Formulation F2 showed release of drug by swelling forms a hydro gel because of

low viscosity grade release rate faster owned to less polymer entanglement and less gel strength. F2 formulation containing HPMC K4M showed slower drug release rate because as the concentration of the polymers increased, there is a decrease in the drug release rates, an increase in polymer concentration cause increase in viscosity of the gel as well as gel layer with longer diffusional path, because of these decrease in effective diffusion coefficient of the drug and a reduction in drug release with controlled manner for 24 hour.

Model fitting data of release profile of F2 formulations

F2 formulation showed high regression coefficients (R^2=0.993) as compare to all formulations fitted to Higuchi model and showed diffusion exponent (n=0.5913) within 0.45 < n <0.89 indicating anomalous (non-fickinin) also F2 formulation showed zero order (R^2= 0.982) which showed release of drug at constant rate because of it F2 batch selected for short term stability study.

Stability studies

Result of accelerated stability study of optimized formulation F2 indicated that physical changes were not observed in the samples at the time intervals of 1 month. The tablet could retain more than 99 % of their active ingredients and revealed no significant change in rate of release of Alfuzosin HCL after 1 month of storage at exaggerated conditions. Dissolution profiles were unaffected during stability study, formulation F2 showed % drug release of 93.56 respectively at the end of 24 hours after 1 month, which proved that dissolution profile of Alfuzosin HCL, was not affected during stability study. Hence F2 was found to be stable during accelerated stability study.

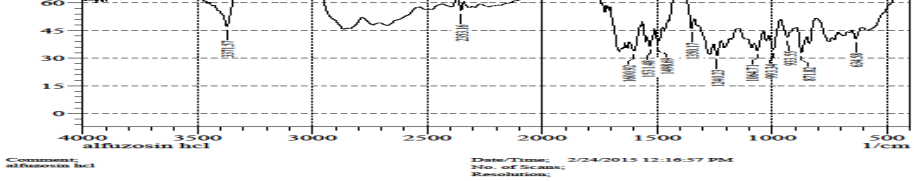

Fig.No 1: IR spectrum of the pure drug Alfuzosin shows in figure No.1

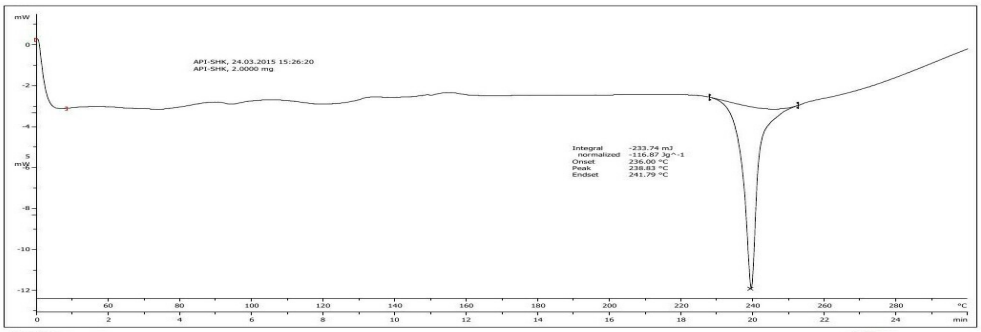

Figure No.2 : DSC Thermogram of Alfuzosin hydrochloride

Table No.2: Pre-Compression Parameter For Powder Blend of F1 – F2 formulation

Batches	F1	F2
Bulk Density(gm/ ml)	0.332±0.2	0.582±0.04
Tapped Density(g/cm³)	0.420±0.6	0.643±0.02
Hausners ratio	1.42±0.2	1.11±0.05
Carrs index(%)	21.42±0.03	14.32±0.04
Angle of Repose(θ)	30.81±0.05	32.02±0.02

Table No.3 : Post-compression parameters for tablets F1 – F2 formulations

Formulations	Tablet Diameter (mm) n=3	Thickness (mm) n = 3	Hardness (Kg/cm²) n = 3	Friability (%) n = 10	Weight variation (n = 20)	Drug contents n = 10
F1	7.0±0.03	2.9±0.07	6.4±0.4	0.74±0.4	99±1.50	99. 8±0.6
F2	7.0±0.02	2.9±0.08	6.4±0.7	0.74±0.1	100±1.00	99 ±0.01

Table No.4: Floating lag time and floating duration of formulations

Formulations	Floating lag time (sec)	Floating duration (hrs)	Matrix integrity
F 1	80	20	+
F 2	89	> 20	+

Table No.5: Swelling Index

Batch	1hr	2hr	4hr	6hr	8hr	10hr	12hr
F 1	0.92	1.53	1.92	2.38	2.85	2.96	3.08
F 2	1.08	1.47	1.95	2.46	2.82	3.4	3.18

Table No. 7 : Percent drug release of Batches F1 to F2

Time(hr)	F2 n= 3	F1 n=3
1Hr	14.80±0.55	13.08±0.92
2Hr	26.82±0.69	24.66±0.48
4Hr	36.82±0.18	37.56±0.38
6Hr	44.88±0.20	45.63±0.12
8Hr	53.03±0.31	51.6±0.26
10 Hr	60.71±0.85	57.48±0.80
12Hr	75.78±0.35	65.73±0.32
18Hr	82.21±0.48	73.02±0.63
24Hr	93.78±0.83	---

Table.No.6: Model fitting data of release profile

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi's (R^2)	Hixon-Crown well (R^2)	Krosmeyer peppas		Best fit model
					(R^2)	(n)	
F2	0.982	0.920	0.991	0.969	0.913	0.5913	Higuchi model

Conclusion

In the present Research work, attempt has been made to develop Alfuzosin HCL floating tablets as matrix forming material utilizing effervescent approach. FTIR spectroscopy revealed that there was no chemical interaction between drug and polymer. The drug content was uniform in all the formulation of the tablets prepared. *In-vitro* release data of F2 optimized formulations were fitted to various kinetics models like Higuchi. Higuchi model describes the release from F2 formulation where the solid is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion. F2 formulations followed anomalous type (Non-fickian transport) and *in-vitro* drug release was found to have followed Higuchi kinetics Stability study of optimized formulations F2 indicated that physical changes were not observed in the samples at the interval of 1 month. Dissolution profiles were unaffected during stability study. From the present study carried out on Gastroretentive drug delivery system of Alfuzosin HCl using Polyox WSR301, HPMC K4M and Xanthan gum by direct compression method, showed following conclusion. The results of current study clearly indicate that the *in vitro* release of Alfuzosin HCL is significantly affected by the amount of Polyox WSR301, HPMC K4M, and Xanthan gum as the concentration a formulations made with different concentrations of polymers showed efficient released profile of the drug. The optimized formulation of batch F2 containing drug - polymer ratio (1:2:5) containing Polyoxwsr301, Hpmck4m and Xanthan gum gave best *in vitro* release of 93.78% in 0.1 N HCL was better than marketed preparation. It was as an ideal formulation and subjected to further short term stability. Optimized formulation of Alfuzosin HCl (F2) was found to be stable at 45^0 c following a 1 month stability study. Finally the formulation of Alfuzosin HCl provides a better option for increasing the bio availability and reliability Alfuzosin for hypertension and in benign prostatic hyperplasia to relive symptoms of urinary obstruction. Hence it can be concluded that Alfuzosin hydrochloride in GRDDS dosage form can be used for its anti hypertensive activity.

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