FORMULATION AND EVALUATION OF ALFUZOSIN HYDROCHLORIDE EXTENDED RELEASE TABLETS

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Summary

The aim of the study was to design extended release tablets which was capable of producing a 20 hrs extended release profile there by eliminating the use of immediate release tablets which require a frequent administration of three tablets containing 2.5 mg of alfuzosin hydrochloride of daily dose. The present study deals with formulation of Alfuzosin Hydrochloride extended release tablets. Benign prostatic hyperplasia is a noncancerous prostate problem in which the normal elements of the prostate gland grow in size and number, requires an alpha-adrenergic blocker which is having optimum therapeutic window concentration for a prolonged duration. With the above characteristics Alfuzosin Hydrochloride was selected as active therapeutic agent. Alfuzosin HCl extended release matrix tablets were prepared by wet granulation method by employing hydrophilic polymers (HPMC K 100 M) and hydrophobic polymers (hydrogenated castor oil and ethyl cellulose). The matrix granules were prepared by mixing the drug along with hydrogenated castor oil using the ethyl cellulose as binder in different amounts. The prepared granules were compressed with HPMC K 100M at optimized concentration of ethyl cellulose. The prepared tablets were evaluated for various physicochemical parameters by official procedures. The *in-vitro* release study of matrix tablets were carried out in 0.01N HCl for 24 hours. To investigate the drug release mechanism, the release data were fitted into kinetic models such as zero order, first order, Higuchi and Peppa's. Analysis of drug release data from the matrix system indicated that the drug release follows zero order kinetics by anomalous (non-fickian) diffusion.

Key words: Extended release tablets, Alfuzosin HCl, Hydroxypropyl methyl cellulose, Hydrogenated castor oil, Ethyl cellulose.

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Introduction

Extended release oral drug formulations have been used since the 1960s to enhance performance and increase patient compliance. By incorporating the dose for 24 hours in to one tablet from which the drug is slowly released, peaks of high plasma concentration and troughs of low concentration can be prevented. This helps avoid the side effects associated with high concentrations and the lack of activity associated with low concentrations giving better overall therapy.

Alfuzosin HCl is a selective antagonist of post-synaptic alpha1 - adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra. Alfuzosin is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia[1]. Alfuzosin is not indicated for the treatment of hypertension. The prostate gland of the patients enlarges in BPH and prevents urine flow from bladder which results in urinary retention. The treatments available are surgical removal of excess tissue or drug therapy[2]. Two classes of drugs are used, 5-alpha reductase inhibitors and alpha adrenergic antagonists. The second class includes terazosin, doxazosin, tamsulosin and alfuzosin.

Alfuzosin is freely soluble in water [3] and thus readily absorbed after administration. The oral absorption is significantly aided by the presence of food. The dose of immediate release alfuzosin tablet is 2.5 mg thrice daily, elimination half life is 3-5hr and pKa is 8.1.[4] Recently 10 mg once daily extended release formulation has become available in the market[5] which is more convenient for older patients. Marketed alfuzosin formulation is a three layered Geo matrix tablet that requires special facilities, high cost, time consuming and complex operation than conventional formulations [6].

In the present study extended-release alfuzosin Matrix tablets were prepared by involving two steps. 1) Alfuzosin HCl granules were prepared with hydrogenated castor oil as hydrophobic polymer by using ethyl cellulose as binder and 2) The prepared granules were compressed into tablets with HPMC K 100M as hydrophilic matrix polymer.

Materials and Methods

Alfuzosin HCl was obtained from (MSN Organics Ltd., Hyderabad). Ethyl cellulose was procured from (Aqualon, Mumbai). Hydrogenated castor oil was procured from (Cognis, Mumbai). HPMC K100 was procured from DOW chemicals. Lactose monohydrate from (Friesland foods Domo Ltd), MCC PH 101 from (Accent microcell industries Ltd) and colloidal silicon dioxide (Aerosil 200) from (Wacker silicons) were procured. All other chemicals and ingredients were used for study are of Analytical grade.

Preparation of Alfuzosin HCl ER Tablets:

Tablet formulations were prepared by wet granulation method. A non-aqueous granulation process was adopted to prepare alfuzosin HCl ER tablets. Granules were prepared as follows. Proportion of excipients with drug was as given in (Table 1). All ingredients were sifted through sieve no. 40. Hydrogenated castor oil, lactose monohydrate and MCC PH 101 were mixed with alfuzosin HCl to form final blend. Ethyl cellulose was dissolved in IPA (5% w/v) and used for wet granulation of the final blend. The wet mass was passed through sieve no. 20 and wet granules were dried at 50°C in an oven for 30 minutes. Dried granules were sized by passing it through sieve no. 20 and mixed with micro crystalline cellulose PH 101, HPMC K100M, hydrogenated castor oil, magnesium stearate and Aerosil. Tablets were compressed using Rotary tablet machine with 9.5 mm standard concave punch. Tablet weight was (380mg) kept constant for all matrix tablets prepared.

Table-1. Composition of alfuzosin HCl Extended-release matrix Tablets

S.No	Name of material	F1	F2	F3	F4	F5	F6	F7
1.	Alfuzosin HCl	10	10	10	10	10	10	10
2.	Lactose monohydrate	132	74.4	74.4	74.4	74.4	74.4	85
3.	Ethyl cellulose	5	19	12	8	8	7	7
4.	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s
5.	Micro crystalline cellulose PH102	120	100	107	121	131	132	131.4
6.	Hydroxy propyl methyl cellulose	106	150	150	140	130	130	120
7.	Aerosil 200	2	1.9	1.9	1.9	1.9	1.9	1.9
8.	Magnesium stearate	7	1.9	1.9	1.9	1.9	1.9	1.9
9.	Hydrogenated castor oil	---	22.8	22.8	22.8	22.8	22.8	22.8
10.	Poly vinyl Pyrrolidine K90	3	---	---	---	---	---	---

Evaluation of granules:

Angle of repose is a relatively simple technique for estimation of the flow property of a powder. Powders with low angle of repose are free flowing and those with a high angle of repose are poorly flowing powders.10 gm of granules were passed through funnel and the pile was formed. The height and weight of the pile was measured and the angle of repose was calculated by using the formula:- Angle of repose (θ) = tan-1

Hausner's ratio was related to interparticle friction and could be used to predict powder flow properties. Hausner's values of the prepared granules ranged from 1.12 to 1.25 were thought to indicate good flow properties.

Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula:

LBD= weight of the powder / volume of the packing.

TBD = weight of the powder / tapped volume of the packing.

Compressibility index of the granules was determined by using the formula

CI (%) = [(TBD-LBD/TBD)] ×100

Evaluation of tablets:

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a Strong- Cobb hardness tester (Tabmachine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by vernier caliper. Weight variation test was performed according to the official method.

Content uniformity:

20 tablets were weighed and finely powdered. Transfer an accurately weighed portion of the powder, equivalent to about 40 mg of Alfuzosin HCl to a 500-ml volumetric flask and add 50 ml of 0.1N hydrochloric acid, and sonicated to dissolve it. Shake by mechanical means for 10minutes, dilute with water to volume, mix, and pass through a filter having a 0.5µm or finer porosity. Drug content was determined by using UV Visible Spectrophotometer at 271nm.

***In-Vitro* Drug Release study:**

In-vitro drug release studies were carried out for extended release alfuzosin HCl formulations using 0.01N HCl as dissolution medium using USP Apparatus-II (Paddle) at 100 rpm (Electrolab, 2000) and temperature was maintained at 37±0.5°C. The dissolution was continued for 24 hours while samples of 5 ml were withdrawn at regular interval and replaced with equal volume of fresh dissolution medium to maintain the volume constant. The samples were filtered,

diluted and analyzed for drug content. The amount of drug released was determined by UV spectrophotometer at 271nm. Drug release at specified time points was calculated.

Kinetic Data analysis:

To study the release kinetics and mechanism for drug release, *In-Vitro* release data was fitted into various kinetic models (Zero order, First order, Higuchi and Korsmeyer Peppas)[7]. The zero order rate Eq. (1), describes the systems where the drug release rate is independent of its concentration[8]**.** The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble Matrix reservoir as a square root of time dependent process based on Fickian diffusion Eq. (3)[9].

$C = k_o t$---------- (1)

Where, K_o is zero-order rate constant expressed in units of concentration/time and‘t’ is the time.

$\text{Log } C = \text{Log } C_o - kt / 2.303$---------- (2)

Where, C_o is the initial concentration of drug and ‘K’ is first order constant.

$Q = Kt^{1/2}$ ---------- (3)

Where, ‘K’ is the constant reflecting the design variables of the system.

Mechanism of drug release:

Korsmeyer et al derived a simple relationship which described drug release from a polymeric system Eq. (4). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model[10].

$Mt / M\,8 = Kt^n$ ---------- (4)

Where Mt / M8 is the fraction of drug released at time t, k is the rate constant and ‘n’ is the release exponent. The ‘n’ value is used to characterize drug release mechanism from the cylindrical shaped matrices.

The following plots were made: cumulative % drug release vs. time (zero order kinetic models); log % drug remain to be released vs. time (first order kinetic model); cumulative % drug release vs. square root of time (Higuchi model) and log cumulative % drug release vs. log time (Peppas model).

FT-IR Spectroscopy Study

The IR spectra of Cefixime trihydrate pure drug and physical mixture of optimised formulation were recorded from 400 to 4000^{-1} on FT-IR spectrophotometer.

Stability studies

The optimized formulation was subjected to stability testing at 40 ± 2^0 C and 75 ± 5% RH, for a period of six months. After each month the tablet samples were analyzed for physical attributes and Invitro drug release profile.

Result and Discussion

The present study investigates the utility of hydrophilic (HPMC K 100) and hydrophobic polymers (Hydrogenated castor oil) for extended delivery of alfuzosin HCl. Lactose monohydrate, micro crystalline cellulose PH101, ethyl cellulose, Aerosil 200 and magnesium stearate are used as diluents, binder, glidant and lubricant, respectively. Seven formulations of alfuzosin HCl extended release matrix tablets were prepared by wet granulation method. To determine the effect of amount of ethyl cellulose on the release of alfuzosin HCl, matrix tablets were prepared by keeping the hydrogenated castor oil and HPMC K 100 amount at constant amounts.

The bulk density, Hausner ratio and compressibility index of all the formulations were confirmed the good flow property (Table.2). The physical properties of compressed extended release tablets, such as weight variation, friability, hardness, and thickness were determined by using standard protocols. These parameters were found to be within standard limits and satisfactory (Table 3).It is observed that the drug content of the tablets was found in between 98.7% and 102.90% of the labeled amounts that reflect good drug distribution and homogeneity.

Table-2. Evaluation data of Alfuzosin ER granules

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner's ratio	Angle of repose (^{o})
F1	0.4	0.476	19	1.19	36.7
F2	0.408	0.50	22.5	1.225	42
F3	0.4	0.512	28	1.28	46
F4	0.416	0.512	23.2	1.23	42.5
F5	0.4	0.487	21.7	1.21	41.7
F6	0.416	0.512	23.27	1.23	43.2
F7	0.411	0.552	25.5	1.34	43

Table-3. Physical properties of Alfuzosin ER tablets

Formulation	Avg weight (mg)	Thickness (mm)	Diametre (mm)	Hardness (kgs/cm^2)	Friability (%)	Drug Content (mg)
F1	380±2	4.2±0.1	11	8±0.5	0.14	99.3±1.4
F2	380±2	4.2±0.1	11	9±0.5	0.09	98.7±1.4
F3	380±2	4.2±0.05	11	6±1.5	0.12	101.6±1.3
F4	380±2	4.2±0.05	11	9±0.5	0.07	101.2±0.9
F5	380±3	4.2±0.1	11	9±0.5	0.2	101.6±1.2
F6	380±3	4.2±0.05	11	6±1.5	0.07	99.3±1.4
F7	380±3	4.2±0.05	11	10±1	0.12	98.7±1.4

All values represent mean ± SD

Drug- Excipient compatibility studies:

There was no characteristic change in the colour of the powder and no additional degradation of products was observed. The increase in impurities at the end of the accelerated condition is not significant. All the active ingredients selected for the development of Alfuzosin HCl tablets are stable and compatible with the active ingredients. Hence it is recommended that the above excipients that are compatible can be used in future formula development trials.

In-vitro drug release studies were performed with all formulations. The results are accordingly tabulated in (Table 4 & Fig 1). The percentage drug release for the formulation $F_5$was found 96% respectively up to 24 hours. Formulation F_5 prepared was found to be the optimised formulation.

Table-4: Dissolution profiles of Batches

Formulations	% drug release				
	1hr	2hr	6hr	12 hr	20hr
Innovator	15	26	67	87	96
F1	51.6	84.16	62	98.78	105.7
F2	8	14	43	65	76
F3	13	20	48	66	80
F4	15	24	53	76	85
F5	17	23	68.2	86	96
F6	10	24	60	71	90
F7	18	25.5	58	70	88.7

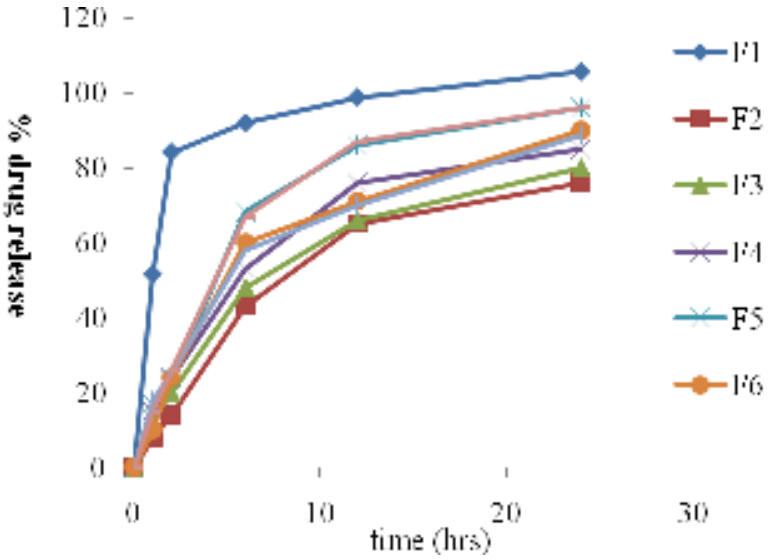


Figure. 1. *In-vitro* release profiles showing the effect of ethyl cellulose and the HPMC K 100M on alfuzosin HCl extended release tablets and innovator product.

In the present work, formulation F5 was selected as optimized formulation because in this formulation drug release pattern was initially rapid and then controlled manner up to 24hrs and this formulation drug release was similar with innovator product.

The mechanism of release for the optimized formulations was determined by finding the R^2 value for each kinetic model viz. Zero-order, First-order, Higuchi, and Korsmeyer-Peppas corresponding to the release data of formulations (Table 5). For most of the formulations the R^2 value of Korsmeyer- Peppas and first-order model is very near to 1 than the R^2 values of other kinetic models. Thus it can be said that the drug release follows Korsmeyer-Peppas and first-order model mechanism. The n-values of Korsmeyer-Peppas model of the best formulations are in between 0.95-0.99. Therefore the most probable mechanism that the release patterns of the formulations followed was non-fickian diffusion or anomalous diffusion.

Table- 5: *In vitro* release kinetics of Alfuzosin ER tablets:

Formulation number	Zero Order(r)	First Order (r)	Higuchi model (r)	Peppas model (r)
Innovator	0.94	0.85	0.99	0.96
F1	0.97	0.92	0.97	0.97
F2	0.96	0.94	0.95	0.98
F3	0.96	0.92	0.99	0.99
F4	0.96	0.9	0.99	0.99
F5	0.94	0.89	0.99	0.96
F6	0.95	0.93	0.96	0.96

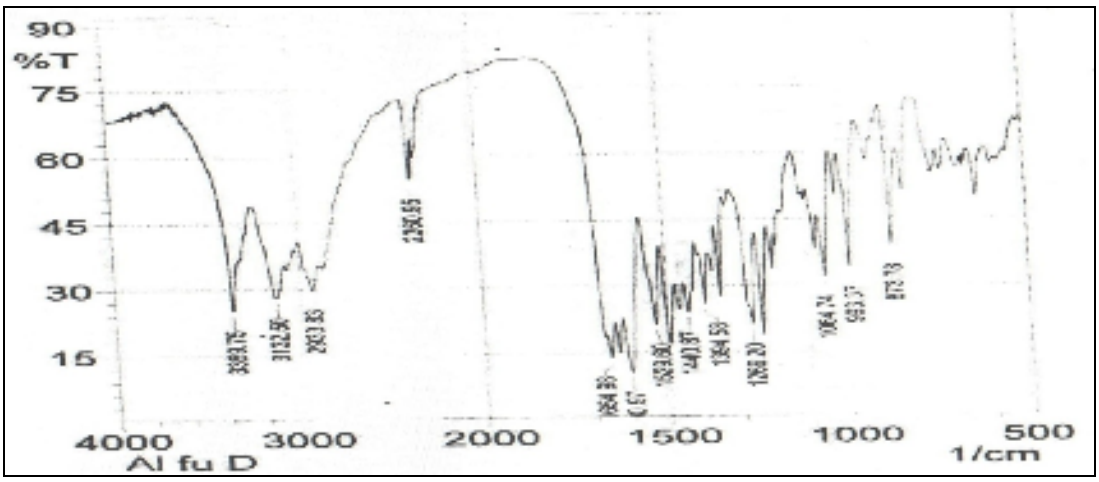
The optimized formulation F5 were selected for accelerated stability studies and the tablets possessed the same parameters even after the stressed conditions, indicates good stability properties of formulation (Table.6)

Table. 6: Stability study data of the Alfuzosin HCl tablets

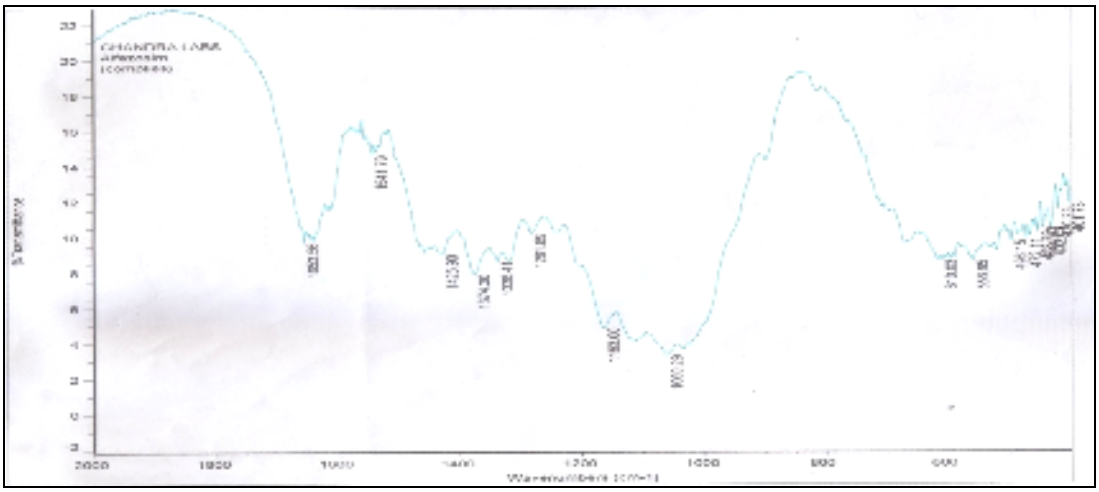
Characteristics tested	Specifications	Testing intervals			
		Initial	1st month	2nd month	3rd month
Description	Off white, round shaped, biconvex tablets	compiles	compiles	compiles	complies
Water content	NMT 0.5% w/w	0.28%	0.33%	0.338%	0.35%
Assay	NLT 99.0% & NMT 101.0 %	99.9%	99.9%	100.6%	100.6%
Hardness	NLT 3kg/cm^2	8±0.5	9±0.5	8±0.5	9±0.5
Thickness	4.2mm	4.2±0.1	4.2±0.1	4.2±0.1	4.2±0.1
Dissolution	1st hr- 10-20%	17	17	17	17
	2nd hr- 20-40%	23	23	23	23
	12th hr-60-85%	86	86	86	86
	20th hr- NLT 85%	96	96	96	96

FT-IR spectra of the alfuzosin and drug with HPMC K 100M revealed that there is no shifting of the peaks indicating the compatibility of the HPMC K100M polymer with the drug (Figure 2,3).

FTIR for Alfuzosin Hydrochloride. Fig-2:



FTIR of Optimized formula: Fig-3:



Conclusion

In conclusion, the results of the present study demonstrated that HPMC K 100 could be a successful hydrophilic polymer for the formulation of extended release tablets of alfuzosin. In-vitro dissolution studies indicated a sustained release pattern throughout the 24 h study period, which was compatible with the theoretical release profile.Hence HPMC K 100, based extended release tablets seem to have a desirable sustained pattern of drug release, in order to reduce the dosing frequency.

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