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Formulation and Evaluation of Extended Release Alfuzosin Hydrochloride Tablets

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ABSTRACT

The conventional oral drug delivery systems are the primary pharmaceutical products commonly seen in the prescription and over-the-counter drug market place. This type of drug delivery system is known to provide a prompt release of drug. Therefore to achieve and to maintain the drug concentration within the therapeutically effective range for treatment of the ailment, it is essential to administer them several times a day. This leads to fluctuations in plasma drug concentrations.[2]

In order to overcome the problems accompanying conventional oral dosage form like poor patient compliance due to frequent dosing and precipitation of adverse effects especially with over medication of a drug having a narrow therapeutic window, it is needful to deliver drug through controlled drug delivery systems.[5]

Keywords: Alfuzosin, controlled drug delivery, formulation, matrix tablets.

BASIC INTRODUCTION:

The most important drug delivery route is undoubtedly the oral route. The oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration and cost effective manufacturing process.[1] The treatment of an acute or a chronic illness by delivery of the drugs to the patients using various pharmaceutical dosage forms, including Tablets, Capsules, Pills, Suppositories, Creams, Ointments, Injectables etc., as drug carriers started years back.[2] About 70% of medicines were prepared in the form of tablets.[3]

A tablet is defined as a solid pharmaceutical dosage form containing active drug substance with or without suitable diluents and prepared by either compression or molding methods. They provide an accurate, stable dose with great precision & least content variability. The manufacturing cost is low as compared to other dosage forms, easy to use & handle.[1, 4]

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MARERIALS AND METHOD:

List of materials used for the study and their category

Materials	Grade	Category	Manufacturer / Supplier
Alfuzosin Hydrochloride	B.P.	Active drug	MSN organics Ltd. Hyderabad.
Lactose monohydrate	U.S.P/N.F.,E.P.	Diluent	Dow chemical's, India.
Ethyl cellulose	I.P.	Binder	Divis laboratories Ltd., Hyderabad.
Isopropyl alcohol	I.P.	Binder solvent	Signet chemical corporation, Mumbai.
Microcrystalline cellulose	U.S.P/N.F.,E.P., J.P.	Diluent	Divis laboratories Ltd., Hyderabad.
Hydroxy propyl methyl cellulose K100M	U.S.P/N.F.,E.P., J.P.	ER polymer	AET laboratories, Hyderabad, India.

Aerosil	U.S.P.	Glidant	Natco Chemie Pvt Ltd. Mumbai, India.
Magnesium stearate	I.P.	Lubricant	Loba Chemie Pvt Ltd. Mumbai, India.
Hydrogenated castor oil	I.P.	Release rate modifier	KMV Enterprises, Hyderabad.

List of equipments and instruments

S. No	Equipments	Manufacturer
1.	Electronic weighing balance	A W 120, Shimadzu Corporation, India.
2.	Tablet compression machine	Cemach, Ahmadabad, India.
3.	Tablet dissolution tester	Electro lab TDT- 08L, Mumbai, India.
4.	Double beam UV/visible Spectrophotometer	Shimadzu UV-1700 PC, Shimadzu Corporation, Japan.
5.	Friabilator	Electro lab EF-2, India.
6.	Digital pH meter 802	Systronics, Ahmedabad, India.
7.	FTIR Spectrophotometer	Jasco 460 plus, Japan.
8.	Tray dryer	Winamac enterprises, Secunderabad, India.
9.	Hardness tester	Electro labs, Mumbai, India.
10.	Disintegration tester	Electro labs, Mumbai, India.
11.	Moisture analyzer	Sartorius, Mumbai, India.
12.	Bulk density apparatus	Electro labs, Mumbai, India.

Fourier Transform Infrared (FTIR) Spectroscopy:

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug & other excipients used in the formulation. First accurately weighed quantity of drug and other excipients were properly mixed. From that 1 mg of the sample was taken and mixed with 10 mg of dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler & the spectrum was recorded by scanning in the wave number region of 4000-400 cm^{-1} in an FTIR spectrophotometer (Jasco 460 plus, Japan). The IR spectrum of the drug was compared with that of the physical mixture to check for any possible drug-excipients interaction.

FTIR Spectrophotometer.

RESULTS AND DISCUSSIONS

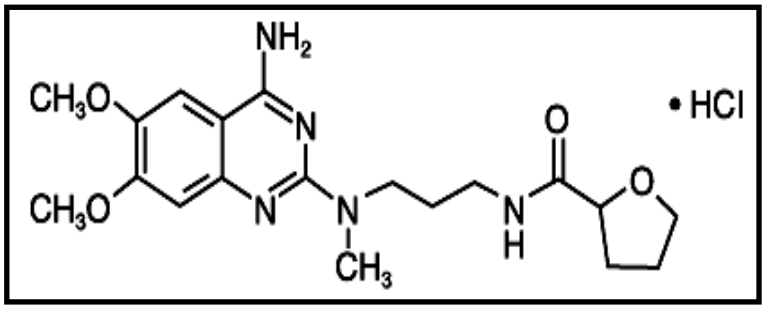
Drug- Excipients interaction studies:

Compatibility studies:

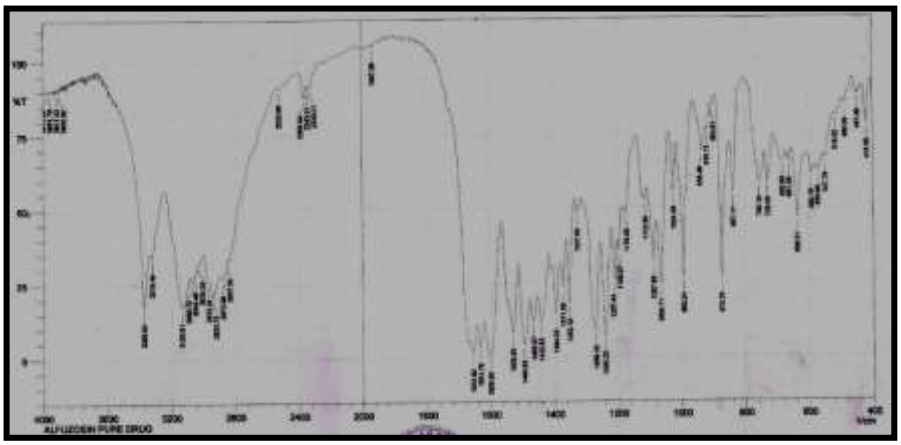
Table; Drug- Excipient compatibility studies

S.No	Ingredients		Description (40ºc ± 2ºc, 75%±5% RH)		
		Ratio	Initial	2weeks	4weeks
1.	Alfuzosin HCl		White powder	White powder	White powder
2.	Alfuzosin HCl +Lactose monohydrate	1:7	White powder	White powder	White powder
3.	Alfuzosin HCl +Ethyl cellulose 7cps	1:1	White powder	White powder	White powder
4.	Alfuzosin HCl +Isopropyl alcohol	Q.S	clear, colorless, flammable	clear, colorless, flammable	clear, colorless, flammable
5.	Alfuzosin HCl +Microcrystalline cellulose PH102	1:13	White powder	White powder	White powder
6.	Alfuzosin HCl +HPMC K100M	1:13	White powder	White powder	White powder
7.	Alfuzosin HCl +Aerosil 200	1:0.2	White powder	White powder	white powder
8.	Alfuzosin HCl +Magnesium stearate	1:0.2	White powder	White powder	White powder
9.	Alfuzosin HCl +Hydrogenated castor oil	1:2	White powder	White powder	White powder

FTIR Spectroscopy:



Structure of Alfuzosin HCl



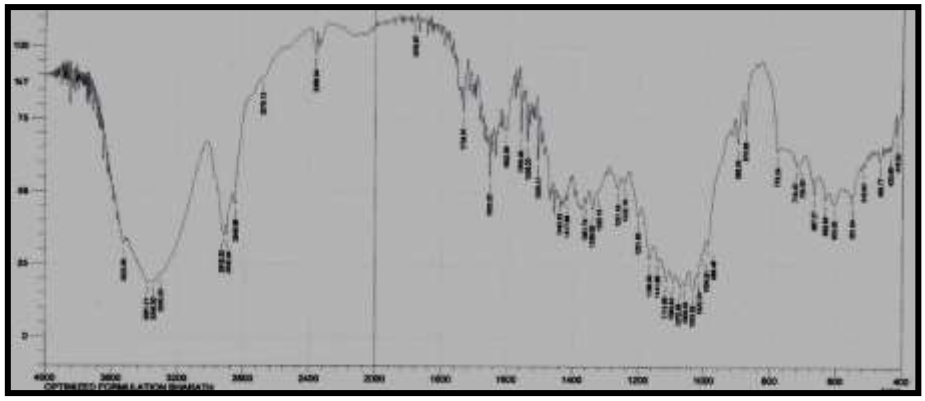
The FTIR spectra of Alfuzosin pure drug

The FTIR spectra of the drug mixed with polymers.

Dose calculation for extended release tablets of Alfuzosin HCl

Calculation of theoretical release profile of Alfuzosin HCl:

Amount of drug needed to be extended = $\frac{0.693 \times D \times T}{t_{1/2}}$ **…….e.q 13**



Where,

D = dose of the drug (2.5mg).

T = duration of time desired for extended release (24h).

$t_{1/2}$ = half-life of the drug (4.5h).

Therefore, 9.24mg of the drug should be extended in each formulation.

Evaluation of extended release matrix tablets

Pre compression parameters:

The pre compression properties of the prepared granules of F4 to F10 Table

Pre compression properties of formulations F4 – F10

Formulation	Poured density* (gm/ml)	Tapped density* (gm/ml)	Carr's index (%)	Hausner's ratio (%)	Angle of repose* (degrees)
F4	0.51 ± 0.006	0.39 ± 0.004	12.82	1.15	23 ± 1.537
F5	0.45 ± 0.007	0.52 ± 0.008	13.46	1.16	25 ± 2.654
F6	0.48 ± 0.013	0.41 ± 0.035	14.63	1.17	26 ± 0.546
F7	0.36 ± 0.02	0.42 ± 0.007	14.28	1.17	24 ± 2.961
F8	0.398 ± 0.006	0.448 ± 0.023	11.16	1.13	23 ± 1.852
F9	0.381 ± 0.016	0.459 ± 0.017	16.99	1.20	25 ± 2.522
F10	0.424 ± 0.004	0.556 ± 0.005	23.74	1.31	23 ± 2.196

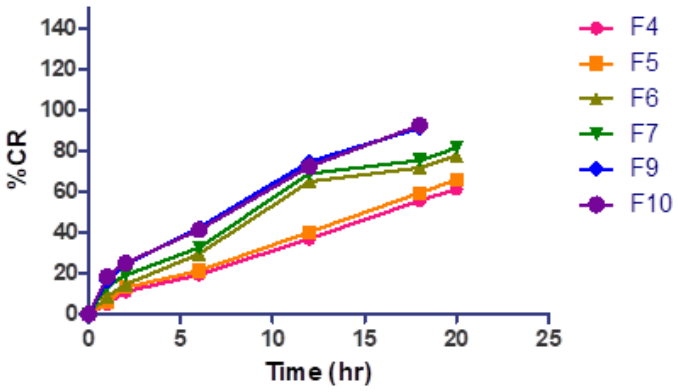
*The values represent mean ± SD, n = 3.

In vitro drug release profiles:

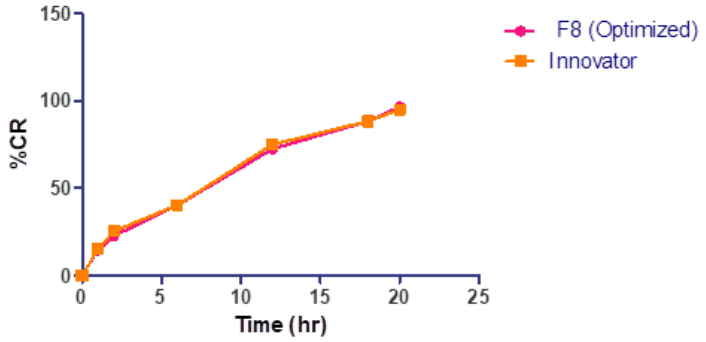
The *in vitro* dissolution data of formulations F1 to F10 and innovator is given in Table, the release profile of formulations F4, F5, F6, F7, F9 & F10 is shown in Fig and F8, and innovator is shown in Fig.

***In-vitro* dissolution data of formulations F1 to F10 and innovator product**

Formulations	**% drug release**						
	0hr	**1hr**	**2hr**	**6hr**	**12hr**	**18hr**	**20hr**
F1	0 ± 0	48.21 ± 1.93828	56.54 ± 2.39846	82.37 ± 0.37292	98.48 ± 2.49361	105.38 ± 3.83910	-
F2	0 ± 0	42.37 ± 2.38462	50.38 ± 2.38193	62.37 ± 1.28394	85.26 ± 2.38457	99.37 ± 2.38716	-
F3	0 ± 0	35.28 ± 2.39871	45.28 ± 2.39738	59.28 ± 2.38109	82.37 ± 1.29374	95.28 ± 1.28367	-
F4	0 ± 0	4.98 ± 0.65054	11.1 ± 4.6502	19.25 ± 2.33456	36.95 ± 2.12132	55.62 ± 1.04628	61.34 ± 3.1537
F5	0 ± 0	6.16 ± 0.51619	13.06 ± 2.59508	21.29 ± 1.28362	40.18 ± 4.7164	59.45 ± 0.27354	65.86 ± 2.54558
F6	0 ± 0	8.56 ± 0.23335	14.55 ± 0.7566	29.58 ± 2.94716	64.91 ± 1.79605	71.73 ± 2.48140	77.74 ± 2.63751
F7	0 ± 0	13.59 ± 1.8809	19.07 ± 5.14067	32.67 ± 3.48104	68.85 ± 2.87793	75.28 ± 2.03849	81.48 ± 3.67696
F8	0 ± 0	14.52 ± 1.1738	22.71 ± 0.51619	40.28 ± 0.28374	72.45 ± 0.42426	88.26 ± 0.29384	96.38 ± 0.51619
F9	0 ± 0	16.49 ± 0.52326	24.4 ± 0.70711	42.49 ± 1.2937	74.71 ± 1.03945	91.13 ± 1.55564	-
F10	0 ± 0	18.39 ± 0.33234	25.06 ± 0	41.41 ± 1.28394	72.25 ± 1.13137	92.51 ± 0.23335	-
Innovator	0 ± 0	15.33 ± 0.42236	25.42 ± 0.13983	40.25 ± 0.49284	75.11 ± 1.03467	88.29 ± 1.38294	95.06 ± 0.67897



***In vitro* drug release profile of formulations F4, F5, F6, F7, F 9 & F10.**



***In vitro* drug release profile of formulations F8 (Optimized) & innovator product.**


Zero hour


1st hour


6th hour


12th hour


18th hour


20th hour

Swelling and erosion of the optimized formulation

Alfuzosin Hydrochloride, a urinary selective □□□adrenergic antagonist is used against Benign Prostatic Hypertrophy. It is freely soluble in water and readily absorbed after oral administration. An extended release formulation of the drug is thought to be more convenient for older patients due to reduced frequency of drug administration which overcomes the problem of patient noncompliance.

In the present work, extended release matrix tables of Alfuzosin HCl were prepared using various rate controlling polymers. The product profile was targeted to match the innovator product ALFUSIN (CIPLA).

The drug exhibited a λ_{max} at 254nm and hence calibration curve was constructed at this wavelength. The calibration curve of Alfuzosin HCl in 0.01N HCl was found to be linear over a concentration range of 2-10 µg/ml with R^2 value of 0.9957.

The innovator product was evaluated for physicochemical properties and *in vitro* drug release. Based on the results the target profile was fixed (Table 5.4).

In the pre formulation studies, the active ingredient Alfuzosin HCl was evaluated for flow properties and compressibility. The values of Hausner's ratio, Angle of repose, Carr's index indicate that the drug exhibit poor flow and hence needs to be granulated before tabulating.

The drug excipient compatibility studies indicated that the physical properties of the drug remain unchanged when mixed with various excipients and stored at accelerated conditions for 4 weeks (Table 5.6). The FTIR spectra of Alfuzosin HCl showed characteristic peaks for different functional groups such as amide C=O, primary & secondary N-H group, Aliphatic C-H group and Cyclic C-O group. When the peaks of physical mixture of the drug with polymer mixture were compared to that of the drug alone, no major shift in the peaks was observed (Table 5.7). This indicates absence of interaction between the drug and selected excipient.

Alfuzosin HCl is freely soluble in water and hence a judicious selection of release retarding polymers was necessary to achieve a constant and sustained release of the drug. The most common method of modulating the drug release is to include it in a matrix system. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance.[43]

The drug release for extended duration, particularly for highly water soluble drugs, using a hydrophilic matrix system is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs with high water solubility, hydrophobic polymers are suitable as matrixing agents for developing sustained release dosage forms. Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well established safe applications.[43]

In the present study Hydroxy propyl methyl cellulose K100M (HPMC K100M) was used as a hydrophilic matrixing agent because it forms a strong viscous gel on contact with aqueous media which is reported to be useful in controlled delivery of highly water soluble drugs. It has also been reported that at higher concentration of HPMC, the drug release was faster which may be due to faster dissolution of the highly water soluble drugs from the core and its diffusion out of the matrix forming the pores for entry of solvent molecules.

Ethyl cellulose (EC) was incorporated in the formulation as the hydrophobic polymer since it cannot be swells like HPMC and can change the permeability of the matrix resulting in modification of drug release.[42]

In formulations F1, F2 and F3, EC & HPMC were used in varying concentrations (Table 4.3). The results indicate that this combination was beneficial in retarding the drug release up to only 18hr. To further retard the drug release, addition of Hydrogenated castor oil (HCO) was investigated. HCO has been used as a sustain release coating material and hardening agent. It has been reported that HCO forms a thin coating on the surface of the drug particles there by controlling the release of the drug. In formulations F4 to F10, HCO was added in a concentration of 5.8% along with varying concentrations of EC and HPMC K100M. HCO was added both intra and extra granularly to further sustain the release of the drug.

The granular properties of formulation F4 to F10 indicate good flow ability and compressibility. The post compression properties of the tablets were found to be satisfactory in terms of weight, hardness and friability. The drug content of the formulations was found to be in the range of 98.7 to 101.06%.

In-vitro release studies indicate that the formulation F4 containing 5% EC and 39.4% HPMC K100M along with 5.8% HCO gave a release of only 61% after 20 hr. When compared to formulation F3 the release was found to be retarded. The slow release of the drug can be attributed due to the uniform coating of HCO on the individual drug particles by the addition of HCO intra granularly and extra granularly.

In formulation F5 the amount of EC was reduced to 3.9%, retaining the amount of HPMC K100M. However, the drug release did not improve considerably. In formulations F6 & F7 the amount of both EC and HPMC were reduced. A substantial increase in the drug release was observed from both the formulations.

The formulation F8 which contained lesser concentration of showed the optimum release which was similar to the innovator product. This formula contained 5.8% HCO, 2.1% EC and 34.2% HPMC K100M.

A further decrease in EC (F9) and HPMC K100M (F10) resulted in sustaining the drug for up to 18 hr only.

Hence F8 was considered to be the optimized formulation in which the release was sustained up to 20 hr and the release profile was similar to the innovator product.

A judicious combination of hydrophilic polymer (HPMC K100M-34.2%) & hydrophobic polymers (EC-2.1% & HCO-5.8%) was thus found to be beneficial in sustaining the release of Alfuzosin HCl for 20 hrs.

When the dissolution data was treated with various models it was found that the release follows Higuchi kinetics and the mechanism of drug release was found to be anomalous diffusion as indicated by ‘n’ value 0.6024 of the korsmeyer’s equation.

The optimized formulation was subjected to stability studies under accelerated conditions for 3 months. The results of stability study indicate no major change with respect to the drug content and percent drug release.

CONCLUSION-

From the present study it can be concluded that control release of a highly water soluble drugs like Alfuzosin HCl can be achieved using a judicious combination of hydrophobic and hydrophilic polymers. A combination of HPMC K100M, EC and HCO was beneficial in extending the release of the drug for 20hr. The mechanism of drug release from the matrix tablet was found to be by anomalous diffusion i.e. the combination of both diffusion and erosion. The developed formulation of Alfuzosin HCl was found to be helpful in reducing dosing frequency and improving patient compliance. Due to the ease in manufacturing the matrix tablets, the formula could be adopted for large scale production.

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