JChrDD | Vol 2 | Issue 1 | 2011: 43-48
ISSN: 2249-6785
Journal of Chronotherapy and Drug Delivery

Received: Nov 12, 2010
Revised: Dec 16, 2010
Accepted: May 5, 2011

Original Research Paper

FORMULATION AND EVALUATION OF ALFUZOSIN HYDROCHLORIDE EXTENDED RELEASE TABLETS

B Chandana*[1], Subal Debnath[1], SY Manjunath[1], Madhu E Nicholas[2]

[1]Srikrupa Institute of Pharmaceutical Sciences, Velkatta, Kondapak, Dist Medak, Siddipet-502277 (India)

[2]MSN Formulations Ltd, Bollram, Medak (India)

* Corresponding author. Tel: +91-9949402406;

E-mail: subal_2007@yahoo.co.in

Abstract

In the present work, an attempt was made to design alfuzosin extended release (ER) tablets using hydroxypropylmethyl cellulose (HPMC) and ethyl cellulose. Seven different formulations were developed by wet granulation method using HPMC K100M and EC 7cps as polymers. All the formulations were evaluated for their micromeritic properties such as compressibility index, Hauser's ratio and flow properties. Dissolution studies of showed that formulation F7 released 96% of drug at 20 h time interval. From the results, it was shown that release followed first order kinetics. All the tablets show good fit for Higuchi (r^2 =0.97 - 0.98) and Peppas' (r^2 = 0.98 - 0.99). Therefore both diffusion and erosion mechanisms play role in alfuzosin release from matrix tablets. Formulation F7 containing alfuzosin hydrochloride, HPMC K100 M, EC 7cps, hydrogenated castor oil, MCC PH 101, lactose monohydrate, aerosil, magnesium stearate and isopropyl alcohol was considered as optimized formulation. Further, *in vitro* release pattern of drug from F7 was found to be super imposable on marketed formulation (the similarity factor f2 was found to be 80.10). F7 was found to be stable during accelerated stability studies conducted at 40°C / 75% RH for three months as per ICH guidelines.

Key Words: HPMC K100M, EC 7cps, Matrix tablets, Wet granulation

Introduction

Alfuzosin, a quinazoline derivative, is a selective alpha-1 blocker that has been used in the treatment of hypertension and benign prostatic hyperplasia. Alfuzosin acts by inhibiting the postsynaptic α_1-adrenoceptors on vascular smooth muscle. This drug inhibits the vasoconstrictor effect of circulating and locally released catecholamines (epinephrine and norepinephrine), resulting in peripheral vasodilatation.[1] The prostate gland of the patient enlarges in the BPH and prevent urine flow from bladder which result in urinary retention, The goal of the therapies is to prepare extended release dosage form to cause enough necrosis so that when the dead tissue is reabsorbed by the body the prostate shrinks, relieving the obstruction of the urethra.

The usual dose of alfuzosin for patients with BPH is 2.5 mg twice or thrice daily of the IR formulation or 5 mg of ER alfuzosin twice daily or 10 mg of ER alfuzosin once daily. The rationale for extended release preparation is to change the absorption characteristics to obtain a more slowly achieved maximal plasma concentration (C_{max}).This promotes a sustained plasma concentration over 20 h, thereby allowing for once-daily dosing and improved tolerability due to the avoidance of high peaks in plasma concentration. For freely soluble drugs like

alfuzosin, large quantity of HPMC is required to control the release that ultimately results in tablet which is difficult to swallow.[1] This problem can be resolved by using water insoluble polymer in the formulation. Therefore ethyl cellulose was used in present study along with HPMC to prepare matrix tablets.

Materials and methods

Materials

Alfuzosin hydrochloride and isopropyl alcohol were obtained from MSN Lab Ltd (India). HPMC K100 M was obtained from Aqualon-Hercules (India), ethyl cellulose (EC) 7cps and hydrogenated castor oil were obtained from Signet (India). MCC PH 101, lactose monohydrate, aerosil, magnesium stearate were obtained from Asakeshi (China), Dow Chemicals (India), Colorcon (India) and Luzanac Pharma (India), respectively.

Preparation of matrix tablets

Alfuzosin hydrochloride tablets were prepared by wet granulation method. The ingredients were passed through 40 mesh sieve and weighed accurately as per the manufacturing formula. An amount of 8 mg of ethyl cellulose was added in a 100 mL of isopropyl alcohol. The binder solution was added to the contents and wet dough mass was obtained by using rapid mixing granulator. Wet mass was dried in fluid bed granulator, where temperature is maintained at 60°C in which dried granules was passed through 16 mesh sieve. Finally, milled granules were passed through 16 mesh sieve. Remaining quantity of hydrogenated castor oil, HPMC K100, aerosil were mixed with the above prepared blend and final lubrication was done with magnesium stearate (60 mesh).

All the batches were compressed on 8 station tablet compression machine (Kambert, India) with 11 mm sub concave punches. To increase the appearance of tablets, coating was done. Instacoat universal white (50 g) was dissolved in 450 mL of water and was subjected to stirring for 45 min. This solution was used to coat the tablets by using autocoater until tablets attained 2% weight gain (i.e., 380-388 mg). The formulae of all batches are shown in Table 1. For comparison, marketed tablets were used.

Physical evaluation of tablets

The physical properties of tablets such as weight variation, friability, hardness and thickness2 were determined. The weight variation of tablets was performed by randomly selecting 20 tablets and weighing them individually and together in electronic single pan balance (Sartorius, India). Friability was tested by Roche fraibilator. Hardness was tested by Monsanto hardness tester. The thickness of tablets was measured using vernier calipers.

Table 1. Formulation of alfuzosin hydrochloride tablets

Ingredients mg/tab	F1	F2	F3	F4	F5	F6	F7	F8*
Alfuzosin HCl	10	10	10	10	10	10	10	10
Lactose	80	80	80	80	80	80	80	80
MCC PH101	181	178	174	94	98	101	125	125
HPMC K 100M	100	100	100	150	150	150	130	130
EC 7cps	5	8	12	19	15	12	8	8
Hydrogenated castor oil	-	-	-	23	23	23	23	23
Magnesium stearate	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	2	2
Total weight	380	380	380	380	380	380	380	380

*Coated with Instacoat universal white

Drug content

The drug content in tablets was determined by randomly choosing 6 tablets of each formulation. A quantity equivalent to 10 mg of alfuzosin hydrochloride was weighed and dissolved in mobile phase. The mobile phase was composed of buffer, acetonitrile and tetrahydrofuran in 800:200:10 ratio (buffer was prepared by dissolving 5 mL of perchloric acid in 900 mL of water with pH 3.5 and finally diluted to 100 mL with milli Q water). The amount of drug was determined by injecting 10 µL of sample in an HPLC system (Shimazdu, Japan) consisting of Intersil OD5-2 (150 x 4.6 mm). The column was maintained at ambient temperature. The compounds were eluted using the mobile phase at the flow rate of 1.5 mL/min. The column effluent was monitored at 254 nm and the retention time was noted.

Dissolution studies[3]

Dissolution studies were carried out for all the formulations, employing USP II paddle method and 900 mL of 0.01N HCl as the dissolution medium at 100 rpm and the temperature was maintained at 37+0.5°C. A sample of 5 mL was withdrawn periodically at 1, 2, 12 and 20 h time intervals and the volume was replaced with an equivalent amount of the dissolution medium. These samples were analyzed by UV-VIS Spectrophotometer at 254 nm.

Kinetics of drug release

The rates of drug release from different batches were evaluated kinetically by using the following equations:

Zero order kinetics: $F = K_0 t$

First order kinetics: $\ln (1-F) = -K_1 t$

Higuchi model: $F = K_2 t^{1/2}$

Peppas' model: $\log F = \log K_3 + n \log t$

F is amount of drug dissolved at time t, K_0, K_1, K_2, K_3 are dissolution rate constants, n is the diffusion exponent indicative of the mechanism of drug release. For the matrix the value of n < 0.45 indicates Fickian (case 1 release) release, n > 0.45 but < 0.89 indicate non Fickian (anomalous) release, and > 0.89 indicates super case II type release. Case II generally refers to the erosion of polymer and anomalous transport refers to both diffusion and erosion controlled drug release.

Accelerated stability studies[4]

The formulated Alfuzosin hydrochloride extended release Tablets were subjected to accelerated stability studies at 40^0C / 75% RH, after packing in HDPE Container, for a period of 3 months.

Results and Discussion

Different batches of formulated alfuzosin HCl extended release tablets were evaluated for uniformity of weight, thickness, hardness, drug content uniformity, friability and all the physical parameters of different batches were within control (Table 2).

Table 2. Physicochemical properties of tablets

Batch code	Average weight (mg)	Thick-ness (mm)	Hard ness (kg/cm^2)	Friabi lity (%)	Drug Content (mg/tab)
F1	378	4.19	12	0.75	101.2
F2	379	4.19	13	0.76	100.8
F3	379	4.18	12	0.74	100.9
F4	380	4.19	13	0.75	100.6
F5	379	4.19	13	0.75	100.7
F6	378	4.18	14	0.76	100.8
F7	380	4.20	14	0.77	100.7
Alfoo*	382	4.20	13	0.76	101.0

* marketed product

Dissolution studies of alfuzosin hydrochloride showed that the formulations released 96% of drug at 20 h of time interval (Fig. 1 to 4). As F1, F2, F3 formulations were not meeting the dissolution specification, i.e., showed 100% of drug release in 2 h only, these batches were not included in the dissolution data fitting. The calculated regression coefficients showed a higher r^2 with first order kinetics (r^2=0.9985) (Table 3). Hence, release data of the tablets obeyed first order[13]. All the tablets show good fit for Higuchi (r^2 =0.97-0.98), from which, it is evident that alfuzosin was released by diffusion process from the matrices. The diffusion exponent of Peppas' model (n) ranged from 0.601-0.784 indicating non-Fickian or anomalous transport. Therefore, both diffusion and erosion mechanisms play role in release of alfuzosin from matrix tablets.

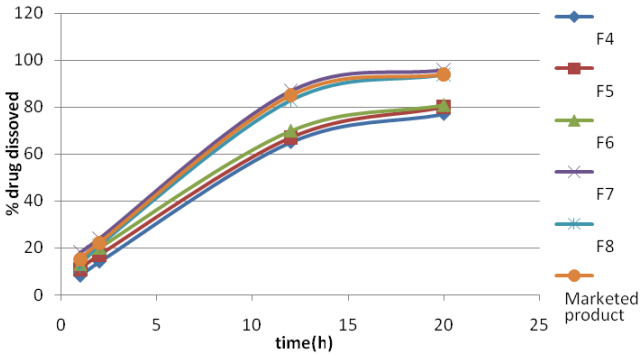

Fig. 1. Zero order plots for dissolution of alfuzosin from different formulations

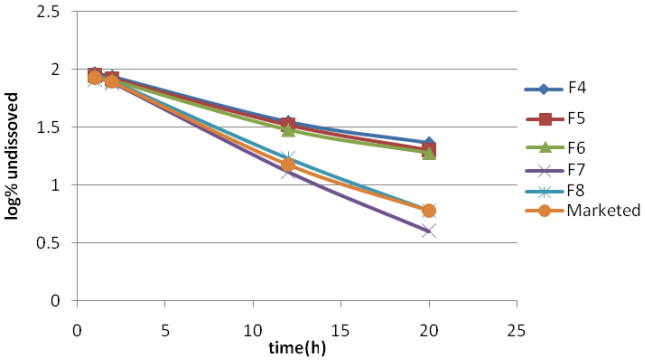

Fig. 2. First order plots for dissolution of alfuzosin from different formulations

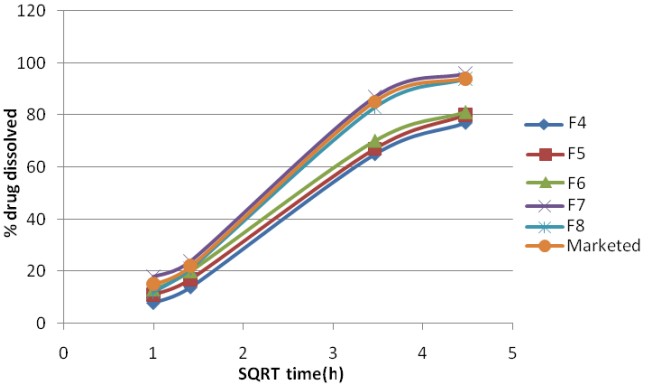

Fig. 3. Higuchi's plots for dissolution of alfuzosin from different formulations

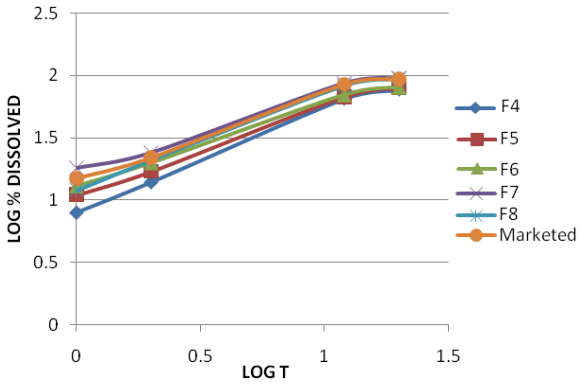

Fig. 4. Peppas' plots for dissolution of alfuzosin from different formulations

Table 3. Dissolution profile comparison of different batches

Batch code	r^2 values				"n" values
	Zero order	First order	Higuchi	Peppas	
F4	0.947	0.9862	0.9865	0.9927	0.784
F5	0.9525	0.9925	0.9892	0.9942	0.690
F6	0.942	0.9859	0.9851	0.9934	0.635
F7	0.922	0.9985	0.9721	0.9850	0.601
F8	0.930	0.9982	0.9791	0.990	0.710
Marketed	0.922	0.9931	0.9721	0.989	0.651

Among the developed formulations, F7 gave a release profile similar to that of innovator product (ALFOO). The dissolution profiles of formulation F7 and innovator product were compared by calculating difference factor (f1) and similarity factor (f2)[14]. The values of f1 and f2 were found to be 4.16 and 80.10 respectively. Formulation-F7 developed is considered similar and equal to the innovator product (Table 4).

Table 4. Dissolution profile comparison of different batches of alfuzosin matrix tablets

Time (h)	Avg Reference	Avg Test	(R-T)
1.00	15	18	3
2.00	22	24	2
12.00	85	87	2
20.00	94	96	2
f1		4.16	
f2		80.10	

Formulation F7 was subjected to accelerated stability testing at 40° C/ 75% RH for 3 months. No significant changes were observed in the physicochemical properties, drug content and the dissolution profiles at the end of storage period of 3 months (Table 5).

The aim of the study was to design a extended release matrix tablets which was capable of producing a 20 h sustained 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. In present study the release of drug was extended by employing semi synthetic derivative of cellulose, hydroxylpropylmethyl cellulose which is swellable and hydrophilic polymer. matrix tablets prepared using HPMC on contact with dissolution media or gastric fluids gets hydrated to form a viscous gel layer through which drug will be released by diffusion or by erosion of matrix.

Numerous studies have been reported on the HPMC matrices to control the release of various drugs[5-10]. Generally by using the combination of high viscosity and low viscosity polymers of HPMC[11], Alfuzosin tablet was already formulated. However, the use of hydrophilic polymer alone for extending drug release for highly soluble drugs was limited due to rapid diffusion of drug through the hydrophilic gel network, for such drugs it becomes essential to incorporate hydrophobic polymer in the matrix system. Among the different polymers Eudragit has been used[12]. In present investigation, ethyl cellulose-7cps was used as a binder, which is hydrophobic in nature hence the binary mixture of hydrophilic and hydrophobic polymer has been used successfully to formulate extended release matrix formulations. As ethyl cellulose-7cps is also having low viscosity when compared with other grades, to obtain more retardant property at low concentrations of ethyl cellulose-7cps hydrogenated castor oil was also incorporated in the formulation. Lactose was used as filler and microcrystalline cellulose was chosen because of the high bulk density and the excellent flow properties thus MCC provide minimum weight variation and good content uniformity. Magnesium stearate and colloidal silicon dioxide are used as lubricant and anti adherent. Formulation F1, F2, F3 were formulated by using both HPMC K100M at constant weight and EC-7cps in increasing order but it does not show useful results as these formulations released 100%

of drug within 2 h, whereas, according to the finished product specification the formulation should release 10-20% of drug in 1st h, 20-40% of drug in 2nd h, 60-85% of drug in 12th h and not less than 85% of drug in 20th h. so in order to get the desired drug release profile the concentration of both HPMC K100M and EC 7cps were increased along with incorporation of hydrogenated castor oil which attributed drug release profile in which the release was retarded but not meeting the specification therefore by altering the concentration of polymers, F7 batch was optimized which shows the desired drug release profile, i.e., 96% at 20th h of time interval, which is similar with that of marketed product ALFOO.

Table 5. Stability study data of the alfuzosin matrix tablets

Test	Specifications	Initial	At the end of		
			1 month	2 months	3 months
Description	Off white, round shaped, biconvex tablets	Complies	Complies	Complies	Complies
Identification	The retention time of major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay.	Complies	Complies	Complies	Complies
Hardness	NLT 3kg/cm^2	14	13	14	13
Thickness	4.2 mm	4.2	4.23	4.19	4.2
Dissolution	1st h - 10-20% 2nd h - 20-40% 12th h - 60-85% 20th h - NLT 85%	17 23 86 96	17 24 86 96	16 24 86 96	16 24 86 96
Assay by HPLC	NLT 380.00mg (90.0%) and 390.0mg (110%)	380.21 mg/tab (100.9%)	381.23 mg/tab (100.5%)	379.91 mg/tab (100.8%)	383.9 mg/tab (100.9%)

Conclusion

HPMC K100M and EC7cps combination successfully yielded alfuzosin hydrochloride extended release tablets in which release pattern was extended the over 20 h. From the stability studies it was found that no significant change in drug content and other physical properties of tablets were observed.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

References

1. British Pharmacopoeia. Vol 1. London: British Pharmacopoeia commission; 2005, p.73.
2. Keith, M. Compression and consolidation of the powdered solids. In: Lachman L, Liberman HA, Kanig JL, editors. Theory and Practice of Industrial Pharmacy. 3rd ed. Mumbai: Varghese Publishing House; 1991. p. 66-72.
3. US-FDA. Dissolution method for drug products. Available at: http://www.accessdata.fd.gov/scripts/cder/dissolution/dsp_SearchResults_dissolution.cfm?PrintAll=1
4. Ravi PR, Ganga S, Saha RN. Design and study of lamivudine oral controlled release tablets. AAPS Pharm Sci Tech. 2007; 8: 101.
5. Kamboj S, Gupta GD, Oberoy J. Oral controlled release dosage forms. Pharmainfo.net 2009; 7: 123-126.
6. Yan G, Li H, Zhang R, Ding D. Preparation and evaluation of a sustained release formulation of nifedipine HPMC tablets. Drug Dev Ind Pharm. 2000; 26: 681-686.
7. Basak SC, Reddy BMJ, Mani KPL. Formulation of the monolithic matrix tablets of ambroxol hydrochloride as sustained release tablets. Indian J Pharm Sci. 2006; 68: 594-598.

8. Harikrishna Boyapally H, Kumar R, Douroumis D. Preparation and evaluation of diltiazem HCl tablets using direct compression method. Drug Deliv. 2009; 16: 67-74.
9. Genc L, Jalvand E. Preparation and evaluation of controlled release matrix tablets of ketorolac tromethamine. Drug Dev Ind Pharm. 2008; 34: 903- 910.
10. Nair A. *In vitro* controlled release of alfuzosin hydrochloride using HPMC based matrix tablets and its comparison with marketed products. Pharm Dev Technol. 2007; 12: 621- 625.
11. Roni MA, Kibria G, Jalil R. Formulation and *in vitro* evaluation of alfuzosin extended release tablets using directly compressible Eudragit. Indian J Pharm Sci. 2009; 71: 252-258.
12. Tiwari SB, Rajbai AR. Extended release oral drug delivery technologies: monolithic matrix systems. In: Jain KK, editor. Methods in molecular biology-drug delivery system. New York: Humana Press; 2008. p. 232.
13. Costa P. An alternative method to the evaluation of similarity factor in dissolution testing. Int J Pharm. 2000; 220: 77-83.