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Design development and evaluation of extended release tablets of Alfuzosin hydrochloride

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Abstract

Alfuzosin hydrochloride(HCl) was formulated as oral extended release matrix tablets using polymers like sodium alginate, ethyl cellulose(EC), hydroxyl propyl methyl cellulose (HPMC K100) and hydrogenated castor oil (HCO).Matrix tablets were prepared by wet granulation method. Tablets were prepared with drug to polymer ratios 1:5, 1:10, 1:15 and 1:20.The formulated tablets were evaluated for various physicochemical parameters by official procedures. The in vitro release study of the matrix tablets were carried out in 0.1N HCl for 2hrs at pH 1.2 and pH 6.8 buffer for the next 22 hours. Based on drug release rate, polymers can be arranged as sodium alginate > EC >HPMC >HCO. Among all the polymers HCO was most suitable to design the extended release formulation of alfuzosin HCl. Analysis of drug release mechanism indicated that the drug release from the matrix tablets was found to be non fickian obeying zero order kinetics.

Key words : Alfuzosin HCl, Extended release, Matrix tablets.

Introduction

Alfuzosin is a selective alfa adrenergic receptor antagonist used for the treatment of symptomatic benign prostatic hyperplasia. The drug is freely soluble in water, has low dose and short biological half life, hence it is suitable for oral extended release formulations.

In the last two decades, extended release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Drug release from these systems should be at a desired rate, predictable and reproducible. Polymers[1] which are used as release retarding materials in the design of extended- release dosage forms play a vital role in controlling the delivery of drug from these dosage forms[2].The chief objective of extended release systems [3]is to reduce the dosing frequency to an extent that a once daily dosage is sufficient for therapeutic management with a uniform plasma concentration at a steady state [4]. The present investigation is aimed at designing an extended release (ER) formulation of alfuzosin HCl, as once a day dosage form using release-retarding polymers.

Materials and Methods

Materials

Alfuzosin HCl and ethyl cellulose were received as gift samples from Cipla, Goa and EDH Private Ltd., Mumbai respectively. Sodium alginate, HPMC K100 and hydrogenated castor oil (HCO) (S.D. fine chemicals Ltd., Mumbai) were procured commercially. All other materials used were of pharmaceutical grade.

Preparation of matrix tablets

The matrix tablets were prepared by the wet granulation method. The composition of the tablet formulations studied is represented in table 1 and 2.The required amount of drug, polymer and other excipients were mixed in a mortar by geometric dilution technique. Required amount of isopropyl alcohol was added and mixed thoroughly to form the wet mass. The wet mass was passed through mesh no.12 to obtain wet granules. The wet granules were dried at 60^{o}Cfor 4 hours. The dried granules were passed through sieve no. 16 to break the aggregates. Dried granules were mixed with the required amount of magnesium stearate (passed through sieve no.100).The tablets were compressed on a cadmach single punch machine.

Table 1.Composition of matrix(sodium alginate /ethyl cellulose) tablets of Alfuzosin HCl Ingredients (mg/tablet)

Formulations	Drug	Sod.Alginate	EC	Lactose	MCC	PVP	Mag.stearate
SA1	5	25		230	125	100	15
SA2	5	50		205	125	100	15
SA3	5	75		180	125	100	15
SA4	5	100		155	125	100	15
EC1	5		25	230	125	100	15
EC2	5		50	205	125	100	15
EC3	5		75	180	125	100	15
EC4	5		100	155	125	100	15

Table 2.Composition of matrix(HPMC/HCO) tablets of Alfuzosin HCl Ingredients (mg/tablet)

Formulations	Drug	HPMC	HCO	Lactose	MCC	PVP	Mag.stearate
H1	5	25		230	125	100	15
H2	5	50		205	125	100	15
H3	5	75		180	125	100	15
H4	5	100		155	125	100	15
HC1	5		25	230	125	100	15
HC2	5		50	205	125	100	15
HC3	5		75	180	125	100	15
HC4	5		100	155	125	100	15
HC5	10		100	155	120	100	15
HC6	10		150	105	120	100	15
HC7	10		200	55	120	100	15

Evaluation of tablets

Weight variation

Twenty tablets were selected randomly and the average weight was determined. Then the individual tablets were weighed and the individual weight was compared with the average weight.

Hardness and Friability

Hardness of the tablets (n=3) was determined using monsanto hardness tester. Friability of the tablets were checked using Roche friabilator. Preweighed sample of tablets (n=10) was placed in the friabilator, it was operated for 100 revolutions. Tablets were then dusted and reweighed. The experiment was repeated three times.

Estimation of drug content

Twenty tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 5 mg/10mg of drug was transferred into 100 ml volumetric flask and extracted with pH 6.8 buffer by keeping in a sonicator for 2 hours, then it was filtered ,suitable dilutions were made and absorbance was recorded by using UV spectrophotometer(Elico) at 245 nm.

In vitro drug release study.

In vitro release studies were conducted by using USP eight station dissolution test apparatus(Electrolab).The dissolution medium consisted of 0.1N HCl (pH 1.2) for the first 2 hours and phosphate buffer (pH 6.8)for the subsequent 22 hours.500 ml of dissolution medium was maintained at 37±0.5^{o}C,at 100 rpm(paddle method).Aliquots of 10 ml were withdrawn at predetermined time intervals and an equivalent amount of fresh buffer maintained at the same temperature was replaced. The samples were suitably diluted and analysed by measuring the absorbance at 245 nm.

Data Analysis

Release data were analysed as per zero order, first order, Higuchi equation[5] and Peppas equation [6] models to assess the drug release kinetics and mechanism of release from the tablets.

Results and Discussion

Marketed formulations contain 5mg/10mg of Alfuzosin HCl. All the formulations contained 5 mg of drug, however ,the final formulations (HC5,HC6,HC7) contained 10 mg of the drug. The fabricated formulations were subjected to weight variation, hardness, friability and estimation of drug content. All the formulated tablets complied with the weight variation test requirement. Hardness of the tablets was in the range of 4-5 Kg/cm^2.Weight loss in the friability test was less than 0.84% in all the cases. All the matrix tablets prepared contained the drug with in 100±2% of the labeled claim. Thus, all the physical parameters of the prepared tablets were practically with in control.

Four different polymers (sodium alginate ,ethyl cellulose, HPMC, hydrogenated castor oil) were studied at different concentrations as drug release retardants. Sodium alginate is an anionic linear polysaccharide that is soluble at neutral pH, forms alginic acid at pH < 3 and does not swell at pH 1.2.However,rapid swelling and erosion are observed in pH 6.8. An increase in the concentration of sodium alginate did not significantly prolong the drug release. Faster release of drug from the sodium alginate matrix system(SA1 to SA4) is due to rapid swelling and erosion.The matrix could release the drug only up to 6 hours(Table 3).

As the concentration of ethyl cellulose was increased (EC1 to EC4),the release rate of the drug was decreased (EC1>EC2>EC3>EC4),this may be due to reduction in the penetration of the solvent into the system because of hydrophobic nature of ethyl cellulose present in the formulation.The matrix could release the drug only up to 10 hours(Table 3).The hydration rate of HPMC increases with an increase in the hydroxy propyl content.the solubility of HPMC is pH independent.In the present study ,HPMC K-100M was used as the hydrophilic matrixing agent because it forms a strong viscous gel on contact with the aqueous media,which may be useful in the controlled delivery of highly water- soluble drugs.As the concentration of HPMC in the formulations(H1 to H4) was increased ,the drug release was significantly prolonged(Table 4).Faster release of drug from the formulation H1 was due to the faster dissolution of the drug and its diffusion out of the matrix forming pores for the entry of the solvent molecules.However,the release of drug from other formulations (H2>H3>H4) was delayed probably due to the decreased penetration of the solvent into the matrix leading to decreased diffusion of drug from the matrix.

HCO has been used as a sustained release coating material and hardening agent .When tablet was compressed HCO forms a thin coat on the surface of the drug particles.Faster release of the drug from HC1 was due to uneven coating of individual particles during granulation and compression.The slow release of drug in the formulations (HC2 to HC7) is due to the formation of a uniform coating on individual drug particles by the hydrophobic polymer during compression.Initial release of the drug from the matrix could be attributed to the dissolution of

the drug from the surface of the tablet ,further penetration of the solvent was hindered due to hydrophobic coating of the HCO on the drug particles leading to slow release for a prolonged period.In formulations (HC5 to HC7), dose of the drug was 10 mg.In tablets (HC5 and HC6) ,the drug to polymer ratio was 1:10 and 1:15 respectively,they achieved 100% release in 18 hours.Finally , tablets with drug to polymer ratio 1:20 (HC7),could retard the drug release up to 24 hours(Table 4).

Table 3.Comparative percentage drug release from various (sodium alginate/ethyl cellulose)formulations of Alfuzosin HCl
Time (hr)

Formulations	1	4	6	8	10
SA1	32±1.22	97.8±0.61	100±0.66		
SA2	29.3±1.18	77.9±1.23	100±0.84		
SA3	27.3±0.62	69.3±1.22	97.33±1.24	100.5±0.46	
SA4	25.9±1.23	67.4±0.92	97.8±0.65	100.6±0.53	
EC1	40.4±1.22	90.2±1.21	100.4±0.61		
EC2	34.1±1.21	65.2±0.88	78.8±0.69	99.7±0.65	100.5±0.42
EC3	20.2±1.25	58.6±1.01	67.9±0.88	79.9±0.65	100.2±0.56
EC4	19.9±1.85	56.9±0.95	65.3±0.82	73.8±0.73	90.2±0.62

Table 4.Comparative percentage drug release from various (HPMC/HCO)formulations of Alfuzosin HCl
Time (hr)

Formulatons	1	4	8	12	24
H1	47.2±1.23	97.8±0.75	100.4±0.42		
H2	19.3±1.23	42.8±1.22	74.0±0.85	99.7±0.73	100.2±0.42
H3	22.0±1.25	43.5±1.21	66.6±0.85	89.2±0.69	100.4±0.31
H4	13.7±1.86	32.6±1.12	57.3±1.02	71.2±0.65	100.5±0.54
HC1	25.5±1.45	64.6±1.22	81.4±0.52	100±0.45	
HC2	24.9±1.86	52.2±1.23	78.8±1.65	100.2±0.64	
HC3	24.0±1.3	46.1±1.13	71.1±0.78	93.5±0.46	100.1±0.63
HC4	19.7±1.5	36.9±1.23	50.1±1.52	63.3±0.84	100.4±0.42
HC5	15.6±1.9	23.1±1.52	37.4±1.4	75.3±1.22	100.2±0.61
HC6	14.7±1.25	23.1±1.12	34.6±1.24	58.4±0.85	100.3±0.43
HC7	14.2±1.36	24.6±1.25	33.1±1.3	56.4±1.26	100.4±0.36
Brand X	16.1±1.23	24.2±1.13	36.1±0.65	53.9±0.6	101.2±0.48

The values of T50 (time taken for 50% drug release) and T90 (time taken for 90% drug release) for all the formulations are indicated in table 5 and 6.From the table 5 and 6 ,it is clearly evident that the r value calculated for Higuchi equation was >0.9(except HC5 and HC6),hence the drug release was diffusion controlled.In all the formulations the n value calculated as per the peppas equation was >0.48 ,hence , the drug release followed non-fickian diffusion.In all the formulations the r value for zero order equation was higher than the r value for the first order equation (except H1);hence drug release mainly followed zero order kinetics.As evident from

the table 4 and 6 ,formulation HC7 gave similar drug release as that of commercial sustained release tablet of alfuzosin HCl (Brand X).

Table 5. Dissolution kinetics and dissolution parameters of Alfuzosin HCl(sodium alginate/EC)Tablets

Formulations	Zero order Eqn.(r)	Higuchis Eqn.(r)	Peppas Eqn.(n)	T50(hr)	T90(hr)
SA1	0.9872	0.9921	0.79	1.4	3.45
SA2	0.9658	0.9731	0.70	1.45	4.35
SA3	0.9126	0.9292	0.63	1.50	5.40
SA4	0.9418	0.9472	0.67	2	5.45
EC1	0.9252	0.994	0.56	1.30	4
EC2	0.9123	0.9822	0.48	1.50	7
EC3	0.9239	0.9891	0.63	3.10	8.4
EC4	0.9081	0.9829	0.57	3.25	9.45

Table 6. Dissolution kinetics and dissolution parameters of Alfuzosin HCl(HPMC/HCO)Tablets

Formulations	Zero order Eqn.(r)	Higuchis Eqn.(r)	Peppas Eqn.(n)	T50(hr)	T90(hr)
H1	0.8822	0.9788	0.48	1.10	3.5
H2	0.9828	0.9721	0.67	5	9.45
H3	0.9481	0.9812	0.58	5	12.30
H4	0.9805	0.9692	0.69	6.55	14.45
HC1	0.8931	0.9777	0.84	2.45	9.20
HC2	0.944	0.9942	0.62	3.5	9.30
HC3	0.9551	0.9894	0.55	4.45	11.30
HC4	0.9552	0.9609	0.51	08	18.10
HC5	0.9162	0.8102	0.71	9.30	13.45
HC6	0.9509	0.8609	0.67	10.45	16.45
HC7	0.9302	0.9326	0.68	11.30	19.30
Brand X	0.9388	0.9338	0.65	11	19.00

Conclusion

Hence, the release rate of drug from the matrix tablets can be governed by the type of the polymer and the concentration of the polymer employed in the preparation of the tablets. The matrix tablets prepared with ethyl cellulose could extend the drug release up to 10-12 hours. The hydrophilic matrix of HPMC could control the drug release for more than 12 hours. The hydrophobic matrix HCO could extend the drug release effectively for 24 hours. The order of increasing release rate controlling efficiency observed with various polymers was HCO>HPMC>EC>sodium alginate. It is evident from the results that a hydrophobic matrix, HCO, is a better system for controlled delivery of highly water- soluble drugs like alfuzosin HCl.

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