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Research Article

"FORMULATION AND DEVELOPMENT OF MULTILAYER AND MONOLITHIC EXTENDED RELEASE MATRIX TABLETS OF ALFUZOSIN HCL"

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ABSTRACT

Objective: In present investigation an attempt has been made to increase therapeutic efficacy, reduce frequency of administration and improve patient compliance, by developing extended release monolithic and multilayered tablets of Alfuzosin hydrochloride.

Methods: Extended release matrix tablets of Alfuzosin were developed by using different drug and polymer ratio with guar gum, Hydroxypropylmethylcellulose, xanthan gum as matrix formers. All lubricated formulations were compressed by wet granulation method.

Results: Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, *invitro* dissolution. All the formulation showed compliance with Pharmacopoeial standards. *In vitro* release studies indicated that matrix multilayer tablets prepared by wet granulation with various proportions of polymer mixtures failed to control the drug release for extended period of time. Controlled delivery of Alfuzosin could be achieved in F8, F9 and to a lesser extent F7 tablet formulations which released 67%, 86%,and 90% of drug, respectively, at the end of 20th hr in 0.01N HCl.

Conclusion: Among these monolithic matrix tablets (F9) prepared with guar gum-HPMC-xanthan gum mixture (1:11:4) shown comparable drug release profiles at 1st and 20th h as 18% and 86% as that of the innovator (Xatral). Drug release kinetics indicated that drug release was best explained by Higuchi as these plots showed the highest linearity (r^2 = 0.9979).

Keywords: Alfuzosin, matrix multilayer, xanthan gum, Methocel, extended release.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of the body, to promptly achieve and then maintain the desired therapeutic drug concentration that elicits the desired pharmacological action and to minimize the incidence and the severity of unwanted adverse effects. To achieve this goal, it would be advantageous and more convenient to maintain a dosing frequency to once, or twice-daily regimen. An appropriately designed extended release dosage form can be a major advance in this direction compared to conventional immediate release dosage form[1,2]. Among various technologies available, monolithic matrices-matrix tablets continue to be popular because of simple processing technologies required, reproducibility, stability of the materials and dosage form as well as ease of scale-up operation. In particular, the interest awakened by matrix type deliveries is completely justified in view of their biopharmaceutical and pharmacokinetics advantages over the conventional dosage forms [3, 4].

Two classes of drugs are used for the treatment of benign prostatic hypertrophy (BPH) in elderly males i.e., 5-alpha reductase inhibitors and alpha adrenergic antagonists. The second class includes terazosin, doxazosin, tamsulosin and Alfuzosin. Alfuzosin a selective alpha adrenergic antagonist is freely soluble in water [5, 6] 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 [7, 8]. Recently 10 mg once daily extended release formulation has become available in the market [9], which is more convenient for older patients. Marketed Alfuzosin formulation is a three layered Geomatrix tablet that requires special facilities, high cost, more time and complex operation than conventional formulations [10].

During the last two decades swelling polymers are being used as sustained or controlled release devices. Low viscosity hydroxyl propyl methylcellulose (HPMC) was used by Nair *et al* [11] to prepare controlled release Alfuzosin tablet (10 mg) that sustained drug release only for 12 h. To obtain once daily dosage form, high viscosity HPMC (such as Methocel K100M) should be used which can sustain for longer period. For freely soluble drugs like Alfuzosin, a large quantity of HPMC is required to control the release that ultimately results in tablets which are difficult to swallow and to resolve this problem a binary mixture of guar gum and xanthan gum was tried. Hence, the objective of the study was to investigate how high viscosity HPMC, guar gum and xanthan gum combination affect the dissolution rate of Alfuzosin matrices of multilayer and monolayer tablets.

MATERIALS AND METHODS

Alfuzosin HCl – IP was procured by Hetero Pharma Ltd. Hyderabad, Lactose monohydrate and Microcrystalline cellulose (vivapur 101) were gifted by FMC Biopolymer. Methocel k100M gifted by colorcon Asia Ltd. Guar Gum (apcol ultra guar), Xanthan gum were procured by DMV International. Pregelatinized starch (starch 1500), magnesium stearate, Colloidal Silicon dioxide (Aerosil 200) were procured by Loba chemie, Cochin.

Preparation method for multilayer tablets by wet granulation method

Formulation F1, F3, F5 shown in **Table 1** were prepared by wet granulation method. The weighed quantities of Lactose, (Microcrystalline cellulose) MCC, guar gum, (Hydroxy propyl Methyl cellulose) HPMC, (pregelatinised starch) PGS and drug were sifted through #40 mesh. Then the mixture was dry mixed in rapid mixer granulator with impellor ON for 10 min and chopper ON for 2 min. The prepared premix was granulated using purified water, then sifted through #14 mesh, obtained wet granules were dried in hot air oven at 60±5ºC until moisture becomes <3%. The dried granules were lubricated with (colloidal silicon dioxide) CCS and Magnesium stearate in octagonal blender for 2 min.

Table 1: Composition of Drug layer by wet granulation

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Alfuzosin Hcl	10	10	10	10	10	10	10	10	10
Lactose monohydrate	11.5	---	11.5	---	---	---	---	---	---
Microcrystalline cellulose	22	204	22	194	36.25	184	174	154	164
Pregelatinised starch	5	---	5	---	25	---	---	---	---
Guar gum	50	30	50	35	175.0	40	45	45	45
HPMC	---	100	---	105	---	110	115	115	115
Xanthan gum	---	---	---	---	---	---	---	20	10
Colloidal silicon dioxide	0.5	2.0	0.5	2.0	1.25	2.0	2.0	2.0	2.0
Magnesium stearate	1	4.0	1	4	2.50	4	4	4	4
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Preparation method of Polymer layer for multilayer tablets

The formula of polymer layer for formulation F1, F3, F5 multilayer tablets was shown in **Table 2**. Lactose, MCC, guar gum, HPMC, PGS was sifted through #40 mesh. Then the mixture is dry mixed in rapid mixer granulator impellor ON for 10 min and chopper ON for 2 min. The prepared premix was granulated using purified water, then sifted through #14 mesh, obtained wet granules were dried in hot air oven at 60±5°C until moisture becomes <3%. The dried granules were lubricated with CCS and Magnesium stearate in octagonal blender for 2 min.

Table 2: Composition of Polymer layer

Ingredients	F1	F3	F5
Guar gum	5.0	60	60
Pregelatinised starch	0.5	10	10
Colloidal silicon dioxide	0.5	0.5	0.5
Microcrystalline cellulose	---	29	29
Magnesium stearate	0.5	0.5	0.5
Purified water	q.s	q.s	q.s

Preparation method for Monolithic tablets by wet granulation method

Formulation F2, F4, F6, F7, F8, F9 shown in **Table 1** were prepared by wet granulation method. The weighed quantities of Lactose, MCC, guar gum, HPMC, PGS and drug were sifted through #40 mesh. Then the mixture is dry mixed in rapid mixer granulator with impellor ON for 10 min and chopper ON for 2 min. The dry mix was granulated using purified water with impellor and chopper ON for around 1min 35 sec, kneading is done while impellor and chopper ON for 30 sec, then wet mix was sifted through #14 mesh, obtained wet granules were dried in hot air oven at 60±5°C until moisture becomes <3%. The dried granules were lubricated with CCS and Magnesium stearate in octagonal blender for 2 min. The total weight of tablet was shown in **Table 3.**

Table 3: Total Tablet Weight

	LAYER	WEIGHT(mg)
1	Drug layer	250.0
2	Polymer layer	100.0
	Total tablet weight	350.0

API Characterization

Physical appearance, bulk density, tapped density, Carr's Index, Hausner's ratio, solubility were performed for API.

Physical parameters of blends:

Bulk density (Db)

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduated measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by

$$D_b = M / V_0$$

Where, M is the mass of powder, V_0 is the bulk volume of the powder.

Tapped density (D_t)

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by,

$$D_t = M / V_t$$

Where, M is the mass of powder.

V_t is the tapped volume of the powder.

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height 'h' above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using following equation,

$$\theta = \tan^{-1} (h/r)$$

Where θ = Angle of repose,

h= Height of pile,

r= Radius of the base of the pile.

Carr's Consolidation Index (I)

Carr's index is an indication of the compressibility of a powder. It is expressed in percentage and is given by

$$I = D_t - D_b / D_t \times 100$$

Where

D_t= Tapped density, D_b= Bulk density.

Evaluation parameters of formulated tablets

Thickness and diameter

Control of physical dimensions of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier Calipers. It is measured in mm.

Hardness

The Monsanto hardness tester was used to determine the tablet hardness .The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. It is expressed in kg/cm².

Friability (F)

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions in 4 min and were dedusted. The

percentage weight loss was calculated by reweighing the tablets. The% friability was then calculated by: -

$(W_{initial})$ - (W_{final}) / $(W_{initial})$ X 100

Weight variation

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit. IP limit for weight variation in case of tablets weighting up to 120 mg is ± 10%, 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%.

PD= $(W_{initial})$ – (W_{final}) / (W_{inital}) x 100

Where PD= Percentage deviation, W_{avg} =Average weight of tablet,

$W_{initial}$ =Individual weight of tablet.

***In vitro* Release studies**

In vitro dissolution studies for all the tablets were carried out using USP type II Dissolution apparatus in 900 ml of 0.01N HCl as dissolution media, maintained at 37±0.5°C at 100 rpm. 5ml aliquots were withdrawn at required intervals and replaced by 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution (if required) at 232 nm using UV-visible spectrophotometer against as 0.01N HCl as blank.

Stability studies

Stability studies were carried out at 40°C/75%RH for a specific period of time upto 3months for the selected formulations and for compatibility studies. Take the drug and excipient in ratio 1:5 in 10ml vial place in initial condition and accelerated condition to testing 40°C±2°C/75% RH to study color, odor, hygroscopic nature for period of one month.

RESULTS AND DISCUSSION:

In the present investigation it is aimed to formulate, evaluate, and optimize an oral extended release formulation of Alfuzosin; development was made to extend the rate of release of drug from solid oral dosage form by using polymers like Guar gum, Xanthan gum, and HPMC.

API characterization was performed. As shown in **Table 4** compressibility index value is more than 25% which exhibits poor flow. The solubility of Alfuzosin hydrochloride drug substance in phosphate buffer of P^H =10 is about 123(mg/ml). Calculated dose solubility volume 10 mg (highest strength)/ 123(mg/ml) = 0.08 ml < 250ml.Therefore Alfuzosin hydrochloride is considered a highly soluble drug according to the Biopharmaceutical Classification System.

Table 4: Characterization of API (Active Pharmaceutical Ingredient)

S. NO	API CHARACTERISATION	RESULTS
1	Physical Appearance	White, hygroscopic and crystalline powder
2	Bulk density	0.184
3	Tapped Density	0.328
4	Carr's index	43.82
5	Haussner's Ratio	1.8
6	Solubility	SOLVENT MEDIA 0.01N HCL pH=2 ACETATE BUFFER pH=4.5 PHOSPHATE BUFFER pH=6.8 PHOSPHATE BUFFER pH=10

Tablets with various compositions were formulated in two strategies i.e., multilayer and monolayer tablets. All the prepared blends, evaluated for physical characteristics were within the limits shown in **Table 5.**

Table 5: Physical parameters of all the prepared blends

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density	0.392	0.342	0.342	0.361	0.392	0.341	0.334	0.355	0.334
Tapped density	0.520	0.480	0.480	0.500	0.520	0.469	0.464	0.501	0.473
Compressibility index	28.76	28.76	28.76	27.71	28.76	27.27	29.90	29.07	29.51
Hausner ratio	1.403	1.403	1.403	1.383	1.403	1.375	1.387	1.410	1.415
Particle size distribution (%)									
#20	2.4	2.4	2.4	3.5	2.4	4.0	2.0	3.2	3.5
#40	9.6	9.6	9.6	9.5	9.6	11.2	9.2	9.2	12.5
#60	8.8	8.8	8.8	8.5	8.8	8.0	8.0	8.0	7.5
#80	6.4	6.4	6.4	9.0	6.4	10.0	10.8	8.8	6.5
Receiver	72.8	72.8	72.8	69.5	72.8	66.8	70.0	70.8	70.8

The prepared tablets were evaluated for weight variation, thickness, hardness, friability and *invitro* drug release profiles. The prepared tablets had acceptable variations in weight and thickness. Since mechanical integrity is importance in successful compared formulation, the hardness of tablets were determined and found to be in the range of 9.5 to 12.2 kp. Friability was observed between 0.13 to 0.15% which was below 1% indicating sufficient mechanical strength of prepared tablets was shown in **Table 6.**

Table 6: Post compression parameters

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation(mg)	351.9	350.3	349.8	350.5	352.3	351.3	348.1	350.6	350.2
Hardness (kp)	9.7	9.1	9.1	9.5 - 10.2	9.1 - 10.6	10.7-12.1	10.8-12.1	1.8 - 12.1	10.7-11.2
Thickness (mm)	5.5	5.7	5.7	5.6	5.7	5.4	5.3	5.3	5.5
Friability (%)	0.14	0.14	0.14	0.15	0.14	0.13	0.13	0.13	0.15`

This study showed that guar gum and HPMC was used to retard the release of the drug for certain period of time. Results shown in **Table 7**, indicated that multilayer matrix Alfuzosin tablets (F1, F3& F5) containing various proportions of guar gum and HPMC showed slower release profiles.

Table 7: Dissolution profile

Time (hrs)	innovator	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	20	11.1	24	11.4	24	19.1	21	20	11	18
2	28	20.6	36	20.5	34	32.3	31	30	17	28
6	52	42	62	42.3	61	54.2	55	54	34	50
12	80	70.9	84	70.3	80	75.1	76	74	51	70
20	97	101.3	95	98.8	95	92.1	91	90	67	86

On the other hand, monolithic matrix formulations F2, F4, F6, F7 were able to release the tablet cores efficiently and extended release was obtained, but at low proportions of Guar gum: HPMC (1:3) (F2)

offered faster release of drug in 1st hr. Innovator dissolution profile was shown in **Table 8**. Comparative dissolution profile of the prepared tablets and innovator were shown in **Figure1.**

Table 8: Dissolution profile of innovator in 0.01N Hcl

Dissolution media	0.01N Hcl
Volume	900ml
Apparatus	Paddle(with sinkers)
Speed	100 rpm
Time	1,2,6,12,20 hrs

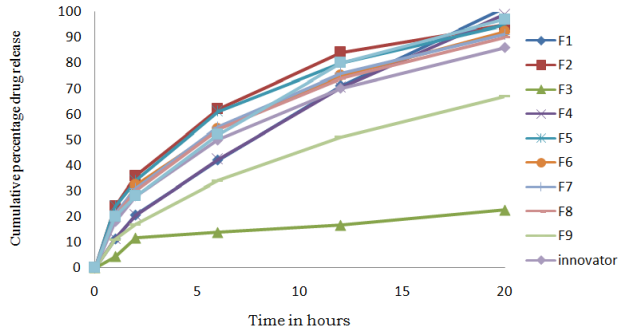

Figure 1: Comparative dissolution profiles of tablets with innovator

Selective delivery of Alfuzosin could be achieved using F8, F9 and, to a lesser extent, F7 tablet formulations which released 67%, 86%, and 90% of drug, respectively, at the end of 20th hr in 0.01N HCl. Among these monolithic matrix tablets (F9) prepared with Guar gum-HPMC-Xanthan gum mixture (1:11:4) shown comparable drug release profiles at 1st and 20th h as 18% and 86% as that of the innovator mentioned in **Table 7**.

Drug release kinetics indicated that drug release was best explained by Higuchi's equation, as these plots showed the highest linearity (r^2 = 0.9979), but a close relationship was also noted with zero-order kinetics (r^2 = 0.9950). Korsmeyer's plots indicated n value of 0.65 to 0.89, which was indicative of an anomalous diffusion mechanism or diffusion coupled with erosion; hence, the drug release was controlled by more than one process.

Storage of these tablets for 3 months at 25°C/40% RH showed no change either in physical appearance or in dissolution profiles, pointing to the potential of matrix monolayer, for providing controlled delivery.

CONCLUSION

Based on the Results and discussion, we can concluded that extended release matrix monolayer tablets of Alfuzosin HCl were prepared successfully by wet granulation using the combination of different concentration of polymers like Methocel K100 M, Guar gum and xanthan gum which shown dissolution profiles as that of the innovator product. Hence the prepared 20 hr controlled release monolithic matrix formulation would provide an extended duration of therapeutic effect and by can improve the patient compliance.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported. No funding was provided for this analysis.

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