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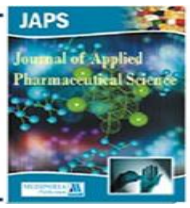

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Formulation and Evaluation of Oral disintegrated tablets of Alfuzosin Hydrochloride using super-disintegrants

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ABSTRACT

In the present work, orodispersible tablets of Alfuzosin Hcl were prepared by direct compression and sublimation methods with a view to enhance patient compliance. In these methods, varying concentrations of crospovidone, sodium starch glycolate and croscarmellose sodium of 3.3, 6.6 and 10% w/w were used, along with camphor used as subliming agent in sublimation method. The prepared batches of tablets were evaluated for hardness, friability, drug content, wetting time, dispersion time, disintegration time and dissolution studies. Based on disintegration time (approximately 13-18 seconds) all the promising formulations (from each method) were tested for *in-vitro* drug release pattern (in pH 6.8 phosphate buffer), drug-excipient interaction (FTIR spectroscopy) and short term stability studies. Among the promising formulations, the formulation F4 and F14 containing 10% w/w Crospovidone emerged as the overall best formulation ($t_{50\%}$1.79 and 1.21 minutes) based on drug release characteristic (in pH 6.8 phosphate buffer) compared to controlled formulation F1 ($t_{50\%>}$10 minutes).

Keywords: Orodispersible tablet, Alfuzosin, Crospovidone, Sodium starch glycolate, Croscarmellose sodium and Camphor.

INTRODUCTION

Patients often experience inconvenience in swallowing conventional tablets when water is not available. Furthermore, patients who have swallowing problems encounter difficulties in taking tablets (Koizumi K, 1997), particularly pediatric and geriatric patients. Such problems can be resolved by means of orally disintegrating tablet. This tablet disintegrates instantaneously when put on oral cavity, releasing the drug, which dissolves or disperse in the saliva (Habib W, 2000). Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. While designing the dispersible tablets it is possible to achieve an effective taste masking along with a pleasant feeling in the mouth. The techniques are mainly used to formulate these tablets, namely freeze drying, granulation and direct compression (Reddy LH, 2002). Alfuzosin (AZ) is an alpha-adrenoreceptor blocker used in the management of hypertension and it also relieves symptoms of urinary obstructions in benign prostatic hyperplasia (Sweetman SC, 2002). The concept of formulating orodispersible tablets containing Alfuzosin offers a suitable and practical approach in serving desired objective of rapid disintegration and dissolution characteristics with increased bioavailability. The main criteria for mouth disintegrating tablets is to disintegrate or dissolve rapidly in oral cavity with saliva in 15 sec to 60 sec, without need of water and should have pleasant mouth feel. The disintegrants used should fulfill the criteria by disintegrating the tablets in specified limit time. In the present study a variety of super

and Sodium starch glycolate were selected and tablets were prepared by direct compression and sublimation methods using different additives.

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MATERIALS AND METHODS

Alfuzosin HCl was obtained from Hetero drugs, Hyderabad and Crospovidone, Croscarmellose sodium (Ozone pharmaceuticals), sodium starch glycolate (Kemphasol, Mumbai), Microcrystalline cellulose (Flocel, Gujarat), Xylitol (Danisco, UK), Aerosil (Evonik industries, Germany), Vanillin flavor (CDV inds. Mumbai).

Preparation of orodispersible tablets of Alfuzosin

Direct compression method

In direct compression method (Bi YX, 1999), all the ingredients including drug, polymers and excipients were weighed accurately according to the batch formula (Table 1). The drug is thoroughly mixed with xylitol on a butter paper with the help of a stainless steel spatula. Then all the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend (150 mg) of each formulation was compressed on rotary tablet punching machine (Cadmach, India) using 8 mm round punches in a controlled environment to get the average weight of 150 mg tablets. The 10 formulations were prepared by different concentrations of disintegrants.The composition of various formulations are given in the Table 1.

Table 1: Composition of different oral dissolving tablets of Alfuzosin by direct compression method.

Ingredient(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Alfuzosin	10	10	10	10	10	10	10	10	10	10
Crospovidone	-	5	10	15	-	-	-	-	-	-
Sodium starch glycholate	-	-	-	-	5	10	15	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	-	5	10	15
Xylitol	62	57	52	47	57	52	47	57	52	47
Aerosil	3	3	3	3	3	3	3	3	3	3
Vanillin	2	2	2	2	2	2	2	2	2	2
MCC (102)	70	70	70	70	70	70	70	70	70	70
Magnesium stearate	3	3	3	3	3	3	3	3	3	3

Sublimation method

In sublimation method (Patel, 2008) camphor was used as subliming agent along with varying concentrations of crospovidone, sodium starch glycolate and croscarmellose sodium . All the ingredients were mixed in geometric proportion in a poly bag for 15 minutes. The resulting powder blend was compressed on single punch tablet press (Cad mach, India) using 8 mm round punches in a controlled environment to get the average weight of 150 mg tablets. The 10 formulations were prepared by different concentrations of camphor and disintegrants.The compressed tablets were then subjected to sublimation at 60±1ºC for 1 hour in hot air oven. During drying the volatile component sublimed and a porous structure was obtained. The end point of drying was indicated by constant weight of the tablet. The composition of various formulations has given in the Table 2.

Table 2: Composition of different oral dissolving tablets of Alfuzosin by sublimation method.

Ingredients(mg/tablet)	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20
Alfuzosin	10	10	10	10	10	10	10	10	10	10
Crospovidone	-	5	10	15	-	-	-	-	-	-
Sodium starch glycholate	-	-	-	-	5	10	15	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	-	5	10	15
Xylitol	62	47	37	27	47	37	27	47	37	27
Aerosil	3	3	3	3	3	3	3	3	3	3
Vanillin	2	2	2	2	2	2	2	2	2	2
MCC(102)	70	70	70	70	70	70	70	70	70	70
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Camphor	-	10	15	20	10	15	20	10	15	20

Evaluation of Tablets

The prepared tablets were evaluated (Banker GS, 1987) for physicochemical parameters like uniformity of thickness using a dial-caliper and hardness test using Monsanto hardness tester. Randomly selected tablets from all the ten formulations were also evaluated for Friability test (using Roche Friabilator), Weight variation test and Drug content uniformity. The tablets were also evaluated for special parameters like,

In vitro disintegration time

The *in vitro* disintegration time was determined using Disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Wetting time

The method reported by Yunixia et al. was followed to measure tablet wetting time. A piece of tissue paper (12 cm ×10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 mL of simulated saliva pH, a tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined (Bi Y, 1999).

In vitro Dispersion time

In vitro Dispersion time (Chaudhari PD, 2005) was measured by dropping a tablet in a measuring cylinder containing 6 mL of pH 6.8 (simulated saliva fluid). Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

Drug content uniformity

Ten tablets from each formulation were weighed and powdered(IP, 1996) .Known quantity of the powder, equivalent to

Table 3: Evaluation of oral dissolving tablets of Alfuzosin by direct compression method (n = 3).

Formulation	Hardness (Kg/cm^2)	Friability (%)	Wt variation (mg)	Drug content (%)	Disintegration time (sec)	Wetting time (sec)	*In vitro* dispersion time(sec)
F1	3.1±0.28	0.61	149±1.20	101.33±0.57	186.2± 1.22	151.2±2.26	159.4±0.21
F2	3.5±0.45	0.79	150±1.22	99.03±0.77	35.9± 2.26	27.46±1.13	29.3±0.65
F3	3.0±0.23	0.82	150±.545	96.66±0.48	26.3± 1.60	19.1±0.71	19.4±0.58
F4	3.2±0.30	0.68	150±.545	98.66±0.23	19.0± 0.92	13.63±0.55	9.4±0.20
F5	3.5±0.45	0.62	150±0.34	97.33±0.61	56.6± 1.28	37.2±2.26	45.3 ±0.22
F6	3.4±0.73	0.65	150±1.08	98.36±0.81	44.7± 1.83	29.46±1.13	38.6 ±0.28
F7	3.1±0.39	0.77	150±1.12	100.13±0.7	28.6± 0.96	24.1±0.72	19.6 ±0.32
F8	3.2±0.32	0.81	150±1.34	99.00±0.37	42.6± 1.25	34.66±1.73	39.6±0.31
F9	3.4±0.26	0.52	150±0.32	98.36±0.67	35.6± 1.03	25.1±0.55	22.1 ±0.35
F10	3.5±0.55	0.66	150±1.02	96.85±0.12	23.3± 0.85	22.6±0.81	17.0 ±0.24

Table 4: Evaluation of oral dissolving tablets of Alfuzosin by sublimation method (n=3).

Formulation	Hardness (Kg/cm^2)	Friability (%)	Wt variation (mg)	Drug content (%)	Disintegration Time (sec)	Wetting time (sec)	*In vitro* dispersion time(sec)
F11	3.26±0.2	0.67	150±1.20	100.23±0.5	172.28±1.2	148.2±2.26	155.2±0.2
F12	3.03±0.43	0.82	150±0.22	99.03±0.77	31.96±2.02	26.56±1.13	27.3±0.65
F13	2.88±0.28	0.70	150±.345	96.76±0.48	24.32±1.6	18.56±0.5	15.4±0.56
F14	3.1±0.20	0.69	150±0.14	98.06±0.23	16.07±0.84	12.23±0.5	7.4±0.24
F15	3.1±0.45	0.66	150±0.34	97.33±0.61	53.20±1.22	38.2±2.20	42.3± 0.2
F16	3.2±0.73	0.62	150±.61	98.56±0.73	42.32±1.60	26.56±1.08	30.6±0.26
F17	3.0±0.31	0.61	150±1.22	99.13±0.65	26.60±0.96	21.1±0.8	22.6±0.30
F18	3.2±0.32	0.63	150±1.34	99.10±0.37	39.62±1.25	30.26±1.7	36.6±0.31
F19	3.0 ±0.26	0.62	150±0.42	98.46±0.37	31.64±1.03	23.1±0.55	20.1±0.32
F20	3.2±0.55	0.59	150±0.52	98.62±0.12	21.30±0.81	20.6±0.81	14.0±0.28

10 mg of Alfuzocin was weighed accurately and dissolved in 100ml of water and 6.8 phosphate buffer. Amount of the active ingredient was determined spectrophotometrically at 248.5 nm, using a UV-Visible spectrophotometer, Shimadzu UV-1700. The percentage content was determined using the standard graph of the pure drug. Six such determinations were performed and standard deviation was also determined.

Dissolution studies

In vitro dissolution of Alfuzosin was carried out in USP type-II dissolution apparatus (Electrolab, model-TDT 06N) employing a paddle stirrer at 50 rpm using 900 mL of pH 6.8 as the dissolution medium maintained at a temperature of 37 ± 0.5ºC. Aliquots of dissolution medium (5 ml) were withdrawn at specified time intervals of time and diluted suitably and analyzed at 248.5nm using Shimadzu UV-Visible spectrophotometer. Cumulative percent of Alfuzosin released was calculated and plotted against time (Bhagwati S, 2005).

Drug-Excipients compatibility studies

FT-IR spectra were obtained on spectrum 100 FTIR (Perkin-Elmer). Samples were prepared in KBr disks and data were collected over a spectral region from 4000 to 400 cm-1.

Stability studies

Short term stability studies on the optimized formulation were carried out by storing the tablets (in amber colored rubber stoppered vials) at 40ºC/ 75% RH for a specific period up to 30 days. At an interval of10 days, the tablets were visually examined for hardness, uniformity of drug content and *in vitro* disintegration time.

RESULTS AND DISCUSSION

The present study was carried out to prepare Alfuzosin hydrochloride oral disintegrating tablets that can be used in the treatment and management of hypertension and benign prostatic hyperplasia. Using various super disintegrants like Crospovidone, Croscarmelose sodium and Sodium starch glycolate, tablets were prepared along with other additives. Direct compression and sublimation methods were used for the preparation of tablets.

A total number of ten formulations from each method were prepared and evaluated. Tablets mean thickness (n=3) was almost uniform in all the formulations. In all the formulations, the hardness was uniformly maintained and it was found to be around 3.5 kg/cm^2. No much variation in the hardness was found which clearly indicates that the blending was uniform. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness. Percent friability of the prepared formulations was less than 1%. The values obtained lies in the range of 0.52 and 0.82 %.

All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ± 7.5% of the weight. The weight variation in all the prepared formulations was found to be 149 ± 1.24 and 151 ± 1.45 mg, which was in pharmacopoeial limits. The percentage drug content of all the formulations were found to be between 96.76 ± 0.48 and 100.23 ± 0.5 of Alfuzosin hydrochloride,

which was within the acceptable limits. The cumulative percentage drug released by each tablet in the *in vitro* release studies was based on the mean content of the drug present in the respective tablet. Further the tablets were subjected for the evaluation of *in vitro* disintegration time. The *in vitro* disintegration time (seconds) for all the formulations varied from 12.0 ± 0.92 and 53. 6 ± 1.28 in case of direct compression method and 14.07 ± 0.8 and 56.2 ± 1.22 in case of sublimation method. The rapid disintegration was seen in the formulations containing Crospovidone, Croscarmellose sodium and Sodium starch glycolate. This is due to rapid uptake of the water from the medium, swelling and burst effect. It was also noticed that as the disintegrant concentration was increased, the time taken for disintegration was reduced. The wetting time (seconds) for all the formulations was performed in triplicate. The values lie between 12.63 ± 0.55 to 37.2 ± 2.26 and 13.23 ± 0.5 to 38.2 ± 2.20. The wetting time was rapid in Crospovidone followed by Croscarmelose sodium and Sodium starch glycolate. Here also it was observed that as the concentration of disintegrant increased the time taken for wetting was reduced. Sodium starch glycolate took a little more time for complete wetting in both the methods when compared to other disintegrants.

The *in vitro* dispersion is a special parameter in which the time taken by the tablet for complete dispersion is measured. The time for all the formulations varied between 7.4 ± 0.24 and 45.12 ± 1.2. The time taken by all the tablets to produce a uniform dispersion was within the limits. The *in vitro* dispersion was rapid in Crospovidone followed by Croscarmelose sodium and Sodium starch glycolate. The values were depicted in Table 3 & 4.

Table 5: *In vitro* dissolution parameters of various formulations in pH 6.8 phosphate buffer.

Formulation	D_5 (%)	D_{10} (%)	$t_{50\%}$ (min)	$t_{90\%}$ (min)
F1	21.19	41.46	>15	>15
F4	76.16	98.12	1.79	7.86
F7	62.25	88.55	2.80	9.45
F10	72.54	92.46	1.93	8.63
F14	79.46	98.51	1.21	7.16
F17	68.83	89.15	2.83	9.28
F20	74.76	99.01	1.86	7.34

The *in vitro* dissolution studies show that an increase in the drug release was observed when the disintegrant concentration was increased in the formulations. The rapid drug dissolution might be due to easy break down of particles and rapid absorption of drug into the dissolution medium. Amongst the formulations prepared by two methods, the formulation F4 and F14 was considered as promising formulations. Amongst the formulations F4 and F14, the formulation F14 was found to be the best as this formulation showed the lowest weight variation, good hardness, short wetting and dispersion time, fast disintegration and good content of active ingredient. By using dissolution data, various dissolution parameters like percent drug dissolved in 5min (D5), 10min (D10), $t_{50\%}$, and $t_{90\%}$ were determined. Among the promising formulations, F14 has shown 8-fold faster drug release ($t_{50\%}$ = 1.21min) compared to control formulation (15min). When the $t_{50\%}$ values were considered, the F14 was the best formulation. The data was depicted in table 5. The dissolution data obtained were subjected to kinetic treatment to know the order of release. The values obtained signify that the release rate follows first order kinetics. The dissolution profiles were shown in Figures 1 and 2.

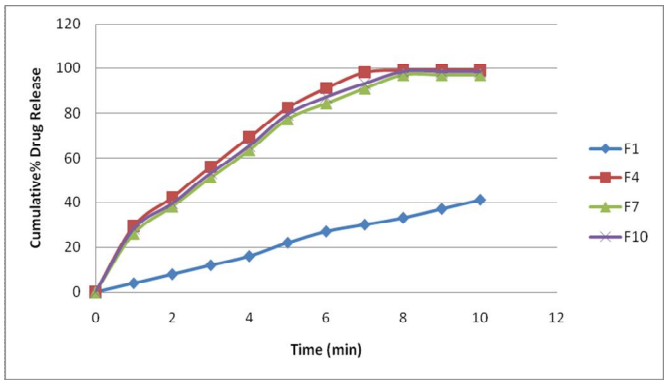

Fig 1: Cumulative percent drug release profiles of promising formulations of Alfuzosin by direct compression method.

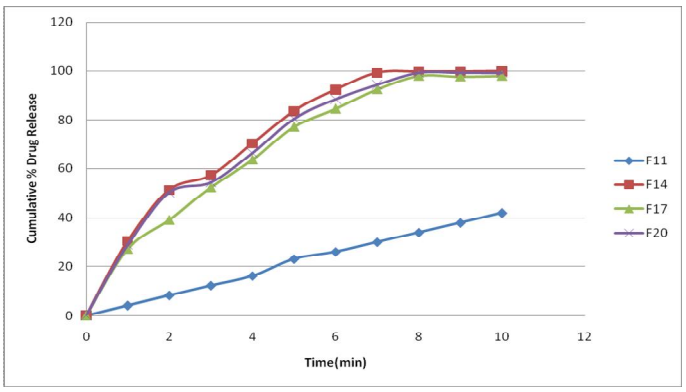

Fig 2: Cumulative percent drug release profiles of promising formulations of Alfuzosin by sublimation method.

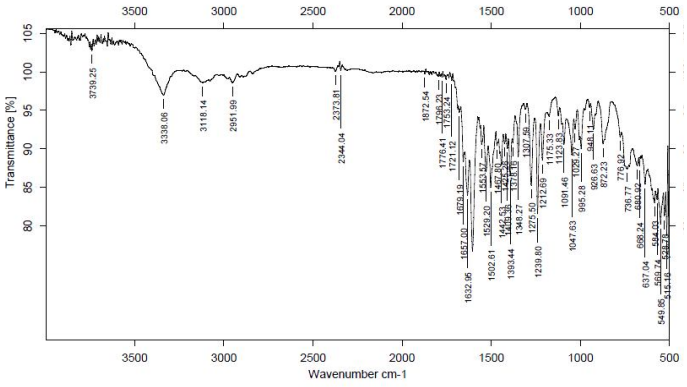

Fig 3: FT IR Spectrum of pure drug Alfuzosin HCl.

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of F14 showed all the characteristic peaks of Alfuzosin, thus confirming that no interaction of drug and the components of the formulation. The spectra were shown in Figures 3 and 4. Stability studies were conducted for the formulations F4 and F14. The reason for selection is, these two formulations have shown good results in *in*

vitro disintegration, wetting time and *in vitro* drug release studies.

The tablets were analyzed for hardness, uniformity of drug content and *in vitro* disintegration time at a time interval of 10 days till a period of 30 days. Both the formulations showed no significant variations in all the parameters and were stable for a period of 30 days.

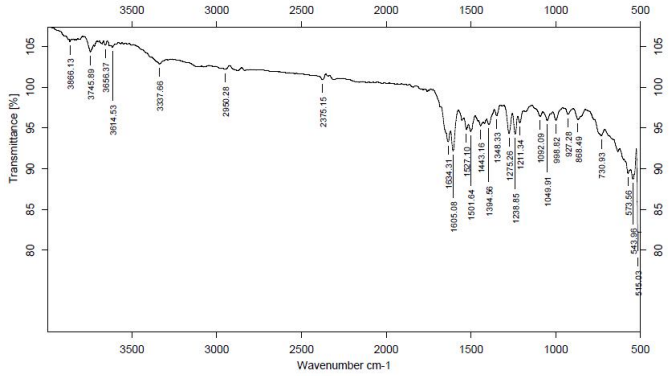

Fig 4: FT IR Spectrum of a formulation (F4) containing Alfuzosin HCl**.**

CONCLUSION

Oral route, the most convenient route of drug administration can be made as an ideal route by overcoming certain drawbacks. Dispersible tablet is one such attempt towards achieving this goal. Due to their rapid disintegration they can be directly placed in the oral cavity or ingested as a solution after dispersing in water especially for administration to pediatric patients. Also orodispersible tablets result in faster and complete dissolution of the drug due to their faster disintegration, rapid absorption and improved bioavailability. The overall results suggests that a 10% disintegrant concentration is suitable for the preparation of Alfuzosin oral dissolving tablets and the tablets containing disintegrants Crospovidone (F4) and F14 containing Crospovidone and camphor are the best formulations.

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