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New Diazo Coupling Reactions for Visible Spectrophotometric Determination of Alfuzosin in Pharmaceutical Preparations

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Abstract: Simple, rapid and sensitive spectrophotometric procedures were developed for the analysis of Alfuzosin hydrochloride (AFZ) in pure form as well as in pharmaceutical formulations. The methods are based on the reaction of AFZ with nitrite in acid medium to form diazonium ion, which is coupled with ethoxyethylenemaleic ester (Method A) or ethylcyanoacetate (Method B) or acetyl acetone (method C) in basic medium to form azo dyes, showing absorption maxima at 440, 465 and 490 nm respectively. Beer's law is obeyed in the concentration of 4-20 µg/mL of AFZ for methods A, B and 3-15 µg/mL of AFZ for method C.The molar absorptivity and sandell's sensitivity of AFZ-ethoxyethylenemaleic ester, AFZ- ethylcyanoacetate and AFZ-acetyl acetone are1.90 x 10^4 , 0.022; 1.93 x 10^4, 0.021and 2.67 x 10^4 L $mole^{-1}$ cm^{-1}, 0.015 µg cm^{-2} respectively. The optimum reaction conditions and other analytical parameters were evaluated. The methods were successfully applied to the determination of AFZ in pharmaceutical formulations.

Keywords: Alfuzosin, Diazo Coupling Reactions, Ethoxyethylenemaleic ester, Ethylcyanoacetate, acetyl acetone.

Introduction

Alfuzosin Hydrochloride (AFZ) [1] is a alpha 1- receptor blocker and is chemically known as *N*-[3-[(4- amino-6, 7-dimethoxy – quinazolin-2- yl)-methyl-amino]propyl]oxolane-2-carboxamide hydrochloride. Figure 1 shows the structure of alfuzosin. It is used for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. Literature survey reveals that, few chromatographic [2-6] methods have been reported for the

estimation of AFZ. To the best of our knowledge, there is no work in the literature reported about the spectrophotometric method for the analysis of AFZ in either biological fluids or pharmaceutical formulations. Hence the author has made an attempt to develop three simple and rapid spectrophotometric methods for the estimation of AFZ in bulk drugs and in pharmaceutical formulations. The methods are based on the reaction of AFZ with nitrite in acid medium to form diazonium ion, which is coupled with ethoxyethylenemaleic ester (Method A) or ethylcyanoacetate (Method B) or acetyl acetone (Method C) in basic medium to form azo dyes, showing absorption maxima at 440, 465 and 490 nm respectively.

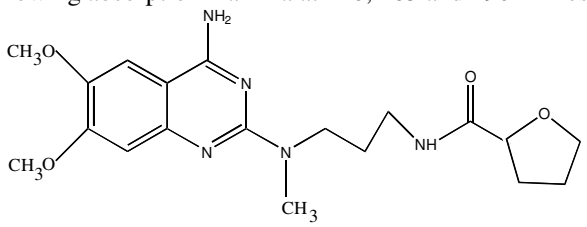

Figure 1. Structure of Alfuzosin

Experimental

Apparatus

All spectral and absorbance measurements were made on a systronic model 117 digital spectrophotometer with 10mm matched quartz cells.

Materials and reagents

All chemicals used were of analytical reagent grade and double distilled water was used for preparing the reagent solutions. AFZ was obtained from Dr.Reddy's labs Hyderabad. Stock solution of AFZ was freshly prepared by dissolving 100mg of AFZ in 100mL of distilled water and then this was further diluted with distilled water so as to obtain working standard solution of 100 µg/mL. A (5%) solution of ethoxyethylenemaleic ester, ethylcyanoacetate (5%), 5% methanolic solution of acetyl acetone, 1% sodium nitrite, 2% sulphamic acid, 2M sodium hydroxide and 5M HCl were used

General procedure for the determination of AFZ

Aliquots of the working standard solution of AFZ (4-20 µg/mL for Methods A&B; 1-15 µg/mL for method C) were transferred into a series of 10 mL calibrated flasks. For all the methods 1 mL of 1% sodium nitrite and 0.5 mL of 5M HCl were added and the solutions were shaken thoroughly for 2 minutes to allow the diazotization reaction to go to completion. Add 1 mL of 2% sulfamic acid, stir the solutions for 3 min and add 1 mL of 2% ethoxyethylenemaleic ester (method A) or ethylcyanoacetate (method B) or 1.5 mL of 5% acetyl acetone (method C). Then add 2 mL of 2M sodium hydroxide solution and the contents were diluted to 10 mL using double distilled water and mixed well. After 5 minutes, the absorbance of the colored azo dyes was measured at 440 or 465 or 490 nm against the reagent blank.

Assay of pharmaceutical tablets

Twenty tablets were powdered and mixed thoroughly. An amount equivalent to 100 mg of the drug was dissolved in water and filtered. The filtrate was made up to 100 mL and appropriate aliquots of the drug solution were treated as described above for the determination of AFZ.

Results and Discussion

Spectral characteristics

Method A, B and C involves the diazotization of AFZ, followed by the coupling of ethoxyethylenemaleic ester or ethylcyanoacetate or acetylacetone in alkaline medium. The absorption spectra of the azo dyes formed between AFZ- ethoxyethylenemaleic ester, AFZ-ethylcyanoacetate and AFZ- acetyl acetone have absorption maxima at 440, 465 and 490 nm respectively (Figures 2, 3 &4).

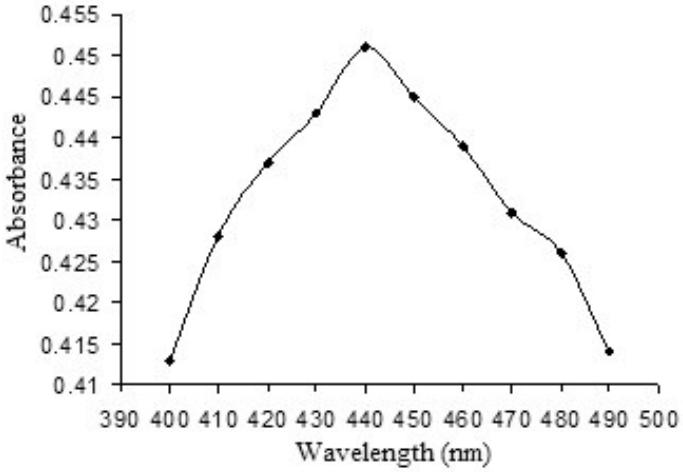

Figure 2.Absorption spectrum of the azo dye formed between AFZ (10µg/mL) and ethoxyethylenemaleic ester

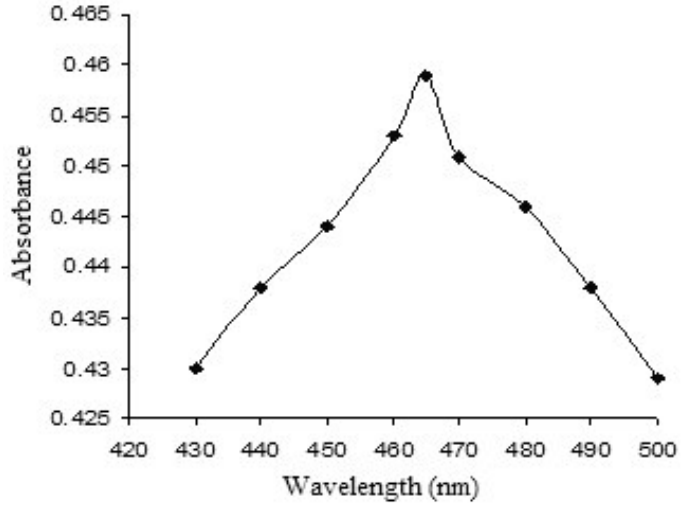

Figure 3. Absorption spectrum of the azo dye formed between AFZ (10µg/mL) and ethylcyanoacetate

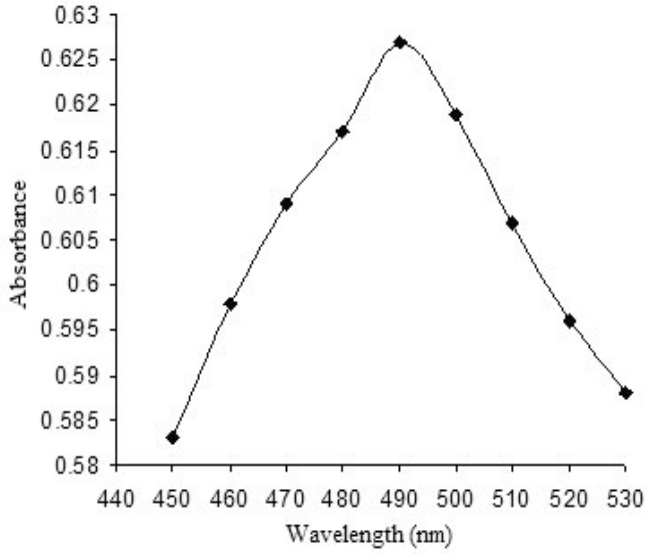

Figure 4. Absorption spectrum of the azo dye formed between AFZ (10µg/mL) and acetyl acetone

Effect of acidity on diazotization

The effect of acidity on the diazotization reaction was studied in the range 1-10 M HCl, and constant absorbance values were obtained in the acidity range 3-8 M HCl. Above this range, a decrease in the absorbance was observed. The minimum time required for diazotization was 2 min. Diazotization was carried out at room temperature and the optimum acidity for the formation of diazonium chloride was fixed to 5M.Other mineral acids were tested and found unsatisfactory.

Effect of sodium nitrite

The optimum concentration of sodium nitrite solution was found to be 1mL of 1% solution of sodium nitrite. The excess of nitrite could be removed by the addition of 1 mL of 2% sulfamic acid. An excess of sulphamic acid has no effect on colour.

Effect of coupling agent

The effect of varying the concentration of coupling agent was studied using the proposed procedure and adding 0.2-2.0 mL of 2% ethoxyethylenemaleic ester or 0.2-2.0 mL of ethylcyanoacetate or 0.2-2.5 mL of acetyl acetone to a series of drug solutions. It was found that maximum and stable color was formed with 1 mL of ethoxyethylenemaleic ester (2%) or 1 mL of ethylcyanoacetate (2%) or 1.5 mL of acetyl acetone (5%) solution in final volume of 10 mL.

Effect of sodium hydroxide concentration

The effect of sodium hydroxide concentration on the absorbance was studied; volumes from 0.5-3.0 mL of 2M sodium hydroxide solutions were examined. The investigations showed that 1-3 mL of sodium hydroxide gave maximum absorbance and 2 mL of 2 M sodium hydroxide was chosen for the procedure. Other alkaline solutions were tried, but best results were obtained by using sodium hydroxide.

Analytical data

The optical characteristics such as Beer's law limits, Sandell's sensitivity, molar absorptivity, percent relative standard deviation (calculated from eight replicate samples containing 3/4th of the amount of the upper beer's law limits) were calculated for all the methods and the results are summarized in Table 1. Regression characteristics like standard deviation of slope (S_b), standard deviation of intercept (S_a), standard error of estimation (S_e), % range of error (0.05 and 0.01 confidence limits) and detection limit were calculated for all the methods and are shown in Table 1.

Table 1. Optical and regression characteristics, precision and accuracy of the proposed methods for AFZ

Parameter	Method A	Method B	Method C
$\lambda_{max,}$ nm	440	465	490
Beer's law limits, µg mL^{-1}	4.0 – 20.0	4.0– 20.0	3.0 - 15
Detection limits, µg mL^{-1}	0.127	0.096	0.127
Molar absorptivity, L mole^{-1} cm^{-1}	1.90 x 10^4	1.93 x 10^4	2.67 x 10^4
Sandell's sensitivity	0.022	0.021	0.015
Regression equation ($Y = a + bC$)			
Slope (b)	4.48 x 10^{-2}	4.57 x 10^{-2}	6.30 x 10^{-2}
Standard deviation of slope (S_b)	0.14 x 10^{-3}	0.11 x 10^{-3}	0.27 x 10^{-3}
Intercept (a)	-0.10 x 10^{-3}	-0.30 x 10^{-3}	-1.60 x 10^{-3}
Standard deviation of intercept (S_a)	1.91 x 10^{-3}	1.47 x 10^{-3}	2.68 x 10^{-3}
Standard error of estimation (S_e)	1.82 x 10^{-3}	1.40 x 10^{-3}	2.56 x 10^{-3}
Correlation coefficient (r)	0.9999	0.9999	0.9999
Relative standard deviation, % [a]	0.064	0.154	0.111
% Range of error(Confidence limits)[a]			
0.05 level	0.054	0.129	0.093
0.01 level	0.080	0.191	0.137
% Error in bulk samples [b]	0.522	0.120	0.513

[a]Average of eight determinations; [b] Average of three determinations
In Y =a + bC, Y is absorbance and C is concentration.

Interference

The extent of interference by common ions was determined by measuring the absorbance of a solution containing 10.0 µg/mL of AFZ and various amounts of diverse species. Majority of the common ions do not interfere. An error of 2% in the absorbance readings was considered tolerable. Some of the common excipients which often accompany the pharmaceutical preparations do not interfere in the present method. The results are given in Table 2.

Analysis of pharmaceutical preparations

Application of the proposed methods to the determination of AFZ in its dosage forms was successfully made; the results are presented in Table 3. The excellent recoveries obtained indicated the absence of any interference from the excipients.

Table 2. Determination of AFZ in presence of excipients

Excipients	Amount Added, mg	% recovery of AFZ* ± % RSD		
		Method A	Method B	Method C
Magnesium stearate	40	99.6±0.42	100.3±0.24	100.4±0.40
Hydroxy propyl methyl cellulose	50	100.1±0.35	99.9±0.32	99.7±0.18
Lactose	30	99.5±0.60	99.8±0.38	99.8±0.55
Glucose	30	99.7±0.26	100.1±0.52	100.2±0.48
Sorbitol	50	100.1±0.70	100.4±0.66	100.2±0.20
Dextrose	30	99.8±0.28	99.6±0.20	99.9±0.68
Sodium alginate	40	99.8±0.25	99.9±0.43	99.7±0.18
Talc	50	99.7±0.65	99.9±0.55	99.6±0.65
Starch	40	99.9±0.18	100.2±0.85	100.1±0.30
Povidone	40	99.8±0.23	100.1±0.33	100.05±0.28
Micro crystalline cellulose	50	100.06±0.22	100.01±0.53	100.2±0.71

Table 3. Results of analysis of tablet formulations containing AFZ

Formulation	Labeled Amount (mg)	Recovery*±%RSD**		
		Method A	Method B	Method C
Tablets-1	10	99.8±0.35	100.1±0.30	100.2±0.35
Tablets-2	10	100.3±0.40	100.2±0.35	100.6±0.60

* Average of 5 determinations; ** Relative standard deviation

Conclusions

The proposed methods were found to be simple, economical, selective and sensitive. The statistical parameters and recovery study data clearly indicate the reproducibility and accuracy of the methods. Analysis of the authentic samples containing AFZ showed no interference from the common excipients. Hence, these methods could be considered for the determination of AFZ in the quality control laboratories.

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