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Research Article

ATOMIC ABSORPTION SPECTROMETRIC DETERMINATION OF ACLIDINIUM BROMIDE USING AMMONIUM REINECKATE

MOHAMMED W.I. NASSAR[1], KHALID A.M. ATTIA[1], AHMED A. MOHAMED, SAMIR MORSHEDY[2], MOHAMEDA SHAHIN[1*]

[1]Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Al-Azhar University, 11751 Nasr City, Cairo, Egypt. [2]Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Damanhour University, Beheira, Egypt.
Email: Mohamed.shahin@pharm.dmu.edu.eg

ABSTRACT

Objective: Atomic absorption spectrometric method has been developed for determination of aclidinium bromide in its pure and pharmaceutical dosage form. Methods: The method was based on the ability of aclidinium bromide to form stable ion pair complex with ammonium reineckate and the amount of chromium in the formed complex, corresponding directly to the concentrations of the reacted aclidinium bromide, has been measured directly at 357.9 nm. Results: The method has been optimized and validated with respect to linearity, accuracy and precision. Conclusion: The proposed method has been successfully applied for the determination of the drug in its commercial preparation.

Keywords: Aclidinium bromide; Atomic absorption; validation.

INTRODUCTION

Aclidinium bromide [ACB], Figure 1, a novel, long-acting, inhaled muscarinic antagonist, has been developed for the treatment of chronic obstructive pulmonary disease [1].

Different analytical techniques have been applied for pharmaceutical analysis with various applicable advantages. These techniques including either chromatographic [2-5], spectrophotometric [6- 12], spectrofluorimetric [13, 14], atomic spectrometry or application of electrochemical methods [15, 16].

Atomic absorption spectrometry has become a powerful method of analysis due to its selective resonance radiation and sensitivity. Hence, determination of trace elements can be performed in most analytical laboratories. The main goals of analytical atomic spectrometry are to attain the broadest dynamic range, suppress the matrix effect, eliminate spectral interferences, minimize the time and cost required for sample preparation [17].

Recently, atomic absorption spectrometry has been utilized for determination of several compounds using precipitating reagents such as ammonium reineckate, cobalt (II) thiocyanate and bismuth (III) tetraiodide to form ion pair associates [18,19].

To date, no analytical methods has been developed for determination of ACB in its pure and pharmaceutical dosage form so the main purpose of this work is to establish a sensitive, accurate and precise atomic absorption spectrometric method for determination of ACB in bulk powder and in pharmaceutical preparation depending on its ability to form stable ion pair complex with ammonium reineckate.

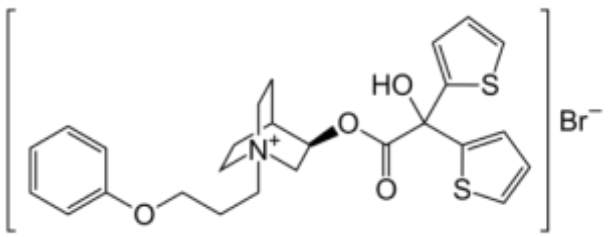

Figure 1: Structure formula of ACB

EXPERIMENTAL

Materials

Pure ACB (99.25%) and Tudorza® Pressair® inhalation powder each inhaler dose containing 400µg of ACB per actuation were kindly supplied by National Organization for Drug Control and Research, Giza, Egypt

Chemicals and reagents

All reagents used were of analytical grade, water used throughout the procedure was freshly distilled and deionized.

- Ammonium reineckate $NH_4[Cr(NH_3)_2(SCN)_4]$, (Sigma-Aldrich, Germany), prepared as 10^{-2} M aqueous solutions.
- Acetone, (Sigma-Aldrich, Germany).
- Methanol, HPLC grade (Sigma-Aldrich, Germany).

Apparatus

GBC Elemental atomic absorption flame spectrometer, model: GBC 932 AA (Australia), equipped with air-acetylene burner, spray chamber, adjustable nebulizer and computed with GBC AAS software. Chromium was measured at wavelength 357.9 nm, slit width 0.2 nm, relative noise 1 nm, lamp current 10 mA, integration time 4 seconds.

Standard solutions

A standard solution of ACB (2 mg/ mL) was prepared by dissolving 200 mg of the drug powder in 50 mL of methanol using a 100-mL volumetric flask and completing to volume with methanol. This standard solution was stable for at least 3 and 7 days when stored at room temperature and in refrigerator, respectively.

Procedures

General procedure

Aliquots of standard aclidinium bromide solution (2 mg/mL) containing (2.5–10 mg) were transferred into a series of 10 mL volumetric flasks and 5 ml of 10^{-2} M ammonium reineckate solution was added. The mixtures were left to react for 60 min under stirring at room temperature. The resulting precipitate was then filtered off

on Whatman filter paper. The precipitate was separated and dissolved in least amount of acetone, and completed to the mark in 100 mL volumetric flasks with methanol. The solutions were then aspirated directly in the atomic absorption spectrometer and measured the chromium ion concentration at wavelength 357.9 nm.

Validation of the method

The methods were tested for linearity, range, limits of detection and quantitation, accuracy and precision according to ICH guidelines.

Procedure for pharmaceutical preparation

A quantity equivalent to 10 mg of ACB was accurately weighed and transferred then the volume was made up to 75 mL with methanol. The solution was shaken vigorously for 20 min then sonicated for 30 min and filtered. The volume was completed to 100 mL with methanol to produce a stock solution labeled to contain 100 µg/mL of ACB. Working solution (10 µg/mL) was obtained by further dilution with methanol, and then analyzed following the general procedure of the method.

RESULTS AND DISCUSSION

In the present study, a simple and sensitive atomic absorption spectrometric method was developed for selective quantitative determination of ACB depending on its reaction with ammonium reineckate.

Spectral characteristics

Ammonium reineckate has a high affinity towards the formation of ion pair complex with the studied drug. This formed complex is insoluble in aqueous solution and can easily be separated by filtration. The precipitates could be dissolved in acetone. Then the amount of chromium in the formed complex of aclidinium bromide-reineckate ion pair can be measured directly by atomic absorption spectrometer at 357.9 nm. These amounts corresponding directly to the concentrations of the reacted ACB.

Based on the elemental analysis results (C, 47.49; H, 4.32; N, 13.04; S, 24.89). It was found that the studied complex is formed based on a 1:1 ratio of ACB and the reineckate salt. Hence, each 25 µg/mL of ACB is equivalent to 2.454 µg/ml of chromium.

METHOD VALIDATION

Linearity and range

Under the described experimental conditions, the calibration graph for the method was constructed by plotting the measured absorbance at 357.9 nm versus the final drug concentrations corresponding in µg/mL. The regression plot was found to be linear over the range of 25-100 µg/mL, the regression data were presented in table (1). The high values of coefficient of determination and the small values of slope and intercept indicated the linearity of the calibration graph.

Limits of detection and quantitation

LOD and LOQ values were calculated and the obtained results indicated the sensitivity of the proposed methods for the analysis of the studied drugs as shown in table (1).

Accuracy and precision

Accuracy of the described method, calculated as the mean percent recovery (%R), was assessed by applying the described procedure for triplicate determination of three concentration levels covering the linearity range of the drug (35, 50, 65 µg/mL). The results in table (1) indicated the accuracy of the proposed methods.

Moreover the standard addition technique was applied to check the accuracy of the described methods. It was done by adding known quantities of ACB bromide in its pure form to already analyzed pharmaceutical preparation and the percent recovery of the pure added concentrations was calculated. The data listed in table (1) proved that the proposed methods could selectively analyze the drugs without any interference from any excipients.

Precision of the methods, calculated as the percent of relative standard deviation (%RSD), was assessed by triplicate determination of three concentration levels covering the linearity range of the drug (35, 50, 65 µg/mL) within one day for repeatability and on three successive days for intermediate precision. The small values of %RSD indicated high precision of the methods as shown in table 2.

Pharmaceutical applications

The proposed procedure was applied for the determination of ACB in Tudorza® Pressair® inhalation powder**.** Satisfactory results were obtained in good agreement with the label claim, indicating no interference from excipients and additives. The obtained results were statistically compared to those obtained by the manufacturing method. No significant differences were found by applying *t*-test and *F*-test at 95% confidence level, indicating good accuracy and precision of the proposed method for the analysis of the studied drug in its pharmaceutical dosage form, as shown in table 3.

CONCLUSION

Atomic absorption spectrometric method was suggested for determination of aclidinium depending on its ability to form stable ion pair complex with ammonium reineckate. Although this method provides acceptable results, the need for the reagent preparation and time consuming to complete the reaction makes it very limited.

Table 1: Regression and validation data for determination of ACB by the proposed atomic absorption spectrometric method

Parameters		Proposed method
Wavelength (nm)		357.9
Linearity range (µg/ml)		25 — 100
- Regression equation		$y^{*} = b\,x^{**} + a$
- Slope (b)		0.002
- Intercept (a)		-0.0013
Coefficient of determination (r^2)		0.9996
LOD (µg/ml)		1.833
LOQ (µg/ml)		5.557
Accuracy (%R)***		101.52
Precision (%RSD)***	Repeatability	1.372
	Intermediate precision	1.541

***y** is the absorbance of chromium.**
x is the concentration of ACB in µg/mL**
***** Values for 3 determinations of 3 different concentrations**

Table 2: Recovery study of ACB by applying standard addition technique

Pharmaceutical take (µg/mL)	Pharmaceutical found(µg/mL)	Pure added (µg/mL)	Pure found (µg/mL)	%Recovery
30	30.8	10	9.87	98.74
		15	15.23	101.54
		20	19.96	99.81
	Mean± %RSD			100.03 ± 1.413

*** Average of five determinations**

Table 3: Determination of ACB in Tudorza® Pressair® inhalation powder by the proposed atomic absorption spectrometric and the manufacturing methods

Parameters	Proposed method	Manufacturing method***
n*	5	5
Average (% Recovery)	100.30	100.04
%RSD	99.75	1.010
t (2.306)**	0.271	——
F (6.388)**	1.071	——

*** Number of measurements**

** **The values in parenthesis are tabulated values of "*t* "and "*F*" at (P = 0.05),** *** **HPLC using C_{18} column, mobile phase was acetonitrile: methanol(45:55, v/v) at a flow rate (1mL/min) and UVdetection at 260 nm..**

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