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Colorimetric determination of astemizole in bulk and in its pharmaceutical dosage forms using flow injection

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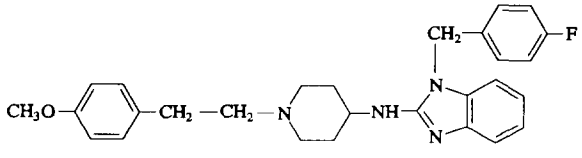
Abstract

A continuous flow spectrophotometric method for determining 0.5–100 μg ml^{-1} of astemizole in pure and in dosage forms is suggested. It depends on forming a pinkish orange product which can be quantified spectrophotometrically at 495 nm. The coloured product was due to the action of *N*-bromosuccinimide on astemizole in alkaline medium and in the presence of a cetyltrimethylammonium bromide micellar medium. The procedure is automated and solutions can be analysed at a rate of 167 h^{-1} with a relative error of about 1.25%. The limit of detection is 0.5 μg ml^{-1} ($\approx 1.09 \times 10^{-6}$ M). The method is evaluated by a recovery study and by the analysis of commercial formulations.

Keywords: Astemizole; Colorimetric determination; Flow injection

1. Introduction

Astemizole (Hismanal®,I),2-(*p*-fluorobenzyl)-2-[(1-(*p*-methoxyphenethyl)-4-piperidylamino] benzimidazole,



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is a potent and long-acting new H_1-antihistamine used to treat the symptoms of allergic disorders. It belongs to a new class of drugs with few centeral or antimuscarinic effects [1,2]. Currently, astemizole and its pharmaceutical dosage forms are not found in any pharmacopoeia and different analytical methods are reported for its determination. These include high performance liquid chromatography (HPLC) [3–6], ultraviolet spectrophotometry [6,7], radioimmunoassay [8], and thin layer chromatography (TLC) [9,10].

In the present study, a colorimetric method for the determination of astemizole in bulk and in pharmaceutical preparations is described based on

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measurement of the absorbance of a pinkish orange product in a flow injection system. This method is simple, accurate and easy to apply to routine usage. In addition, it needs no preliminary treatment, such as extraction or ashing, and needs no sophisticated or costly instruments.

2. Experimental

2.1. Reagents

Distilled, deionized water was used throughout. All the chemicals were of analytical reagent grade, unless otherwise stated. A stock solution of 1000 μg ml^{-1} astemizole (Lot No. ZR 43512 D 0301) was prepared by dissolving 0.1000g of the drug in 100 ml of 0.035 M acetic acid. A solution of 0.05 M *N*-bromosuccinimide (NBS) was prepared by dissolving 0.8899 g of the *N*-bromosuccinimide (BDH, UK) in 100 ml of 0.1 M KOH. This solution was used within 30 min of its preparation. Cetyltrimethylammonium bromide (CTABr) solution of 0.04 M was prepared by dissolving 3.645 g of the CTABr (BDH, UK) in 250 ml of water. A Stock solution of 1 M KOH (Merck, Germany) was used.

2.2. Apparatus

Spectrophotometric measurements were made with an LKB Ultrospec II spectrophotometer equipped with a flow cell (volume, 80 μl; light path, 10 mm). The components, including injection valve, pump and manifold, were as reported earlier [11].

2.3. Flow injection manifold and procedure

The manifold used for the determination of astemizole is shown in Fig. 1. A pump (Gilson Minipuls 3, Anachem) was used to propel the reagents. Astemizole solutions (100 μl) were injected via a Rheodyne 5020 injection valve. The obtained absorbance was measured at 495 nm.

3. Results and discussion

3.1. Optimization of parameters

Astemizole was found to yield a clear pinkish orange product with NBS in aqueous basic medium and in the presence of a micellar medium of CTABr. The coloured product is probably due to oxidation of the drug as NBS is known to be an oxidising reagent. Therefore, investigations were carried out to establish the most favourable conditions for the formation of the coloured product. The influence of some variables on the reaction has been studied. Such variables, which were changed individually, include concentration of the reagents, flow rate of reagents and analyte, and sample volume. Solubility of NBS was studied by using different diluents, e.g. H_2O, CH_3COOH, NaOH and KOH. The salt when dissolved in KOH yielded greater absorbance readings compared to the other tested diluents. The effect of changing the concentration of NBS over the range of 0.001–0.125 M was examined. The peak height absorbance increased as the concentration of NBS is increased and started to decrease above 0.05 M, which concentration was used in further studies.

A study of the influence of sample volume over the range 10–150 μl showed that there was a slight increase in peak height absorbance with increasing sample volume. Best peak height absorbance was obtained by using 100 μl as a sample volume, which was used in further investigations.

The influence of flow rate over the range 3.0–11.9 ml min^{-1} was studied. The peak height absorbance increased slightly with increasing flow rate, indicating that the reaction is not very fast.

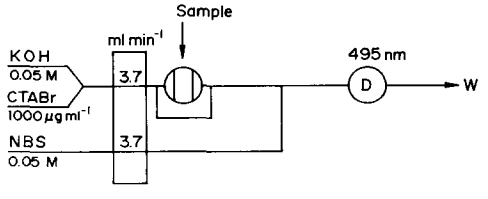

Fig. 1. Manifold used for determination of astemizole: W, waste; D, detector.

Best response was obtained at a total flow rate of 7.4 ml min^{-1}.

The effect of coil length was examined over the range 0–200 cm. The peak height absorbance decreased by approximately 14% from 0 to 200 cm, probably because of the dilution of the sample. Therefore, no reaction coil was included in the manifold, in order to achieve a reasonable sensitivity.

The selected values for the FIA variables are: total flow rate, 7.4 ml min^{-1}; injection volume, 100 μl; and no reaction coil. The reaction time from injection to measurement under these conditions is 21.5 s.

3.2. Analytical performance

Series of standard solutions were prepared from the stock solution of astemizole and run in triplicate by the FIA procedure under the conditions specified above. A typical FIA run for astemizole is shown in Fig. 2, from which a calibration graph of astemizole concentration vs. peak absorbance was extracted. A typical computer regression of this plot resulted in the calibration equation:

$$A = 5.42 \times 10^{-4} + 3.16 \times 10^{-3}C$$

where A is absorbance, C is concentration of the drug (μg ml^{-1}) and with a correlation coefficient of 0.999 and a relative standard deviation of 1.25% (based on 15 repeated injections) indicating a fairly good straight line that passes through the origin with an insignificant intercept. This equation can be used to calculate unknown astemizole concentrations in the range 0.5–100 μg ml^{-1}, within which the equation was found to be linear.

A sample throughput of 167 h^{-1} could be attained; this was calculated by measuring the peak width, which was found to be 21.5 s at the baseline and 3.0 s at 60% at the peak height, indicating minimal dispersion.

3.3. Interference

The effect of other substances on the accuracy of the astemizole determination with NBS was studied. Because astemizole and its active metabolites have a rapid and extensive distribution in the human body (e.g. pancreas, adrenal glands, liver, lung, kidney tissue, testes, etc.), the effect of some common excipients generally present in pharmaceutical preparations, and some amino acids

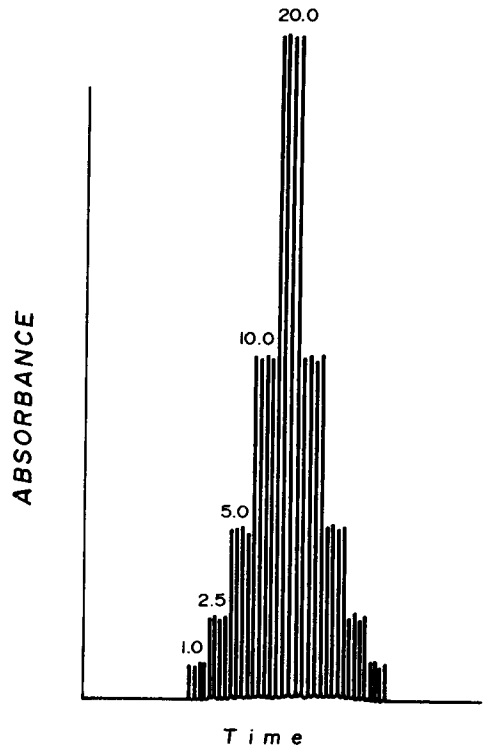

Fig. 2. Typical recorder outputs for a series of Astemizole standards under the recommended conditions; numbers on the peaks are astemizole concentrations (μg ml^{-1}).

Table 1
Effect of other substances (all 250 μg ml^{-1}) on the absorbance of 25 μg ml^{-1} astemizole

Interferent	Absorbance[a]	Recovery (%)[b]
Astemizole (pure)	0.068	100
D(−)-Fructose	0.068	100
D(+)-Galactose	0.067	98.5
D(+)-Glucose	0.064	94.1
Sucrose	0.066	97.1
Starch	0.068	100
L-Cysteine	0.022	32.4
DL-Tyrosine	0.048	70.6
Casein	0.044	64.7

[a] Each result is the average of three injections.
[b] Relative to astemizole.

Table 2
A statistical comparison of the results of determination of pharmaceutical products containing astemizole by FIA with those obtained by SP

Drug proprietary name and supplier	Active material as $\mu g\ ml^{-1}$ astemizole analysed	Recovery ± SD[a](%)		
		FIA	SP	t[b]
Hismanal tablet (Janssen, Belgium)	40	99.6 ± 1.30	100.5 ± 2.1	0.8
	50	100.1 ± 1.15	98.4 ± 1.8	1.4
Hismanal suspension (Janssen, Belgium)	40	102.1 ± 1.28	99.5 ± 1.2	1.8
	50	99.5 ± 1.26	97.7 ± 0.9	1.2

[a] Calculated as mean of four determinations.
[b] Student t-test calculated; theoretical value: 3.18 ($P = 0.05$).

which are normally found in the biological samples, was investigated. However, excipients such as fructose, glucose, sucrose, galactose and starch showed no significant interference. Other interferents tested such as L-cysteine, DL-tyrosine and casein interfered severely but their interference can be reduced easily through dilution, because they interfered when present at high concentrations. The results obtained are shown in Table 1.

3.4. Application

The present FIA method was applied to the determination of astemizole in its pharmaceutical formulations: Hismanal® tablet (Lot No. 88J 12/433) and oral suspension (Lot No. 88A 07/879). Two solutions of 40 and 50 $\mu g\ ml^{-1}$ concentrations of each dosage form were injected four times. Results obtained are shown in Table 2. The same batch of samples was analysed by another spectrophotometric method (SP) [7], and percentage recovery, SD and Student t-test values were calculated (Table 2). Statistical analysis of the results using Student's t-test for paired data revealed no significant differences between the two methods at the 95% confidence level for tablets and suspension. Excipients such as glucose, starch and other drug components do not interfere. However, the new procedure has the advantage of being quicker, since there is no need for an extraction step, and easier to use for routine analysis.

The present method is superior to other reported methods with respect to simplicity and sample throughput. In addition, it satisfies the need for a rapid and sensitive procedure for the determination of astemizole in drug formulations suitable for routine quality-control purposes.

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