Department of Instrumental Analysis, University of Łódź, Łódź[1], Technical Chemistry School, Zgierz[2], Poland

Coulometric titration of ketotifen in tablets

W. Ciesielski[1], R. Zakrzewski[1], U. Żłobińska[2]

Received September 20, 2004, accepted September 24, 2004

Prof. Dr. Witold Ciesielski, Department of Instrumental Analysis, University of Łódz, ul. Pomorska 163 PL-90-236 Łódz, Poland
zaiciesielski@hotmail.com

Pharmazie 60: 237–238 (2005)

A method for the determination of ketotifen involving its reaction with iodine in an alkaline medium is presented. In coulometric titration using biamperometric end-point detection 0.25–2 μmol (77–618 μg) of ketotifen was successfully determined. The elaborated method was applied to the determination of ketotifen in drugs.

Ketotifen (4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10 H-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one) is an active component of pharmaceutic products of antihistamine and antiasthmatic efficiency. Several methods for the determination of ketotifen in pharmaceutic products have been reported e.g. potentiometric titration with chloric(VII) acid (Mikotic-Mihun 1983), ion-selective electrodes (Hopkała 1999), UV spectrophotometry (Mikotic-Mihun 1983; Vachek 1987; Szczepaniak 1992; Sane 1993; Sastry 1997; El-Kousy 1999), spectrofluorimetry (Sastry 1998), differential pulse polarography and adsorptive stripping voltammetry (Bersier 1992), densitometric high-performance thin-layer chromatography (Sanghavi 1995), and HPLC (Zarapkar 1992; Nnane 1998).

Table 1: Results of the coulometric titration of ketotifen (n = 6)

Taken (μmol)	Found (μmol) $\bar{x} \pm t_{0.95} \cdot \frac{s}{\sqrt{n}}$	RSD (%)
0.2556	0.2572 ± 0.0007	0.27
0.5086	0.5063 ± 0.0075	1.41
1.017	1.018 ± 0.008	0.73
2.034	2.038 ± 0.003	0.14

Table 2: Results of coulometric determination of ketotifen in tablets (n = 6)

Drug	Declared content (mg)	Found (mg) $\bar{x} \pm t_{0.95} \cdot \frac{s}{\sqrt{n}}$	RSD (%)
"Ketotifen" Polfa PL	1	1.003 ± 0.002	0.2
"Pozitan" Glaxo Wellcome	1	1.001 ± 0.007	0.7
"Zaditen" Novartis CH	1	0.998 ± 0.002	0.2

It has been found that in alkaline medium one molecule of ketotifen reacts with four iodine atoms. In acid or neutral media the reaction of iodine with ketotifen is slow and titration is impossible.
Water soluble tablet excipients remaining after filtrations do not interfere under the conditions of the proposed application. A high concentration of potassium iodide was used in the coulometric titration in an alkaline medium in order to obtain 100% current efficiency. Moreover, such a solution is stable. Oxidation of iodide ions occurs only in acidic solution and is not observed in alkaline.
In all the investigated drugs the amount of ketotifen determined by the coulometric method was in good agreement with the declared content.
The titration presented here is the only coulometric method available for the determination of ketotifen. Comparing the iodometric determination of ketotifen with the methods previously reported, one may conclude that this method is characterised by a short analysis time, high precision and accuracy, a simple procedure and commonly available reagents. The coulometric method is partly automated and requires no standard solutions.

Experimental

1. Chemicals and apparatus

Doubly glass-distilled water, KI, NaOH, were used. A standard solution of ketotifen (Polfa-Warsaw) was prepared by dissolving a weighed amount of reagents in water. A type OH-404 universal coulometric analyser was obtained from Radelkis (Budapest, Hungary).
An electolysis cell with two platinum electrodes each with an area of 5 cm^2, working in a generation circuit and an OH-9381 double electrode in a biamperometric indicator circuit was used. The cathode and anode compartments of the electrolysis cell were separated by a sintered glass G-4 disc. The levels of liquids in both compartments were the same in order to avoid the mixing of electrolytes. A mechanical stirrer was employed.

2. Procedure

2.1. Determination of ketotifen in solution

The coulometric determination was carried out in the reaction solution containing 1 mol · l^{-1} KI and 2 mol · l^{-1} NaOH. A sample solution containing ketotifen was introduced into 25 ml of the reaction solution placed in the anode compartment of the electrolysis cell. The polarisation voltage applied to the indicator system electrodes was 150 mV. After starting the mechanical stirrer, a stabilized current 5 mA was passed through the solution. The charge (Q) was noted after completing the titration of ketotifen up to an indicator current of 0.4 μA.
The ketotifen content (μmol) in the tested sample was calculated according to Faraday's law:

$$n = \frac{\Delta Q}{zF} \cdot 10^3 \qquad (1)$$

where:
$\Delta Q = Q - Q_0$ (mC), Q_0 – the charge corresponding to blank titration, z – the number of electrons transferred (z = 4), F – the Faraday constant (96 485 C · mol^{-1}).

2.2. Determination of ketotifen content in tablets

Ten tablets were weighed and crushed in a mortar. A mass of powder equivalent to the average mass of one tablet was dissolved in 10 ml of water and the solution was filtered. Then 1 ml of this solution was introduced into 25 ml of the reaction solution placed in the anode compartment of electrolysis cell and titrated in the same way as the pure substance. The content of the ketotifen in one tablet was calculated according to the equation:

$$m = \frac{10\,\Delta QM}{zF} \qquad (2)$$

where:
m – content of the tested substance in one tablet (mg),
$\Delta Q = Q - Q_0$ (mC), z – the number of electrons transfered (z = 4), F – Faraday's constant (96485 C · mol^{-1}), M – formula mass (309 g · mol^{-1}).

References

Bersier PM, Szczepaniak W, Ren M (1992) Direct differential pulse polarographic and adsorptive stripping voltammetric assay of ketotifen in tablets. Arch Pharm (Weinheim) 325: 253–259.

El-Kousy NM, Bebawy LI (1999) Determination of some antihistamine drugs by atomic-absorption spectrometry and colorimetric methods. J Pharm Biomed Anal 20: 671–679.

Hopkała H, Drozd J (1999) Ion-selective electrodes for the determination of antihistaminic drug ketotifen. Chem Anal (Warsaw) 44: 603–609.

Mikotic-Mihun Z, Kuftinec J, Hofman H, Zinic M, Kajfez F, Meic Z (1983) Physico-chemical and analytical characteristics of ketotifen. Acta Pharm Jugosl 33: 129–142.

Nnane IP, Damani LA, Hutt AJ (1998) Development and validation of stability indicating high-performance liquid chromatographic assays for ketotifen in aqueous and silicon oil formulations. Chromatografia 48: 797–802.

Sane RT, Chonkar NL, Surve SR, Gangrade NG, Bapat VV (1993) Extractive colorimetrics estimation of (i) ticlopidine hydrochloride, (ii) buspirone hydrochloride, (iii) nefopam hydrochloride and (iv) ketotifen fumarate from pharmaceutical preparations. Indian Drugs 30: 235–239.

Sanghavi NM, Puranik KA, Samarth MM (1995) Analysis of ketotifen fumarate by high-performance thin-layer chromatography. Indian Drugs 32: 53–54.

Sastry CSP, Naidu PY (1997) Spectrophotometric estimation of ketotifen fumarate in pharmaceutical formulations. Mikrochim Acta 127: 219–223.

Sastry CSP, Naidu PY (1998) Spectrofluorimetric estimation of ketotifen and terfenadine in pharmaceutical formulations. Indian Drugs, 35: 147–149.

Szczepaniak W, Cychowska T, Prządka T (1992) Spectrophotometric determination of ketotifen in pharmaceutical preparations after isolation on ion-exchanger. Acta Polon Pharm 49: 3–5.

Vachek J (1987) Photometric determination of ketotifen. Cesk Farm 36: 168–169.

Zarapkar SS, Bhounsule NJ, Halkar UP (1992) High-performance liquid-chromatographic determination of ketotifen hydrogen fumarate in pharmaceuticals. Indian Drugs 29: 365–366.

Department of Pharmaceutical Sciences, Shenyang Pharmaceutical University, Liaoning, P.R. China

Surface modification of liposomes for cardiomyocytes targeting *in vitro*

Y. CHEN, Y. J. DENG, Y. L. HAO

Received August 3, 2004, accepted September 13, 2004

Department of Pharmaceutical Sciences, Shenyang Pharmaceutical University, No. 103, Wenhua Road, P.O. Box 52, Shenyang City, Liaoning Province, 110016, People's Republic of China
w.chenyan@263.net

Pharmazie 60: 238–240 (2005)

The effect of novel 3-{4-[2-hydroxyl-(1-methyl ethylamine) propyl oxygen]phenyl}propionic acid cetylester (PAC) as a surface modification ligand on the delivery of liposomes into cultured cardiomyocytes was investigated. Small unilamellar liposomes with and without PAC (PAC-liposome and Plain-liposome) were labeled with a fluorescence marker. The cultured neonatal cardiomyocytes were incubated with liposomes under normoxia or hypoxia conditions, and then the cell-associated fluorescence was measured. A high affinity of the PAC-liposomes to cardiomyocytes was observed. The amount of cell uptake of PAC-liposomes under normoxia conditions was 4-fold higher than that of plain-liposome, and the increase was 8.5-fold when hypoxia occured. The results suggested that PAC is a potential surface modification ligand for liposome targeting the ischemic myocardium.

Liposomes have been suggested as efficient carriers for the delivery of drugs into ischemic myocardium (Caride and Zaret 1977; Phelan and Lange 1991; Smalling et al. 1995; Silva et al. 2001). This targeting phenomenon can be explained by the fact that in hypoxic areas of infarcted myocardium with increased permeability, liposomes ranging from 10 to 500 nm in size can extravasate and accumulate inside the interstitial space as a reservoir of the drug (Torchilin 2000). To enhance their activity of targeting to an ischemic myocardium or cardiomyocytes, liposomes with different characters (size, surface charge, permeability can be designed) and modified with various kinds of ligands (antibody, receptor ligand, sugar residues, etc).

It was reported that the β_1-adrenoreceptor (1-AR) predominated in mammalian ventricular cardiomyocytes (ranging from 80% in various rats, canine, and feline cardiac preparations to 60% in baboon ventricular myocytes) and its levels significantly increased when hypoxia occured (Bae et al. 2003). To improve the efficiency of liposomal drug delivery into the ischemic myocardium, 3-{4-[2-hydroxyl-(1-methyl ethylamine) propyl oxygen]phenyl}propionic acid cetylester (PAC) was synthesized, which has a homologous structure as esmolol (a selective β_1-adrenoreceptor blocker). Its effect as surface modification on the delivery of liposomes into cultured cardiomyocytes was studied.