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Electrochemical oxidation of fesoterodine and identification of its oxidation products using liquid chromatography and mass spectrometry

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ABSTRACT

The electrochemical behavior of fesoterodine (FES), an antimuscarinic drug used for the treatment of urge incontinence and overactive bladder, was investigated using linear sweep and cyclic voltammetry at a stationary and rotating disc glassy carbon electrodes. A single two-electron anodic signal of FES was observed in neutral buffered aqueous methanolic solutions. Kinetics of alkaline hydrolysis of FES to its active metabolite 5-hydroxymethyl tolterodine was investigated by time dependent linear sweep voltammetry. Controlled potential electrolysis of FES solutions was performed at platinum gauze electrode in aqueous-methanolic media. Electrolyzed solutions were analyzed using ultra performance liquid chromatography with electrospray ionization quadrupole time-of-flight mass spectrometry. Two main products of electrochemical oxidation of fesoterodine were identified as 5-formyl fesoterodine (isobutyric acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-formyl-phenyl ester) and *N*-desisopropylated fesoterodine (isobutyric acid 4-hydroxymethyl-2-(3-isopropylamino-1-phenyl-propyl)-phenyl ester). The mechanism of the electrochemical oxidation of FES has been proposed and confirmed using on-line electrochemistry/mass spectrometry with porous glassy carbon electrode.

1. Introduction

Fesoterodine fumarate (FES, **1** in Scheme 1) is a muscarinic receptor antagonist used for the treatment of urinary urge incontinence (UUI) and other symptoms associated with an overactive bladder. This drug also increases functional bladder volume [1]. Isobutyric acid 2-((*R*)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl) phenyl ester hydrogen fumarate (IUPAC) is the form of FES used in pharmaceutical preparations commercially available under the trade name Toviaz. Fesoterodine fumarate is white to off-white powder freely soluble in methanol (574 mg cm^{-3}), water (542 mg cm^{-3}), acetone (205 mg cm^{-3}), 0.9% NaCl solution (551 mg cm^{-3}), very slightly soluble in toluene (0.14 mg cm^{-3}) and practically insoluble in heptane (0.03 mg cm^{-3}). The melting point of FES is 105 °C and the pK_a value is (10.31 ± 0.01) at 23.4 °C [2].

According to recent studies, fesoterodine, a novel drug, proves superior efficacy in treatment of UUI over an older antimuscarinic drug tolterodine [3,4]. With tolterodine, FES shares the main active metabolite, 5-hydroxymethyl tolterodine (5-HMT, **2** in Scheme 1). After oral administration, FES is hydrolyzed in plasma by nonspecific esterases to 5-HMT, which is further metabolized principally via cytochromes P450 2D6 and P450 3A4 in the liver to its inactive metabolites – namely carboxy, carboxy-*N*-desisopropyl and *N*-desisopropyl metabolite [5]. All of the pharmacodynamic effects of FES in human body are thought to be mediated via 5-HMT [6].

Knowledge of drug stability is important not only for the pharmaceutical application but also for its analysis. It can prevent incorrect interpretation of the results. The stability of FES was investigated under acidic, basic, thermal, oxidative, and photolytic stress conditions. 10 % and 32 % of the drug was degraded after 6 h in 1 M HCl and 2 M HCl, respectively, 100 % after 36 h in 2 M HCl. FES was found to be highly susceptible to alkaline hydrolysis (Scheme 1) as its complete degradation occurred already after 15 min in 0.01 M NaOH (95 % after 10 min). FES was quite stable under oxidative conditions (in 2% H_2O_2).

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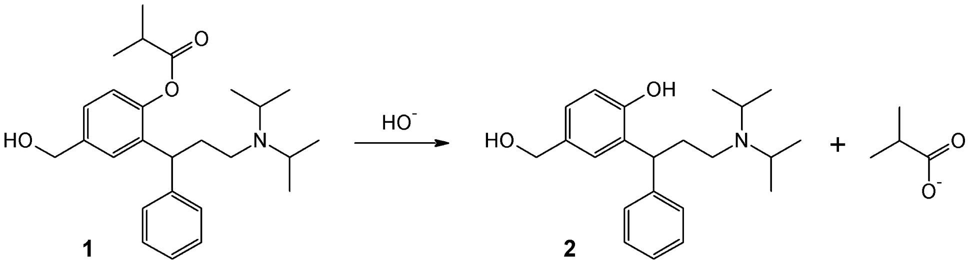

Scheme 1. Hydrolysis of fesoterodine (**1**) to 5-hydroxymethyl tolterodine (**2**).

Under thermal conditions, 17 % of FES was degraded after 36 h at 60 °C. UV-A light (365 nm) had no significant photodegradation effect on FES. On the other hand, its exposure to UV-C light (254 nm) for 6 h resulted in full degradation (for 45 min 60% degradation). The main degradation product was 5-HMT (*m/z* 342), minor products with *m/z* 356, 175, 284, 365 and 393 were also formed and identified using LC/ESI-MS [7]. Its photodegradation products appeared at *m/z* 265, 284, 293, 311, 342, 365 and 370 [8].

A limited number of publications have been focused on the determination of FES. Sangoi et al. developed methods for its determination in pharmaceutical formulations using liquid chromatography-tandem mass spectrometry with positive electrospray ionization (LC-ESI-MS/MS) [9], second-order derivative UV spectrophotometric method [10] and capillary zone electrophoresis [11]. Parekh at al. carried out the first simultaneous determination of FES and 5-HMT in human plasma samples using LC-ESI-MS/MS [12].

Combination of electrochemical methods with LC/MS identification of reaction products is increasingly used for the study of electrochemical oxidation pathways of various drugs [13–16]. LC/ESI-MS has been recently used for elucidation of electrochemical oxidation of the structurally related drug tolterodine [17]. To the best of our knowledge, no electroanalytical study of FES has been published yet. In this work, electro-oxidation of FES was studied using voltammetric techniques and coulometry. Controlled potential electrolysis was used for the preparation of FES oxidation products (OP) and ultra performance liquid chromatography with electrospray ionization mass spectrometry (UPLC/ESI-MS) for their identification.

2. Experimental

2.1. Reagents

(*R*)-fesoterodine fumarate (99%) was obtained from IS Chemical Technology, China. 5-hydroxymethyl tolterodine was synthesized from (*R*)-fesoterodine fumarate [17]. Methanol (p.a., Lach-Ner Czech Republic), acetonitrile (HPLC gradient grade, Sigma–Aldrich, Czech Republic), ammonium acetate (p.a., >98.0%, Lach-Ner Czech Republic) and ultrapure water (Merck Millipore, Darmstadt, Germany) were used. Britton-Robinson (BR) buffers were prepared from phosphoric acid, acetic acid and boric acid (0.04 mol dm^{-3} each, analytical grade, Lachema, Czech Republic), pH values were adjusted with 0.2 M NaOH (analytical grade, Lach-Ner Czech Republic). Ammonium formate buffer solutions were prepared from 0.1 mol dm^{-3} formic acid (p.a., for HPLC, 50% in water, Fluka) and ammonia (p.a, 25% in water, Lach-Ner Czech Republic). Aqueous calibration standards Duracal, pH 4, 7 and 10 (Hamilton, Bonaduz, Switzerland) were used for calibration of a pH-meter inoLab720 pH with a combined glass electrode SenTix41 (all WTW, Weilheim, Germany).

2.2. Voltammetric measurements

Voltammetric measurements were performed using Autolab PGSTAT128N with 663 VA Stand and NOVA 1.10 software (Metrohm Autolab, the Netherlands). A three-electrode system consisted of a glassy carbon working electrode (GCE, Bioanalytical Systems, USA, disk diameter 3.0 mm, surface area 0.077 cm^2) or rotating GCE (Metrohm, disc diameter 2.0 mm, surface area 0.033 cm^2), a platinum wire auxiliary electrode and a saturated calomel reference electrode (SCE). The surface area of the working electrodes was estimated by voltammetry of 5 mmol dm^{-3} potassium ferrocyanide in 0.1 mol dm^{-3} potassium chloride (diffusion coefficient $0.656 \times 10^{-5}\,cm^2\,s^{-1}$ [18]). The working electrodes were polished with 0.05 μm alumina slurry on wet microcloth (Buehler, USA) and sonicated in distilled water for 10 s before each measurement. Linear sweep (LSV) and cyclic voltammograms (CV) were recorded at a scan rate of 100 mV s^{-1} or at arbitrary scan rates ranging from 5 to 500 mV s^{-1} where appropriate. Hydrodynamic measurements were carried out with angular velocity ranged from 52 rad s^{-1} to 314 rad s^{-1} and scan rate 5 mV s^{-1}. All experiments were performed in supporting electrolytes containing BR buffer solution of desired pH and methanol (1:1, v/v). To obtain convolution voltammograms LSV data were processed using eL-Chem Viewer software [19].

2.3. Controlled potential electrolysis

An apparatus for controlled potential electrolysis consisted of an OH-404 potentiostat (Radelkis, Budapest, Hungary) with a three-electrode system: platinum gauze working electrode (a cylinder 8 mm high and 8 mm diameter, surface area 11 cm^2), platinum auxiliary electrode placed in a separate cathode compartment and reference SCE. The electrolysis was performed at various values of constant potential in supporting electrolyte containing aqueous BR buffer solutions of pH 4 or 7 and methanol (1:1, v/v) under nitrogen atmosphere. The potential values 500, 1000 and 1150 mV were chosen for pH 4 and 200, 600 and 1000 mV for pH 7. All samples were electrolyzed in stirred solutions containing 0.5 mmol dm^{-3} fesoterodine fumarate (0.26 mg cm^{-3}) in a total volume of 1.2 cm^3 until the current decreased to its residual value.

Controlled potential coulometry was performed on Autolab PGSTAT128N (Metrohm Autolab) with a three-electrode system comprising of spectral graphite rod as a working electrode (surface area 5.42 cm^2), reference SCE and Pt auxiliary electrode placed in a cathode compartment separated from the anode part by a vycor frit. Supporting electrolyte containing BR buffer solutions of pH 7 and methanol (1:1, v/v) was electrolyzed at potential 1000 mV until the current reached its residual value (typically 3 μA). Then 0.05 mg of fesoterodine fumarate was added ($c = 0.1$ mmol dm^{-3}) and the solution was electrolyzed at 900 mV for about 2 h to reach the residual current value.