Journal of Photochemistry and Photobiology A: Chemistry 256 (2013) 16–22

Contents lists available at SciVerse ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

Photochemistry of a novel antimuscarinic drug fesoterodine and identification of its photodegradation products by LC–ESI–MS studies

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ARTICLE INFO

Article history:
Received 9 August 2012
Received in revised form 19 January 2013
Accepted 9 February 2013
Available online 19 February 2013

Keywords:
Fesoterodine
Photochemistry
Isolation and identification
Degradation products
LC–ESI–MS studies

ABSTRACT

Fesoterodine (FESO) is a novel muscarinic receptor antagonist for the treatment of overactive bladder syndrome. The aim of this work was to study the photodegradation of FESO, to determine its kinetics and to identify the photodegradation products. The photochemistry of FESO was investigated in sample solutions exposed to a UV-A (320–400 nm) and UV-C irradiation (100–280 nm) at room temperature. The photodegradation process was monitored by means of liquid chromatography method equipped with monolithic column and photodiode array detector. This drug is more photolabile under UV-C light. In methanol–water solution (1:1, v/v), approximately 62.5% of FESO decomposes after 60 min of UV-C irradiation, whereas under 6 h of UV-A light only 4.9% decomposes. FESO was shown to be photolabile and its photodegradation reaction followed the zero-order kinetics with the rate constant $k = 0.5503\ min^{-1}$, and $t_{1/2}$ and $t_{90\%}$ obtained were 46.92 min and 9.38 min, respectively. The main degradation products were isolated by semi-preparative liquid chromatography and identified by liquid chromatography coupled to an electrospray ionization mass spectrometry. The powdered and intact tablets were also exposed to UV-C irradiation. Based on the obtained results, a complete drug photodegradation pathway was proposed.

1. Introduction

Fesoterodine (FESO), 2-(3-(diisopropylamino)-1-phenylpropyl) -4-(hydroxyl-methyl)phenyl isobutyrate, is an oral, nonselective antimuscarinic that is rapidly and extensively converted by ubiquitous nonspecific esterases to its active metabolite, 5-hydroxymethyltolterodine (5-HMT), indicated for overactive bladder (OAB) treatment [1,2]. OAB is defined by the International Continence Society as a syndrome associated with symptoms of urgency with or without urgency urinary incontinence, which is usually accompanied by frequency and nocturia [3].

The interest in the photostability studies has been increasing steadily because is an integral part of the drug development process and are widely recognized as one of the most important procedures in registration of pharmaceutical products [4]. Knowledge of the photochemical and photophysical properties of the compound is necessary for appropriate handling, packaging and labeling the drug substance and drug product [5]. Most pharmaceuticals contain chromophores which absorb energy in the UV region through the excitation of electrons within the molecular structure to a higher energy state [6]. Radiation has two main effects on drugs. The first is the influence of light on the stability of the drug substances and drug formulations [7]. The second aspect of drug-light interactions is that of the biological effects caused by the reaction of drugs, photoproducts or metabolites of drugs with light and biomolecules, resulting in drug induced photosensitivity [8,9]. Nowadays, some studies have been published about photochemical of the pharmaceuticals, identification of its degradation products and proposition of its degradation pathways [10–12].

Preliminary stability investigations realized by our research group revealed that FESO undergo degradation upon exposure to light, and its photolability was established by forced degradation testing. The stability-indicating LC method was developed and validated for determination of FESO in commercial tablet dosage form and forced degradation studies (hydrolysis, oxidation and photolysis) have been reported; however, the photodegradation kinetics of FESO in pharmaceutical formulations and the identification of all photoproducts were not described [13]. Moreover, the drug was also determined by validated liquid chromatography–tandem mass spectrometry and capillary electrophoresis methods, but the degradation products were not fully identified [14,15].

The identification of the chemical structures of the compounds is not possible by LC alone. Therefore, the use of LC coupled to electrospray ionization mass spectrometry (LC–ESI–MS) profiling method which permits the rapid cataloging and identification of potential degradants is an attractive alternative to rapidly characterize degradation products and impurities [13,16]. Although the traditional methods involving process scale-up, isolation, and

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http://dx.doi.org/10.1016/j.jphotochem.2013.02.003

purification of components such as degradants are expensive and time-consuming, these methods, e.g., semi-preparative LC, are essential for complete product isolation and identification.

The purpose of this study was to investigate the photochemical transformation processes of FESO under UV-A and UV-C irradiation in neutral conditions and to estimate the rate of the photodegradation process by kinetic determinations. Besides, we also report the structure identification of the main photoproducts by selective LC–ESI–MS method, and the drug photodegradation pathway was postulate.

2. Experimental

2.1. Chemicals

The fesoterodine fumarate reference substance was purchased from Toronto Research Chemicals Inc. (Toronto, ON, Canada). Toviaz® (Pfizer Inc., Zwickau, Germany) tablets for oral administration, containing 8 mg of fesoterodine fumarate per tablet (6.2 mg fesoterodine base, excipients: glyceryl behenate, hypromellose, indigo carmine aluminum lake, lactose monohydrate, soya lecithin, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and xylitol), were obtained from commercial sources. Phosphoric acid 85% and LC-grade acetonitrile and methanol were obtained from Tedia Company Inc. (Fairfield, OH, USA). Ammonium acetate was purchased from Spectrum Chemical Corp. (Gardena, CA, USA). Ultrapure water (Milli Q Gradient System, Millipore Corp., Bedford, MA, USA) was used for all the analyses.

2.2. LC method

The LC apparatus was a Shimadzu LC system (Shimadzu Corp., Kyoto, Japan) equipped with an SCL-10A$_{VP}$ system controller, an LC-10AD$_{VP}$ binary pump, a SIL-10AD$_{VP}$ autosampler, a CTO-10AC$_{VP}$ column oven, and an SPD-M10A$_{VP}$ photodiode array (PDA) detector. The peak areas were integrated automatically by computer using the Class VP software (v 6.12). The experiments were performed on a reversed-phase Phenomenex Inc. (Torrance, CA, USA) Onyx C18 monolithic column (100 mm × 4.6 mm i.d.). The Shimadzu LC system was operated isocratically at controlled temperature (45 °C) using a mobile phase of acetonitrile–methanol–0.03 mol L^{-1} ammonium acetate (pH 3.8) (30:15:55, v/v/v), run at a flow rate of 2.4 mL min^{-1} with detection at 208 nm. The injection volume was 10 μL of a solution containing 50 μg mL^{-1} for the reference substance and sample solutions [13]. The quantitation was performed using the absolute area of the peak. Standard curve was obtained by plotting the peak area of FESO versus the theoretical concentration over a range of 5–150 μg mL^{-1}. The data were subjected to the least squares regression analysis. Inspection of the plotted calibration curve described by equation: $y = 11711.55x + 17019.76$ and determination coefficient ($r^2 = 0.9995$) confirmed that the calibration curve was linear over the concentration range [13].

2.3. Preparation of reference and sample solutions

The stock solution of FESO was prepared by weighing accurately, 25 mg of fesoterodine fumarate (purity 98%) and diluted to volume with methanol, obtaining a concentration of 1 mg mL^{-1} of fesoterodine base. The stock solution was stored at 2–8 °C, protected from light and daily diluted to an appropriate concentration in mobile-phase. To prepare the sample solutions, tablets containing 8 mg of fesoterodine fumarate were accurately weighed and crushed to a fine powder. Appropriated amounts were transferred into individual 50 mL volumetric flasks. After adding 30 mL of methanol, the flasks were vortex mixed for 3 min. Then the samples were made up to volume with methanol, transferred to appropriate tubes and centrifuged at 3000 × *g* for 10 min. Aliquot of the clear supernatant liquid at final concentration of 200 μg mL^{-1} of the active pharmaceutical ingredient was filtered through a 0.45 μm membrane filter (Millipore Corp.).

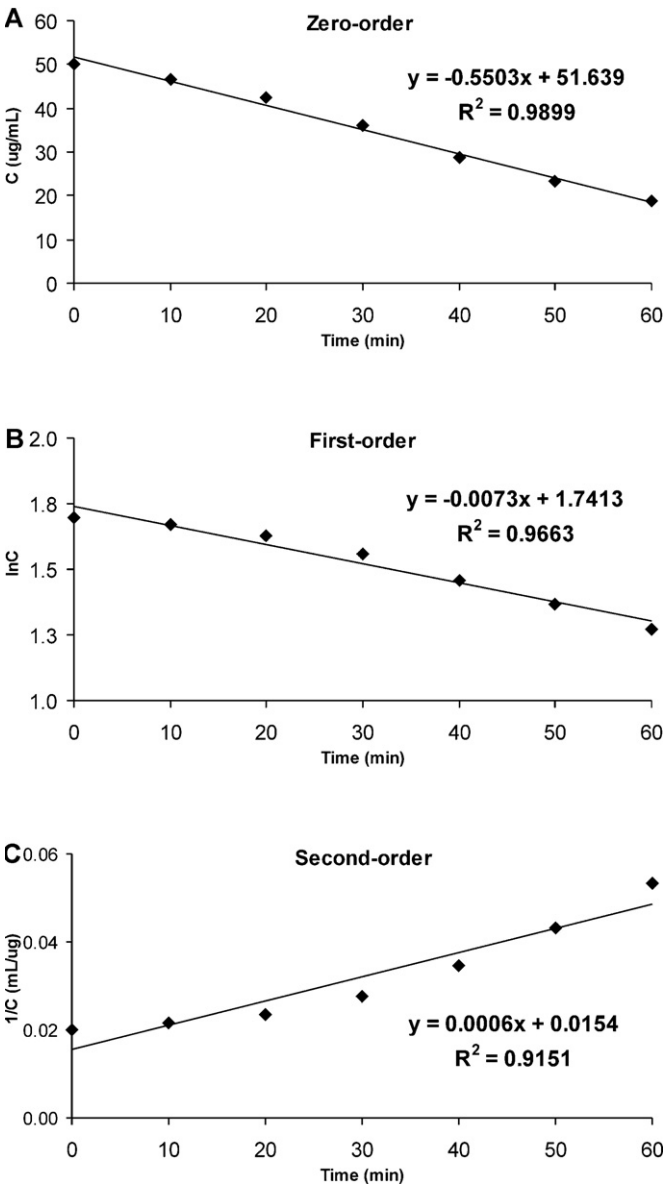

Fig. 1. Plots of concentration (a; zero-order reaction), log of concentration (b; first-order reaction) and reciprocal of concentration (c; second-order reaction) of remaining fesoterodine versus time.

2.4. Photodegradation studies

The effect of light was studied exposing the pharmaceutical formulation solutions in 1 cm disposable cuvettes (Brand GmbH, Germany). The light sources were an UV-A (center of emission 360 nm, bandwidth 40 nm) and an UV-C (emission spectra centered at 254 nm) 30 W lamps (Philips, Amsterdam, Holland) fixed to the chambers in a horizontal position, in order to compare the degradation under the two different radiation sources. The chambers