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Montelukast photodegradation: Elucidation of Φ-order kinetics, determination of quantum yields and application to actinometry

Mounir Maafi *, Wassila Maafi

Leicester School of Pharmacy, De Montfort University, The Gateway, Leicester LE1 9BH, UK

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ABSTRACT

A recently developed Φ-order semi-emperical integrated rate-law for photoreversible AB(2Φ) reactions has been successfully applied to investigate Montelukast sodium (Monte) photodegradation kinetics in ethanol. The model equations also served to propose a new stepwise kinetic elucidation method valid for any AB(2Φ) system and its application to the determination of Monte's forward ($\Phi_{A\rightarrow B}^{\lambda_{irr}}$) and reverse ($\Phi_{B\rightarrow A}^{\lambda_{irr}}$) quantum yields at various irradiation wavelengths. It has been found that $\Phi_{A\rightarrow B}^{\lambda_{irr}}$ undergoes a 15-fold increase with wavelength between 220 and 360 nm, with the spectral section 250–360 nm representing Monte effective photodegradation causative range. The reverse quantum yield values were generally between 12 and 54% lower than those recorded for $\Phi_{A\rightarrow B}^{\lambda_{irr}}\Phi_{A\rightarrow B}^{\lambda_{irr}}$, with the *trans*-isomer (Monte) converting almost completely to its *cis*-counterpart at high irradiation wavelengths. Furthermore, the potential use of Monte as an actinometer has been investigated, and an actinometric method was proposed. This study demonstrated the usefulness of Monte for monochromatic light actinometry for the dynamic range 258–380 nm.

1. Introduction

Montelukast sodium (Monte), sodium 1-(1(*R*)-(3-(2-(7-chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl)3-(1-hydroxy-1-methylethyl) phenyl)propyl)thio)methyl)cycloproprane) acetate, is an oral drug used in the treatment of asthma and to relieve the symptoms of seasonal allergies (Schoors et al., 1995). Pharmacologically, it is classed as a leukotriene receptor antagonist as it acts by binding to the cystenyl leukotriene receptor $CysLT_1$ in the lungs and bronchial tubes (Schoors et al., 1995). As such it blocks the action of leukotriene D4 on these receptors thereby reducing bronchoconstriction and inflammation (Schoors et al., 1995).

Monte has been reported to be highly photolabile, especially in solution (Smith et al., 2004). Exposure of this drug even to very low levels of UV radiation, results in its degradation. It obeys a *trans–cis* photoisomerisation mechanism whereby its (*E*)-ethenyl moiety rotates to the (*Z*) geometry (Smith et al., 2004). The overall reaction is labelled here AB(2Φ) as it involves two reversing photochemical reactions between the drug and its photoisomer (Maafi and Maafi, 2014) (Scheme 1).

Thus, special handling precautions were proposed to protect the drug from exposure to light in order to avoid photodegradation, such as by using amber glass vials (Zhao et al., 1997), wrapping with black paper (Radhakrishna et al., 2003) or aluminium foil paper (Thibert et al., 1996) and storing in the dark, or analysing under amber/red light conditions (Arison et al., 1999).

The kinetic studies that have been conducted on Monte photodegradation have employed classical thermal kinetic models and found it to obey either the zeroth or first-order kinetics (Roman et al., 2011; Alsarra, 2004; Al Omari et al., 1999). However, to the best of our knowledge, no attempts have so far been devoted to determining the quantum yields of Monte photodegradation. This is the case for a number of AB(2Φ) photoreversible drugs including some antipsychotics, tricyclic antidepressants, cephalosporin antibiotics, and corticosteroids (Ming, 2012).

In fact, the lack of quantum yields' determination is common for a ubiquitous number of AB(2Φ) photoreversible systems used in the pharmaceutical field despite the fact that such systems have found a wide range of applications in numerous research areas ranging from photodynamic materials and photo-nanomedicine (Fomina et al., 2012; Feliciano et al., 2010) to photoresponsive hydrogels and polymeric capsules (Wohl and Engbersen, 2012; Tomatsu et al., 2011). Research in targeted drug delivery, for instance, has recently turned its attention towards triggered drug delivery through the use of stimuli-responsive delivery devices

* Corresponding author. Tel.: +44 116 257 7704; fax: +44 116 257 7287.
E-mail address: mmaafi@dmu.ac.uk (M. Maafi).

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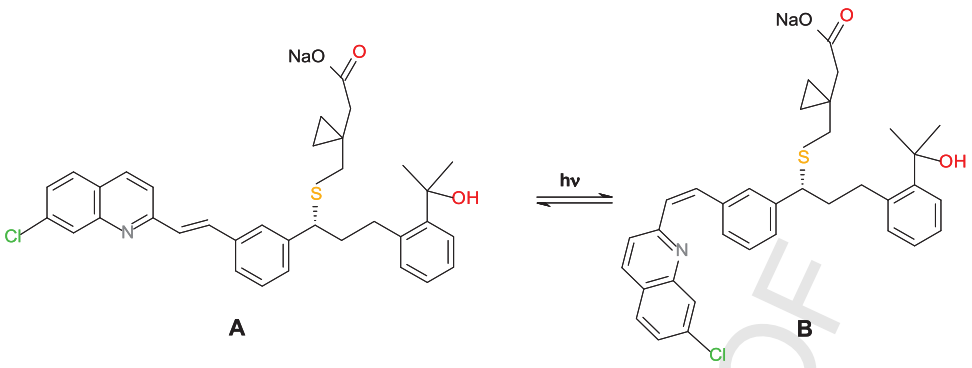

Scheme 1. *Trans* to *cis* photoisomerism of Monte upon exposure to UV-irradiation.

(Fomina et al., 2012; Wohl and Engebersen, 2012; Tomatsu et al., 2011; Feliciano et al., 2010). Light-stimulus represents a particularly attractive means which is currently being actively explored as it can be remotely applied and controlled in space and time thereby affording more precise control over drug release site and dosage (Fomina et al., 2012; Tomatsu et al., 2011). In general, a number of advantages are procured by these delivery devices, including a reduction of undesirable side effects, higher drug levels reaching the target sites, enhanced *in vivo* action, reduced drug degradation and a precise control over dosage regimen (Fomina et al., 2012; Tomatsu et al., 2011). It therefore becomes imperative for the design and/or application of such photoreversible systems to have an accurate knowledge of the photoreactions' attributes and their photokinetic behaviour.

In a recent study (Maafi and Maafi, 2014) it has been shown that AB(2Φ) systems obeyed Φ-order kinetics as does the unimolecular AB(1Φ) nifedipine photodegradation (Maafi and Maafi, 2013). These new kinetic treatments overcome the drawbacks of the classical procedures by not only providing a specific mathematical framework to deal with photodegradation reactions (replacing the integrated rate-laws developed for thermal reactions (Piechocki and Thoma, 2010)) but also by allowing better and more reliable insight into the reactions' kinetic behaviour and physico-chemical attributes.

The aim of this study was to investigate Monte kinetics and to propose a new method for the elucidation of the Φ-order kinetics using Monte as an example for AB(2Φ) systems. The strategy is further employed in determining wavelength-dependent values for the reaction's forward and reverse quantum yields. Finally, the potential of the mathematical framework is put to advantage towards demonstrating the usefulness of Monte in actinometry.

2. Materials and methods

2.1. Materials

Montelukast sodium, 2-[1-(*R*)-[3-[2(*E*)-(7-chloroquinolin-2-yl) vinyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl]propyl-sulfanylmethyl]cyclopropyl] acetic acid sodium salt (Monte), and spectrophotometric grade ethanol were purchased from Sigma–Aldrich.

2.2. Monochromatic continuous irradiation

For irradiation experiments, a Ushio 1000 W xenon arc-lamp light source housed in a housing shell model A6000 and powered by a power supply model LPS-1200 was used. This setting was cooled by tap water circulation through a pipe system. The lamp housing was connected to a monochromator model 101 that allows the selection of specific irradiation wavelengths as it consists of a special f/2.5 monochromator with a 1200 groove/300 nm blaze grating. The excitation beam was guided through an optical fibre to impinge from the top of the sample cuvette, i.e. the excitation and the analysis light beams were perpendicular to each other. The set up was manufactured by Photon Technology International Corporation.

2.3. The monitoring system

A diode array spectrophotometer (Agilent 8453) was used to measure the various absorption spectra and kinetic profiles for the irradiation and calibration experiments. This spectrophotometer was equipped with a 1-cm cuvette sample holder and a Peltier system model Agilent 8453 for temperature control. As such, the sample was kept at 22 °C, stirred continuously during the experiment, and almost completely shielded from ambient light. The spectrophotometer was monitored by an Agilent 8453 Chemstation kinetics-software.

A radiant power/energy meter model 70260 was used to measure the radiant power of the incident excitation beams.

2.4. Kinetic data treatment

In order to carry out non-linear fittings and to determine best-fit curves, a Levenberg–Marquardt iterative program within the Origin 6.0 software was used.

2.5. HPLC measurements

The HPLC system consisted of a reversed-phase Jupiter 5μ C-18 300A Phenomenex (250 × 4.60 mm) column equipped with PerkinElmer Series 200 pump, UV/vis detector, vacuum degasser and a PerkinElmer type Chromatography Interface 600 series Link linked to a computer system.

The mobile phase consisted of 15% water adjusted to pH 3.18 with glacial acetic acid and 85% methanol. A flow rate of 1 ml/min and an injection loop of 20 ml were used. The detector wavelength was set at 254 nm.

2.6. Monte solutions

A 7.4×10^{-4} M stock solution of Monte in ethanol was prepared by weighing the solid. The flask was protected from light by aluminium foil wrapping and was kept in the fridge. The stock solution was diluted to prepare fresh analytical solutions (ca. $> 2 \times 10^{-6}$ M) for analysis of irradiation experiments performed at various wavelengths.

For actinometric studies, Monte solutions of the same concentrations (ca. $> 2 \times 10^{-6}$ M) were exposed to specific wavelengths irradiations (258, 328, 345 and 360 nm) using a series of different

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