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Actinometric and Φ-order photodegradation properties of anti-cancer Sunitinib

Mounir Maafi *, Lok Yan Lee

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

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ABSTRACT

The photodegradation reaction of Sunitinib (SUT), occurring via *Z*–*E* photoisomerisation, has been evaluated in this study using the recently developed Φ-order kinetics. In ethanol, the forward ($Z \rightarrow E$) photoreaction of SUT was invariant with irradiation (its quantum yield, $\Phi^{\lambda irr}_{Z \rightarrow E} \approx 0.019$) in contrast to the $E \rightarrow Z$ isomerisation whose $\Phi^{\lambda irr}_{E \rightarrow Z}$ undergoes a 30-fold, sigmoid-shaped, increase with increasing irradiation wavelength. This situation limited usefully the extent of *Z*-SUT photodegradation at the photostationary state to a maximum of *c.a.* 30% of the initial concentration. Nevertheless, these results support a strong recommendation for a complete protection of SUT from light at all stages. Furthermore, a SUT-actinometer was developed and was proven to be useful for the 320–480 nm spectral range. The latter wavelength interval defined as well SUT photodegradation causative range. The formalism of Φ-order kinetics proves to be a useful investigative tool for drugs' photodegradation studies.

1. Introduction

Z-Sunitinib malate [N-[2-(diethylaminino)ethyl]-5-[(*Z*)-(5-fluoro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide L-malate], (*Z*-SUT), is an orally active multiple tyrosine kinase and angiogenesis inhibitor [1,2]. It is part of a new emerging cancer targeted therapies which are characterised by a unique mechanism of action and a high specificity for key biological pathways involved in the cancer process [3]. It is prescribed for metastatic renal cell carcinoma and for the treatment of gastrointestinal stromal tumours [4,5]. Some results suggested that *Z*-SUT might be active against breast cancer and its efficacy and toxicity do not appear to be affected by patient age, including children and elderly [4]. Its presence in patients skin and sweat was evidenced [6], and its effects in skin photoirritation and phototoxicity have also been reported [7].

A few literature reports indicated its sensitivity to light [8,9]. The mostly descriptive data available thus far, reveals that *Z*-SUT photodegradation consists of a photoisomerisation around the double bond linking the 2-oxyindole and the pyrrole rings leading to *E*-SUT as a single identified photoproduct in organic media, Scheme 1 [8]. The anti-cancer drug was however found to be thermally stable in methanol in the dark [3,8,9]. Despite *Z*-SUT recognised photodegradation, a number of studies did not report on practical handling precautions that should have been taken to protect the solutions from light during preparation and analysis [3,6,10–12].

To the best of our knowledge, there are no published kinetic studies on the photodegradation of *Z*-SUT [13–15]. Zhao et al. [8] studied the effects of various solvents on the degradation of *Z*-SUT, and Etienne-Grimaldi [9], reported that *Z*-SUT phototransformation was completed within 5 min of exposure to ambient light in methanolic solutions, but no treatment of the kinetic data was proposed in both these studies. Also, the quantum yields of the photoreaction steps have not yet been reported for this drug.

Recently, a new method of studying photoreversible reactions of drugs has been proposed [16,17]. This type of systems, labelled here *AB*(2Φ), involves two photoactive species (A and B) each transforming into the other through a single photoprocess characterised by a specific quantum yield (Φ), Scheme 1. Under non-isosbestic irradiation, the overall photoreaction obeys Φ-order kinetics. A description of the mathematical framework of such a reaction is provided in later sections.

The photoreversible reaction is a process responsible for many drugs' degradation [13] and a basis for a number of pharmaceutical and technological systems [18–20]. However, little is known on the reactivity attributes of such processes, especially on their photochemical yields.

The Φ-order kinetic approach [16,17,21], presents a double advantage in proposing a simple mathematical set of equations that simplifies the treatments of the data and provides tools to facilitate both the determination of reaction quantum yields, the quantification of many reactivity aspects, in addition to allowing

* 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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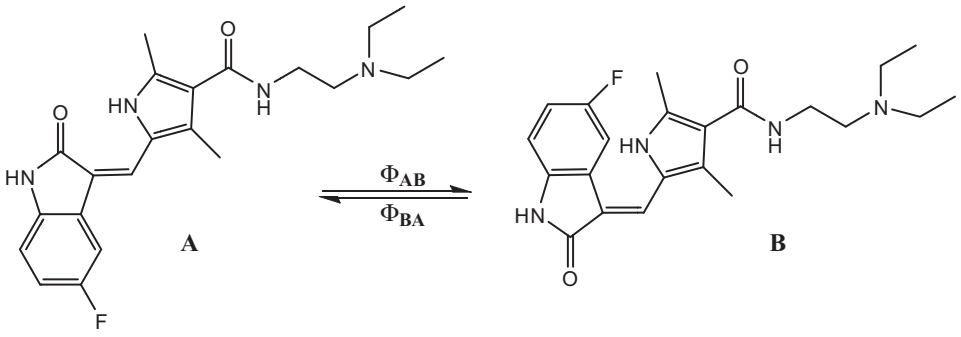

Scheme 1. Reversible photoisomerisation of *Z*-SUT (A) and *E*-SUT (B).

the prospection and development of new drug-actinometers. In this respect, *Φ*-order kinetics stands as a better alternative to the classical treatments using thermal reaction orders.

In this study, the photokinetics of SUT is investigated with the aims of characterising its reaction photochemical quantum yields relative to the irradiation wavelength and its potential for actinometry.

2. Materials and methods

2.1. Materials

Sunitinib maleate, (*Z*-SUT), and spectrophotometric grade ethanol were purchased from Sigma–Aldrich (Dorset, UK).

2.2. Monochromatic continuous irradiation

An 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 for the irradiation experiments. The 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 since it consists of a special *f*/2.5 monochromator with a 1200 groove/mm at 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 (London, Ontario, Canada).

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 (Agilent Technologies, Lakeside, Cheshire, UK).

An Oriel Radiant Power/Energy meter model 70260 was used to measure the radiant power of the incident excitation beams (Darmstadt, Germany).

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 (Bucks, UK).

2.5. Chromatographic HPLC measurements

Sunitinib and its photoproduct were separated on a Gemini C_{18} reverse phase column 5 μm, 2.1 mm × 50 mm (Phenomenex, Cheshire, UK) fitted to a PerkinElmer Series 200 Pump and UV/Vis Detector, and a 600 Series Link interface. The set up was remotely controlled by TotalChrom software (PerkinElmer, USA).

Separation of *Z*- and *E*-isomers was achieved at a flow rate of 1 ml/min with a mobile phase of 67% water (adjusted to pH 3 with glacial acetic acid) and 33% acetonitrile. An injection loop of 20 μl was used and the detector wavelength was set at 350 nm. The overall run time of the assay was 6 min, the retention times of *Z*- and *E*-SUT were 2.17 and 1.84 min, respectively. The linearity range (of the calibration graph, peak area = $5 \times 10^9 \times C + 15376$) ranged between 5×10^{-6} and 2.15×10^{-4} M.

2.6. SUT solutions

A stock solution of *Z*-SUT (*c.a.* 3×10^{-4} M) 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 served to prepare diluted fresh analytical solutions (ca. 9×10^{-6} M) for analysis of irradiation experiments at various wavelengths and ca. 6×10^{-5} M for HPLC analyses.

For actinometric studies, fresh *Z*-SUT solutions of the same concentrations (ca. 9×10^{-6} M) were exposed to monochromatic beams of ten different irradiation wavelengths (480, 460, 440, 420, 400, 380, 360, 345, 340, and 320 nm) using a series of different intensities for each wavelength. The kinetic traces were observed at the irradiation wavelength and subsequently fitted with the *Φ*-order equations.

Experiments were conducted at least in triplicates.

3. Results and discussion

3.1. The mathematical background

3.1.1. *Φ*-order kinetics for non-isosbestic irradiation

Usually, the investigations of drugs' photodegradation were performed using 0th-, 1st-, and 2nd-order kinetics [14]. The inadequacy of such photokinetic data treatments in quantifying photodegradation reactions was previously discussed [16,21,22]. Instead, the newly proposed approach that was based on *Φ*-order kinetics, has been proven to faithfully describe the time evolution of the species concentrations or any related quantity such as the medium absorbance [16,17]. The equations of the *Φ*-order kinetic model apply when the reactive medium is subjected to non-isosbestic and monochromatic irradiation at constant temperature. The *Φ*-order approach brings three main advantages in that it allows a unique characterisation of the kinetic data, provides an