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Φ-order kinetics of photoreversible-drug reactions

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ABSTRACT

Background: Drug photodegradation data are usually treated by zero-, first- or second-order kinetic equations. Such treatments would lack reliability since the aforementioned equations have been originally developed for pure thermal reactions. In this respect, it has recently been shown that unimolecular photodegradations obey Φ-order kinetics (Maafi and Maafi, 2013). However, no similar information is, thus far, available for other reactions including photoreversible AB(2Φ) systems. This paper aims at filling this gap for AB(2Φ) kinetics.

Methods: Runge–Kutta numerical integration data for photoreversible reactions traces were combined with a template equation in order to derive an optimized (semi-empirical) integrated rate-law equation for AB(2Φ) reactions. The proposed model equation was test by examining its ability to fit synthetic Runge–Kutta data that have not been used for the optimization. The obtained fitting parameters are then compared to their theoretical counterparts.

Results: Both an integrated rate-law and an analytical equation for the overall reaction rate-constant were set for photoreversible drug reactions. The values of overall reaction rate-constant and initial velocity obtained theoretically correlated well with those obtained by fitting the kinetic traces of reactions with the derived integrated rate-law. AB(2Φ) photodegradation reactions have been proven to obey Φ-order kinetics. The equation proposed describes faithfully their kinetic behaviour in solution. The formula of the overall rate-constant involves both reagents' characteristics and experimental parameters. These equations facilitated the rationalisation and prediction of the individual effects of each reaction parameter. Specially, our results proved a self-photostabilisation with increasing initial drug-concentration and demonstrated the potential for actinometry of drugs obeying AB(2Φ) mechanism.

1. Introduction

The ICH recommendations for photostality testing of drugs and formulations (ICH, 1996) do not provide clear specifications or protocols on the treatment and analysis of the kinetic data of drug photodegradations. In the literature, the photokinetic data of the initial drug, usually extracted by a separation method, were treated according to the well-known classical zero-, first- or second-order kinetic model equations (Ming, 2012; Piechocki and Thoma, 2010; Tashtoush et al., 2008; Tonnesen, 2004; Albini and Fasani, 1998). These three kinetic options were used irrespective of the photochemical overall mechanism governing the drug and its photoproducts, and despite the fact that the aforementioned equations were originally developed for pure thermal reactions. It is also noticeable that most often the application of this approach meant that only data corresponding to the early stages of the reaction (up to the half-life time) were effectively used for the kinetic treatment (Piechocki and Thoma, 2010). In addition, the determined overall rate-constants of drug photodegradation reaction could neither be compared to those obtained by other studies or lead to the determination of the photochemical quantum yield of the reaction (the overall rate-constant and the quantum yield are generally achieved by separate experiments).

Recently (Maafi and Maafi, 2013; Maafi, 2010; Maafi and Brown, 2007), it has been shown that a drug unimolecular AB(1Φ) photodegradation reaction, where the initial species (A) photo-transforms into a product (B) with an efficiency $\Phi_{A\rightarrow B}$, obeys a specific kinetic order, the so-called Φ-order, that significantly differs from the mathematical formulation of 0th-, 1st- and 2nd-order equations. The Φ-order kinetic was found to describe well the whole set of AB(1Φ) photodegradation data and readily allows the determination of the reaction photochemical quantum yield from the reaction overall rate-constant. Nonetheless, the above findings have a limited application as they are specific to unimolecular drug photodegradations of the AB(1Φ) type.

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Despite the relative mathematical similarity of the differential equations (DE) of drug photoreactions obeying more elaborate mechanisms than AB(1Φ), there are no known procedures to achieve their solutions, *i.e.* deriving the corresponding integrated rate-laws of such systems, through a closed-form integration (Maafi and Maafi, 2013; Maafi, 2010; Klan and Wirz, 2009; Mauser and Gauglitz, 1998). In this respect, it has been shown that it is not even possible to solve the DE of AB(1Φ) systems for the case where both (A and B) species absorb the incident light at a non-isosbestic wavelength (Maafi and Maafi, 2013).

In order to circumvent this tedious problem, a new approach (Maafi and Maafi, 2013) was proposed to develop semi-empirical rate-law equations for drug photodegradation DEs that cannot conventionally be solved. It combines the results generated by a numerical method, such as Runge–Kutta (RK) method, to a plausible template equation. The various parameters involved in the rate-law equation would then be optimised and their analytical expressions defined.

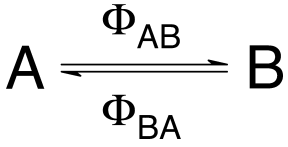
In order to explore further the usefulness of the above approach, it is applied in the present study to propose an integrated rate-law equation for drugs that obey a photoreversible AB(2Φ) photodegradation reactions, as given in Scheme 1.

A wide range of important drugs and formulations undergo photoreversible reactions. A recent review (Ming, 2012) has listed a number of examples for drugs that degrade through E/Z photo-isomerisation. Such drugs have varied therapeutic activities including but not limited to the treatment of depression (Tammilehto and Torniainen, 1989), Alzheimer disease (Azevedo Fihlo et al., 2010), neuroleptic disorders and psychosis (Stehfest et al., 2010; Maquille et al., 2010; Li Wan Po and Irwin, 1980), asthma (Al Omari et al., 2007; Radhakrishna et al., 2003) and infections (Lerner et al., 1988). In most cases, the produced photoisomer is much less or not biologically active compared to its counterpart, the initial drug isomer. Small photoisomerisable molecules have also been employed in neurobiology to target the $GABA_A$ receptor (Feliciano et al., 2010) for potential development of photo-nanomedicine and photodynamic materials. Another fast developing field is the incorporation of photoreversing systems in formulations and delivery systems such as photoresponsive hydogels for biomedical applications (Tomatsu et al., 2011), photoresponsive materials for drug delivery (Wohl and Engebersen, 2012) and light-triggered release from nanocarriers (Fomina et al., 2012).

Therefore, rationalising the kinetics of such photoreversible reactions is of importance to quantitatively evaluate the reactivity of the systems studied and shed light on their performance. This can best be achieved by the development of adequate integrated rate-laws.

2. Materials and methods

The method used here of deriving integrated rate-law equation for photodegradation drug systems whose differential equations cannot be integrated in a closed-form, has been recently developed in our team (Maafi and Maafi, 2013), and is applied here for AB(2Φ) photodegradation reactions. It is based on the principle of using synthetically calculated data (representing the temporal variation of the species' concentrations or any other measurable variable such as absorbance), as model datasets to test, optimise and validate the proposed formula of the integrated rate-law and overall rate-constant. The RK-4 calculation is fed with plausible reaction parameters to produce the kinetic traces. The reliability of RK-4 in solving differential equation makes it a powerful tool to deliver photodegradation reaction traces with high accuracy. The theoretical numerical integration used in this study has been constructed on the basis of the fourth-order Runge–Kutta (RK-4) method (results obtained from a homemade programme).



Scheme 1. Generic photodergadation drug-systems obeying an AB(2Φ) mechanism.

Around 50 traces were fitted with the proposed template formula for the integrated rate-law in order to optimise the analytical expressions of the exponential and the pre-logarithmic factors (*vide infra* Eqs. (2) and (3)). This procedure is also meant to provide good indications on the limits of applicability of the proposed integrated rate-law equation. Once the complete formula has been derived, it has been tested against *c.a.* 100 more RK-4 traces for validation and for application purposes.

The validation of the optimised integrated rate-law formula is achieved by not only recording a good fit of the RK-4 traces by the formula but also by ensuring that the values of reactions' overall rate-constants and initial velocities obtained from the fitting, differ by no more than 10% of those values calculated using the theoretical equations.

A Levenberg–Marquardt iterative programme within the Origin 6.0 software package were used to run the non-linear fitting and the determination of the best fit curves.

3. Results

3.1. The semi-empirical model for AB(2Φ) kinetics

The differential equation expressing the time variation of the concentrations of species A and B ($C_A(t)$ and $C_B(t)$, respectively, Scheme 1), considering that the solution, subjected to a monochromatic and continuous irradiation, is homogeneously and continuously stirred, the concentration of the excited-state is assumed to be negligible, the medium temperature is constant, and at the (non-isosbestic) irradiation wavelength (λ_{irr}) species A and B absorb different amounts of light (P), *i.e.*, the absorption coefficients (ε) of the species are different and have non-zero values ($\varepsilon_A^{\lambda_{irr}} \neq \varepsilon_B^{\lambda_{irr}} \neq 0$), is (Maafi, 2008; Maafi and Brown, 2008)

$$\frac{dC_A(t)}{dt} = -\frac{dC_B(t)}{dt} = \left(\Phi_{B\to A}^{\lambda_{irr}} \times \varepsilon_B^{\lambda_{irr}} \times C_B(t) - \Phi_{A\to B}^{\lambda_{irr}} \times \varepsilon_A^{\lambda_{irr}} \times C_A(t)\right) \times l_{\lambda_{irr}} \times P_{\lambda_{irr}} \times F_{\lambda_{irr}}(t) \quad (1)$$

where $\Phi^{\lambda_{irr}}$ are the forward and reverse quantum yields of the photochemical steps realised at the irradiation wavelength (λ_{irr}), $P_{\lambda_{irr}}$ is the radiant power, $l_{\lambda_{irr}}$ is the optical path length of the irradiation beam inside the sample, and $F_{\lambda_{irr}}$ the photokinetic factor.

Because $F_{\lambda_{irr}}$ is a time dependent function, Eq. (1) is not possibly integrated in a closed-form (Maafi and Brown, 2008).

To circumvent this situation, the model equation previously developed for the unimolecular photoreaction AB(1Φ), (Maafi, 2010; Maafi and Brown, 2007) which has been obtained by a closed-form integration, can be used as a template to approach the model equation for AB(2Φ) kinetics. Provided that irradiation (λ_{irr}) and observation (λ_{obs}) wavelengths are clearly set (to define the specific $\lambda_{irr}/\lambda_{obs}$ condition), an expression (Eq. (2)) can be proposed as an integrated rate-law that describes the time