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Invited feature article

Cyclodextrine-nanoencapsulation of niclosamide: Water solubility and meaningful enhancement of visible-light—Mediated sensitized photodegradation of the drug

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ABSTRACT

A kinetic and mechanistic study of the daylight-mediated photooxidation of the multifunctional drug Niclosamide (NSD) was carried out in aqueous solutions. NSD is a frequent contaminant suspended in natural waters. The aqueous dissolution of the practically insoluble NSD was driven by the presence of 2-hydrxypropyl-β-cyclodextrin (HPβCD). The already proposed formation of an inclusion complex between NSD-HPβCD was confirmed through theoretical studies. NSD-nanoencapsulation within the oligosaccharide occurs with a 1:2 stoichiometry, being the drug embedded into a cavity of two HPβCD molecules, in a so called head-to-head orientation.

The Reactive Oxygen Species singlet molecular oxygen, superoxide radical anion and hydrogen peroxide, generated through the visible-light absorber sensitizers Riboflavin and Rose Bengal, are effectively intercepted by the encapsulated biocide and contribute to its photodegradation. The overall NSD photooxidation rate, determined through oxygen consumption indicates that the process is relatively highly efficient in the microheterogeneous aqueous media as compared to NSD in MeOH solution, and to phenol (PHE) in pure water. The paradigmatic water-contaminant PHE was taken a as reference in order to evaluate the persistence of the NSD under photosensitized irradiation in aqueous medium. The photooxidation mechanism of NSD is affected by cyclodextrin complexation, due to dynamic limitations, electrostatic interactions and pH changes upon NSD dissolution in aqueous HPβCD. In this sense, the NSD-HPβCD complex can be seen as a sort of nanoreactor that enables the photodegradation of the biocide in water, under daylight conditions.

1. Introduction

Niclosamide (5-Chloro-N-(2-Chloro-nitrophenyl)-2-hydroxy-benzamide, NSD), a water-insoluble multifunctional drug, widespread employed as a biocide is frequently found as a contaminant, suspended in surface waters [1].

Considering the environmental relevance of light-induced degradative processes, a kinetic and mechanistic study of the daylight-mediated photooxidation of NSD, in methanolic solution, has been recently undertaken by ourselves [2]. The mentioned research work was important as an initial approximation towards the possible natural fate of the contaminant in solution, under daylight photoirradiation. Riboflavin (Rf, vitamin B2) was employed as photosensitizer. The vitamin constitutes an archetypal natural photosensitizer, profusely employed to model the oxidative photodegradation of numerous water contaminants [3–5]. The reactive oxygen species (ROS) singlet molecular oxygen ($O_2(^1\Delta_g)$) and superoxide radical anion ($O_2^{\bullet}-$) were responsible for the NSD photodegradation. Nevertheless, the use of a non-natural solvent, such as MeOH, in a study on contaminated waters, constitutes an approach that, from the environmental point of view, deserves to be improved.

In the present work we attempt to overcome the limited NSD water-solubility by means of the employment of cyclodextrins (CD). It is known that these oligosaccharides form macrocycles

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joined by glycosidic linkages whose hydrophobic inner space and hydrophilic external surface offers the possibility to form inclusion complexes with different liposoluble substrates, in a kind of "host-guest" association [6].

It is also well known that the inclusion of a given hydrophobic substrate into a cyclodextrin cavity frequently leads to physicochemical changes on the guest substrate. These changes are not only limited to effects on water solubility. They can also affect the chemical behavior of the encapsulated molecule towards different physicochemical stimulations, including photoinduced reactivity [6–9].

All these considerations sparked our interest in the re-evaluation of the Rf-photosensitized degradation of NSD, performed in the presence of aqueous 2-hydrxypropyl-β-cyclodextrin (HPβCD). This oligosaccharide was chosen because it has been reported that, although the vitamin and HPβCD forms a hydrogen-bonded noninclusion complex, with a stability constant of 5.75 M^{-1}, the association does not produce noticeable modifications in the physicochemical properties of Rf. [10].

In the present study, the formation of inclusion complexes between NSD and HPβCD, already experimentally examined by Devarakonda et al. [11], was systematically characterized through theoretical studies. Following, the effect of such an association on the kinetic and mechanistic aspects of Rf-sensitized NSD photodegradation was evaluated, under visible light irradiation. Results clearly show significant changes in the photodegradation rate of the contaminant as compared to what we found in methanolic homogeneous medium [2].

Summarizing, the present work addresses two important topics: (a) The physicochemical understanding of CD-inclusion complexes with environmentally relevant molecules and (b) The influence on water-solubility on the efficiency of NSD daylight-mediated photodegradation.

In addition to the environmental importance of the research work, the combined results also lead to the possibility of optimizing the efficiency of low-energy demanding reactors for remediation of stored residual waters containing water-insoluble suspended contaminants.

2. Experimental

2.1. Materials

Riboflavin, the proteins catalase (CAT, from bovine liver) and superoxide dismutase (SOD; from bovine erythrocytes) were purchased from Sigma Chem. Co. Furfuryl acetate (FFAc) and phenol were purchased from Sigma Chem. Co., Rose Bengal (RB), deuterium oxide (D_2O; 99.9 atom% D) were from Aldrich. (2-Hydroxypropyl)-β-cyclodextrin, average M_w ~1541.56 was from Sigma-Aldrich.

2.2. Apparatus and methods

In all the cases, pHs/pDs were controlled with a MP220 Mettler-Toledo pH-meter.

Ground state absorption spectra were registered in a Hewlett Packard 8453 diode array spectrophotometer.

2.2.1. Continuous photolysis

Continuous aerobic photolysis of aqueous solutions containing the substrates plus sensitizers were carried by means of blue leds (for Rf-sensitization) and green leds (for RB-sensitization) with irradiation wavelengths of 465 ± 25 nm and 510 ± 40 nm respectively. Oxygen uptake experiments were performed employing a home-made photolyser provided with a quartz-halogen lamp (150-W) and a cut-off filter at 450 nm.

The reactive rate constant, k_r, for the chemical reaction of $O_2(^1\Delta_g)$ (see further process ((13) in Scheme 2) was evaluated as described by Scully and Hoigné [12], using the expression slope/$slope_R = k_r$ [NSD-HPβCD]/k_{rR} [R]. In this case the knowledge of the rate constant value (k_{rR}) for the photooxidation of a reference compound R, is required. Slope and $slope_R$ represent the slopes of

$$\text{Rf- HP}\beta\text{CD} + h\nu \rightarrow {}^1\text{Rf- HP}\beta\text{CD}^* \rightarrow {}^3\text{Rf- HP}\beta\text{CD}^* \quad (5)$$

$${}^3\text{Rf- HP}\beta\text{CD}^* + \text{NSD-(HP}\beta\text{CD)}_2 \rightarrow \text{Rf- HP}\beta\text{CD}^{\bullet-} + \text{NSD-(H}\beta\text{PCD)}_2^{\bullet+} \quad (6)$$

rate constant k_{q3}

$$\text{Rf- HP}\beta\text{CD}^{\bullet-} + \text{H}^+ \rightarrow \text{RfH- HP}\beta\text{CD}^{\bullet} \quad (7)$$

$$2\ \text{RfH-HP}\beta\text{CD}^{\bullet} \rightarrow \text{Rf} + \text{RfH}_2\text{- HP}\beta\text{CD}_2 \quad (8)$$

$$\text{RfH}_2\text{- HP}\beta\text{CD} + O_2({}^3\Sigma_g^-) \rightarrow \text{RfH}_2\text{- HP}\beta\text{CD}^{\bullet+} + O_2^{\bullet-} \quad (9)$$

$$O_2^{\bullet-} + \text{NSD-(HP}\beta\text{CD)}_2 \rightarrow \text{P10} \quad (10)$$

$$\text{RfH}_2\text{-HP}\beta\text{CD}^{\bullet+} + O_2^{\bullet-} \rightarrow \text{Rf} + H_2O_2 \quad (11)$$

$$H_2O_2 + \text{NSD-(HP}\beta\text{CD)}_2 \rightarrow \text{P(12)} \quad (12)$$

$${}^3\text{Rf- HP}\beta\text{CD}^* + O_2({}^3\Sigma_g^-) \rightarrow \text{Rf-HP}\beta\text{CD} + O_2({}^1\Delta_g) \quad (13)$$

rate constant k_{ET}

$$O_2({}^1\Delta_g) \rightarrow O_2({}^3\Sigma_g^-) \quad (14)$$

rate constant k_d

$$O_2({}^1\Delta_g) + \text{NSD-(HP}\beta\text{CD)}_2 \rightarrow O_2({}^3\Sigma_g^-) + \text{NSD-(HP}\beta\text{CD)}_2 \quad (15)$$

rate constant k_q

$$O_2({}^1\Delta_g) + \text{NSD-(HP}\beta\text{CD)}_2 \rightarrow \text{P16} \quad (16)$$

rate constant k_r

Being $k_r + k_q = k_t$

Scheme 1. Possible pathways for a Rf- HPβCD – sensitized process in the presence of a hypothetical electron donor (NSD), transparent to the photoirradiation wavelength. For simplicity, natural decay processes from the species ^{1}Rf- HPβCD* and ^{3}Rf- HPβCD* have been ignored.