Photodegradation of Lincomycin in Aqueous Solution

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Aqueous solutions of lincomycin were irradiated with UV light in homogeneous and heterogeneous systems. Lincomycin disappeared in both systems but the presence of TiO_2 noticeably accelerated the degradation of the antibiotic in comparison with direct photolysis. The rate of decomposition was dependent on the concentration of lincomycin and followed a pseudo-first-order kinetics. Photolysis involved only the oxidation of lincomycin without mineralization. Differently, the treatment with TiO_2 and UV light resulted in a complete mineralization of the antibiotic. The degradation pathways involved S- and N-demethylation and propyldealkylation. The mineralization of the molecule led to the formation of sulfate, ammonium, and nitrate ions.

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1. INTRODUCTION

In recent years, there has been a growing interest in the presence of pharmaceutical substances in the aquatic environment [1–8]. These molecules are often excreted via urine or feces because they are nonmetabolised [9] and enter into wastewater and eventually reach drinking water if they are not biodegraded or eliminated during sewage treatments.

Many substances are hardly degraded and appear to be quite persistent [6]. Residues of pharmaceuticals and their metabolites can be expected in the environment everywhere in the world where humans use drugs. A large variety of pharmaceutical compounds have been frequently found in sewage treatment plant effluents and river water at concentrations up to several $\mu\text{g L}^{-1}$ [10]. Pharmaceutical substances have been detected in small creeks and big rivers such as Rhine, Elbe, Neckar, Danube, and Po [11].

Antibiotics are an important group of pharmaceuticals employed for the treatment of human infections and in veterinary medicine. Antibiotics are largely used in farming and in aquaculture as growth promoters and thus are permanently added to the feed. Animal husbandry discharges antibiotics and their metabolites into the environment through liquid manure. These substances may contaminate soil and ground water as well as river water via run-off drainage from the fields when the manure is used as fertiliser. The most prominent effect of antibiotics in the environment is the development of resistances in bacterial strains causing a serious

threat for public health as more and more infections can no longer be treated with the presently known antidotes [10].

Lincomycin is an antibiotic active against the gram-positive bacteria [12], widely used by humans and for veterinary purposes [13–15]. Laboratory tests have proved that lincomycin is toxic to brine shrimp (*Artemia salina*) nauplii employed as a teratogen test system [16–18]. Recently, lincomycin concentrations approaching 250 ng L^{-1} were found in the river Po (Italy) [19]. The level of contamination noticeably exceeded the trigger value (10 ng L^{-1}) suggested by a recent document on the environmental risk assessment of medicinal products in EU [20]. The high lincomycin load was most probably due to the large number of animal farms in the river subbasins [19].

Lincomycin is hardly modified by the common chemicals. Sztaricskai et al. [21] reported that lincomycin was not oxidized by strong oxidants as NaIO_4 and H_2O_2 . Lincomycin sulfoxide was obtained by microbial transformation [22]. Two isomeric sulfoxides, which differed in the configuration of the sulfur chiral center, were prepared with low yield by oxidation with dimethyldioxirane [21]. The corresponding sulfones were obtained by oxidation of the lincomycin sulfoxides with OsO_4 in the presence of N-methylmorpholine-N-oxide [21].

Pospíšil et al. [23] prepared lincomycin sulfoxides and lincomycin sulfones by biotransformation or by chemical oxidation with H_2O_2 under mild acid or neutral conditions. N-oxide sulfoxide and two isomeric N-oxide-sulfones were

prepared by oxidation of lincomycin with H_2O_2 in alkaline media [24].

Advanced oxidation processes allow the complete oxidation of inorganic and organic species. The objective of the present study was to investigate the possible application of photodegradation methods for transforming lincomycin into harmless substances. The photooxidation of the drug was carried out by irradiation with UV light in the absence and in the presence of TiO_2 that has been successfully employed as photocatalyst to oxidise many organic pollutants [25] and drugs [26, 27] in aqueous solutions.

2. MATERIALS AND METHODS

Lincomycin was purchased from Aldrich and was used without further purification. The structural form is shown below:

SCHEME 1

The irradiation experiments were carried out in a 0.5 L Pyrex batch photoreactor with a 125 W medium pressure Hg lamp (Helios Italquartz) immersed in the reacting solution in axial position. The IR component of the incident beam as well as any radiation below 300 nm was eliminated by the circulation of cooling water through a Pyrex jacket surrounding the lamp. The photon flux emitted by the lamp, measured by using a radiometer (UVX digital) leaned against the external wall of the photoreactor containing only pure water, was 10 mW cm^{-2} .

The initial concentrations of lincomycin were 50, 20, and 10 mg L^{-1} and the natural pH values ranged between 5.6 and 6.5. Oxygen was continuously bubbled in the reacting system before and throughout the duration of the runs. The temperature inside the photoreactor was about 313 K during all the experiments.

Commercial TiO_2 Degussa P25 (specific surface area $\approx 50 \text{ m}^2 \text{ g}^{-1}$, 80% anatase, 20% rutile) was used as the photocatalyst for the heterogeneous photodegradation experiments. The amount of catalyst able to absorb almost all the impinging photons was determined by performing measurements of the light transmitted through aqueous suspensions containing different quantities of TiO_2 powder. The optimal

amount of catalyst was 0.4 g L^{-1} . The suspensions were magnetically stirred during the runs.

Samples were withdrawn from the photoreactor at fixed intervals of time. Before analysis, the samples were separated from the catalyst by filtration through a $0.45 \mu\text{m}$ cellulose acetate membrane (HA, Millipore). The quantitative determination of lincomycin was performed by an HPLC equipped with a 9012 Varian pump and a Phenomenex Luna 5μ Phenyl-Hexyl, $4.60 \times 250 \text{ mm}$ column. A mixture of acetonitrile, methanol, and an aqueous solution (40 mM) of potassium dihydrogenphosphate (20:20:60 v/v) was used as the eluent at the flow rate of $0.8 \text{ cm}^3 \text{ min}^{-1}$. A Varian 9050 UV detector measuring at 210 nm was used.

The mineralization of the drug was monitored by determining the total organic carbon (TOC) by means of a TOC Shimadzu 5000 A analyzer, provided with an automatic auto sample injector ASI 5000 A. Absorption spectra of the samples withdrawn during the course of the reaction were recorded with a UV-visible Shimadzu 2401 PC spectrophotometer.

Ionic species were determined by ionic chromatography using a Dionex DX 120 instrument equipped with an Ion-Pac AS14 4 mm column (250 mm long, Dionex). The eluent was an aqueous solution of NaHCO_3 (8 mM) and Na_2CO_3 (1 mM). A flow rate of $1 \text{ cm}^3 \text{ min}^{-1}$ was maintained during the analyses. Ammonium ion was determined by an ion sensitive electrode (Oriel mod. 9512) in an expandable ion analyser (Orion EA 920).

3. RESULTS AND DISCUSSION

Preliminary investigations were carried out in order to establish if some decomposition or chemical modification of lincomycin occurred in the dark, under the same experimental conditions of the irradiation experiments. No reaction took place without O_2 or UV illumination.

3.1. Homogeneous photodegradation

The results revealed the occurrence of a slow photolytic reaction but no evidence of mineralization was found. Figure 1 shows the disappearance of lincomycin irradiated with UV light. The percentages of drug transformed after 5 h were ca. 70, 40, and 20% for 10, 20, and 50 mg L^{-1} , respectively. The total organic carbon values did not vary under irradiation and this finding is in accord with the formation of photodegradation products having the same number of carbon atoms of the initial molecule.

There are two possible sites for oxidative attack in lincomycin: the thiomethyl group and the pyrrolidine nitrogen. Tertiary amines are known to be oxidized slowly under acid conditions, so that under UV irradiation and in the presence of dissolved oxygen, the photochemical oxidation of lincomycin could be attributed to the conversion of the thiomethyl group into sulfoxide and sulfone derivatives [27]. The presence of these oxidized products having the same number of atoms of C of lincomycin would justify the constancy of the TOC values during irradiation.

FIGURE 1: Photochemical degradation of aqueous solutions of lincomycin.

FIGURE 2: Photocatalytic degradation of aqueous solutions of lincomycin.

3.2. Heterogeneous photodegradation

Figure 2 shows the disappearance of lincomycin irradiated with UV light in the presence of TiO_2 . The complete degradation of the drug was achieved in times noticeably shorter than that by homogeneous irradiation. The photocatalytic reaction obeyed a pseudo-first-order kinetic law, as previously reported in the literature for most organic substrates [28–32].

Figure 3 shows the temporal evolution of the spectral changes taking place during the photocatalytic degradation of 50 mg L^{-1} of lincomycin. Spectrum 1 was obtained in

FIGURE 3: Changes in absorption spectra during the photocatalytic degradation of a 50 mg L^{-1} aqueous solution of lincomycin: spectra 1–5 denote irradiation for 0, 30, 90, 120, and 300 min, respectively.

FIGURE 4: Variation of TOC during the photocatalytic degradation of aqueous solutions of lincomycin.

the presence of TiO_2 particles before irradiation. Absorption slowly increased till 120 min accompanied by the appearance of a little broad band at about 270 nm. With increasing irradiation time this band disappeared due to the continuous transformation of the substrate and of the intermediate species in the presence of TiO_2 and oxygen.

Figure 4 shows the variation of the TOC values determined during the photocatalytic degradation of lincomycin. Different from the homogeneous treatment, lincomycin was completely mineralized when the photocatalyst was present. The slow mineralization rate is indicative of the existence of long-lived intermediates during the mineralization process.

FIGURE 5: Time evolution of the organic ionic species formed during the photocatalytic degradation of a 20 mg L⁻¹ aqueous solution of lincomycin.

Ionic chromatography revealed the presence of inorganic and organic anionic species formed during the photodegradation of lincomycin. The various species were identified by peak spiking and comparing the retention times observed for standard anion solutions. Ammonium ions were also detected during the course of the irradiation process.

Figures 5 and 6 show the evolution of the ionic species formed during the degradation of a solution containing 20 mg L⁻¹ of lincomycin. Formate and propionate ions increased rapidly in the early stages of the degradation process. Their concentration reached a maximum value and then disappeared under irradiation.

Sulfate ions continuously increased during the run but long-time irradiation led only to a partial recovery (ca. 70%) of the total inorganic sulfur. The lack of sulfur mass balance can be linked to the presence of white colloidal sulfur.

Ammonium ions were quickly formed and accumulated throughout the reaction period. The amount of ammonium ions reached approximately 75% of the corresponding quantity of initial organic nitrogen. Nitrate ions appeared later and accounted the 25% residual of the stoichiometric amount of nitrogen species.

Heterogeneous photocatalysis involves photoexcitation that causes charge separation in the semiconductor particles followed by simultaneous oxidation of the adsorbed organic substrate. Two possible pathways are possible: the one involving direct oxidation of the organic molecule and the other proceeding through free $\cdot\text{OH}$ radical mediated reactions. Hydroxyl radicals are formed from the oxidation of surface-adsorbed water molecules and/or hydroxyl ions and to a lesser extent from hydrogen peroxide formed as a byproduct from the superoxide radical anion $\text{O}_2^{\cdot-}$ produced by reaction of the photoelectrons with adsorbed oxygen. In aqueous solutions, most of the mechanisms propose the hydroxyl free radicals as the primary charge transfer intermediates in the mineralization of the organic com-

FIGURE 6: Time evolution of the inorganic ionic species formed during the photocatalytic degradation of a 20 mg L⁻¹ aqueous solution of lincomycin.

pounds and consider the essential role of oxygen as electron scavenger [33].

The ability of TiO_2 to promote the total photooxidation of a large variety of organic compounds is attributed to the favourable position of its valence and conduction bands. At pH = 7, the redox potential of the photogenerated holes is +2.53 V versus the standard hydrogen electrode (SHE) [34]. After reaction with water the holes can produce hydroxyl radicals $\cdot\text{OH}$ whose redox potential is only slightly lower (+2.27 V). Both potentials are far more positive than that of H_2O_2 (+1.35 V).

The $\cdot\text{OH}$ radical can react in different ways with the organic compounds, namely, by hydrogen abstraction and by electrophilic addition. These reactions are nonspecific as a result of the high electron affinity of the $\cdot\text{OH}$ radical. The heteroatomic sites are oxidized more efficiently than the C-C or C-H bonds are.

The nature of the ionic species produced after short irradiation times reveals that a large part of the initial photocatalytic reactions takes place at the sulfur and nitrogen containing substituents. The appearance of formate ions is attributable to S- and N-demethylation of lincomycin. The methyl groups adjacent to nitrogen or sulfur are easily hydroxylated by an active species as $\cdot\text{OH}$ and they rearrange to release formaldehyde that is quickly oxidized to formic acid. Similarly, the hydroxylation of the propyl group adjacent to the tertiary carbon of the pyrrolidine moiety should lead to the formation of propionic acid.

The high propionate concentration reached after 1 h of irradiation (more than 3 times the initial lincomycin concentration) clearly indicates that the majority of the propionate ions derives from other demolition steps involving fragmentation of the molecule and oxidation of unknown aliphatic intermediates.

In weakly acidic media, as in the present experiments, the nitrogen atom of the pyrrolidine moiety [24] is hardly

oxidized so that N-demethylation can occur. It is worth noting that N-dealkylation of lincomycin and its analogs with platinum catalyst and air or oxygen were also reported by Birkenmeyer et al. [35].

The desulfuration of lincomycin justifies the presence of sulfate ions from the beginning of irradiation. The amount of sulfur recovered as SO_4^{2-} was less than 70% of the original sulfur concentration. Typically, only sulfate is produced from the photocatalytic oxidation of organic compounds containing sulfur atoms. At the best of our knowledge, a partial transformation to colloidal sulfur has never been reported.

As shown by Calza et al. [36], the photocatalytic transformation of the nitrogen moieties to N_2 , NH_4^+ , NO_2^- , or NO_3^- depends on the initial oxidation state of nitrogen and on the structure of the organic molecules. Ammonium ions are generally formed directly when the oxidation state of the bound nitrogen is -3 [36], whilst nitrate formation occurs through a sequence of oxidative steps. The relative concentrations of these species depend largely on the nature of the nitrogen atom in the compound [36–38]. Low et al. [37] found that the aliphatic amines produced a higher ammonium to nitrate concentration ratio than the compounds containing ring nitrogen. This indicates that the reactions involving ring nitrogen are more complex and that there are significant reaction paths leading to nitrate ion in addition to ammonium ions.

The presence of nitrate ions during the degradation of lincomycin begins to be significative when more than 60% of the initial nitrogen concentration is converted into ammonium ions. This could mean that one of the two nitrogen atoms of the antibiotic is transformed more rapidly than the other one. The oxidation attack probably involves the introduction of $\cdot\text{OH}$ radicals in the pyrrolidine moiety and the cleavage of the amide bond [24]. Nitrogen contained in the amide group is easily and predominantly transformed to ammonium ions [39] whereas both NH_4^+ and NO_3^- ionic species are generated in the case of the tertiary amine [36]. Several steps of nitrogen oxidation and consequently an induction period are necessary before nitrate ions are formed from the pyrrolidine nitrogen [36, 37].

The progressive addition of $\cdot\text{OH}$ radicals leads to the formation of oxygenated aliphatic intermediates and ultimately to CO_2 . The sugar moiety is easily oxidized and mineralized.

4. CONCLUSION

Heterogeneous photocatalysis appears to be a good method for the decomposition of aqueous solutions of lincomycin. Simple irradiation with UV light leads to the complete disappearance of the antibiotic but does not cause the mineralization of lincomycin. The presence of TiO_2 improves the effectiveness of the photodegradation and allows the complete mineralization.

Formate and propionate ions formed in the early stages of the process were converted into carbon dioxide and water. Different transformation pathways were followed by the nitrogen atoms according to the nature of the C-N bonds:

the amide group was principally transformed to NH_4^+ ions whilst both NH_4^+ and NO_3^- ions were formed from the pyrrolidine nitrogen. Sulfur and sulfate ions were obtained from the oxidation of the thiomethyl group.

The photocatalytic process could be applied to degrade many pharmaceuticals that cannot be completely eliminated by biological treatment and are emitted into the aquatic environment.

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