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Photocatalytic degradation of cholesterol-lowering statin drugs by TiO_2-based catalyst. Kinetics, analytical studies and toxicity evaluation

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ABSTRACT

The photocatalytic degradation of simvastatin, lovastatin, and pravastatin, cholesterol-lowering statin drugs, by TiO_2-based catalyst in aqueous solutions has been studied. In all cases the degradation was found to be efficient and was clearly owing to the formation of hydroxyl radicals. When present in their open forms, the life times were evaluated, in aerated conditions, to 8.1 ± 1.2, 10.4 ± 1.3 and 19.2 ± 2.1 min for simvastatin, lovastatin and pravastatin respectively. In their lactone forms, in non-aerated conditions, the life times were found to be higher: 12.4 ± 1.1 and 15.6 ± 2.0 min for simvastatin and lovastatin. Several primary and secondary photoproducts were elucidated by means of LC–MS technique. They were obtained as a result of the addition of the hydroxyl radical to the double bonds leading to the formation of different hydroxy derivatives. Under prolonged irradiation, efficient mineralization of statin solutions was observed by means of total organic carbon (TOC) evolution. A detailed mechanism for the degradation of statins and the formation of photo-products is proposed and discussed, together with toxicity evaluation. It is stressed that photocatalysis appears to be an alternative to other chemical or biological methods for statins removal in aqueous solutions.

1. Introduction

Cholesterol lowering statins are a group of pharmaceuticals, which are the most frequently prescribed agents for reducing morbidity and mortality related to coronary heart disease. Lovastatin is a natural product; while simvastatin and pravastatin are semi-synthetic compounds [1]. Due to high persistence and widespread occurrence of lipid-regulating agents in aquatic environments, their presence in drinking water has been widely reported [1–6].

Several methods enable the analysis of lipid regulators at concentration levels of ng L^{-1} [2,5,7–11]. Quantification of statins and their human metabolites in biological matrix such as blood and urine has been extensively studied [12–21]. Similar methods development concerning statin residues in environmental samples (natural waters) present more difficulties and has not been widely investigated [1,2]. Owing to the extensive use of statins and their large scale production municipal sewage treatment plants as well as sewage treatment plants of the pharmaceutical industry might therefore be important point sources of contamination [2]. Available data for the statin class refers to the detection of atorvastatin (Lipitor) in wastewater from municipal sewage treatment plant (1–117 ng L^{-1}) and in rivers at low levels of ng L^{-1} [1,2]. Despite of common use the fate and effects of statin drugs in the environment are largely unknown.

Pharmaceuticals in general may enter the environment through different pathways, resulting in the contamination of waste or fresh water, where bacteria are most likely the primarily affected organisms. Once they are present in aqueous solutions, they can undergo photochemical transformations with sunlight via direct or indirect photoreactions [22–24]. Such photochemical degradation can be one of the major transformation processes and one of the factors that control the fate of the organic pollutants in the environment.

In this context it is useful to apply various technologies to purify aqueous municipal and industrial effluents containing pharmaceutical substances, before they enter surface waters. Among them, advanced oxidation processes (AOPs) have been the subject of major interest in recent years. These processes are characterized by the formation of the highly oxidizing species, namely hydroxyl radicals. They ensure high reactivity with low selectivity, as they are required for the degradation of different pollutants. Heterogeneous photocatalysis represents an example of AOPs capable of achieving a complete oxidation of organic and inorganic species, including pharmaceutical substances. It takes advantage of some semiconductor solids, which can be used as photocatalysts suspended in the water effluent that has to be treated, or immobilized on various types of supports. Among various solids, polycrystalline anatase

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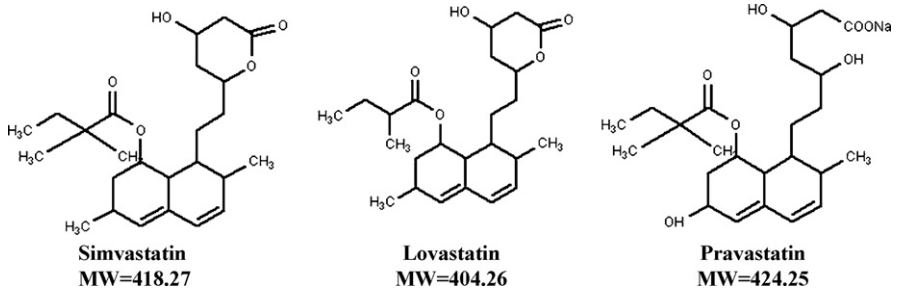

Fig. 1. Chemical structures of statins.

TiO_2 is largely used because of its low cost and its (photo)stability [25]. It is also remarkably active, cheap, non-toxic and chemically stable over a wide pH range. In general, the goal of the application of photocatalysis in water treatment is the transformation, deactivation and finally mineralization of environmentally persistent compounds or xenobiotics. A large number of studies have been dedicated in our laboratory to develop transparent TiO_2-anatase films [26]. They were efficiently used to initiate the photocatalytic degradation of various organic compounds, such as pesticides and also their metabolites [27–29].

The results of our previous study [30] revealed that statin might be persistant under environmental conditions, partially being degraded in aqueous solutions, and partially converted to various, more stable transformation products. Thus, we decided to broaden our research to the field of photocatalysis of a group of possible pollutants–statins. The aim of this work was to study the photocatalytic degradation of simvastatin, lovastatin and pravastatin cholesterol-lowering statin drugs, irradiated in the presence of TiO_2 catalyst, in order to get a better insight into the mechanism of their degradation. Mass spectrometry and toxicity assessment (bioluminescence inhibition of *Vibrio fischeri* bacteria) were devoted to elucidation of the photodegradated products and to the evaluation of their toxicity activity.

2. Experimental

2.1. Materials

The statin drugs used for our research were at least 99.9% pure, so no further purification was required. Simvastatin and lovastatin (as lactones) and pravastatin (as sodium salt of active hydroxy acid form) (Fig. 1) were kindly provided by one pharmaceutical company. Hydrochloric acid, sodium chloride; sodium hydroxide and glacial acetic acid were purchased from Carlo Erba Reagents (Rodano, IT), acetonitrile (highest grade available) from Sigma–Aldrich Company Ltd (Gillingham, GB). They were used without further purification. Double de-ionized water was prepared through the Milli_Q Plus Ultra-Pure water system (Millipore, Billerica, USA) and its purity was controlled by its resistivity.

For the preparation of sol–gel derived TiO_2 films tetraethoxysilane (Acros Organics, Geel, Belgium), ethanol (Riedel-de Haen, Hanover, Germany), and concentrated (65%) nitric acid (Acros Organics, Geel, Belgium) and for TiO_2 sol: titanium (IV) isopopoxide (Acros Organics, Geel, Belgium), ethyl acetoacetate (Riedel-de Haen, Hanover, Germany), 2-methoxyethanol (Fluka, Buchs, Switzerland), ND The Triblock Copolymer Pluronic F-127 Sigma–Aldrich Company Ltd (Gillingham, GB) were used.

Transparent TiO_2-anatase films deposited on both sides of SiO_2-precoated soda lime glass slides (175 mm × 12.5 mm × 2 mm) were produced by sol–gel processing route, as described elsewhere [26]. The photocatalytic cell consisted of a DURAN glass tube (240 mm, inner diameter 40 mm), which was closed on the lower side with a glass frit and the valve for purging with oxygen. The effective volume of the glass tube was 250 mL. The spinning basket was made entirely of Teflon and fitted into the photocatalytic cell. Six glass slides with immobilized catalyst were fastened around the axis by the help of two holders. The glass slides and the axis were not joined together. There was a gap of 1.5 mm in between to enable homogenous mixing of the solution in all segments of the cell. The spinning basket with immobilized TiO_2 placed in the glass tube could freely rotate around its axis. A detailed description of the photoreactor and the cell (both developed in our laboratory) is given elsewhere [27]. The photocatalytic activity of the prepared TiO_2 films was evaluated in a tailor-made chamber photoreactor using 3 low-pressure mercury fluorescent lamps as a UVA radiation source (CLEO 20 W, 438 mm × 26 mm, Phillips; broad maximum at 365 nm). The photocatalytic cell was put in the centre, between the lamps. The motor on the top of the reactor rotates the spinning basket with the variable speeds (0–300 rpm).

2.2. Instruments and methods

The degradation of the statins and the formation of by-products were followed by HPLC system. It consisted of a HP 1090 series chromatograph, coupled with DAD detector (Agilent Technologies, Santa Clara, USA). Zorbax Eclipse XDB-C18 column (4.6 mm × 150 mm, 5 μm) was provided by Agilent Technologies (Santa Clara, USA). Detection was performed at 238 nm. The eluents consisted of acetonitrile (Eluent A) and grade water (pH 4.0 acidified with glacial acetic acid) (Eluent B) with flow rate 1 mL min^{-1}. The injection volume was 50 μL. Simvastatin and lovastatin were separated at the isocratic conditions as follows: 70% A, 30% B and pravastatin at 30% A, 70% B. Working solutions were prepared daily, in order to avoid hydrolysis, by diluting the stock solutions with double-deionised water.

LC–MS studies were carried out with a Waters Alliance 2695 (Milford, USA) high performance liquid chromatography system coupled to a Quattro LC triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with a pneumatically assisted electrospray ionisation source (ESI) in positive ion mode and a Waters photodiode array detector. Each single experiment permitted the simultaneous recording of both UV chromatogram at a preselected wavelength and an ESI-MS full scan. The capillary voltage was set to 3.0 kV, while the sampling cone voltage was equal to 35.0 V. Source and desolvation temperature were set to 120.0 °C and 300.0 °C respectively. MS data were acquired over an m/z range 50–800 at collision energy of 10.0 eV, by MassLynx NT 3.5 Waters system. Mobile phase consisted of acetonitrile (mobile phase A) and water, acidified with acetic acid to pH 4.0 (mobile phase B) with gradient programme as follows: 0 min 5% A; 15 min 95% A; 25 min 95% A, 35 min 5% A. The flow rate was equal to 0.2 mL min^{-1} and the injection volume was equal to 30 μL.

LUMIStox system, produced by Hach-Lange (Dusseldorf, Germany) was applied for the toxicity experiments. Total organic