

## SAŽETAK

### Primjena $\text{TiO}_2$ fotokatalizatora za uklanjanje citostatika iz vode

Zaštita i očuvanje vodenih resursa izazov je na globalnoj razini s kojim se današnjica susreće. Uz konvencionalne postupke obrade voda razvijaju se i napredni oksidacijski procesi koji su se zbog svog neselektivnog ponašanja pokazali učinkovitijim za uklanjanje malih organskih molekula poput farmaceutika čija prisutnost u okolišu više ne iznenađuje. Među raznim vrstama lijekova, svoj put u okolišu, ponajviše kroz otpadne vode pronašli su i lijekovi protiv raka (citostatici) koji zahtijevaju pažnju zbog povećane potrošnje i bioloških učinaka na organizme, već pri niskim koncentracijama. U ovome radu izabrana su dva citostatika, imatinib i krizotinib čija se mogućnost uklanjanja iz vode ispitala kroz sorpcijsku i fotokatalitičku aktivnost primjenom  $\text{TiO}_2$  fotokatalizatora. Prema mehanizmu fotokatalitičkog procesa, ispitivana komponenta podlijegat će razgradnji ako se prethodno sorbira na katalizator pa se sukladno tome, u prvom nizu eksperimenata proučavao sorpcijski afinitet citostatika prema različitim oblicima  $\text{TiO}_2$  fotokatalizatora, koristeći nekoliko modela sorpcijskih izoterma. Općenito se, na temelju određene količine sorbirane tvari, ispitala i primjenjivost sorpcije kao jednostavnije i jeftinije metode za uklanjanje imatiniba i krizotiniba iz vode ili kao preteča neke druge oksidacijske metode. Priroda procesa sorpcije, provedenog pri tri različite temperature opisana je promjenom početne koncentracije analita, pH-vrijednosti i ionske jakosti otopine te promjenom mase sorbensa. Visoke vrijednosti regresijskog koeficijenta,  $R^2$  upućuju na prikladnost linearne, Freundlichove i Langmuirove izoterme za opisivanje sorpcije citostatika na suspendirani i imobilizirani oblik  $\text{TiO}_2$ . Oba analita pokazuju rastući trend koeficijenta sorpcije s porastom vrijednosti pH u rasponu od 5 do 9 s naglaskom na veću mobilnost imatiniba u slučaju imobiliziranog  $\text{TiO}_2$ . Pozitivna korelacija određena je i između temperature, mase sorbensa i koeficijenta sorpcije, dok je porastom ionske jakosti otopine krizotinib pokazao suprotan trend. Termodinamika sorpcije opisana je kao spontan proces fizikalne prirode koji slijedi kinetiku pseudo-drugog reda.

Što se tiče eksperimenata fotokatalize, prvo su se odredile vrijednosti početne koncentracije analita i pH otopine pri kojoj citostatici postižu optimalnu razgradnju, primjenom modeliranja odzivnih površina (RSM). Pri dobivenim uvjetima (pH 5 i 5 mg/L) ispitan je mehanizam fotokatalitičke reakcije, određivanjem radikalskih vrsta odgovornih za razgradnju. Vodeću ulogu u razgradnji imatiniba i krizotiniba pokazali su hidroksilni radikali i singletni kisik. U sljedećim eksperimentima pokazana je važnost provođenja fotokatalize u prisustvu raznih

anorganskih i organskih tvari kao sastavnica matice vode koji su većinski usporili razgradnju. Kao i svaki drugi proces razgradnje, fotokataliza imatiniba i krizotiniba također je bila popraćena stvaranjem nusprodukata čije su strukture i putevi razgradnje predloženi korištenjem spektrometrije masa visokog razlučivanja. Potencijalna opasnost razgradnih produkata procijenjena je testom akutne toksičnosti prema morskoj bakteriji *Vibrio fischeri*, pri čemu je postignuta značajna inhibicija luminiscencije tijekom fotokatalitičke razgradnje krizotiniba u razdoblju od 90. do 180. minute. Kao fotokatalizator koristio se TiO<sub>2</sub> imobiliziran na staklene mrežice koji je olakšao samu provedbu eksperimenata pritom misleći na filtriranje uzoraka.

**Ključne riječi:** citostatici, imatinib, krizotinib, titanijev (IV) oksid (TiO<sub>2</sub>), sorpcija, fotokataliza, razgradni produkti, toksičnost

## ABSTRACT

### Application of TiO<sub>2</sub> photocatalyst for the removal of cytostatic drugs from water

The protection and conservation of water resource is a global challenge facing humanity today. In addition to conventional water treatment, advanced oxidation processes are also being developed to non-selectively and efficiently remove small organic molecules such as pharmaceuticals, whose presence in the environment is no longer surprising. Among the different classes of pharmaceuticals, anti-cancer drugs (cytostatics) have also found their way into the environment, mostly through wastewater, which requires attention due to their increased consumption and biological effects, even at low concentrations. In this work, two cytostatics, imatinib and crizotinib, were selected and their ability to be removed from water was tested by sorption and photocatalytic activity with TiO<sub>2</sub> photocatalysts. The prerequisite step of the photocatalytic process is the sorption of the tested component on the catalyst, so in the first series of experiments the sorption affinity of cytostatics to different forms of TiO<sub>2</sub> was investigated. In addition, based on the studied sorption affinity, the applicability of sorption as a simpler and less expensive method for the removal of imatinib and crizotinib or as a complementary method to some oxidation processes was tested. The nature of the sorption process was described by changing the initial concentration of the analyte, the pH value and the ionic strength of the solution, and by performing experiments at three different ambient temperatures and different sorbent dosages. The suitability of the linear, Freundlich, and Langmuir isotherm models for describing the sorption of cytostatics on the suspended and immobilized forms of TiO<sub>2</sub> was indicated by high values of the regression coefficient,  $R^2$ . Both analytes showed an increasing trend in the sorption coefficient with increasing pH values in the range of 5 to 9, highlighting the greater mobility of imatinib in the case of immobilized TiO<sub>2</sub>. A positive correlation was also observed between temperature, sorbent mass and sorption coefficient, while the increase in ionic strength of crizotinib solution showed the opposite trend. The thermodynamics of sorption is described as a spontaneous process of physical nature that follows pseudo-second-order kinetics.

In the first step of the photocatalytic experiments, the initial concentration of the analyte and the pH of the solution, at which the cytostatic reaches the optimal degradation, were tested using response surface modelling (RSM). Under the conditions obtained (pH 5 and 5 mg/L), the mechanism of the photocatalytic reaction was studied by determining the main radical species involved in the degradation. Hydroxy radicals and singlet oxygen played the main

role in the degradation of imatinib and crizotinib. The importance of performing photocatalysis in the presence of various organic and inorganic substances as common components of the water matrix was also demonstrated, since most of them slow down the degradation. Like any other degradation process, photocatalysis of imatinib and crizotinib was accompanied by the formation of by-products, whose structures and degradation pathways were suggested by high-resolution mass spectrometry. The hazard potential of the degradation products was assessed by an acute toxicity assay with the marine bacterium *Vibrio fischeri*, with significant inhibition of luminescence during photocatalytic degradation of crizotinib over period of 90 to 180 minutes. TiO<sub>2</sub> immobilized on glass meshes was used as the photocatalyst, which facilitated the performance of the experiments by avoiding filtering of the samples.

**Keywords:** cytostatics, imatinib, crizotinib, titanium (IV) oxide, sorption, photocatalysis, degradation products, toxicity