

# Kinetics of 5-Fluorouracil Degradation by Heterogenous TiO<sub>2</sub> Photocatalysis

LUCIAN ALEXANDRU CONSTANTIN<sup>1\*</sup>, INES NITOI<sup>1</sup>, IONUT CRISTEA<sup>1</sup>, PETRUTA OANCEA<sup>2</sup>

<sup>1</sup> National Research and Development Institute for Industrial Ecology – ECOIND Bucharest, 71-73 Drumul Podul Dambovitei Str., 060652, Bucharest, Romania

<sup>2</sup> University of Bucharest, Faculty of Chemistry, 4-12 Elisabeta Av., 030016, Bucharest, Romania

*Cytostatic drugs represents a category of pharmaceutical products used in cancer treatment, and among them 5-fluorouracil is the most common. Drugs used in cancer treatment are inhibiting and even destroying the cells, acting in a non-selective manner and therefore being considered to present carcinogenic, genotoxic, mutagenic and teratogenic potential. About 15% of the administered 5-fluorouracil is eliminated from human body without any transformation and therefore ends up in the wastewater system. Due to the fact that removal of 5-fluorouracil and other pharmaceutical products using conventional wastewater treatment is incomplete and inefficient, there is a need for more performant degradation technologies such as advanced oxidation processes. Among them, photocatalytic oxidation using titanium dioxide represents one of the most efficient removal technology for hazardous organic compounds. UV/TiO<sub>2</sub> degradation of 5-fluorouracil was investigated in the aim to optimize process operational parameters: pH = 7, photocatalyst dose = 100 mg/L, irradiation time = 180 min. The degradation kinetic of 5-fluorouracil was found to follow Langmuir-Hinshelwood model and degradation rate constant  $k_r = 3.74 \times 10^{-6} \text{ M min}^{-1}$  and equilibrium constant of 5-fluorouracil adsorption on photocatalyst particles  $K_{ad} = 9505 \text{ M}^{-1}$  were determined.*

**Keywords:** 5-fluorouracil, photocatalysis, TiO<sub>2</sub>, photocatalyst

Cytostatic drugs are representing a class of pharmaceutical products used on a large scale in cancer treatment, the most commonly used worldwide being 5-fluorouracil (5FU) [1]. The drugs for cancer treatment are acting against human cells inhibiting or even destroying them [2]. 5FU is the active substance from capecitabine (CAP) which in human body is rapidly metabolized and converted to the active compound. About 15% of administered 5FU is eliminated by human body without transformation and ends in to the sewerage system [3]. Research studies performed in the last decade proved that cytostatic drugs presents a low biodegradability in the secondary stage of wastewater treatment plants [4,5]. Cytostatic drugs residues were found in hospital sewerage systems in concentrations up to  $\mu\text{g/L}$  [5-7]. Concentrations of 5FU between 5-140  $\mu\text{g/L}$  were detected in European hospitals local wastewater treatment plants [5,8].

Due to the fact that removal of 5FU and other pharmaceutical products through conventional physical/chemical and biological wastewater treatment processes is incomplete and inefficient [3, 9], there is a need for more performant treatment technologies [10] such as advanced oxidation processes (AOPs).

Among AOPs, photocatalytic oxidation using TiO<sub>2</sub> represents one of the most efficient treatment process used for removal of organic compounds from aqueous systems [11-13]. In the last decade photocatalytic oxidation was studied for degradation of pharmaceutical compounds like anti-inflammatory agents and endocrine disruptors [14,15]. TiO<sub>2</sub> anatase form presents the best photo-activity and photo-stability [16].

Nowadays there is limited information related to photocatalytic degradation of 5FU, the research objectives aimed to:

- optimize operational parameters of the photocatalytic process: photocatalyst dose, irradiation time
- investigate the effect of 5FU initial concentration upon photocatalytic process efficiency
- investigate photocatalytic process kinetics

## Experimental part

Photocatalysis experiments were performed using a Heraeus UV reactor equipped with a TQ150 medium pressure Hg lamp with an incident photon flow of  $1.05 \times 10^{-6} \text{ einstein s}^{-1}$  determined via ferrioxalate actinometrical method. The variation domain for the main operating parameters were:

- 5FU concentration = 0.89-19.74 mg/L;
- photocatalyst dose = 10 – 200 mg/L;
- irradiation time = 30-180 min.

Identification of 5FU was realized via GC-MS technique using a Agilent 7890A gas chromatograph coupled with an Agilent 240MS ionic trap mass spectrometer. 5FU determination was made based on its derivatization reaction with pentafluorobenzyl bromide (PFBBR), showed in figure 1.

Water sample 50-350 mL was adjusted to pH=5 with K<sub>2</sub>HPO<sub>4</sub> 20% and afterwards extracted with ethyl acetate (AcOEt). After separation and drying on anhydrous Na<sub>2</sub>SO<sub>4</sub> was concentrated in nitrogen flow at ~ 0.5 mL. Concentrated sample is entered in GC vial and 0.5 mL acetone, 100  $\mu\text{L}$  PFBBR 10% in acetone, 50  $\mu\text{L}$  2-Cl-phenol 100 mg/L, 30 mg anhydrous K<sub>2</sub>CO<sub>3</sub> fine powder are successively added. The vial is sealed with Teflon septum lid, and kept at 60°C minimum 2 h, under easy stirring at each 20 min. 1  $\mu\text{L}$  from the processed sample is automatically injected into GC. All used reagents were of analytical grade purity.

\* email: lucian.constantin@incdecoind.ro

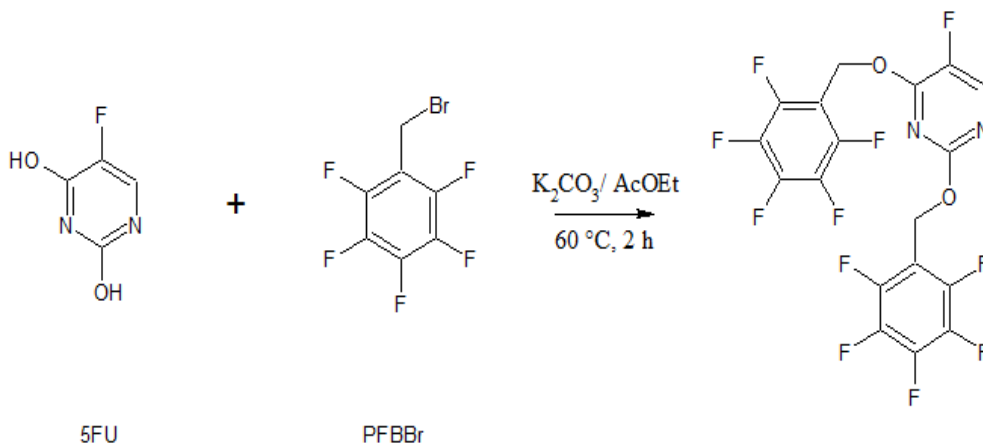


Fig.1 Derivatization reaction of 5FU with PFBBR

[TiO <sub>2</sub> ] <sub>0</sub> (mg/L)	[5FU] <sub>0</sub>		F <sup>-</sup> (mg/L)	N (NH <sub>4</sub> <sup>+</sup> NO <sub>3</sub> <sup>-</sup> ) (mg/L)	η <sub>5FU</sub> (%)	η <sub>F</sub> (%)	η <sub>N</sub> (%)
	(M x 10 <sup>5</sup> )	(mg/L)					
10	5.75	7.48	0.11	0.09	23.07	7.75	4.29
20	5.20	6.76	0.15	0.14	30.45	10.56	6.67
50	4.09	5.32	0.24	0.22	45.24	16.90	10.48
100	3.35	4.36	0.31	0.28	55.12	21.83	13.33
200	4.44	5.78	0.21	0.19	40.58	14.79	9.05

**Table 1**  
PHOTOCATALYST DOSE INFLUENCE UPON 5FU DEGRADATION EFFICIENCY AND ORGANIC FLUORINE AND NITROGEN MINERALIZATION EFFICIENCIES, pH=7, [5FU]<sub>0</sub> = 9.73 mg/L = 7.48 x 10<sup>-5</sup> M, irradiation time=30 min

The GC conditions were:

- column: DB-5MS 60 m, 0.25 μm ID, split 5:1, injector temperature 300°C;

- temperature program: 60°C for 1 min, increase with 10°C/min up to 300°C, maintain 5 min at 300°C (total time 30 min).

The MS conditions were:

- ionic trap temperature: 110 °C, transfer line: 280°C, ion source: 280°C

- characteristic ion for 5FU derivative 490 m/z, retention time 23.78 min

Determination of F<sup>-</sup>, NO<sub>3</sub><sup>-</sup> and NH<sub>4</sub><sup>+</sup> was made via ion chromatographic technique using an ICS 300 ion chromatograph.

## Results and discussions

### Effect of photocatalyst dose

Photocatalyst dose represents an important parameter in heterogeneous photocatalysis influencing photons efficient adsorption and pollutant degradation. Photocatalytic degradation experiments were performed in order to investigate this parameter in the following conditions: initial pollutant concentration [5FU]<sub>0</sub> = 9.73 mg/L = 7.48 x 10<sup>-5</sup> M at pH=7 and initial photocatalyst doses [TiO<sub>2</sub>]<sub>0</sub> between 10-200 mg/L. For each photocatalyst dose, 5FU, F<sup>-</sup>, N-NH<sub>4</sub><sup>+</sup> and N-NO<sub>3</sub><sup>-</sup> concentrations were determined after 30 min irradiation time. Pollutant degradation efficiency, fluorine and nitrogen mineralization efficiencies were calculated and presented within table 1.

The results showed that both 5FU degradation efficiency and organic fluorine and nitrogen mineralization efficiencies have an ascendant trend with the increase of photocatalyst dose up to a [TiO<sub>2</sub>]<sub>0</sub> = 100 mg/L value. This behavior is due to the increased number of active sites available for 5FU adsorption. At photocatalyst doses above 100 mg/L the light scattering phenomenon appears, with a negative impact upon the photocatalytic oxidation efficiency. Presented data confirm existence of two domains for 5FU degradation rate vs. initial photocatalyst dose, one with ascendant profile [TiO<sub>2</sub>]<sub>0</sub> ≤ 100 mg/L and other with descendent profile [TiO<sub>2</sub>]<sub>0</sub> ≥ 100 mg/L. [TiO<sub>2</sub>]<sub>0</sub>

= 100 mg/L was selected as optimum dose that assures the substrate degradation [5FU]<sub>0</sub> = 7.48 x 10<sup>-5</sup> M with highest degradation rate  $r_0 = 0.138 \times 10^{-5} \text{ M min}^{-1}$ . Optimum photocatalyst dose assures 5FU degradation efficiency of 55.12% and organic fluorine and nitrogen mineralization efficiencies of 21.83%, and 13.33% respectively, after irradiation time of 30 min.

### Effect of irradiation time

Irradiation time was varied in the domain 30-180 min for an initial pollutant concentration [5FU]<sub>0</sub> = 9.73 mg/L = 7.48 x 10<sup>-5</sup> M, at pH=7 and optimum photocatalyst dose [TiO<sub>2</sub>]<sub>0</sub> = 100 mg/L.

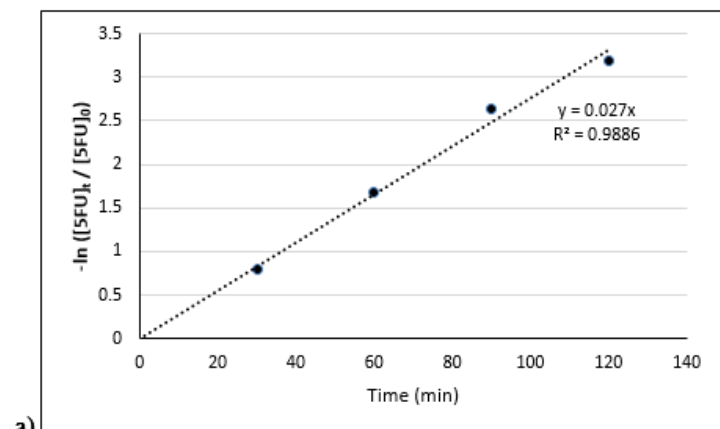
Prolonged irradiation time showed a positive effect upon both pollutant degradation efficiency and organic fluorine and nitrogen mineralization efficiencies. 5FU degradation efficiency reached a value of 96.4% at an irradiation time of 180 minutes. Formation of fluorine and nitrogen organic intermediary products in the process of 5FU oxidative degradation is emphasized by mineralization efficiencies that are permanently lower compared with pollutant's degradation efficiency: 68.66% for fluorine mineralization and 44.76% for nitrogen mineralization.

5FU degradation and organic fluorine and nitrogen mineralization curves were linearized using a pseudo-first order kinetics for an initial pollutant concentration [5FU]<sub>0</sub> = 9.73 mg/L = 7.48 x 10<sup>-5</sup> M and first rate order constants were calculated:  $k_{5FU} = 2.7 \times 10^{-2} \text{ min}^{-1}$ ,  $k_{F^-} = 8.2 \times 10^{-3} \text{ min}^{-1}$ ,  $k_N = 4.7 \times 10^{-3} \text{ min}^{-1}$ .

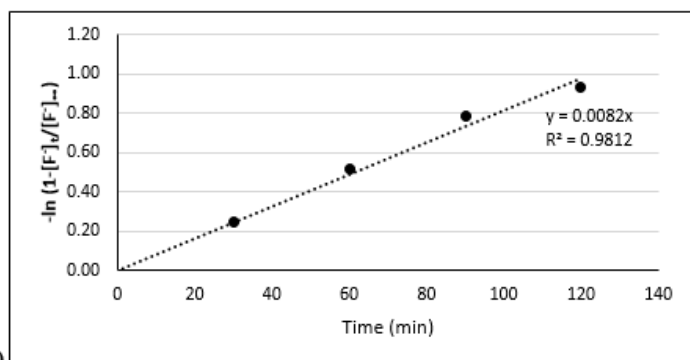
### Kinetics

Many studies on TiO<sub>2</sub> assisted photocatalytic oxidation proved the limitative character of initial pollutant concentration increase upon pollutant's degradation rate. The influence of this parameter was investigated for initial pollutant concentrations varying between [5FU]<sub>0</sub> = 0.89 - 19.74 mg/L = 6.84 x 10<sup>-6</sup> - 1.52 x 10<sup>-4</sup> M at pH = 7, photocatalyst dose [TiO<sub>2</sub>]<sub>0</sub> = 100 mg/L at 30 min irradiation time.

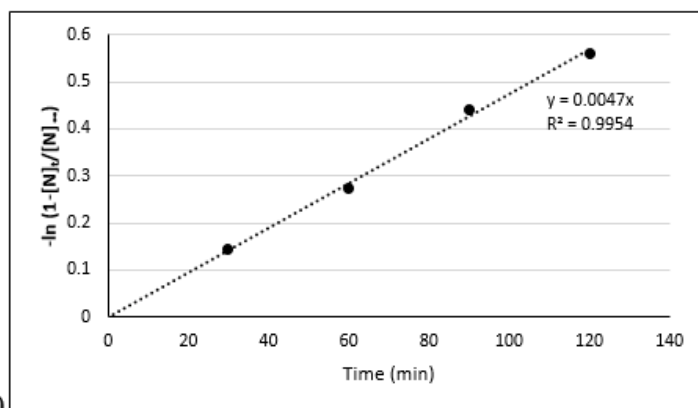
Increase of 5FU initial concentration results in a decrease of pollutant degradation efficiency, revealing the need to



a)



b)



c)

Fig. 2. Pseudo-first order kinetic in UV/TiO<sub>2</sub> system for  
a) 5FU degradation, b) organic fluorine mineralization,  
c) organic nitrogen mineralization

[5FU] <sub>0</sub>		[5FU] <sub>30 min</sub>		η <sub>5FU</sub>
(mg/L)	(M)	(mg/L)	(M)	
0.89	6.84 × 10 <sup>-6</sup>	0.0013	1.0 × 10 <sup>-8</sup>	99.85
2.12	1.63 × 10 <sup>-5</sup>	0.12	9.23 × 10 <sup>-7</sup>	94.33
9.73	7.48 × 10 <sup>-5</sup>	4.36	3.35 × 10 <sup>-5</sup>	55.12
19.74	1.52 × 10 <sup>-4</sup>	9.97	7.67 × 10 <sup>-5</sup>	49.49

**Table 2**  
INITIAL POLLUTANT  
CONCENTRATION INFLUENCE  
UPON 5FU DEGRADATION IN  
UV/TiO<sub>2</sub> SYSTEM  
pH = 7, [TiO<sub>2</sub>]<sub>0</sub> = 100 mg/L,  
IRRADIATION TIME = 30 min

prolong irradiation time in order to obtain good substrate degradation efficiency. This behaviour is explained by the competition between 5FU and its degradation products for the consumption of radical species involved in photo-oxidation reaction, which leads to pollutant's degradation efficiency decrease.

Due to the fact that organic compounds degradation via heterogeneous catalysis can be described by Langmuir - Hinshelwood model, this model was also applied in the case of 5FU degradation. The degradation rate can be described by the following equation:

$$r_0 = \frac{k_r K_{ad} [5FU]_0}{1 + K_{ad} [5FU]_0} \quad (1)$$

where:

- $r_0$  = initial degradation rate of 5FU;
- $[5FU]_0$  = initial substrate concentration;
- $k_r$  = 5FU degradation rate constant;
- $K_{ad}$  = equilibrium constant of 5FU adsorption on TiO<sub>2</sub> particles.

Rearrangement of degradation rate equation (equation1) led to following linear equation:

$$\frac{1}{r_0} = \frac{1}{k_r K_{ad} [5FU]_0} + \frac{1}{k_r} \quad (2)$$

From equation 2 plot rate constant  $k_r$  and equilibrium constant  $K_{ad}$  values can be calculated.  $1/k_r$  is representing the intercept and  $1/k_r K_{ad}$  is representing the slope of plotted equation 2.

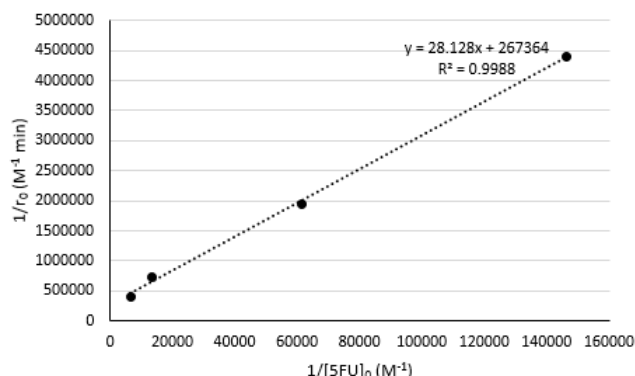


Fig. 3. Linearization of Langmuir - Hinshelwood equation for 5FU degradation in UV/TiO<sub>2</sub> system

Initial pollutant degradation rate  $r_0$  ( $M \text{ min}^{-1}$ ) was calculated from kinetic curve for experimental values obtained in the first 30 min of irradiation.

The obtained constants values were:

-  $k_f = 3.74 \times 10^{-6} M \text{ min}^{-1}$ ;

-  $K_{ad}^r = 9505 M^{-1}$ .

Langmuir - Hinshelwood model verification shows that the degradation of adsorbed 5FU occurs at TiO<sub>2</sub> particles surface, where radical species generated by TiO<sub>2</sub> irradiation are also adsorbed.

### Conclusions

Photocatalytic degradation of 5FU via UV/TiO<sub>2</sub> system was studied and the following optimum operating parameters were set:

-  $pH = 7$ ,

- photocatalyst dose  $[TiO_2]_0 = 100 \text{ mg/L}$ ,

- irradiation time = 180 min.

5FU degradation and organic fluorine and nitrogen mineralization follows a pseudo-first order kinetic:

-  $k_{5FU} = 2.7 \times 10^{-2} \text{ min}^{-1}$ ,

-  $k_F = 8.2 \times 10^{-3} \text{ min}^{-1}$ ,

-  $k_N = 4.7 \times 10^{-3} \text{ min}^{-1}$ .

Organic fluorine and nitrogen mineralization efficiencies are always lower than pollutant's conversion, showing the formation of intermediary fluorine and nitrogen organic derivatives that are further degraded. Verification of Langmuir-Hinshelwood model proves that pollutant

degradation occurs on photocatalyst surface. The values of pollutant adsorption - desorption constant  $K_{ad} = 9505 M^{-1}$  and rate constant  $k_f = 3.74 \times 10^{-6} M \text{ min}^{-1}$  were calculated.

Obtained results attest that TiO<sub>2</sub> assisted heterogeneous photo-catalysis constitute a performant method for degradation of cytostatic drugs from aqueous systems.

*Acknowledgements: The work has been funded by National Authority for Scientific Research and Innovation through Programme Nucleu 13N/2009, Project PN 09-13.03.15.*

### References

1. LIN, H., LIN, A., Water Res., **48**, 2014, p. 559-568.
2. LUTTERBECK, C, WILDE, M., BAGINSKA, E., LEDER, C., MACHADO, E., KUMMERER, K., Sci.Total Environ., **527**, 2015, p. 232-245.
3. ZHANG, J., CHANG, V., GIANNIS, A., WANG, J., Sci. Total Environ., **445**, 2013, p. 281-298.
4. BUERGE, I., BUSER, H., POIGER, T., MULLER, M., Environ. Sci. Technol., **40**, no. 23, 2006, p. 7242-7250
5. MAHNIK, S., LENZ, K., WEISSENBACHER, N., MADER, R., FUERHACKER, M., Chemosphere, **66**, no. 1, 2007, p. 30-37.
6. KOVALOVA, L., McARDELL, C., HOLLENDER, J., J.Chromatogr. A, **1216**, no. 7, 2009, p. 1100-1108.
7. MULLOT, J., KAROLAK, S., FONTOVA, A., HUART, B., LEVI, Y., Anal. Bioanal. Chem., **394**, no. 8, 2009, p. 2203-2212.
8. VERLICCHI, P., GALETTI, A., PETROVIC, M., BARCELO, D., J. Hydrol., **389**, no. 3, 2010, p. 416-428.
9. TIRON, O., BUMBAC, C., PATROESCU, I., BADESCU, V., POSTOLACHE, C., Water Sci. Technol., **71**, no. 6, 2015, p. 832-839.
10. WANG, X., LIN, A., Environ. Pollut., **186**, 2014, p. 203-215.
11. CONSTANTIN, L., NITOI, I., CRISTEA, I., OANCEA, P., ORBECI, C., NECHIFOR, A.C., Rev. Chim.(Bucharest), **66**, no. 5, 2015, p. 597
12. NITOI, I., OANCEA, P., CRISTEA, I., CONSTANTIN, L., NECHIFOR, G., J. Photochem. Photobio. A, **298**, 2015, p. 17-23.
13. SAGGIORO, E., OLIVEIRA, A., PAVESI, T., MOREIRA, J., Rev. Chim.(Bucharest), **65**, no. 2, 2014, p. 237
14. ZHANG, X., WU, F., WU, X., CHEN, P., DENG, N., J. Hazard. Mater., **157**, no. 2, 2008, p. 300-307.
15. PALOMINOS, R., MONDACA, M., GIRALDO, A., PENUELA, G., PEREZ-MOYA, M., MANSILLA, H., Catal. Today, **144**, no. 1, 2009, p. 100-105.
16. MAXIM, F., POENARU, I., TANASESCU, S., Rev. (Chim.Bucharest), **64**, no. 10, 2013, p. 1135

Manuscript received: 15. 12. 2015