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Solubility and degradation of paracetamol in subcritical water

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Abstract: In this study, solubility and degradation of paracetamol were examined using subcritical water. The effect of temperature and static time was investigated during the solubility process in subcritical water at constant pressure (50 bar). The experimental results showed that temperature and static time have crucial effects on the degradation and solubility degrees. The maximal solubility of paracetamol was obtained at 403 K as $(14.68 \pm 0.74) \times 10^3$. An approximation model for the solubility of paracetamol was proposed. O₂ and H₂O₂ were used for the degradation of paracetamol. The maximum degradation degree was found as 68.66 ± 1.05 % and 100 ± 0.00 % using O₂ and H₂O₂, respectively.

Keywords: subcritical water medium; approximation model; paracetamol; degradation; solubility.

INTRODUCTION

In recent times, pharmaceuticals have been detected in surface water, ground water, drinking water and sewage effluents due to their intensive usage.^{1,2} The presence of pharmaceuticals in drinking water and aquatic environments endangers human health and causes various health problems.³ Thus, the treatment of water contaminated with pharmaceuticals, such as anticonvulsants, antipyretics, antidepressants, cytostatic drugs, chemotherapy agents and antibiotics, has become a serious problem.^{4–6}

Paracetamol (acetaminophen, *N*-(4-hydroxyphenyl)acetamide) is a major analgesic and antipyretic agent and is widely used as an intermediate agent in the azo dyes industries and photographic chemicals worldwide.^{7,8} Although paracetamol, used as fever reduction drug and for pain relief, is relatively safe at lower doses, it has various hazards, such as gastrointestinal disease, liver failure, hepatotoxic potential, and centrilobular necrosis in the liver.^{9,10}

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Paracetamol has been found in sewage treatment plant with concentration up to 6 and 10 ppb in natural waters.^{7,11,12} Thus, efficient degradation techniques are required to avoid potential risks of contaminated waters polluted by pharmaceuticals, particularly by paracetamol. Conventional methods, such as chemical coagulation, biological remediation, adsorption and advanced oxidation processes, have been applied for the treatment of wastewaters containing various contaminants.^{13–15} Moreover, subcritical water oxidation, with or without oxidants, is an effectual method for the degradation of hazardous compounds that exist in aquatic environments.^{16,17} Using subcritical water with oxidizing agents, such as oxygen, permanganate, hydrogen peroxide, *etc.*, various potential pollutants that are difficult to oxidize with conventional methods can be efficiently oxidized.^{16–18} Hydrogen peroxide is a relatively innocuous oxidation agent that decomposes to O₂ and H₂O at room temperature. It produces reactive hydroxyl radicals (HO•) which are able to efficiently degrade most organic pollutants present in wastewaters.^{19,20} Although oxygen is not as effective as hydrogen peroxide, it has been employed in many studies concerned with wastewater treatments due to its environmentally friendly nature.²¹ Thus, hydrogen peroxide, and oxygen were used as oxidizing agents in the present study.

In addition, the solubility of pharmaceuticals is essential for their removal from contaminated sites. Dissolving hazardous organic compounds in subcritical water appears to be an effective method for remediating contaminated water.²² Many literature studies focused on using several methods for determining the solubility of paracetamol in various solvents.⁷ These methods were often toxic and required an additional solvent removal step. Herein, subcritical water was used as a unique alternative and environmentally friendly method that offers many advantages.²³

In the literature, there are several investigations about the solubilities of pharmaceuticals in single and binary solvent mixtures, which is important for pharmaceutical industry. Approximation model equations are useful to predict the solubilities of the pharmaceuticals over a wide range of temperatures. These equations are obtained using experimental data for the pharmaceuticals. Various physicochemical parameters affect the approximation models, such as pressure, pH, salt and co-solvent concentration, dissolution enthalpy, entropy, *etc.* Moreover, the decomposition temperature of pharmaceuticals obtained through these models seems to be important.^{14,24,25} Thus, the mentioned models are recommended as useful for determining appropriate operating parameters by performing a limited number of experiments in decontamination treatments.

Paracetamol was degraded using O₂ and H₂O₂ in subcritical water. The solubility characteristics of paracetamol in subcritical water were investigated. In addition, an approximation model for the solubility of paracetamol was obtained using reported models for organic molecules.²³

EXPERIMENTAL

Reagents and apparatus

Paracetamol was supplied by Sigma–Aldrich, glacial acetic acid and H₂O₂ (35 vol. %, $\rho = 1.13 \text{ g cm}^{-3}$) were from Merck, and methanol from J. T. Baker. Deionized water (18 M Ω cm at 25 °C) was obtained from a Millipore Milli-Q Advantage A10. The HPLC column ACE 5 C18 (250 mm \times 4.6 mm id) was supplied by Mac-Mod (USA). An empty HPLC column (150 mm \times 4.6 mm i.d.) was used as an extraction cell. A Teledyne ISCO 260 D series syringe pump system (USA) was used for delivering water and providing pressure. O₂ and N₂ gases were supplied from Linde gas (Turkey). An Agilent 1200 model HPLC apparatus was used for the HPLC analyses.

Solubility experiments procedures

A syringe pump system and a self-made oven system were used for the solubility experiments, as described in a previous work.²⁶ An empty cylindrical HPLC column was filled with 0.25 g of paracetamol. Both ends of the column were covered with 0.45 μm mesh size frits and the cell was tightened to prevent leakage. The filled column was placed in a Tekno-sem TF R400 model oven. The syringe pump system was used to deliver water in the pressure mode fixed to 50 bar. Fractions (3 mL) were collected at 5, 10, 15 and 30 min after 60 min equilibration at each temperature. Solubility experiments were performed in triplicate to ensure accuracy of the experimental solubility data and were performed at six different temperatures ranging from 293 to 433 K.

Degradation experiments procedures

A self-made system, a so-called reactor, was used for the degradation experiments, as shown in a previous work.²⁷ The reactor was filled with 120 mL of 5 ppm aqueous paracetamol solution. Degradation experiments were performed at four different temperatures ranging from 373 to 433 K. The samples were collected at 5, 15, 30 and 60 min. The pressure was maintained at 30 bar with nitrogen to keep the water in liquid form, and 0.035 mL of H₂O₂ were used as oxidizing agent in each degradation experiment. In the other batch of degradation experiments, the pressure was maintained at 30 bar with oxygen, which also acted as an oxidizing agent in this case.

HPLC analysis

Paracetamol was analyzed using a mobile phase consisting of a mixture of 28 vol. % of methanol and 3 vol. % of glacial acetic acid in water at a flow rate of 1.5 mL min⁻¹ at ambient temperature. A UV-DAD detector was used at a wavelength of 275 nm. Paracetamol standards were prepared in deionized water.

RESULTS AND DISCUSSION

Effect of temperature on solubility

Experimental mole fraction solubilities (x_2) of paracetamol in subcritical water obtained at different temperatures are summarized in Table I. It is clearly seen that the temperature has a significant effect on the solubility as stated in previous studies.^{15,28}

However, the mole fraction solubility of paracetamol decreased dramatically to $x_2 < 10$ at 413 K due to possible degradation of paracetamol at higher temperature.

TABLE I. Comparison of experimental mole fraction solubility ($x_2 \times 10^3$) of paracetamol in subcritical water obtained in a static time (t) of 30 min according to Eqs. (1)–(6) defined later

T / K	Exp. ^a $x_2 \pm SD$ (30 min)	Eq. (1)	Eq. (2)	Eq. (3)	Eq. (4)	Eq. (5)	Eq. (6)
293	1.52±0.01	1.52	1.52	1.52	1.52	1.52	1.52
298	1.77±0.00	1.69	2.29	0.25	4.91	1.69	1.74
303	2.06±0.00	1.88	2.55	0.31	5.97	1.88	1.98
373	10.06±1.37	6.10	8.27	2.83	52.75	6.55	9.44
383	10.92±1.13	6.97	10.76	3.58	67.49	7.71	11.39
393	11.37±0.85	7.91	14.35	4.47	85.26	9.09	13.65
403	14.68±0.74	8.91	19.72	5.48	106.47	10.73	16.26

^aThe experiments were performed in triplicate

Effect of static time on solubility

The highest mole fraction solubility of paracetamol was obtained at 403 K as 12.78 ± 0.51 , 14.36 ± 0.59 , 14.44 ± 0.46 and 14.68 ± 0.74 , in static times of 5, 10, 15 and 30 min, respectively. The static time is an effectual parameter for the solubility of organic molecules, as stated in previous papers.²³ It was found that a static time above 10 min had a minor effect on the rates so that an adequate time was provided to the system to attain equilibrium.

Approximation models

Miller *et al.* proposed a new equation (Eq. (1)) for the solubility of polycyclic aromatic hydrocarbons in subcritical water.¹³ The mole fraction solubility at elevated temperatures can be predicted using the mole fraction solubility obtained at ambient temperature (T_0) as shown in Eq. (1):¹³

$$\ln x_2(T) \approx \left(\frac{T_0}{T}\right) \ln x_2(T_0) \quad (1)$$

where $x_2(T)$ demonstrates the mole fraction solubility at any temperature (T), $x_2(T_0)$ demonstrates the ambient mole fraction solubility and T_0 demonstrates ambient temperature.

The authors developed the equation by adding a cubic term to the base equation, Eq. (1), as is shown in Eq. (2):

$$\ln x_2(T) = \left(\frac{T_0}{T}\right) \ln x_2(T_0) + 15 \left(\frac{T_0}{T} - 1\right)^3 \quad (2)$$

Mathis *et al.* developed Eq. (3), which was employed for determining the solubility of liquid apolar organic compounds in subcritical water, as follows:¹⁴

$$\ln x_2(T) = \left(\frac{T_0}{T}\right) \ln x_2(T_0) + 2 \left(\frac{T - T_0}{T_0} - 1\right)^3 \quad (3)$$

Kayan *et al.* developed an approximation model, Eq. (4), for the solubility of benzoic and salicylic acids, which Yabalak *et al.* successfully applied for the solubility of sebacic acid:^{15,23}

$$\ln x_2(T) = \left(1.85 \frac{T_0}{T} - 1\right) \ln x_2(T_0) \quad (4)$$

Kapalavavi *et al.* developed a new model, Eq. (5), for the solubility of paraben in subcritical water:²⁸

$$\ln x_2(T) = \frac{T_0}{T} \ln x_2 T_0 + 0.5(C-1) \left(\frac{T_0}{T} - 1\right) \quad (5)$$

As is shown in Table I, none of the five equations could correctly predict the mole fraction solubility of paracetamol. Thus, a new modified approximation model (Eq. 6) was obtained, which correctly predicts the mole fraction solubility of paracetamol:

$$\ln x_2(T) = \frac{T_0}{T} \ln x_2 T_0 + 8/5 \left(\frac{T - T_0}{T_0}\right) \quad (6)$$

The developed model ensures a comprehensive prediction for the solubility of paracetamol at most of the temperatures compared with experimental ones, as illustrated in Table I.

Degradation of paracetamol with O₂

The degradation process was performed in subcritical water medium under O₂ atmosphere. Using O₂ in subcritical water medium offers a powerful and eco-friendly method that is widely used in the water recycling process and other environmental treatments.^{29,30} Dissolving oxygen in subcritical water initiates the formation of hydroxyl and other reactive radicals that participate in the reaction process, thereby increasing the degradation degree.³¹

Degradation experiments were realized at four selected temperatures, specifically at 373, 393, 413 and 433 K, as demonstrated in Table II. The degradation degree of paracetamol during 60 min were determined as 52.20±1.42 % without using oxidant at 433 K, and 68.66±1.05 % using the same conditions but under 30 bar of O₂ pressure.

TABLE II. Effect of temperature on the degradation degrees of paracetamol using O₂ in 60 min

T / K	433 (without O ₂)	373	393	413	433
Degradation, %	52.20±1.42	10.13±1.98	42.62±1.88	64.11±1.71	68.66±1.05

The effect of static time on degradation degree was investigated at four selected times (5, 10, 30 and 60 min), as shown in Table III. Increasing the static time from 5 to 60 min increased the degradation degree of paracetamol from 64.45±1.11 % to 68.66±1.05 % at 433 K. High static time might have enhanced the interaction of O₂ and other radicals formed by O₂ with paracetamol, thereby increasing the degradation degree.

TABLE III. Effect of static time on the degradation degrees of paracetamol using O₂ at 433 K

<i>t</i> / min	60 (without O ₂)	5	10	30	60
Remaining amount, ppm	2.18±0.08	1.77±0.06	1.68±0.09	1.62±0.07	1.57±0.05
Degradation degree, %	52.20±1.42	64.45±1.11	66.31±1.81	67.61±1.31	68.66±1.05

Degradation of paracetamol with hydrogen peroxide

Hydrogen peroxide is a unique alternative oxidant to air or pure oxygen in degradation of organic compounds to carbon dioxide and water.^{32,33} While H₂O₂ is reduced to H₂O and O₂ at room conditions, both of H₂O and O₂ do not have any effect on degradation degrees.^{34,35} It decomposes to form highly reactive hydroxyl radicals in subcritical water medium.^{36,37} Once hydroxyl radicals are produced, they initiate chain reactions in which reactive radicals are formed.³⁸ Generally, temperature and static time play an important role in the degradation process.¹⁶ High temperature enhances the decomposition rate of H₂O₂ to the aforementioned reactive radicals, thereby increasing the degradation rate of the target molecules. Adequate static time is essential for the effective interaction of oxidative species and the target molecules.¹⁶

Degradation experiments were performed at four selected temperatures, *i.e.*, 373, 393, 413 and 433 K, as shown in Table IV. The degradation degree of paracetamol in 60 min was determined as 52.20±1.42 % without using an oxidant at 433 K and 100±0.00 % under the same conditions using 0.035 mL H₂O₂, under nitrogen pressure fixed at 30 bar, as shown in Table IV.

TABLE IV. Effect of temperature on the degradation degrees of paracetamol using H₂O₂

<i>T</i> / K	373	393	413	433
Degradation degree, %	98.28±1.94	100±0.00	100±0.00	100±0.00

In addition, increasing static time from 5 to 60 min increased the degradation degree of paracetamol from 93.81±0.14 % to 98.28±1.94 % at 373 K, as shown in Table V.

TABLE V. Effect of static time on the degradation degree of paracetamol using H₂O₂ at 373 K

<i>t</i> / min	5	10	30	60
Remaining amount, ppm	0.31±0.01	0.30±0.01	0.21±0.02	0.09±0.10
Degradation degree, %	93.81±0.14	94.07±0.11	95.73±0.30	98.28±1.94

CONCLUSIONS

This study demonstrated that subcritical water has a remarkable effect on the degradation and solubility of paracetamol. It was found that the static time is an effective parameter along with temperature in both the degradation and solubility processes.

The experimental solubility results show a good consistency with the developed approximation model (Eq. (6)). The mole fraction solubility of paracetamol was determined as $(14.68 \pm 0.74) \times 10^3$ at 30 min static time and 403 K.

Furthermore, O_2 has a significant impact on the degradation degrees of paracetamol, enhancing the degrees by up to 18 %. While 100 % degradation was obtained using H_2O_2 , the attained degradation of 68 % using O_2 should not be underestimated due to its environmentally friendly nature.

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ИЗВОД

РАСТВОРЉИВОСТ И РАЗГРАДЊА ПАРАЦЕТАМОЛА У ПОДКРИТИЧНОЈ ВОДИ

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Испитани су растворљивост и разградња парацетамола коришћењем подкритичне воде. Проучен је утицај температуре и времена стајања на процес растварања при константном притиску (50 bar). Експериментални резултати показују да температура и време стајања имају пресудан утицај на разградњу и растворљивост. Максимална растворљивост од $(14.68 \pm 0.74) \times 10^3$ за парацетамол постигнута је на 403 K. Предложен је апроксимативан теоријски модел за растворљивост парацетамола. При разградњи парацетамола коришћени су кисеоник и H_2O_2 . Максимални степен разградње од $68,66 \pm 1,05$ и $100 \pm 0,00$ % постигнут је разградњом помоћу O_2 , односно H_2O_2 .

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