Phosphorus recovery from fosfomycin pharmaceutical wastewater by wet air oxidation and phosphate crystallization

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\section*{Abstract}
Fosfomycin pharmaceutical wastewater contains highly concentrated and refractory antibiotic organic phosphorus (OP) compounds. Wet air oxidation (WAO)-phosphate crystallization process was developed and applied to fosfomycin pharmaceutical wastewater pretreatment and phosphorus recovery. Firstly, WAO was used to transform concentrated and refractory OP substances into inorganic phosphate (IP). At 200 °C, 1.0 MPa and pH 11.2, 99% total OP (TOP) was transformed into IP and 58% COD was reduced. Subsequently, the WAO effluent was subjected to phosphate crystallization process for phosphorus recovery. At Ca/P molar ratio 2.0:1.0 or Mg/N/P molar ratio 1.1:1.0:1.0, 99.9% phosphate removal and recovery were obtained and the recovered products were proven to be hydroxyapatite and struvite, respectively. After WAO–phosphate crystallization, the BOD/COD ratio of the wastewater increased from 0 to more than 0.5, which was suitable for biological treatment. The WAO–phosphate crystallization process was proven to be an effective method for phosphorus recovery and for fosfomycin pharmaceutical wastewater pretreatment.

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1. Introduction

The occurrence of pharmaceutical and personal care product residues, especially antibiotics in environment has received considerable attention in recent years (Loganathan et al., 2009). They are considered to be emerging pollutants because they are bioactive, polar and persistent which may cause adverse effects on aquatic life and humans (Rozas et al., 2010). Additionally, antibiotics and their transformation products may result in the development of antibiotics resistant bacteria and genes (Kümmerer, 2009). Moreover, many of these pharmaceuticals are designed to be persistent and lipophilic (Loganathan et al., 2009), and are often not eliminated by wastewater treatment or biodegraded in environment (Sirtori et al., 2009). A solution to this water pollution problem has now become very urgent. Today, most drugs are manufactured through chemical synthesis. The chemical synthesis-based pharmaceutical wastewater contains a variety of organics including spent solvents, catalysts, additives, reactants, intermediates and finished products, which are refractory and microbial toxic (Oktem et al., 2007). It is estimated that approximately half of the pharmaceutical wastewaters produced worldwide are discharged without specific treatment (Chen et al., 2008). The effective disposition of these pharmaceutical residual effluents has become a challenging task.

Fosfomycin (1R-2S-epoxypropyl phosphonic acid) is a broad-spectrum antibiotic, originally isolated from fermentation broth of \textit{Streptomyces fradiae}. Now, fosfomycin is mainly produced by chemical synthesis. Fosfomycin wastewater is the residual mother liquor effluent of the chemical synthesis-based fosfomycin pharmaceutical process. The main pollutants in the wastewater are a variety of organic phosphorus (OP) intermediates, by-products and finished products, i.e. propargyl phosphonic acid, propenyl phosphonic acid, epoxypropenyl phosphonic acid, etc., as well as some raw materials and solvents like alcohols, anilines and EDTA. Extremely high concentrations of antibiotic OP compounds in the wastewater make it recalcitrant, non-biodegradable and toxic to the biological culture. However, few related studies up to date focus on fosfomycin pharmaceutical wastewater treatment. Therefore, the development of effective methods for fosfomycin wastewater treatment becomes urgent.

Wet air oxidation (WAO) is the liquid phase oxidation of organics at elevated temperatures (125–320 °C) and pressures (0.5–20 MPa) using oxygen as oxidant (Yang et al., 2010), and it is known to have great potentials for the treatment of wastewaters containing high contents of organic matters, or toxic contaminants for which direct biological purification is unfeasible and too diluted for incineration (Oliviero et al., 2001). Till 2007, over 400 WAO
plants had been in operation worldwide to treat preferential wastewaters from petrochemical, chemical and pharmaceutical industries as well as residual sludge from biological treatment plants (Levec and Pintar, 2007). It has been considered as one of the most promising and the simplest techniques for partial oxidation of parent pollutants into more biologically amenable intermediates (Katsoni et al., 2008), particularly for toxic organics (Suarez-Ojeda et al., 2008).

Phosphate crystallization technologies including calcium phosphate (CP) (Song et al., 2002; Bellier et al., 2006; Kim et al., 2006; Song et al., 2006) and magnesium ammonium phosphate (MAP) crystallization processes (Wang et al., 2006; Moerman et al., 2009; Saidou et al., 2009) are economically feasible, technically robust and operationally simple processes for phosphorus removal and recovery from waste streams (Shu et al., 2006). In recent years, phosphorus recovery by phosphate crystallization has become a hot topic and has been extensively studied for the treatment of a variety of phosphorus intensive wastewaters like supernatant of anaerobically digested activated sludge (Sibel and Maaazua, 2009), swine wastewater (Suzuki et al., 2007), landfill leachate (Gunay et al., 2008). Nevertheless, the application of phosphorus recovery technology to industrial wastewater treatment is still limited.

In this study, WAO–phosphate crystallization process was developed for fosfomycin pharmaceutical wastewater pretreatment and phosphorus recovery. Firstly, WAO was used to transform concentrated and refractory OP substances in the fosfomycin pharmaceutical wastewater into inorganic phosphate (IP); subsequently, the WAO effluent was subjected to CP and MAP crystallization processes for phosphorus removal and recovery. The aim of this study was to find the best way of treating harmful pollutants and recovering valuable phosphorus element from wastewaters like fosfomycin pharmaceutical wastewater containing concentrated OP compounds.

2. Materials and methods

2.1. Fosfomycin pharmaceutical wastewater

The wastewater used in this study was taken from a chemical synthesis-based fosfomycin pharmaceutical plant in Liaoning Province, the Northeastern China. The wastewater was generated from the epoxidation and chiral separation processes of fosfomycin manufacturing, which contained a variety of OP intermediates (i.e., propargyl phosphonic acid, propenyl phosphonic acid, epoxypropenyl phosphonic acid, etc.) and a little amount of finished fosfomycin products, as well as some alcohols, anilines and EDTA. The generation rate of the wastewater was 15 t d\(^{-1}\). The wastewater possesses a COD content of 60–80 g L\(^{-1}\), total OP (TOP) content of 8–10 g L\(^{-1}\), PO\(_{3}^-\)-P content of 0.8–1.2 g L\(^{-1}\), pH value of 11.0–12.0, but the BOD of the wastewater could not be detected (lower than the detection limit).

2.2. WAO experiments

Batch experiments were carried out in an autoclave equipped with a magnetically driven stirrer and two valves for sampling (GSH-1, Dalian Tongda, China). The autoclave was made of stainless steel, with an inner volume of 2.0 L. The reaction temperature was measured by using a thermocouple and controlled by PID regulator. Typically, 800 mL of fosfomycin pharmaceutical wastewater was introduced into the reactor. After flushing with nitrogen, the reactor was heated to the desired temperature. This procedure was used to minimize unwanted conversion during the heating-up period. Pressurization with oxygen was then completed and the reaction started at “zero time”. Throughout the reaction, procedure of 180 min, the reactor contents were stirred at 800 rpm to ensure good mass transfer from the gas phase to the liquid phase (Katsoni et al., 2008). Liquid samples of approximately 2.5 mL were periodically withdrawn from the reactor through a tube inside the reactor vessel, the COD and the TOP contents were measured. In order to investigate the effect of the reaction temperature, experiments were performed at 125–250 °C with a fixed oxygen partial pressure of 1.0 MPa (all at a reference temperature of 25 °C) and initial pH 11.2 (the original pH value of the raw wastewater). Subsequently, in order to study the influence of oxygen partial pressure, experiments were carried out from 3.0 to 6.0 MPa, with the temperature keeping constant at 200 °C and initial pH value of 11.2. Finally, the wastewater pH value was adjusted to 7.0 and 9.0 by using 6.0 M HCl, and the influence of initial pH values of the wastewater was tested at 200 °C, and 1.0 MPa. Experiments were repeated for three times to check the reproducibility of results.

2.3. Phosphate crystallization experiments

Batch experiments were performed on a magnetic stirrer with a stirring rate of 1000 rpm at room temperature of 22–25 °C (Song et al., 2007). 500 mL WAO effluent (WAO reaction parameters: temperature, 200 °C; oxygen partial pressure, 1.0 MPa; initial pH value, 11.2; reaction time, 180 min). The pH value of the WAO effluent was 6.8 was used. According to different Ca/P or Mg/N/P molar ratios designed, the CaCl\(_2\) solution or both MgCl\(_2\) and NH\(_4\)Cl solutions were added to the above effluent. Throughout the reaction, the pH value of the mixture was kept at 9.0 ± 0.1 for CP crystallization and 8.5 ± 0.1 for MAP crystallization by NaOH supplement. The reaction lasted for 30 min, and water samples of 1.0 mL were removed at frequent intervals and filtrated rapidly with 0.45 μm membranes. 2 μL of 6.0 M HCl was added to the filtrate rapidly to prepare samples for component analyses. The precipitate formed was dried naturally at room temperature. All the reagents were analytically pure reagents and deionized water was used in the experiments.

2.4. Analysis methods

The water samples were analyzed according to standard methods (SEPA, 2002). The concentrations of COD, PO\(_3^-\)-total phosphorus (TP) were analyzed colorimetrically with a spectrophotometer (752 N, China. Specify wavelength: COD at 600 nm, PO\(_3^-\) and TP at 700 nm). COD was measured with potassium dichromate digestion colorimetric method. PO\(_3^-\) was measured with molybdate–ascorbic acid colorimetric method, TP was measured with persulfate digestion molybdate–ascorbic acid colorimetric method, and TOP content was determined by subtracting the PO\(_3^-\)-P content from the TP value. In all the WAO experiments the TP content of the wastewater kept stable, and all TOP removed was considered to be transformed into PO\(_3^-\).

The concentrations of organic acids formed in the WAO were determined by gas chromatography (GC–7890A, Agilent, America) equipped with a capillary column (DB–FFAP 122–3232, 30 m × 0.25 mm × 0.25 μm) and a flame ionization detector. The oven and detector temperature was 120 and 250 °C, respectively. The split–splitless ratio was 30 and helium was used as a carrier gas at the flow rate of 1.8 mL min\(^{-1}\), and the air flow rate was set at 400 mL min\(^{-1}\).

The morphology of the precipitates obtained was observed by using scanning electron spectroscopy (SEM, KYKY-2800, China), and the structure of the crystals was analyzed with X-ray diffraction (XRD, Rigaku DMAX-RB, Japan).
The recovered solids were dissolved by using 0.10 M HNO₃, and the contents of heavy metals (Zn, Cu, Cr, Cd, Pb and Hg) were determined with an inductive coupled plasma emission spectrometer (Spectro Arcos Eop, Germany).

3. Results and discussion

3.1. WAO

3.1.1. Influence of reaction temperature

Fig. 1 showed TOP and COD decreases of the wastewater as the function of reaction time at a series of reaction temperatures (125–250 °C). The initial TOP and COD concentration were 8.23 and 72.7 g L⁻¹, respectively.

From Fig. 1a, when the temperature increased from 125 to 200 °C, TOP conversion significantly increased from 20% to 99% after 180 min reaction. Moreover, with the increase of the reaction temperature the apparent rate constants of TOP conversion increased from 1.4 × 10⁻³ to 3.4 × 10⁻² min⁻¹, it was evident that higher TOP conversion rates resulted from higher temperature. When the temperature was above 200 °C, the final conversion of TOP all could reach 99% within 180 min, nearly all OP substances were converted to IP. Nevertheless, drastic changes of TOP deple-

For COD (Fig. 1b), the reaction processes presented fast degra-

dation at the beginning without any initial induction period and then slowed down until it was terminated. In WAO, the oxidation of organic compounds generally fell into two steps: refractory organics were degraded into low-molecule-weight carboxylic acids (Oliviero et al., 2001) (i.e. formic, acetic and propionic acids, etc.), and short chain organic acids were mineralized into CO₂ and H₂O (Cybulski, 2007). Short chain organic acids were much more resistant to WAO even under severe conditions (Abussaud et al., 2008). Hence the oxidation of short chain organic acids became a major limitation of the WAO process. From Fig. 1b, when the temperature increased from 125 to 200 °C, the COD removal increased from 10% to 58%. Referring to TOP conversion (Fig. 1a), an experimental fact could be deduced that the oxidation of OP compounds was mainly in the first step, i.e. the breakup of C–P bands in OP compounds formed short chain organic acids and IP. At the temperatures of 200 and 225 °C, the COD removal results were comparable. In this temperature interval, nearly a complete transformation of TOP was obtained (Fig. 1a), whereas the temperature was still not high enough for an effective oxidation of short chain organic acids (Debellefontaine and Foussard, 2000). No significant changes of COD removal were observed after 60 min (Fig. 1b). When the temperature increased from 225 to 250 °C, the COD removal efficiency was promoted from 58% to 80%; it could be deduced that, short organic acids oxidation occurred. GC analysis showed that the acetic acid and propionic acid concentrations of the WAO effluent at 225 °C were 4.60 and 3.38 g L⁻¹, respectively; and for 250 °C, they were 3.31 and 1.84 g L⁻¹, respectively. The sum of two organic acids accounted for 42% and 65% of the residual COD of WAO effluent at 225 and 250 °C, respectively. Acetic acid and propionic acid were the main reaction intermediates. In previous studies, propionic acid oxidation occurred at temperature as low as 232 °C (Day et al., 1973), but acetic acid was stable in WAO environments at temperature as high as 275 °C (Shende and Mahajani, 1997).

Then, on purpose of TOP conversion, the temperature of 200 °C would be enough, and for further COD removal the reaction temperature should be kept above 250 °C. Although high temperature would enhance TOP and COD removals, the increase of operation temperature would also significantly increase the operating cost of WAO. Then 200 °C was used for further experiments.

3.1.2. Influence of oxygen partial pressure

Fig. 2a illustrated the TOP conversion under different oxygen partial pressures. As oxygen partial pressure increased from 1.0 to 6.0 MPa, little influence on the TOP final conversion but evident improvement of the TOP depletion profiles were observed, and the apparent rate constants of TOP conversion increased from 3.4 × 10⁻² to 5.3 × 10⁻² min⁻¹. Increased oxygen partial pressure enhanced the saturated oxygen concentration. Studies also reported that the dissolved oxygen increased in the solution could be helpful for the formation of strong oxidation species (Rivas et al., 1998). Therefore, high oxygen pressures could accelerate the oxidation of C–P bands, leading to a higher reaction rate of TOP conversion.

For COD removal, as shown in Fig. 2b, it increased from 57% to 67% with the increase of oxygen partial pressure from 1.0 to 4.0 MPa after 180 min. High oxygen partial pressure favored the oxidation of COD, which was consistent with previous researches (Chung et al., 2009; Yang et al., 2010). Nevertheless, no appreciable influence of COD removal (only from 67% to 69%) was noticed when the oxygen partial pressure increased from 4.0 to 6.0 MPa, indicating that the process expired not because of a lack of oxygen, but because of the presence of non-oxidizable matter under the operating conditions.

Although a high oxygen partial pressure as above 4.0 MPa would enhance the TOP conversion. The pressure effect was only marginal for COD removal. In fact, according to practical design experiences, higher operating pressure above 3.0 MPa usually should be avoided because above that pressure level, there was a very rapid increase in the capital cost of the WAO system (Lin et al., 1996). Then 1.0 MPa was considered to be a more cost efficient oxygen partial pressure.
3.1.3. Influence of initial pH value

Solution pH value had a significant effect on both WAO reaction rate and pathway. In WAO, the oxidation proceeded through a radical mechanism (Cybulski, 2007), the solution pH value had an effect on both the type of free radical reactions that occurred during the WAO and on the stability of the free radical intermediates formed (Abussaud et al., 2008). Another reason was attributed to the effect of pH value on the oxygen solubility (Bhargava et al., 2006). In this study, the influence of the initial pH value was assessed by adjusting pH value from 7.0 to 11.2. Fig. 3 depicted the results obtained.

The WAO reactions were run without pH value control. Consequently, the evolution of different chemical species throughout the WAO reaction changed the liquid-phase pH value with time. For most WAO reactions, many acidic species formed during the oxidation, acidifying the reacting solution. As shown in Fig. 3b, the pH values decreased as expected in the course of the WAO reactions. At initial pH values of 9.0 and 11.2, the pH values rapidly dropped to 7.4 and 8.0 after 15 min reaction, proving a fast formation of numerous acidic species at the beginning, and then the decrease of pH values slowed down and stabilized at 6.5 and 6.8 at the end of WAO. For initial pH value of 7.0, the solution pH value decreased slowly throughout the experiment with a final pH value of 5.8. In WAO, since about 20–40% of the intermediates were organic acids pH variations during WAO experiments also indicated low acid formations at low pH values.

As the initial pH value increased from 7.0 to 11.2, TOP conversion slightly increased from 94% to 99% and the COD removal was significantly enhanced from 44% to 57% in 180 min, high pH values promoted TOP conversion and COD removal. Nevertheless, the effect of initial pH values on TOP conversion was less notable than on COD removal, which might indicate that certain substances that were more sensitive to pH values existed in fosfomycin pharmaceutical wastewater besides OP compounds. Studies showed that, for some organic compounds like phenol, faster reaction rate was observed when the pH value was set above their dissociation constant (Kolaczkowski et al., 1997). Mantzavinos et al. (1996) also found that the oxidation of p-coumaric acid significantly increased as the pH value increased from 7.0 to 12.0. Since the fosfomycin wastewater was complexly composed, these kinds of organic compounds should benefit from high pH values with respect to the COD removal.

The original pH values of the fosfomycin wastewater were 11.0–12.0, so these pH values were favorable for the WAO of the wastewater.

3.2. Phosphate crystallization for phosphorus recovery

3.2.1. Effects of phosphorus recovery

WAO effluents (reaction parameters: temperature, 200 °C; initial pH value, 11.2; reaction time, 180 min) were subjected to phosphate crystallization experiments. Fig. 4 showed the PO$_4^{3-}$/C$_0$ removal profiles and the final PO$_4^{3-}$/C$_0$ removal efficiencies at different Ca/P and Mg/N/P molar ratios, respectively. The equilibrium for phosphate crystallization was established within 10–15 min in both CP and MAP processes at all molar ratios and no significant changes in the residual phosphate concentrations were observed during the rest time of the experiments.

High percent removals of PO$_4^{3-}$ obtained were 99.5 and 99.6% for CP and MAP processes at Ca/P molar ratio 1.0:1.00 and Mg/N/P molar ratio 1.0:1.0:1.0 (the exact molar ratios of hydroxyapatite (Ca$_5$(PO$_4$)$_3$OH, HAP) and struvite (MgNH$_4$PO$_4$·6H$_2$O, MAP)), respectively. Although the percent removals of PO$_4^{3-}$ were high, it should
be noted that the effluent still had considerably high concentration of PO$_4^{3-}$. Additional experiments were conducted to improve the removal of PO$_4^{3-}$ by increasing Ca/P and Mg/N/P molar ratios. From Fig. 4a and b, at the Ca/P molar ratio of more than 2.0:1.0, or at the Mg/N/P molar rate of more than 1.1:1.0:1.0, both CP and MAP crystallization processes could achieve more than 99.9% PO$_4^{3-}$ removals. The residual PO$_4^{3-}$ was lower than 5.0 mg L$^{-1}$. The PO$_4^{3-}$ removal profiles and the final PO$_4^{3-}$ removal efficiencies were promoted by increasing Ca/P or both Mg/P and N/P molar ratios. And for MAP process, at Mg/N/P molar ratio 1:1.0:1.0 and 1.0:1.1:1.0, the residual PO$_4^{3-}$ was 3.1 and 34.3 mg L$^{-1}$, showing that increasing Mg/P molar ratio was more effective for PO$_4^{3-}$ removal than increasing N/P molar ratio. Nevertheless, studies also showed that significant formation of hobierrite (Mg$_3$(PO$_4$)$_2$·8H$_2$O) would occur when Mg/P molar ratio > 2.5:1.0 (Warmadewanthi and Liu, 2009). Since the PO$_4^{3-}$ -P content of the WAO effluent was about 9.5 g L$^{-1}$, all could be removed and recovered by phosphate crystallization.

In the study, the BOD of the fosfomycin pharmaceutical wastewater was below the detection limit, suggesting that the raw wastewater was not suitable for biological treatment. After the WAO–phosphate crystallization, the BOD/COD ratio increased to 0.59 (WAO-CP process, WAO reaction parameters: temperature, 200 °C; oxygen partial pressure, 1.0 MPa; initial pH value, 11.2; reaction time, 180 min. CP reaction parameters: Ca/P molar ratio, 2.0:1.0) and 0.54 (WAO-MAP process, WAO reaction parameters: the same as the WAO-CP process, and the Mg/N/P molar ratio for MAP crystallization was 1.1:1.0:1.0), indicating that toxic organic compounds in the raw wastewater were eliminated and converted to easily biodegradable intermediates during the WAO, and the biodegradability of the fosfomycin pharmaceutical wastewater was significantly improved via WAO–phosphate crystallization pretreatment.

### 3.2.2. Products of phosphate crystallization

The morphology of recovered solids was observed by SEM, and the structure of the solids was detected with XRD. The results of the crystals collected at all molar ratios showed similar results. The MAP products were irregular shaped, being different from the familiar needle-like ones (Song et al., 2007). From XRD results, the pattern of the recovered solids and struvite match almost exactly, showing clearly that the crystal was basically struvite, and the purity was high.

Comparatively, the CP products took on much looser appearance. From the XRD results, CP products showed both obvious diffraction characteristics and strong background scattering. The peaks of CP products agreed well with the hydroxyapatite patterns, showing that the CP product might be a mixture of HAP and amorphous calcium phosphate (ACP). HAP was the most thermodynamically stable CP form (Pastor et al., 2010), whereas, in most cases, during the crystallization of CP, a precursor phase often more easily formed as ACP. In this study, the CP products showed certain HAP characteristics, which might be related to the conversion of the metastable ACP to HAP, and the conversion of ACP to HAP was favorable for the separation and recovery of CP crystals.

The recovered CP or MAP products could be recycled to phosphorus or fertilizer industries (Shu et al., 2006), but they should not contain too much hazardous contents like heavy metals. In order to determine the purity of the CP and MAP products, the heavy metal contents (in terms of Zn, Cu, Cr, Cd, Pb and Hg) of the recovered CP and MAP products were measured, and the results were shown in Table 1. It showed that both CP and MAP products contained only a very few amounts of Zn, Cu, Cr, and Cd, but Pb and Hg were not detected. The heavy metal contents met the requirements of phosphorus or fertilizer industries, and then could be recycled to these applications.

### 4. Conclusions

WAO–phosphate crystallization process was developed and applied for fosfomycin pharmaceutical wastewater pretreatment and phosphorus recovery. 99% TOP was transformed into IP and 58% COD could be reduced by WAO. And 99.9% IP was removed and recovered from WAO effluents by phosphate crystallization. After WAO–phosphate crystallization pretreatment, the BOD/COD ratio of the wastewater increased from 0 to above 0.5. The WAO–phosphate crystallization process was proven to be an effective method for fosfomycin wastewater pretreatment and phosphorus recovery. It was also expected to be a good alternative for other OP wastewater treatment like some organophosphorus pesticide production wastewaters.

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