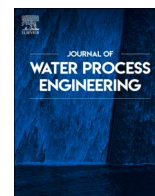




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## Effervescent ferrate(VI)-based tablets as an effective means for removal SARS-CoV-2 RNA, pharmaceuticals and resistant bacteria from wastewater

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### ABSTRACT

Waterborne pathogens including viruses, bacteria and micropollutants secreted from population can spread through the sewerage system. In this study, the efficiency of unique effervescent ferrate-based tablets was evaluated for total RNA and DNA removal, disinfection and degradation of micropollutants in hospital wastewater. For the purpose of testing, proposed tablets (based on citric acid or sodium dihydrogen phosphate) were used for various types of hospital wastewater with specific biological and chemical contamination. Total RNA destruction efficiency using tablets was 70–100% depending on the type of acidic component. DNA destruction efficiency was lower on the level 51–94% depending on the type of acidic component. In addition, our study confirms that effervescent ferrate-based tablets are able to efficiently remove of SARS-CoV-2 RNA from wastewater. Degradation of often detected micropollutants (antiepileptic, antidepressant, antihistamine, hypertensive and their metabolites) was dependent on the type of detected pharmaceuticals and on the acidic component used. Sodium dihydrogen phosphate based tablet appeared to be more effective than citric acid based tablet and removed some pharmaceuticals with efficiency higher than 97%. Last but not least, the disinfection ability was also verified. Tableted ferrates were confirmed to be an effective disinfectant and no resistant microorganisms were observed after treatment. Total and antibiotic resistant bacteria (coliforms and enterococci) were determined by cultivation on diagnostic selective agar growth media.

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## 1. Introduction

The hospital wastewaters play significant role as important source of viruses and their fragments, bacteria and also pharmaceutical residues [1,2]. Conventional biological treatment processes such as nitrification or denitrification have limited or minimal options for elimination of antibiotic-resistant bacteria (ARB) and of virus RNA [3]. Presence and spread of ARB is becoming one of the problems endangering public health. Although this threat has fallen behind the current pandemic, it could seriously complicate treatment of many COVID-19 patients and may increase mortality [4]. COVID-19 pandemic contributes and enhances development and dissemination of antibiotic resistance due to widespread biocide use and increased consumption of antibiotics also by COVID 19 patients. From this point of view, efficient disinfection of wastewater is needed [5]. The presence of viruses and their fragments in wastewaters raises considerable concern due to their ability of possible resistance to disinfection procedures [6]. The recent studies declare that 2–49.5% of COVID-19 positive cases had diarrhea [7] and actually, it is known that some viruses can spread through wastewater into which they are excreted together with human excrements in amount of  $10^2$  to  $10^{12}$  copies per gram of excrement [6]. Currently, there is assumption that some types of coronaviruses can survive several days in the environment and the question about the possible transmission via wastewater, must be asked [8]. SARS-CoV-2 RNA was detected in 40–89% of excrement from COVID positive patients [9–12]. Duration of faecal viral shedding was 1–33 days after negative nasopharyngeal swab [13]. Also, the positive detection of SARS-CoV-2 RNA in wastewater was observed in several recent studies [1,14–17]. The problem of hospital wastewaters is also closely related to occurrence of micropollutants such as pharmaceuticals and illicit drugs [18,19]. These micropollutants may be harmful mainly to aquatic organisms, but also to environment including humans, because they can infiltrate into the groundwater and expose drinking water sources [20,21]. Many pharmaceuticals occurred in hospital wastewater are very stable, non-biodegradable and resistant against conventional wastewater treatment [22]. To improve the quality of wastewater treatment, especially in places with a higher occurrence of pharmaceuticals, advanced oxidation processes (AOPs) were designed as possible tertiary wastewater treatment process. Among various AOPs, ferrates have been gaining popularity. Ferrates are very strong oxidative agents with a redox potential of 2.2 V in acidic environment [23]. Ferrates have unique disinfection properties and have shown the great potential in wastewater treatment as a coagulant and disinfectant, what can be used also in viral RNA elimination [24]. Recently, in addition to pure ferrate(VI), various water soluble polymeric capsules containing ferrate(VI) powder were designed [25,26]. Capsules were used for wastewater treatment not only in the case of various pharmaceuticals (efficiency over 80%), but also for antibiotic resistant bacteria elimination with promising results (complete removal) [5,25]. During the current pandemic situation, the issue of the virus occurrence in wastewater arises as a risk factor for spreading of infectious diseases. Virus surveillance in wastewater offer promising results with possible prediction of disease outbreaks [27]. On the other hand, the usage of ferrates as the wastewater treatment method can help prevent the spread of particles of viruses through the sewage system providing the safety solution in the case of new pandemic situation similar to the actual SARS-CoV-2. The uniqueness of this paper lays in special design of tableted ferrates with effervescent effect and their application for the removal of RNA viruses from hospital wastewater. Ferrate-based tablets present complex method of wastewater treatment. There is an urgent need to obtain more information on the possibilities of spreading SARS-CoV-2 and the ability of wastewater treatment plant (WWTP) to remove fragments of this virus, which is not currently achieved with conventional methods. Our study provides an interesting, cheap and effective solution to several problems associated with the presence of micropollutants and pathogens in wastewater including viral fragments focusing on SARS-CoV-2.

**Table 1**

Characterization of wastewater samples.

Wastewater	Psychiatric clinic (effluent)	Central hospital (influent on hospital WWTP)
Parameter/label	PC	CH
COD (mg/L)	56.3	1650
pH	8.2	7.0
NH <sub>4</sub> -N (mg/L)	3.3	19.8
NO <sub>3</sub> -N (mg/L)	12.8	4.9
PO <sub>4</sub> -P (mg/L)	4.2	6.5
Cl <sup>-</sup> (mg/L)	62.8	88.5
Number of beds	150	500
Treatment method	Nitrification	Nitrification/chlorination
Temperature (°C)	12	14
Flow (m <sup>3</sup> /day)	58	90
COVID-19 cases	0	20
Sampling date	20/11/2019	17/11/2020

## 2. Experimental

### 2.1. Preparation of effervescent ferrate(VI)-based tablets

Potassium ferrate(VI) tablet was prepared using hydraulic hand press (Trystom H62) with die for tablet (13 mm), according to [28]. Three types of tablets with purity of ferrate(VI)  $33 \pm 7\%$  were designed based on potassium ferrate: citric acid, anhydrous: sodium hydrogen carbonate (mass ratio 1:2:1; labeled A), potassium ferrate: sodium dihydrogen phosphate: sodium hydrogen carbonate (mass ratio 1:4:1; labeled B) and pure potassium ferrate tablet (125 mg; labeled F). One tablet per 100 mL of wastewater was dosed. As controls were used tablets without ferrates, i.e. tablets based on acidic component and sodium hydrogen carbonate. Reaction time was 5 min. All experiments were carried out in triplicate.

### 2.2. Quantification of RNA and DNA

Water samples were processed according to [29]. Nucleic acids were isolated by Trizol. Qubit Fluorometer, Qubit RNA and DNA HS Assay Kits (Thermo Fisher Scientific, Waltham, MA, USA) were used for the quantification of total RNA and total DNA. The presence of SARS-CoV-2 fragments were assessed using QuantiTect SYBR Green RT-PCR kit (Qiagen, Hilden, Germany) with primers specific for N1 gene (F: GAC CCC AAA ATC AGC GAA AT; R: TCT GGT TAC TGC CAG TTG AAT) and N3 gene (F: GGG AGC CTT GAA TAC ACC AAA; R: TGT AGC ACG ATT GCA GCA TTG). All experiments were carried out in triplicate.

### 2.3. Antibiotic resistance detection

Detection of total and antibiotic resistant enterococci and coliform bacteria in raw wastewater samples was performed according to [30]. Ampicillin, gentamicin, tetracycline, chloramphenicol, ciprofloxacin and vancomycin were applied in concentrations equal to resistance breakpoints for studied bacteria given by EUCAST [31]. All experiments were carried out in triplicate.

### 2.4. Wastewater sampling and HPLC-MS/MS analysis

Wastewater samples from hospital effluent (Table 1) were collected from the sampling point by an automatic sampling device from 7 to 10 a. m., decanted samples in 10-minute intervals with a total volume of 1800 mL. The samples were collected in plastic bottles and were frozen ( $-18\text{ }^{\circ}\text{C}$ ) 2 h after the sampling or stored in the fridge ( $9\text{ }^{\circ}\text{C}$ ; samples for disinfection study). The wastewater samples were let to thaw at room temperature, filtered through to the syringe filter (0.20  $\mu\text{m}$  regenerated cellulose, Labicom, Czech Republic) and a mixture of isotopically labeled internal standards was added before in-line SPE-LC-MS/MS

**Table 2**  
Removal efficiency of selected pharmaceuticals and their metabolites using ferrate-based tablets.

Sample Compound/tablet	Hospital wastewater Initial concentration (ng/L)	Removal efficiency (%)		
		A	B	F
Carbamazepine <sup>a</sup>	1550	13–29	91–99	36–39
Cetirizine	250	8–16	73–91	26–41
Dihydro CBZ	140	13–31	88–98	35–37
Epoxy CBZ	1530	9–27	17–30	0
Metoprolol acid	1000	0	43–50	32–39
Mirtazapine	320	53–62	>99	77–86
O-desmethylvenlafaxine	530	0	>96	>98
Oxcarbamazepine	940	0	>97	>89
Trazodone	120	41–47	>98	>98
Venlafaxine	450	7–22	22–26	67–69

<sup>a</sup> CBZ - carbamazepine.

analysis. The analytical method has been previously described [32]. All experiments were carried out in triplicate. This paper discusses selected – in wastewater often detected, pharmaceuticals or their metabolites from different therapeutic classes such as antiepileptic, antidepressant, antihistamine and hypertensive. Disinfection of wastewater in the Central hospital is currently carried out by chlorine gas. Its concentration in the effluent is kept at the level 4–5 mg/L and removal efficiency of total RNA fragments is about 60%.

### 3. Results and discussion

#### 3.1. Quantification of total RNA and DNA and their removal from hospital wastewater

The following data summarize results of the quantification of total RNA and total DNA in the samples before and after ferrate-based tablets treatment. The initial concentration of SARS-CoV-2 was 6400 copy/L. The removal efficiency of designed tablets was high, especially in the case of pure ferrate(VI) (tablet F) up to 100%. Pure ferrates are very strong oxidants and can completely destroy viruses, including SARS-CoV-2, and their fragments. Tableted ferrate (VI) showed lower efficiency caused by the presence of the acidic substance which has been preferentially degraded by the ferrates. RNA removal efficiency was 80–100% for A tablets, and 70–94% for B tablets. Similar results were obtained for DNA removal. The removal efficiency was 80–94% for A tablets and 51–82% for B tablets. The efficiency of the A tablets (based on citric acid) was significantly higher than B tablets (based on sodium dihydrogen phosphate) in all cases. Ferrate-based tablets seem to be the suitable option for the destruction of RNA parts of viruses as the samples were positively tested for SARS-CoV-2 before the usage of tablets and negatively tested afterwards. The options currently in use are for example a set of disinfection tanks – directly on site with infectious cases – but the disadvantage of these tanks is the high consumption of chlorine-based preparations and the need for multiple disinfection steps [33]. By removing RNA and DNA fragments does not occur the horizontal transfer of genetic information through wastewater [34]. The presence of SARS-CoV-2 RNA confirmed by RT-PCR analysis in wastewater does not automatically imply the presence of infectious virus. However, studies on the related SARS-CoV virus suggest that these types of coronaviruses may be infectious in wastewater for some time. According to this study, this virus retains infectivity in wastewater for up to 14 days at 4 °C under certain conditions, but at 20 °C for 48 h [35]. There are only few studies on inactivation of SARS-Cov-2 in wastewater so far. Chan et al. [36] reported that the genome of the SARSCoV-2 strains are phylogenetically closest to the bat SARS-related coronaviruses, and the Spike protein has a 78% nucleotide identity with the human SARS-CoV-1. Due to the similarities between SARS-CoV-1 and SARS-CoV-2, the SARS-CoV-2 might also be sensitive to either environment factors or disinfectants. Our results show that the designed

tablets have the ability to destroy viruses very quickly, effective and without hazardous radical by-products, what is a typical advantage of ferrates. There was also confirmed the ability of tableted ferrates to remove SARS-CoV-2 RNA directly from the hospital wastewater.

#### 3.2. Efficiency of effervescent ferrate-based tablets in antibiotic resistant bacteria elimination

Number of total and antibiotic resistant coliform bacteria in untreated water ranged from  $2.21 \pm 0.03$  to  $3.69 \pm 0.03$  log CFU/mL and number of total enterococci was  $1.00 \pm 0.02$  log CFU/mL. No antibiotic resistant enterococci were detected in raw effluent water. Treatment of wastewater with tableted ferrate caused a decrease of all detected antibiotic resistant bacteria below the detection limit.

#### 3.3. Effervescent ferrate-based tablets used for wastewater treatment

Prepared tablets (A, B and F) were also used for the study of removal of selected pharmaceuticals and their metabolites present in wastewater samples. Only compounds occurred in collected wastewater at concentration above 100 ng/L are reported. Obtained results are summarized in Table 2.

Presented pharmaceuticals are often occurred in wastewater and in surface water and are difficult to degrade [37,38]. Pure ferrate was very effective in trazodone, oxcarbamazepine and O-desmethylvenlafaxine removal with efficiency between 89 and 98%. Ferrate-based tablets treatment resulted in higher removal efficiency in some cases for carbamazepine and its metabolites, cetirizine, metoprolol acid, mirtazapine and lamotrigine compared to pure ferrate experiment. Generally, the highest pharmaceuticals removal efficiency was achieved using tablets containing sodium dihydrogen phosphate (labeled B). Removal efficiency by ferrates depends on the way in which the oxidation of individual pharmaceuticals takes place. It also depends on the oxidative potential of the pharmaceuticals, thus whether the redox potential of ferrates is high enough to oxidize a particular class of pharmaceuticals.

### 4. Conclusions

Our study for the first time reported the unique effervescent ferrate-based tablets for the complex wastewater treatment including viral RNA destruction and disinfection. Viruses like a SARS-CoV-2 or their RNA fragments can be embedded in excrements as well as urine and conventional disinfection procedures are not effective enough to destroy them [39]. Designed ferrate-based tablets effectively removed up to 90% of total RNA and 87% of total DNA. Fragments of SARS-CoV-2 were completely removed using ferrate-based tablets. Prepared tablets removed at least 99.9% of bacteria from wastewater and tested antibiotic resistant bacteria were below limit of detection. Proposed tableted ferrates are also very effective (96–99%) in wastewater treatment of



some pharmaceuticals and their metabolites (*O*-desmethylvenlafaxine, oxcarbamazepine, trazodone and mirtazapine). Obtained results indicate higher removal efficiency when sodium dihydrogen phosphate was used as an acid substance balancing of pH of ferrates reaction. Tableted ferrates with effervescent effect offer the fresh look at the way of potentially infectious hospital wastewater treatment. Simple dosage and effervescent effect that replace the stirring are unique benefits of tableted ferrates. The absence of dangerous radical by-products, unlike disinfection using chlorine compounds, advises ferrates on environmental friendly technology and their price increases this rank. Designed tablets can be used for quick disinfection after using the toilet in hospitals or medical centres with infectious cases, in household for wastewater treatment as replacement for chlorine-based tablets but also for drinking water treatment if a reliable source of water is not available.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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