Research, Society and Development, v. 9, n. 8, e411985425, 2020
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v9i8.5425

Degradação de citarabina, creatinina e uréia na urina artificial pelo processo fotoelétrico de sono-eletroquímico

Degradation of cytarabine, creatinine, and urea in artificial urine by a photo-assisted sono-electrochemical process

Degradación de citarabina, creatinina y urea en orina artificial mediante un proceso de electro-química foto asistida

Recebido: 08/06/2020 | Revisado: 25/06/2020 | Aceito: 07/07/2020 | Publicado: 11/07/2020

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Resumo

O presente trabalho teve como objetivo a avaliação da combinação de técnicas eletroquímicas, fotoquímicas e sonroquímicas (sono-eletroquímica fotoassistida) aplicadas à degradação da citarabina (droga quimioterapêutica) na urina simulada que continha creatinina e uréia, através de uma pesquisa laboratorial quali e quantitativa. Um reator eletroquímico de filtro prensa de fluxo contínuo foi empregado usando o ânodo dimensionalmente estável (DSA® - Ti / Ru0.3Ti0.7O2) como material do eletrodo. O delineamento fatorial 23 foi utilizado para otimizar melhores degradações dos compostos orgânicos contidos na urina artificial (creatinina e uréia) juntamente com a citarabina, variando a corrente elétrica, o tempo de retenção e a vazão; a resposta variável foi o carbono orgânico total (TOC). Além disso, as análises UHPLC demonstraram a remoção da ancitabina (precursora da citarabina), corroborando com os dados obtidos pelo delineamento experimental. O uso da urina artificial como suporte eletrônico interfere no processo eletroquímico, levando o TOC a níveis elevados. No entanto, observou-se que houve remoção significativa da carga orgânica presente na solução de efluente, mesmo quando é utilizada uma matriz de degradação mais complexa (urina artificial).

Palavras-chave: Processo oxidativo avançado; Quimioterapêutica; Eletroquímica; Planejamento fatorial; Efluentes hospitalares; Fotoquímica; Sonoquímica.

Abstract

The present work had as its objective, the evaluation of the combination of electrochemical, photochemical and sonrochemical techniques (sono-electrochemical photoassisted) applied to degradation of cytarabine (chemotherapeutic drug) in a simulated urine that continues with creatinine and laboratory research. The paper involved laboratory research with both a qualitative and quantitative approach. A continuous-flow filter-press electrochemical reactor was employed using Dimensionally Stable Anode (DSA® - $Ti/Ru_{0.3}Ti_{0.7}O_2$) as the electrode material. A 2^3 factorial design was used to optimize the degradation of organic compounds contained in artificial urine (creatinine and urea) together with cytarabine, varying applied current, retention time and flow rate, the response variable was total organic carbon (TOC) removal. Additionally, UHPLC analyses demonstrated the removal of ancitabine (precursor of cytarabine), corroborating with the data obtained by the from the experimental design. The use of artificial urine as an electronic support interferes with the electrochemical process, taking TOC to high levels. However, it was observed that there was significant removal of the organic load present in the effluent solution, even when a more complex degradation matrix is used (artificial urine).

Keywords: Advanced oxidation process; Chemotherapeutics; Electrochemistry; Factorial planning; Hospital effluent; Photochemistry; Sonochemistry.

Resumen

El objetivo del presente fue evaluar la combinación de técnicas electroquímicas, fotoquímicas y sonoquímicas (foto-asistidas del sueño-electroquímicas) aplicadas a la degradación de citarabina (fármaco quimioterapéutico) en orina simulada que contiene creatinina y urea, a través de investigaciones de laboratorio cualitativas y cuantitativas. Se empleó un reactor electroquímico de filtro-prensa de flujo continuo utilizando Ánodo Dimensionalmente Estable (DSA® - Ti / Ru0.3Ti0.7O2) como material del electrodo. El diseño factorial 23 se utilizó para optimizar mejores degradaciones de compuestos orgánicos contenidos en orina artificial (creatinina y urea) junto con citarabina, corriente eléctrica variable, tiempo de retención y velocidad de flujo, la respuesta variable fue el carbono orgánico total (TOC). Además, los análisis de UHPLC demostraron la eliminación de ancitabina (precursor de citarabina), corroborando con los datos obtenidos por el diseño experimental. El uso de orina artificial como soporte electrónico interfiere con el proceso electroquímico, llevando el TOC a niveles altos. Sin embargo, se observó que hubo una eliminación significativa de la carga orgánica presente en la solución del efluente, incluso cuando se usa una matriz de degradación más compleja (orina artificial).

Palabras clave: Proceso oxidativo avanzado; Quimioterapia; Electroquímica; Planificación factorial; Efluentes hospitalários; Fotoquímica, Sonoquímica.

1. Introduction

The increase in the number of people diagnosed with cancer is a reality experienced in several health units worldwide (Costa, 2010). The higher incidence of cancer increases the consumption of anti-cancer drugs, as chemotherapy is one of the most frequently used treatment options (Shewach and Kuchta, 2009). Chemotherapy consists of the use of chemical compounds, called chemotherapeutics (Costa, 2010), also known as cytotoxic or antineoplastic agents (Rabii, Segura, et al., 2014) primarily used in hospitals and are administered to outpatients and inpatients (Allwood, Stanley & Wright, 2002). The effluents from hospitals disposed of without previous treatment, containing cytostatic drugs and metabolites excreted by humans, are responsible for environmental impacts caused by health units (Michelini, 2013).

As a result, drugs and their metabolites have been classified as a subclass of organic contaminants, known as emerging pollutants. These are constantly being inserted into the aquatic environment through the inadequate disposal of residues from pharmaceutical industries, untreated hospital effluents and through the excretion of drugs by countless consumers. (Yu and Wu, 2011).

There are reports of the presence of emerging pollutants in water sources in several countries, such as Germany (Molinari, Pirillo, et al., 2006), United States (Jamil Akhtar, Ataullah Khan, et al., 2003), Italy (Molinari, Pirillo, et al., 2006) and Brazil (Molinari, Pirillo, et al., 2006; Stumpf, Ternes, et al., 1999). Brazil is one of the largest consumers of drugs in the world, along with the United States, France, and Germany (Stumpf, Ternes, et al., 1999).

As it is known that many cytostatic drugs are resistant to the degradation processes by conventional treatments (Moura and Silva, 2016). New Environmental decontamination processes are being developed, among them, advanced electrochemical oxidative processes (AEOPs) that can be used as alternative techniques due to their efficiency in the treatment of pollutants in aqueous media (Malpass, Miwa, et al., 2007; Parra , Gul, et al., 2016)

Electrochemical processes are characterized by the “in situ” generation of oxidizing species without the need for adding chemical substances, which is one of the main advantages of this process, pollutants can also be destroyed by direct anodic oxidation, by reactive species of oxygen or oxidants generated from the anodic oxidation of water or electrolytic anions (such as $Cl_2^{\bullet}/OCl^-$ produced at the anode from the Cl^- ion during electrolysis) (Pereira De Sousa, Pinto, et al., 2019).

Some studies have demonstrated that electrolysis can eliminate the cytotoxicity, mutagenicity, and antibacterial activity of clinical wastewater containing antineoplastics (Kobayashi, Hirose, et al., 2012; Hirose, Kondo, et al., 2005). A combination of electrochemical degradation, in the presence of Cl^-, and simultaneous UV irradiation of the reaction mixture, known as photo-assisted electrochemical degradation, can reduce toxicity when compared to isolated methods (Parra, Gul, et al., 2016; Pereira De Sousa, Pinto, et al., 2019; Xiang, Fang, et al., 2016).

Pinto et al. (2019) proved that the combination of three techniques, photochemistry, electrochemistry and sonochemistry, called photo-assisted electrochemical sleep, generated highly oxidizing species, allowing an effective degradation of atrazine, achieving a TOC removal of approximately 98%. Also presenting a greater energy efficiency when compared with isolated techniques.

In view of the above, the present study proposes the application of combined electrochemical, photochemical and ultrasound processes to promote the degradation of the cytarabine (chemotherapeutic drug), creatinine and urea in artificial urine, which is a highly complex degradation medium, and investigate the efficiency of this process for the treatment of effluents.

2. Metodology

The work was a laboratory research on a quali/quantitative basis (Pereira et al., 2018).

2.1.Simulation clinical wastewater containing antineoplastic

The simulated urine (Table 1) presented the following characteristics: pH 6; total organic carbon (TOC) = 5462.25 $mg.L^{-1}$, and conductivity at 13.75 $mS.cm^{-1}$ (298.95 K). Creatinine anhydrous (P.A), urea (99-100) and the artificial urine salts (Laube, Mohr, et al., 2001) were obtained from Labsynth®. Cytarabine was purchased from Sigma Aldrich®. All reagents were used as received.

Table 1. Composition of the simulated effluent.

Substance	**$g.L^{-1}$**
$CaCl_2.2H_2O$	1.103
NaCl	2.925
Na_2SO_4	2.25
KH_2PO_4	1.40
KCl	1.60
NH_4Cl	1.00
Urea	25.00
Creatinine	1.10
Cytarabine (anti-cancer drug)	0.003

Source: Authors (2020).

As can be observed from Table 1, the simulated urine contains large amounts of inorganic salts. This can be helpful in an electrochemical process as the salts provide electrical conductivity, avoiding the addition of further reagents. On the other hand, the presence of urea and creatine increases the organic load and this may lead to difficulties in removal of Total Organic Carbon.

2.2.Analytical methods

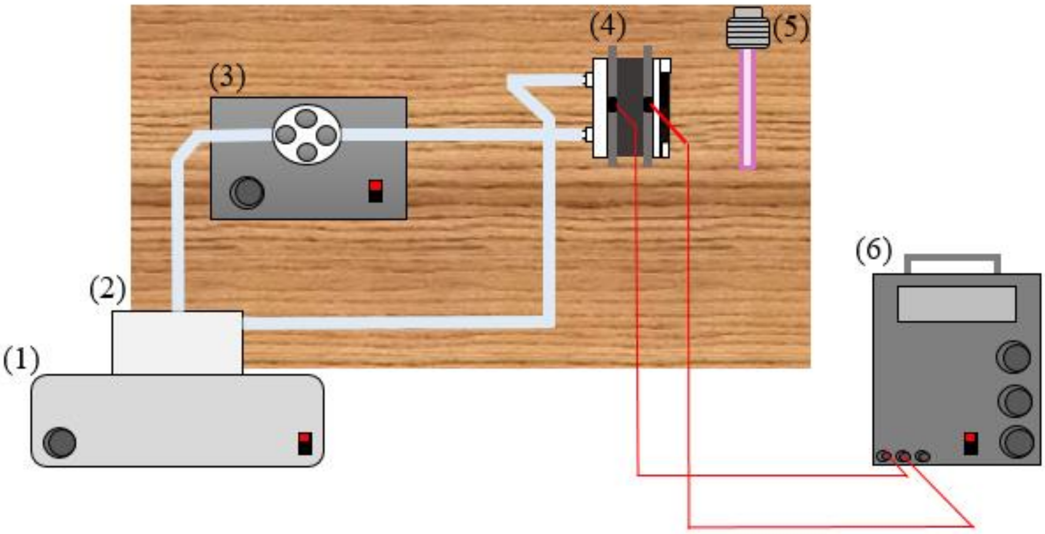
Total organic carbon (TOC) analysis was performed using a Sievers InnovOx carbon analyser, General Electric Company. Creatinine analysis was determined in the artificial urine by the modified Jaffé reaction method (Campins Falcó, Tortajada Genaro, et al., 2001). Urea analysis was determined by spectrophotometric method (Knorst, Neubert, et al., 1997) both performed on the Shimadzu MultSpec-1501 spectrophotometer. Cytarabine was analysed by ultra-high-performance liquid chromatography (UHPLC) equipment with Xevo TQ-s Micro mass spectrometer (Waters). In addition, measurements of iodometric titration according to the standard methodology (AWWA, APHA, et al., 2017), completed the data collection used for analysis.

2.3. Photo-Assisted Sono-Electrochemical reactor

A continuous-flow, filter-press electrochemical cell using a Dimensionally Stable Anode (DSA® -$Ti/Ru_{0.3}Ti_{0.7}O_2$) from De Nora Brazil as the anode material and a Ti-mesh as the cathode as previously used (Pinto, Antonelli, et al. , 2019). The system was mounted with a spacing between electrodes of 4.36 mm (reaction volume of 6.1 cm^3). A peristaltic pump (Masterflex® L/STM 77200-60) was used to pump solution through the cell and an ultraviolet light source (375 W) was irradiated directly into the cell. The ultrasonic energy was employed by an ultrasonic vessel (Cristofoli) with frequency of 42 kHz (**Figure 1**).

As can be seen in Figure 1, the system is composed of various components. The simulated urine solution is present in a reservoir (2) which is maintained in an ultrasonic bath (1). The solution is pumped from the reservoir by a peristaltic pump (3) to the electrochemical reactor (4). In experiments with combined electrochemical and photochemical techniques, UV radiation is provided by a UV lamp (5). Electrical current was supplied by a stabalized source (6).

Figure 1. General scheme of the system, where: (1) ultrasonic bath; (2) effluent solution reservoir; (3) pump; (4) electrochemical cell; (5) UV light source; (6) stabilized source



Source: Authors (2020).

2.4.Experimental Design

The initial factorial design 2^3 was carried out, with two levels and three variables, using the software STATISTICA®. The three operational variables used in this study were flow rate (X1), electric current (X2) and time (X3). The level of factor coded for these parameters was designated as -1 (low) and +1 (high), which are given in Table 2.

Table 2. Variables studied with coded and real values for the factorial design (2^3)

Variable	Symbol	Level	
		-1	+1
Flow (mL min^{-1})	X_1	3.24	4.67
Current (A)	X_2	0.5	1.0
Circulation time (min)	X_3	30	60

Source: Authors (2020).

The experimental range was determined based on the data found in the literature (Pinto, Antonelli, et al. , 2019), using as a response variable the percentage of total organic carbon removal (TOC%). The repetitions were performed at all points, from a 95% confidence interval.

3. Results and Discussions

3.1.Factorial Design (2^3)

The removal of TOC was used as a response factor in the factorial design, thus being able to analyse the mineralization of all organic pollutants present in the studied effluent, knowing that the organic compounds in question are: creatinine, urea and cytarabine and the results can be seen in ANOVA (Table 3).

Table 3. Analysis of Variance (ANOVA) referring to Factor planning 2^3 for TOC%

	Sum of square	df	Mean square	F	p
current	253,6056	1	253,6056	56,59861	0,000068
Flow rate	68,1450	1	68,1450	15,20831	0,004546
time	25,5530	1	25,5530	5,70281	0,043989
1 by 3	98,1090	1	98,1090	21,89555	0,001583
2 by 3	60,7620	1	60,7620	13,56061	0,006197
Lack of fit	19,3666	2	9,6833	2,16108	0,177669
Pure error	35,8462	8	4,4808		
Total SS	561,3876	15			

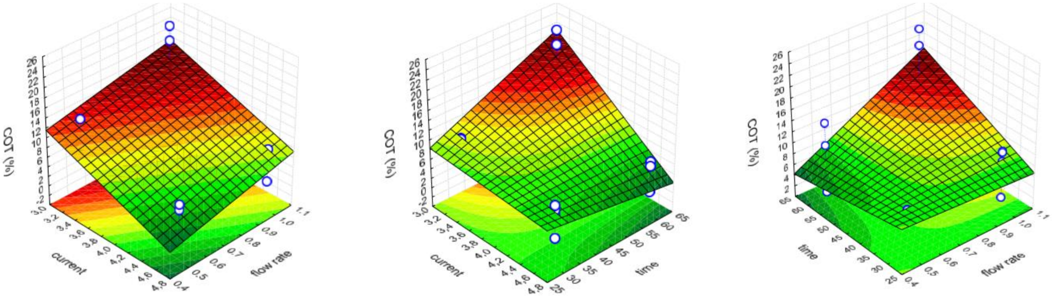
Source: Authors (2020).

From Table 3 is possible to verify the adequacy tests, the p value was <0.05, which indicates that the model is statistically significant (Singla, Verma, et al., 2018), with an R^2 value of 0.90174 for removing TOC. The insignificant terms of the model in the manual regression method were automatically discarded, which, in turn, provided the summary results of the analysis of variance. After treating the results, the estimation and validation of the mathematical model are expressed by equation 1.

$$\%COT= 9{,}06-4{,}95X_1+4{,}13X_2+2{,}53X_3-7{,}96X_1X_3+3{,}89X_2X_3 \qquad 1$$

To assess the influence of variables in relation to TOC removal, response surfaces were constructed (Figure 2).

Figure 2. Response surface graphs for (a, b, c) for TOC (%).



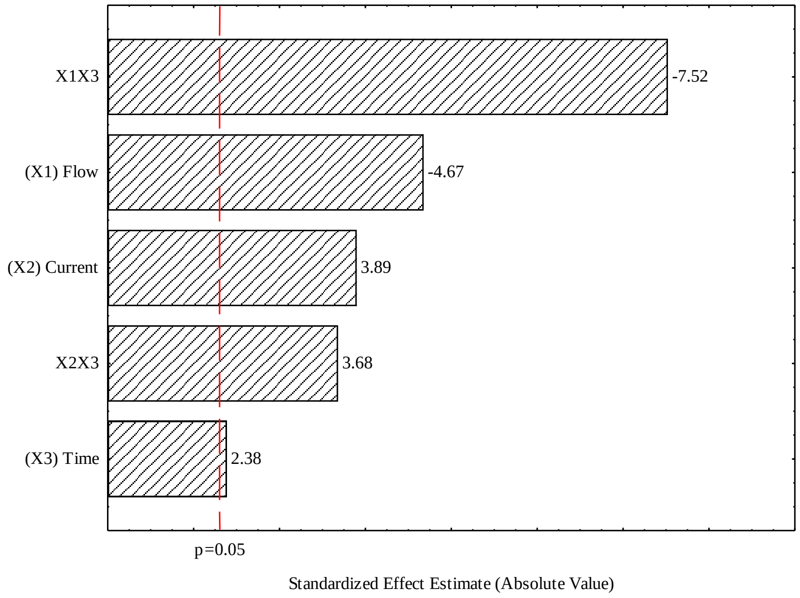
Source: Authors (2020).

It is possible to verify that the pump flow has a negative effect on the response, that is, the lower the pump flow, the greater the removal of TOC this can be explained, since the increase in flow decelerates the mineralization of organic compounds (de Mello Florêncio, de Araújo, et al., 2016). Electric current and time, on the other hand, present positive influences on the process response, that is, with increased time and current, chlorine/hypochlorite production can be increased, this is due to the longer residence time of chloride ions in the reactor, generating higher concentrations of free chlorine species (Singla, Verma, et al., 2018).

The literature describes more expressive results in the removal of organic matter in systems where degradation is carried out in aqueous medium containing NaCl as a supporting electrolyte. According to Pinto (2019), when the photo-assisted sono-electrochemical technique was used, it promoted removal of atrazine (> 99%) in less than 30 minutes of treatment. Parra et al. (2016) studied the degradation of tetracycline in aqueous medium and in artificial urine and observed that in aqueous medium (NaCl) that an increase in the rate of degradation of approximately 16 times was observed. These facts can be explained due to the presence of creatinine and urea interfering in the electrochemical process, due to the decrease of electroactive sites on the electrode and causing the degradation to present lower pollutant removal speeds.

In agreement with that observed in the response surface graphs, Figure 3 presents the Pareto chart for the initial factorial design.

Figure 3. Pareto's chart for the initial 2^3 factorial design.



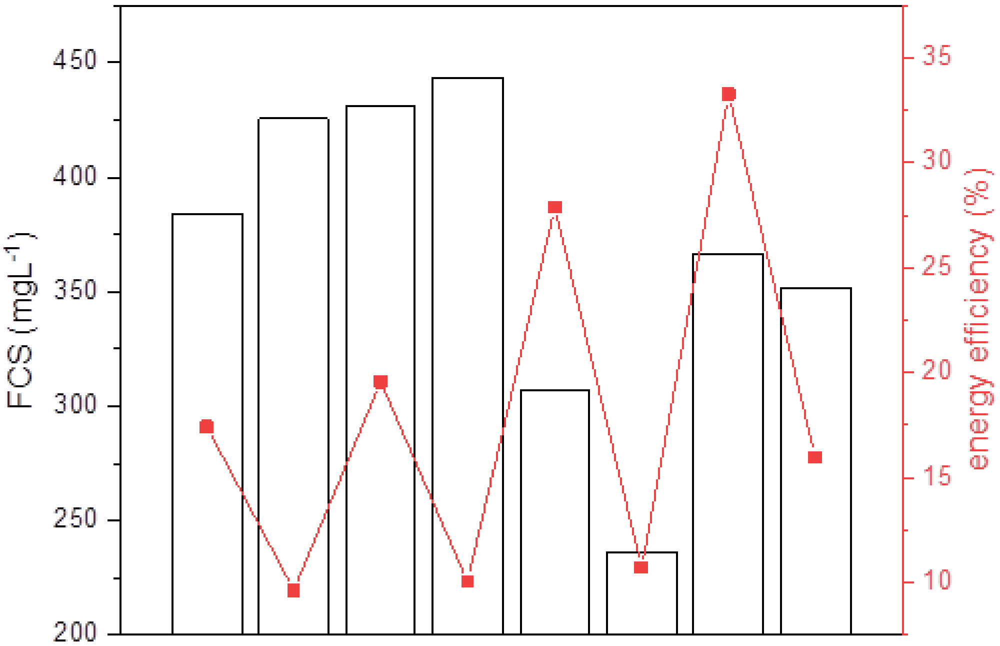
Source: Authors (2020).

The negative behaviour of the flow-rate indicates that lower flow rates favour the removal of TOC. The electric current and the reaction time present positive behaviour, and the increase of these variables favours the removal of TOC. Even though the time has a lower significance among the observed variables, the terms of the time interactions with the pump flow (X_1X_3) and the electric current (X_2X_3) were significant in the process.

3.2. Free chlorine production versus energy efficiency

The highest concentrations of free chlorine species (FCS) (Figure 4) were obtained with the high values of current (1.0 A) and time (60 min), and low value of flow (3.24 mL min-1).

Figure 4. Concentration of free chlorine species (FCS) and energy efficiency at different flow-rates (mL/min), currents (A) and time (min) during the 2^3 experimental design.



4.67	4.67	3.24	3.24	4.67	4.67	3.24	3.24	(mL min^{-1})
0.5	1.0	0.5	1.0	0.5	1.0	0.5	1.0	(A)
60	60	60	60	30	30	30	30	(min)

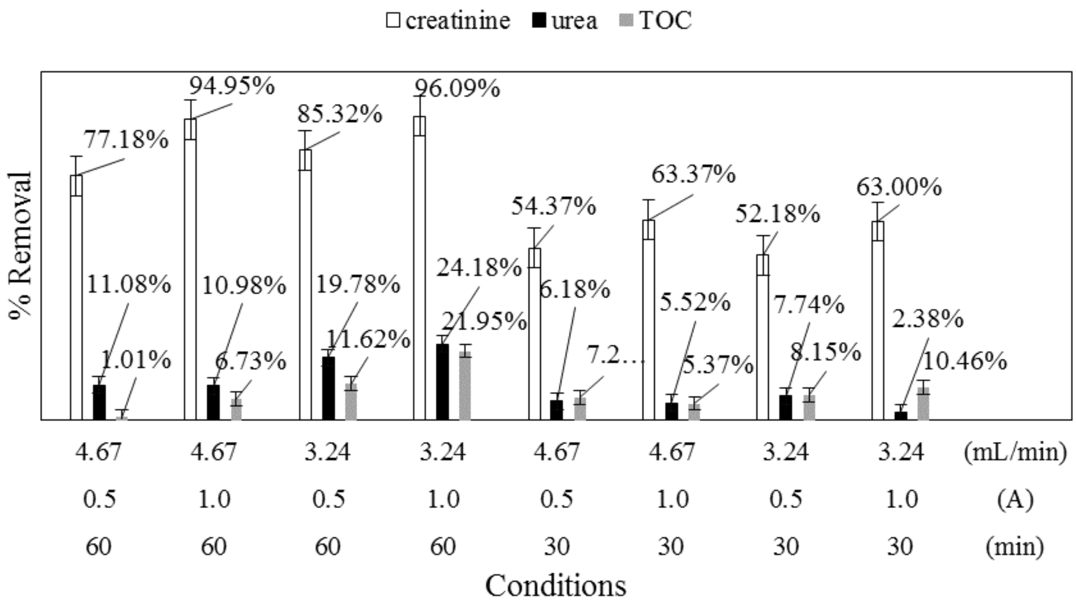
Source: Authors (2020).

This is due to the longer residence time of the chloride ions in the reactor, generating higher concentrations of free chlorine species. Such efficiency is based on Faraday's laws, the first law says that the amount of material released at both the anode and the cathode is proportional to the amounts of electrical energy used, whereas the second law states that, for the same amount of electrical energy, the amount of material released in the anode and cathode is proportional to the equivalent masses of the substances formed (Sousa, Tonhela, et al., 2017). And to achieve the best energy efficiency, these effects have a negative significance, so a better response is observed when there are low values of flow-rate, current and time, justifying the study of the energy consumption of the process to obtain economically viable values. This fact can be verified based on the studies by Reis et al. (2012) in which the energy consumption for the electrochemical technique is proportional to the applied current.

3.3.Removal of cytarabine, urea and creatinine

The best results for the removal of creatinine (96.09%) and urea (24.18%), with initial concentrations of 1.1 and 25 g L^{-1}, respectively, were observed in this condition (Figure 5).

Figure 5. Percentage of degradation of creatinine, urea, and COT.

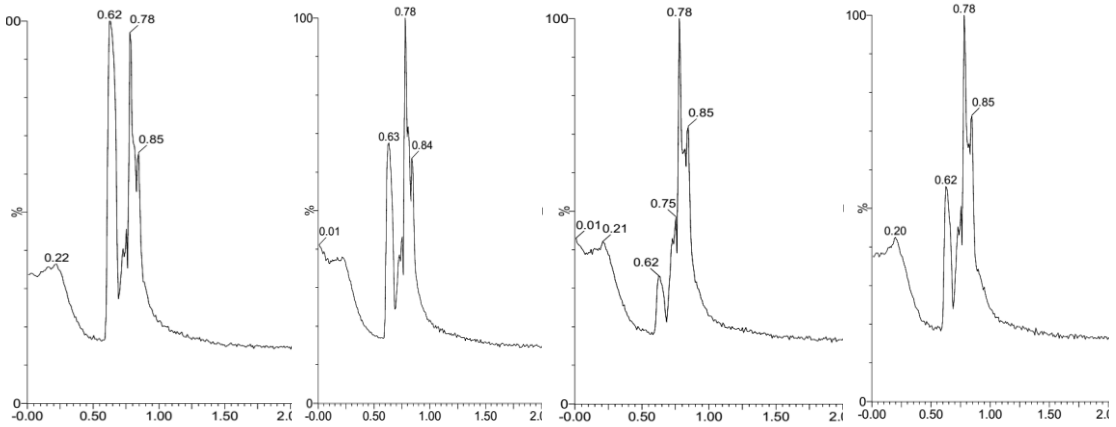


Source: Authors (2020).

According to Parra (2016), urea and creatinine adsorb under the surface of the electrode and can compete with the electrogenerated oxygen, and also with the reaction of chloride detachment, thus decreasing the formation of active chlorine species and consequently the oxidation by indirect processes. Such phenomena further reduce the efficiency of individual processes, so the presence of interferents makes it difficult to break down specific target molecules into natural waste.

Greater removals of organic compounds were obtained in a longer retention time. Because of this, to assess the presence and approximate intensity of cytarabine after the degradation process, the time was fixed at 60 minutes and was carried out under different flow and current conditions. The presence and approximate intensity of cytarabine (chemotherapeutic pollutant) was evaluated by UHPLC (Figure 6).

Figure 6. Chromatographic separation of cytarabine in artificial urine.



A	**B**	**C**	**D**
3.24 mL min^{-1}	4.67 mL min^{-1}	3,24 mL min^{-1}	4,67mL min^{-1}
0.5 A	0.5 A	1.0 A	1.0A
removal TOC :11.62%	removal TOC :1.01%	Removal TOC: 21,95%	removal TOC :6,7

Source: Authors (2020).

Initially cytarabine (0.85 minutes) had approximately 62% intensity. The presence of cytarabine at this peak was confirmed by the mass spectrum with molecular ion peak in m/z 244 and base peak in m/z 112 (Hsieh, Duncan & Brisson, 2007). After degradation, in Figure 6 C and D, the peak intensity relative to cytarabine increased to approximately 72%. According to the literature (Kissinger and Stemm, 1986) the cytarabine in aqueous solution degrades slowly by hydrolysis (less than 1% in 5 days) resulting in the uracil arabinoside deamination product. However, the study demonstrated that in the chromatographic separation of a cytarabine sample, in addition to the presence of the peak of this compound and its degradation product, a peak in retention time lower than the peak of cytarabine is observed, which is relative to ancitabine (probably at 0.62 minutes), which is a precursor of cytarabine. The presence of ancitabine in cytarabine samples is medically useful to maintain effective doses in chemotherapy, since it undergoes rapid deamination in the body for arabinoside uracil.

Initially, the intensity of ancitabine is approximately 85%. Already after degradation this intensity varies from approximately 100%, 68%, 32% and 55% in Figure 6 A, B, C and D, respectively. Thus, the best degradation condition is obtained with high current (1.0 A) and time (60 min) values and low flow-rate (3.24 mL min^{-1}) (Figure 6 C), because despite high intensity of cytarabine, the lowest intensity of the peak that, possibly, refers to the ancitabine. The high intensity of the cytarabine peak suggests that a much longer degradation time will be required to obtain the conversion of ancitabine to cytarabine and subsequent degradation thereof.

Condition C (Figure 6), among all analysed conditions, is also the condition that presents the best TOC removal (21.95%) (Figure 5), which is the best degradation condition of the sample components. Thus, the evaluation by UHPLC-MS corroborates with the data obtained during the experimental design.

4. Conclusions

The use of urine as a supporting electrolyte increases the total organic carbon content in the medium and interferes in the electrochemical process, due to the reduction of the electroactive sites, requiring higher retention times for the complete degradation of the organic compounds present. However, significant removal of the organic compounds present in the effluent by the photo-assisted sono-electrochemical process is observed, even in a more complex environment, with a high content of total organic carbon (artificial urine) in relation to the aqueous medium. Conscious that most drugs are eliminated through the urine, this medium would allow advancements in the studies of electrochemical degradation, since it has high concentrations of salts (sulphates, phosphates, and chlorides) capable of increasing the degradation of pollutants.

In future studies it would be interesting to understand the effect of the presence of urea and creatinine on the rate of removal of the target compound. It would also be interesting to study real urine samples

Acknowledgements

The authors thank FAPEMIG and CNPQ for the financial support. The company Ourofino Agrociência in Uberaba/MG for the help with the UHPLC evaluation of the samples. The authors are grateful to the Hospital of Clinics of UFTM and Hospital Hélio Angotti for share information for the research.

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