DOI: 10.24850/j-tyca-13-06-03

Articles

Primary treatment and ozonation of model wastewater from the production of soft capsules

Tratamiento primario y ozonización de aguas residuales modelo de la producción de cápsulas blandas

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Abstract

The lipid extract of fruits of the royal palm Cubana (*Roystonea regia*), developed at the National Center for Scientific Research (CNIC), will be used in the treatment of benign prostatic hyperplasia (BPH). The product is a liquid oil to be encapsulated in soft gelatin capsules. In Cuba, there was no industrial plant for soft capsule production; a plant was built for this purpose, which was necessary for the previous study of the wastewater model. A treatment scheme to laboratory scale of three stages: Trap of fat, primary sedimentation, and ozonation was evaluated. In the first two stages, hydraulic retention times of 15, 30, and 45 minutes were studied, obtaining the best condition for 30 minutes. The ozonation process was carried out with an experimental design 2^3, with two ozone concentrations in the gas (40 and 60 mg O_3/l), two gas flows (10 and 20 l/h), and two pH values (3 and 7); the ozonation time was 30 min. Ozone doses of 330, 500, and 660 mg O_3/l were applied. Statistical analysis showed that the best results were obtained with ozone concentration: 60 mg O_3/l; gas flow: 10 l/h, and pH: 3. The combination of the treatment stages allowed achieve a total efficiency of reduction of COD (51.6 %), BOD_5 (64.7 %), ST (21 %), SSed (100 %), fats and oils (79.3 %), detergents (91.6 %), nitrogen

(30.1 %), phosphorus (93.1 %), turbidity (85.8 %) and color (90.1 %), guaranteeing compliance with the Cuban NC standard 27: 2012.

Keywords: The trap of fat, sedimentation, ozonation, soft capsules, wastewaters treatment.

Resumen

El Centro Nacional de Investigaciones Científicas de Cuba desarrolló un medicamento a partir del extracto lipídico de frutos de la palma real cubana (*Roystonea regia*) destinado al tratamiento de la hiperplasia prostática benigna. El producto es un líquido oleoso que será encapsulado en cápsulas blandas de gelatina. En Cuba no existía instalación industrial para producir cápsulas blandas, por lo que se construyó una planta con este propósito, siendo necesario el estudio previo de aguas residuales modelo. Se evaluó un esquema de tratamiento a escala de laboratorio de tres etapas: trampa de grasas, sedimentación primaria y ozonización. En las dos primeras etapas se estudiaron tiempos de retención hidráulica de 15, 30 y 45 minutos, obteniéndose la mejor condición para 30 minutos. El proceso de ozonización se estudió con un diseño experimental 2^3, con dos concentraciones de ozono en el gas (40 y 60 mgO_3/l), dos flujos de gas (10 y 20 l/h), y dos valores de pH (3 y 7); el tiempo de ozonización fue de 30 min. Se aplicaron dosis de ozono de 330, 500 y 660 mg O_3/l de agua tratada. El análisis estadístico mostró que los mejores resultados se obtuvieron con concentración de ozono: 60 mg O_3/l; flujo de gas: 10

l/h, y pH: 3. La combinación de las etapas de tratamiento permitió alcanzar una eficiencia total de reducción de DQO (51.6 %), DBO_5 (64.7 %), ST (21 %), S_{Sed} (100 %), grasas y aceites (79.3 %), detergentes (91.6 %), nitrógeno (30.1 %), fósforo (93.1%), turbidez (85.8 %) y color (90.1 %), garantizando cumplir con la norma cubana NC 27:2012.

Palabras clave: trampa de grasa, sedimentación, ozonización, cápsulas blandas, tratamiento de aguas residuales.

Received: 05/03/2021

Accepted: 08/15/2021

Introduction

The National Center for Scientific Research (CNIC) developed a drug obtained from lipid extracts of Royal Palm (Roystonea regia) fruits, indicated for the treatment of benign prostatic hyperplasia (BPH). This product contains fatty acids (oleic, lauric, palmitic, and myristic), common in the diet and components of any vegetable oil.

This product is an oily liquid, so its most suitable pharmaceutical form is the soft gelatin capsule (CBG), where the active pharmaceutical ingredients (API) are coated by a thin film consisting of gelatin (35-45 %), water (40 %) and plasticizer (glycerol, sorbitol 15-25 %). In addition, colorants (iron oxide red ci77491, iron oxide black ci77499), preservatives, opacifiers, and flavorings can be added. Gelatin is a protein of animal origin obtained mainly from bovine bones and pig skin; this type of gelatin is clear and plastic (Brian & Fridrun, 2004; Carolina, 2010). CBG has a water-soluble character, high disintegration speed, and resistance to oxidation (Fridrun, 2004).

In Cuba, it was decided to build an industrial factory for the production of CBG; however, since there is no industrial facility of this type, the physical, chemical, and microbiological composition of the liquid waste generated in the process is unknown, as well as the treatments used to reduce or eliminate contamination levels. From the literature consulted, CBG production methods and cleaning processes are known (Brian, 2004; Carolina, 2010; DICT-CNIC, 2015), but they do not provide information on the composition of the waste generated nor the treatment systems employed, so the study of these residuals and their treatment are essential and novel.

It has been shown that several pharmaceutical compounds are not completely removed in the treatments, which have been found in the effluents of conventional treatment factorys (Ternes *et al*., 2002; Miao, Bishay, Chen, & Metcalfe, 2004; Stackelberg *et al*., 2004; Hernando,

Mezcua, Fernández-Alba, & Barceló, 2006; Manaia, Novo, Coelho, & Nunes, 2008; Deblonde, Cossu-Leguille, & Hartemann, 2011; Rivera-Utrilla, Sánchez-Polo, Ferro-García, Prados-Joya, & Ocampo-Pérez, 2013; Baresel *et al*., 2015; Rodríguez-Narvaez, Peralta-Hernandez, Goonetilleke, & Bandalac, 2017); as well as surface water, groundwater and drinking water in several countries (Kolpin *et al*., 2002; Boyd, Reemtsma, Grimm, & Mitra, 2003; Wiegel *et al*., 2004; Dougherty, Swarzenski, Dinicola, & Reinhard, 2010; Stuart, Lapworth, Crane, & Hart, 2012; Leung *et al*., 2013; Blair, Crago, Hedman, & Klaper, 2013; Chang, 2015; Sorensen *et al*., 2015; Ebele, Abdallah, & Harrad, 2017; Gogoi *et al*., 2018).

Some of the adverse effects of pharmaceutical waste contamination include aquatic toxicity, development of resistance in pathogenic bacteria, genotoxicity, and the emergence of compounds considered endocrine disruptors that affect human health (Leung *et al*., 2013; Vasquez, Lambrianides, Schneider, Kümmerer, & Fatta-Kassinos, 2014; O'Neill, 2016; Rubio, Delgado, & Amaya, 2017; Hogerzeil *et al*., 2018).

Because conventional treatment processes, especially biological ones, sometimes do not represent a safe barrier against several recalcitrant drugs or industrial toxicants, there is a need to introduce advanced treatment technologies that can be considered tertiary or safe treatments. Several technologies have been evaluated for this purpose

with good results. Table 1 presents a summary by several authors with the types of treatment used, contaminants, and main results.

Table 1. Examples of technologies evaluated to reduce toxic and recalcitrant pollutants.

Types of Wastewater	Contaminants	Treatment	Results	Author
Municipal wastewater	Pharmaceuticals and endocrine disruptors	Ozonation	Doses O_3: 2-5 mgl^{-1} Efficiency: 90-99 %	Huber *et al.* (2005)
Surface and underground	Pesticides: Carbamates, Chlorophenoxy Compounds, Organochlorine Organophosphates	Ozonation Ozone/H_2O_2 Ozone/UV	• Aldicarb (9.5 mg/l^{-1}) Doses O_3: 1 mgl^{-1}, pH: 8.3. Ef:100 % • Carbofurans: O_3/UV. COD >85 %. • Dicamba 6.4 μgl^{-1}: 3 mgO_3/7 mgH_2O_2. Ef: 100 % • Dicofol 6.4 $\mu g\ l^{-1}$: 1.5 mgO_3/0.75 mgH_2O_2, pH: 9.4. Ef: 100 %.	Ikehata & Gamal-El-Din (2005)
Superficial and drinking water Municipal	Pharmaceutical Compounds: Antipyretics Analgesics	Ozonation Ozone/H_2O_2 Ozone/UV	<u>Removal efficiency 100%:</u> • Cefazolin and Cephalosporin: H_2O_2/UV: 26 mg/l/2.8x10^{-6} Einst s^{-1}	Ikehata, Jodeiri y Gamal-El-Din

wastewater	Antibiotics Antidepressants Anticonvulsants Contraceptive Cytostatics	H_2O_2/UV TiO_2/UV	Azithromycin: Doses O_3: 3.5 mg l^{-1} • Lincomycin (50 mgl^{-1}): TiO_2/UV: 1 gl^{-1}/8.5 $mW.m^{-2}$, pH: 6.2h. • Ofloxacin (560 μg l^{-1}): Doses O_3: 14 mgl^{-1}, pH:7.4 H_2O_2/UV: 5-10 mM/2.5x10^{-6} Einst s^{-1} • Sulfadiazine 2 μgl^{-1},O_3: 2 mgl^{-1} ,pH: 7 • Carbadox and Trimethoprim: Doses O_3: 0.3 mgl^{-1}, pH: 7.5 • Carbamazepine (118 mg l^{-1}): Doses O_3: 1 mgl^{-1}, pH: 5.5. • Ibuprofen (2 μgl^{-1}): 5 mgO_3l^{-1} and 1.8 mgH_2O_2 l^{-1}. • Propanolol and estrone: Doses O_3: 5 mgl^{-1}, pH: 7	(2006)
Effluents from wastewater treatment plants	Aquatic ecotoxicity. Estrogens and 17β-Hydroxyandrogen	Ozonation pilot plant (30-36 m^3/h)	Doses O_3: 0.6-1.1 gO_3/gCOD Decrease in estrogen-immunoreactivity in 97.7 % and androgen-immunoreactivity in 56.3 %. Reduction of steroid	Altmann *et al.* (2012)

			hormones	
Effluents from wastewater treatment plants	Medicament (47) and drugs (11)	Ozonation and ultrasound pilot plant (50 m^3 h^{-1})	Ozone doses: 7-12 mg/l, High efficiency in most of the investigated drugs. Low efficiency with ultrasound	Abellán-Soler (2013)
Aqueous solutions. Drinking waters. Effluents from treatment plants	Benzotriazole N, N-diethyl-m-toluamide Chlorophene, 3-Methylindole Nortriptyline	UV, UV-H_2O_2 UV-Fe^{2+}-H_2O_2 UV-TiO_2 UV-$S_2O_8^{2-}$ Foto-Fenton Fenton-Like Foto-Fent-Like O_3/H_2O_2	UV-$S_2O_8^{2-}$>UV-TiO_2 >UV-H_2O_2 >UV. Foto-Fenton>Foto-Fenton-Like >Fenton> Fenton-Like. Better results in real waters: UV-TiO_2, O_3/H_2O_2, Foto-Fenton	Benitez, Acero, Real, Roldán y Rodríguez (2013)
Industrial and urban wastewater	Organic material Heavy metals Organic acids Inorganic anions	Ozone (O_3). O_3-Solar (Sol). O_3-Photocatalytic (O_3-Sol-Cat).	O_3-Solar-Cat > O_3-Solar> O_3	Chávez *et al*. (2019)
Aqueous solutions	Sulfamethoxazole Carbamazepine Ibuprofen	Nanofiltration membranes	Retention efficiencies: 98-100 %	Nghiem, Schafer y Elimelech, (2005)
Ultrapure water Municipal	Pharmaceutical contaminants and	Ultrafiltration (UF) Nanofiltration	NF: Retention of 70 % of most of the contaminants evaluated.	Acero, Benítez, Teva y

effluents	pesticides	(NF)	UF: Retention less than 50 %	Leal (2010)
Municipal secondary effluents	Pharmaceutical contaminants and pesticides	Activated carbón (PAC). Granul. Activ.Carbon (GAC). Ultrafiltration (UF). Coagulation.	Best results: - PAC + UF - UF + GAC Coagulation: Low efficiency	Acero, Benítez, Real y Teva (2012)
Municipal secondary effluents	Pharmaceutical Contaminants and Personal Use (Total: 31)	Sand filter (SF). O_3/H_2O_2. Biological Activated Carbon (BAC).	Average efficiency (28 pollutants) SF: 25 % O_3/H_2O_2: 85 % BAC: 90 %	Gerrity *et al.* (2011)
Aqueous solutions	Cephalexin	Granular activated carbón (GAC) and ozonation	GAC: 3 g/l Doses O_3: 15-20 mgl^{-1}, pH: 7-8 100 % Cephalexin elimination 60 % COD reduction	Akhtar, Imran, Zahoor y Amin (2016)
Municipal secondary effluents	Pharmaceutical Contaminants and Personal Use	Sand filtration (SF). Granular Activated Carbon (GAC)	Efficiencies: SF: Low retention. GAC:> 90 % contaminant removal 35-65 % COD reduction	Reungoat, Escher, Macova y Keller (2011)

Among the treatment technologies, ozonation and advanced oxidation processes (AOPs) provide good results for the removal or reduction of pharmaceutical pollutants in drinking water and wastewater treatments (Fernández *et al*., 2020). These processes are efficient for municipal and industrial wastewater containing biorefractory and toxic organic pollutants such as pesticides, tannins, and phenolic compounds (Alvares, Diaper, & Parsons, 2001; Ikehata & Gamal-El-Din, 2005; Ramírez, Espinosa, Fernández, Véliz, & Ramos, 2016; Cabrera *et al*., 2016), cleaners (Ikehata & Gamal-El-Din, 2004) and other industrial chemicals (Chávez *et al*., 2019), achieving in many cases the reduction of high organic loads and partial or complete mineralization of pollutants. Likewise, ozonation reduces or eliminates pathogenic microorganisms (Veliz, Bataller, Fernández, & Fernández, 2012; Nasser, 2017).

Due to the oxidizing power of ozone, it has been used as a chemical reagent for the oxidation of organic substances (Alvares *et al*., 2001; Beltrán, 2004) and mixtures of organic compounds to increase their biodegradability (Paul & Debellefontaine, 2007). As well as to obtain oxygenated compounds such as aldehydes, short-chain acids, and alcohols. Ozone is able to react with most elements and bring the lowest oxides to their highest oxidation state (Ikehata & Gamal-El-Din, 2008). Similarly, it is very effective in reducing or eliminating color and odor. In addition, it contributes to improving the efficiency of various

stages of wastewater and sludge treatment (Paul & Debellefontaine, 2007).

The combination of treatment and ozonation processes has been evaluated with good results in wastewater from the pharmaceutical industry (Abellán-Soler, 2013; Marcelino, Leao, Lago, & Amorim, 2017; Rodríguez-Narvaez *et al*., 2017; Kıdak & Doğan, 2017) and from industrial laundries (Seo, Moon, & Lim, 2001), with high contents of cleaning products and production residues. Also, in domestic wastewater for reuse (Bataller, Veliz, Fernández, Fernández, & Espinosa, 2014; Veliz, Fernández, Llanes, & Bataller, 2016).

Considering the above, the present work aims to characterize the model wastewater generated in the production of soft capsules at a laboratory scale and establishes the operating parameters of a treatment scheme that combines processes of fat retention, primary sedimentation, and ozonation, which ensures compliance with the Cuban discharge standard NC 27: 2012. Based on the results obtained, an alternative for the treatment of this wastewater on a larger scale is proposed.

Materials and methods

Three stainless steel reactors of 500 mL were used to obtain model wastewater. One reactor contains the active pharmaceutical ingredient (API) –Palmex; in another, the mixture of gelatin and dye is prepared, and in the last, the prepared gelatin is stored.

In the three reactors, the filling and emptying process were carried out with the products, leaving their walls impregnated with remains of API oils, gelatin, and colorants. After, these reactors were washed and sanitized following the cleaning procedures and chemical products established in the factories of oily drug production (Oleozón® Production Factory of CNIC), which are similar to those that will be produced in the SCGs Factory. The cleaning products used and their dosage is presented in Table 2. The final wastewater was obtained by mixing the waters from washing the three reactors in a plastic tank of 30 l. Subsequently, the physical-chemical characterization of the water was carried out.

Table 2. Products used for cleaning reactors.

Product	Dosage
Hot drinking water (60-80 °C)	2 l water /l reactor
Industrial cleanser	30-60 g/l
Industrial degreaser	150 ml/l

Industrial descaler	5-10 %
Industrial disinfectant	70 %
Rinse with drinking water (~ 25 ºC)	10 l water /l reactor

The fat trap treatment processes, primary sedimentation, and ozonation of the model wastewater of the production of soft capsules were carried out in an experimental installation at a laboratory scale (Figure 1).

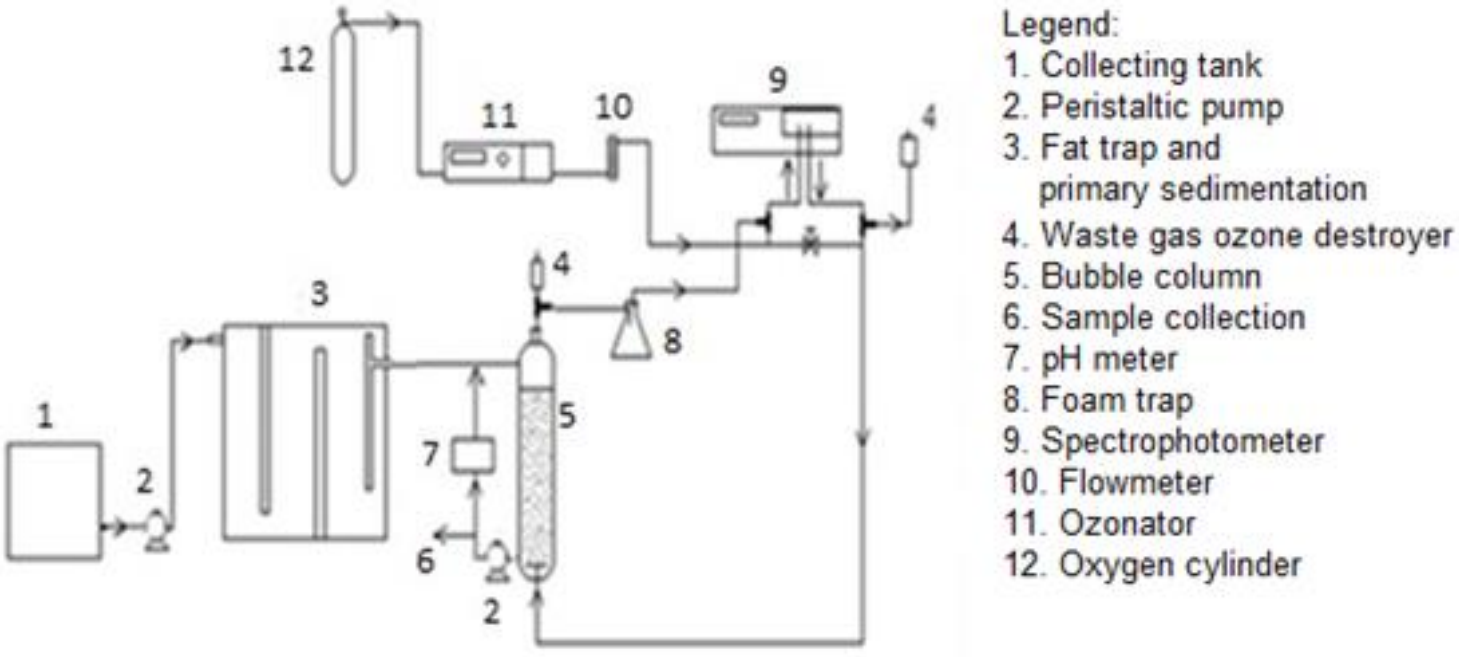

Figure 1. Scheme of the experimental installation.

Figure 2 shows the diagram and photograph of the tank with intermeddle panels at a laboratory scale. This tank groups the processes of fat trap and primary sedimentation. Their treatment zones are:

-Zone I: Retention of fats and oils. Downward flow.

-Zone II: Retention of settleable solids. Upward flow.

-Zone III: Retention of settleable solids. Downward flow into the compartment and upward through the outlet tube.

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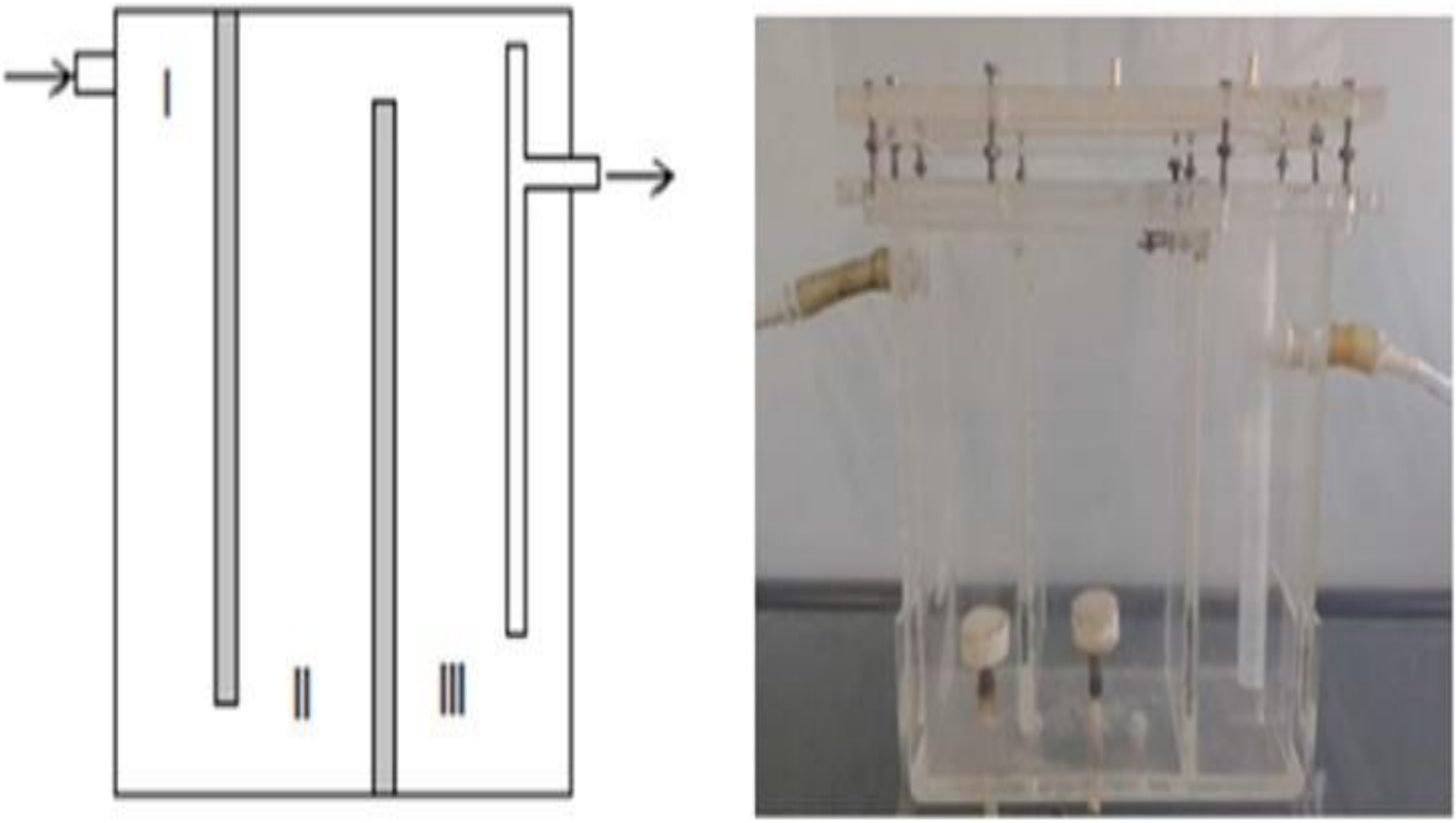

Figure 2. Scheme and picture of the tank for fat trap and primary sedimentation. Zones I, II, and III.

The wastewater model was pumped into the bulkhead tank through a Masterflex peristaltic pump (model 7553-75, USA) with flows that evaluated three hydraulic retention times (HRT): 15, 30, and 45 min. Taking into account the effective volume of the tank (Table 3) and the selected HRT, the flows were calculated: 0.167, 0.083, and 0.055 l/min, respectively. For the evaluation of the fat trap and the primary

settler, the following indicators were selected as response variables: fats and oils, chemical oxygen demand (COD), biochemical oxygen demand (BOD), detergents (active substances to methylene blue: ASMB), total settleable solids (SS), turbidity and color.

Table 3. Dimensions of the partition tank.

Compartment	Zone	Transversal area (cm)	Liquid height (cm)	Liquid volume (L)
1	I	8 x 5	18	0.72
2	II	8 x 8	18	1.22
3	III	8 x 5	14	0.56
			Total effective volumen	2.50

To evaluate the natural sedimentation capacity of the solids contained in the residual and establish the HRT, sedimentation tests were carried out in Imhoff cones. The sedimentation efficiency was evaluated regarding the volume of settled particles and turbidity in the wastewater.

The effluents from the tank were collected and subjected to an ozonation process. A glass bubble column with a useful volume of 600 ml (d = 4 cm and h = 48 cm) was used in the semi-continuous

operation. It has a porous borosilicate gas disperser at the bottom (porosity 0) and a gas outlet at the top.

The oxygen-ozone mixture was obtained from ozone generator equipment (AQOZO-LAB. Cuba) and fed with compressed oxygen, with a maximum ozone generation capacity of 5 g/h. The residual ozone gas that does not react is destroyed at the outlet of the column with an attachment that contains a catalyst with nickel oxide produced at the CNIC. Gas flow was measured with a Gilmont model flowmet), a quartz gas flows cuvette, and a 1mm optical path at standard temperature and pressure conditions. The spectrophotometric determination is based on the Lambert-Beer Law, with the same operating principle as commercial ozone gas analyzer equipment. The European Committee has accepted this method for Standardization (ISO 13964: 1998 standard).

The pH control of the residual to be treated was carried out with an Orion pH meter, model 720. The pH measurement was carried out during the experiments in a recirculation line in the ozonation column. The wastewater treated with ozone was adjusted to pH at the beginning of the experimentation and was kept under control by adding 1N HCl or 5 % NaOH.

Figure 3 shows, from left to right: the peristaltic pump, pH electrode, ozonation column, foam trap, pH meter, and ozonator equipment.

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Figure 3. Ozonation system.

In the study of the ozonation stage, preliminary tests were carried out with treatment times of 1 and 2 h. Subsequently, the process was evaluated with an experimental design 2^3 (Table 4) and ozonation times in all experiments of 30 min. The following response variables were selected: COD, detergents (ASMB), turbidity, and color.

Table 4. The experimental design applied to the ozonation study.

Factor	Nivel	
Ozone concentration in gas (mg/l)	40	60
Gas flow (l/h)	10	20
pH	3	7

The best-operating conditions obtained in each stage studied were used to evaluate the treatment scheme working together. The untreated water samples at the exit of each treatment stage were subjected to a physical-chemical characterization, considering a more significant number of contamination indicators to compare with the discharge standard NC 27: 2012.

The analytical tests were realized. In triplicate according to Standard Methods (APHA, AWWA, & WEF, 2005). Turbidity: 2130-A; Color: 2120-C; COD: 5220-D; BOD_5: 5210-Ñ; Detergents (Active substances to methylene blue. ASMB): 5540; Total Solids (ST): 2540-B; Settleable Solids (SS): 2540-F; Fats and oils (F/O): 5520-D; Total nitrogen: 4500-N; Total phosphorus: 4500-P-C; pH and Electrical Conductivity (EC). The computer program Microsoft® Excel and the statistical program STATGRAPHICS Centurion XV were used for the statistical processing of the results.

The calculation equations used are presented below:

- Applied ozone dose (AD) (mg/l):

$$AD = \frac{CO_3\ g\ (in) \times Gf}{V_L} \times t \qquad (1)$$

where:

CO_3 g (in): Ozone concentration in the gas at the column inlet (mg/l).

Gf: Gas flow (l/h).

V_L: Volume of wastewater to be treated (l).

T: Time of ozonation (h).

- Consumed ozone dose (CD) (mg):

$$CD = \frac{(CO_3\ g\ (inlet) - CO_3\ g\ (outlet)) \times Gf}{V_L} \times t \qquad (2)$$

where:

CO_3 g (in): Ozone concentration in the gas at the column inlet (mg/l).

CO_3 g (out): Ozone concentration in the gas at the column outlet (mg/l).

Gf: Gas flow (l/h).

V_L: Volume of wastewater to be treated (l).

t: Time or period of ozonation (h)

- Gas-liquid transfer efficiency TE (%):

$$\mathrm{TE} = \frac{\mathrm{CD}}{\mathrm{AD}} \times 100 \qquad (3)$$

where:

CD: consumed ozone dose (mg/l).

DA: applied ozone dose (mg/l).

Results

Physical and chemical characterization of model wastewater

Table 5 shows the average values of the parameters analyzed in the model wastewater for producing soft capsules (untreated) and their comparison with the Cuban standard for discharge of liquid waste NC 27: 2012 (Sewerage).

Table 5. Average values of model wastewater from soft capsule production.

Parameters	Unit	Average	NC 27:2012
Temperature	°C	54.9 ± 1.8	< 50
pH	units	7.60 ± 0.02	6-9
Electric conductivity	µS/cm	1752 ± 13	< 4 000
COD	mg O_2/l	1 010.4 ± 27.3	< 700
BOD_5	mg O_2/l	519.0 ± 26.7	< 300
Total solids	mg/l	1990 ± 9.3	-
Settleable solids	ml/l	4.0 ± 0.23	< 10
Fats and oils (F/O)	mg/l	102.1 ± 29.1	< 50
Detergents (ASMB)	mg/l	27.9 ± 1.6	< 25
Total nitrogen	mg/l	95.2 ± 2.5	-
Total phosphorus	mg/l	20.0 ± 0.1	-

Turbidity	UNT	238.4 ± 22.8	-
Color	U Pt-Co	776.9 ± 17.2	-

It is appreciated that the model wastewater has high concentrations of compounds that provide COD and BOD_5, as well as high contents of fats, oils, and detergents. Similarly, the turbidity of water is considerable, and its color is due to the iron oxide used as a colorant in the composition of the capsules, which, when diluted in the wash water, gives it a pink hue. BOD_5/COD ratio is 0.51, a value higher than 0.4, which indicates that the residual is moderately biodegradable (Menéndez & Pérez, 2007).

Fat trap and primary sedimentation treatment process

Table 6, Figure 4, and Figure 5 show the sedimentation efficiency for different hydraulic retention times. It is observed that after 30 min, there is a stabilization in the volume of sediments and in the turbidity of the water, which is why the sedimentation efficiency is maintained. However, particles in suspension persist that contribute approximately 150 NTU.

Table 6. Sedimentation efficiency for different times.

Time (min)	Sedimentation volume (ml/l)	Turbidity (NTU)	Turbidity reduction (%)
0	0	254.00	0
15	2.0	165.45	34.86
30	2.8	154.04	39.35
45	2.9	153.40	39.60
60	3.0	152.76	39.85
75	3.0	151.47	40.36
90	3.0	145.95	42.53

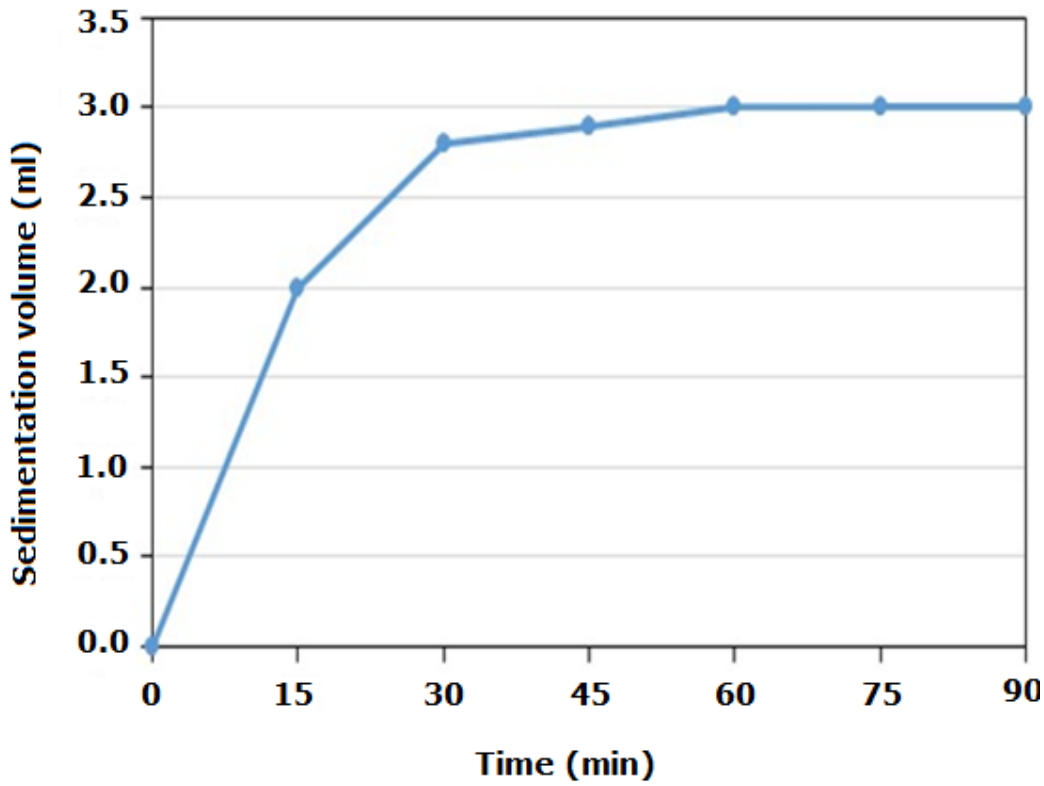

Figure 4. The volume of settled solids obtained for different treatment times.

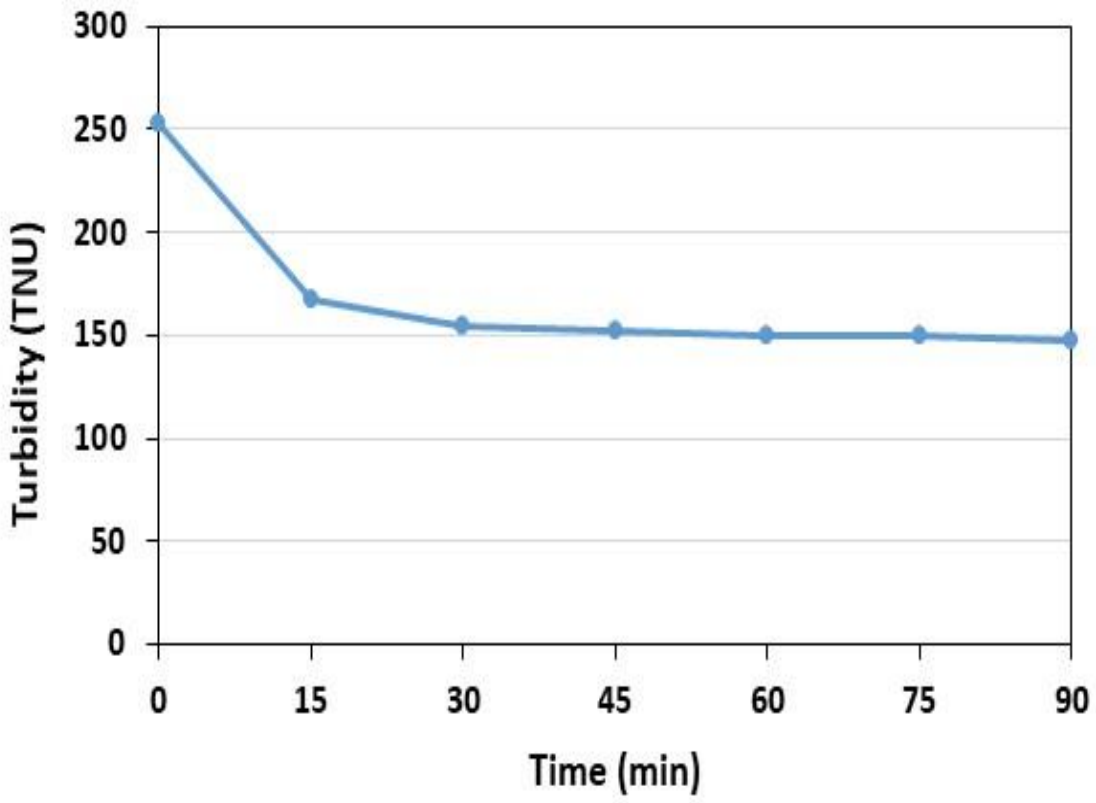

Figure 5. Turbidity of the water samples obtained at different treatment times.

According to the results obtained in the sedimentation tests, it was decided to study the fat trap operation and the settler for a shorter and longer time than that obtained (30 min), establishing the HRT of 15, 30, and 45 minutes.

The average values and statistical comparison of the physical and chemical parameters at different HRT evaluated in the treatment by

fat trap and primary sedimentation are presented in Table 7. Considering that the values of parameters such as fats and oils, turbidity, and present color differences are statistically significant with respect to the residual without treatment (HRT = 0 min) and to the one treated with 15 min, which in turn do not differ statistically with the values obtained at 45 min, the 30 min HRT is suggested for future escalations of these processes of treatment. The rest of the evaluated parameters show significant differences with 15 min of HRT with respect to the untreated water.

Table 7. Physical and chemical parameters of the residuals treated by fat trap and primary sedimentation at different HRT.

HRT (min)	F/O (mg/l)	BOD_5 (mg/l)	COD (mg/l)	ASMB (mg/l)	SS (ml/l)	Turbidity (NTU)	Color (U Pt-Co)
0	102.1 ± 29.1 [a]	519.0 ± 26.7 [a]	1010.4 ± 27.3 [a]	27.9 ± 0.6 [a]	4 ± 0.2 [a]	238.4 ± 22.7 [a]	776.9 ± 17.2 [a]
15	89.0 ± 3.0 [a]	491.6 ± 2.6 [b]	1006.7 ± 3.7 [ab]	18.4 ± 2.6 [b]	0 [b]	173.8 ± 4.5 [b]	531.6 ± 7.5 [b]
30	27.7 ± 2.7 [b]	485.0 ± 5.0 [b]	984.7 ± 3.6 [b]	16.5 ± 2.9 [b]	0 [b]	154.2 ± 5.3 [c]	467.9 ± 4.6 [c]
45	25.6 ± 1.5 [b]	481.3 ± 4.4 [b]	980.5 ± 5.9 [b]	15.8 ± 2.8 [b]	0 [b]	151.8 ± 4.6 [c]	465.5 ± 5.3 [c]

F/O: fats and oils; ASMB: detergents; SS: settleable solids

Equal letters in the same column: There are no statistically significant differences between the means.

Different letters in the same column: There are statistically significant differences between the means.

Table 8 shows that the best fats and oils retention efficiencies (72.9 and 74.9 %), turbidity reduction (35.3 and 36.3 %), and color (39.8 and 40, 1 %) of treated wastewater are achieved at 30 and 45 min of HTR, respectively. Similar values of fat and oil reduction efficiencies in pharmaceutical wastewater treatment factories are reported in the literature: 50-77 % (Mariño & Constanza, 2017); 77 % (Ramos *et al*., 2005); 69 % (Chamorro & Lorena, 2020) and in other lower cases, 21 % (Pineda, 2020). None of the cases reviewed are HRT-reported.

Table 8. Reduction (%) of physical and chemical parameters evaluated in the fat trap treatment and primary sedimentation.

HRT (min)	F/O %	BOD_5 %	COD %	MBAS %	SS %	Turbidity %	Color %
15	12.8	5.3	0.4	34.1	100	27.1	31.6
30	72.9	6.6	2.5	40.8	100	35.3	39.8
45	74.9	7.3	2.9	43.3	100	36.3	40.1

Regarding the elimination of detergents (MBAS) and settling solids (SS), a significant reduction is achieved after 15 min of HRT. The treatment is very efficient for the elimination of the settling solids contained in these waters (100 %) because these solids are fundamentally constituted by gelatin particles that, when cooled in the water, compact and precipitate. In the case of COD and BOD_5, very low elimination efficiencies of these indicators are obtained because organic pollutants are fundamentally dissolved and are not eliminated in these stages of physical treatments. However, the values present statistically significant differences with respect to the untreated residual.

Study of the ozonation process

Under the selected pretreatment conditions, wastewater treated in the fat trap and primary sedimentation (primary treatment system) was used for the ozonation study.

Considering the advantages of the advanced oxidation processes described in the literature, it was decided to preliminarily evaluate the ozonation of the model wastewater at pH 7 and 9, keeping these pH

values constants during the process. In both cases, an ozone concentration of 60 mg/l and a gas flow of 20 l/h were applied to the oxygen gas stream for 1 and 2 hours. Each experiment was performed in triplicate.

The results are shown in Figure 6, in which it can be seen that there are statistically significant differences in the reduction of the COD of the treated waters at pH 7 and 9 in the first hour of ozonation. Still, this difference becomes non-significant at the two hours of treatment, and COD levels cannot be reduced below the limit established by NC 27: 2012 (700 mgO_2/l). The efficiency in terms of reduction of COD was 31.1 % and 23.4 % for pH 7 and 9, respectively, during 2 h of reaction time.

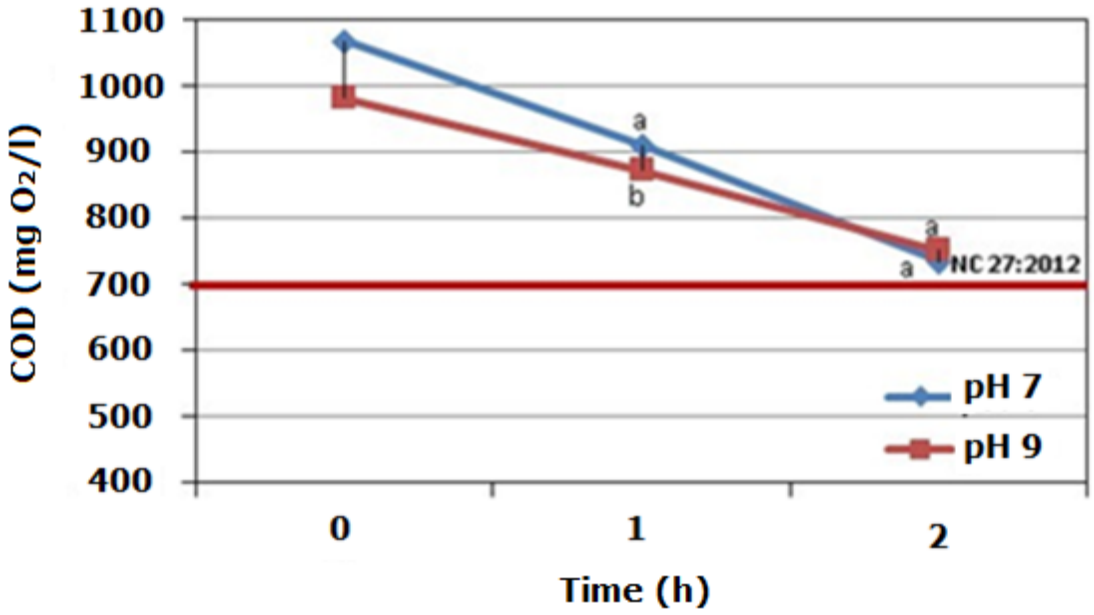

Figure 6. The behavior of COD during the ozonation time at pH 7 and 9.

Authors such as Ikehata *et al*. (2006) and Akhtar *et al*. (2016) report COD reductions between 50 and 82 % for various drugs in solutions with pH values between 7 and 11 and ozonation times of up to 1 h. Pedreros-Calvo, Valderrama, Agudelo, Pérez, and Campo (2021) refer to real pharmaceutical wastewater efficiencies of 30.73 % reduction of COD, at pH 9 and ozonation times of up to 4.5 h, with ozone doses of up to 10 g/h.

The discrete results reported in Figure 5 contradict what was stated by other authors (Alvares *et al*., 2001; Beltrán, 2004; Ikehata *et al*., 2006; Jung, Kim, Yoon, Hwang, & Kang, 2012), who refers that the

efficiency of the application of ozone is more significant as the pH of the water to be treated since ozone decomposes at basic pH to form a greater quantity of $OH^{\cdot}$ radicals, which have the ability to oxidize a wide variety of organic and inorganic compounds.

However, this is not always true since this efficiency increase depends on the wastewater's characteristics to be treated, such as the high levels of natural alkalinity that the residuals present in this study (> 350 mg/l $CaCO_3$). According to Alvares *et al*. (2001), Beltran-Heredia (2001), Beltrán (2004), and Kıdak and Doğan (2017), the presence of ozone-resistant compounds and compounds that inhibit or sequester hydroxyl radicals $OH^{\cdot}$, such as carbonates and bicarbonates present in the residual, can cause the elimination of the $OH^{\cdot}$ radicals generated with the increase in the pH. The level of alkalinity present, in this case, could cause radical ozone oxidation not to be favored. Consequently, high percentages of elimination of compounds measured as COD are not obtained.

In this sense, Yasar, Ahmad, Chaudhry, Rehman, and Khan (2007) argue that with the increase in pH, greater speed should be achieved in the elimination of compounds that provide COD. However, in his experimental results, it is observed that when comparing the reduction percentages of COD at pH 7 and 9, only an increase from 64 to 68 % is achieved, which indicates that in this case, with the increase in pH, no significant differences were reached. At the same time, the author refers that with treatment at pH values above 9, the efficiency of COD removal

is reduced. This behavior was also reported by Pedreros-Calvo *et al*. (2021), with pH values above 9.5.

Considering that ozonation at pH 9 does not obtain the expected results, it was decided to apply ozonation with the reaction by a molecular route at pH 3, maintaining the same experimental conditions as the previous tests. The results are shown in Table 9, in which it is observed that in the first 30 minutes of ozonization, a significant reduction in COD (43.5 %) is achieved, with statistically significant differences to the untreated sample.

This effect on the reduction of COD at acidic pH could be due, in addition to chemical oxidation, to other factors associated with the nature of the gelatins and the pH of the water. Mojgan, Hamid, and Christian (2007) report that both acidic and basic conditions lead to net charges of gelatin molecules (positive at pH 3 and negative at pH 11), causing electrostatic repulsion between the chains, the expansion of their conformation and a weaker tendency of the molecules to form a helix or three-dimensional network and therefore to their denaturation.

Gelatins have a high content of proteins, which tend to denature at low pH values and form solids that agglomerate and settle so that in the treated samples, they are not determined as organic matter by COD, one of the causes of the effectiveness of the system. Luque (2009) states that all denatured proteins have the same conformation, very open and with a maximum interaction with the solvent, so that a water-soluble protein becomes insoluble and precipitates when denatured.

This effect was observed during the ozonization experiments. When acidifying the waters, small solids are formed in suspension inside the column, which, due to the gas flow, are dragged to the surface and adhere to the walls of the ozonation column.

Another condition that could favor the process is the presence of iron in the water, contributed by the colorants applied to the gelatins (red or black iron oxide), which can catalyze the oxidation process with ozone, mediated by radicals or directly by ozone.

Table 9 shows that an increase in the ozone dose from 1 to 4 g/l only increases the efficiency of the treatment by 12 %, so based on the cost/benefit criteria, ozonating at higher doses of 1 g/l is not justified.

Table 9. COD reduction during the ozonation stage at pH 3, ozone concentration in the gas of 60 mgO_3/l, and gas flow of 20 l/h.

Ozonation time (h)	Ozone applied dose (g/l)	COD (mg/l)	Efficiency (%)
0	–	987.8 ± 31.6 [a]	–
0.5	1	557.8 ± 17.9 [b]	43.5
1	2	474.5 ± 9.9 [c]	51.9
2	4	438.6 ± 11.6 [d]	55.6

Different letters in the same column: There are statistically significant differences between the means.

Figure 7 shows that after 30 min of ozonation, it is possible to reduce the COD to values lower than those required by the NC 27: 2012 standard. Because most of the reactions occurred in the first 30 min of treatment, it was decided to set this time for the evaluation of the proposed experimental design (2^3), taking into account economic considerations and the reduction of the ozone dose applied.

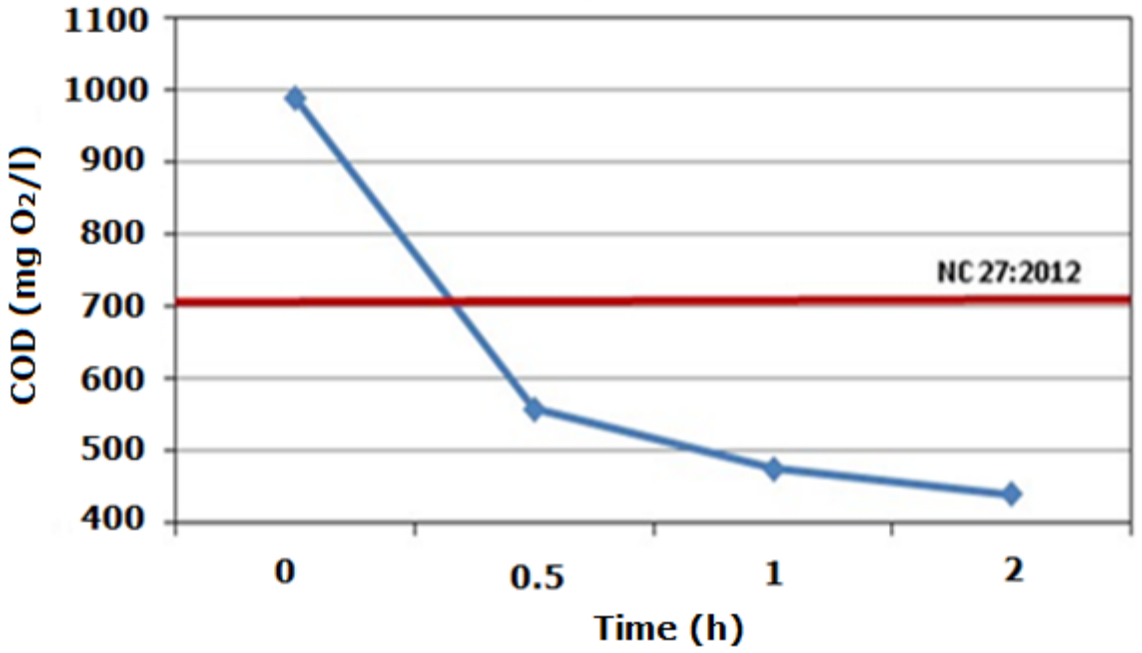

Figure 7. COD variation by ozonation at pH 3.

Taking the point that the best results of the previous ozonation study were obtained with pH 3, ozone concentration, and relatively high

gas flow, it was decided to evaluate an experimental design that grouped these three factors into two levels (2^3), including a concentration of ozone and lower gas flow. This design allowed the evaluation ozone doses lower than 1 g/l (0.66, 0.50, and 0.33 g/l) in terms of reduction of COD, detergents, turbidity, and color, as dependent variables or responses.

In Figure 8 and Figure 9, it is observed that for the reduction of COD and detergents (ASMB), all the factors and interactions (AB, BC, AC) are significant, observing an important effect with the decrease in pH, an increase in the concentration ozone CO_3g and a decrease in the gas flow (Gf). This is evident in the main effects graphs for both parameters.

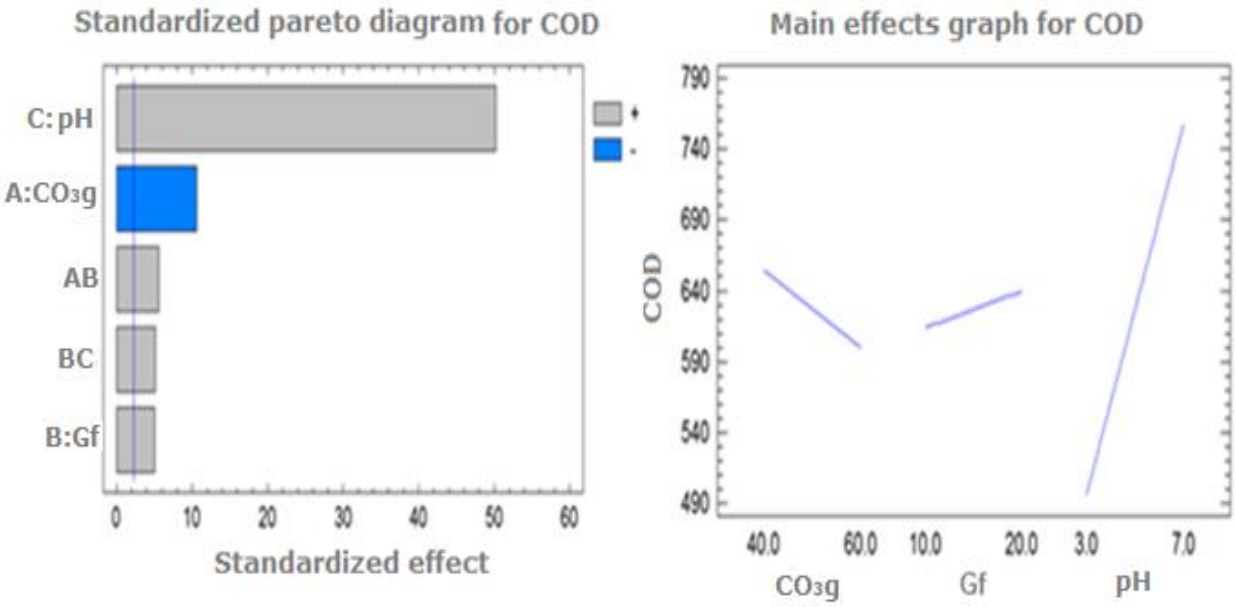

Figure 8. Standardized Pareto diagram and main effects graph for COD.

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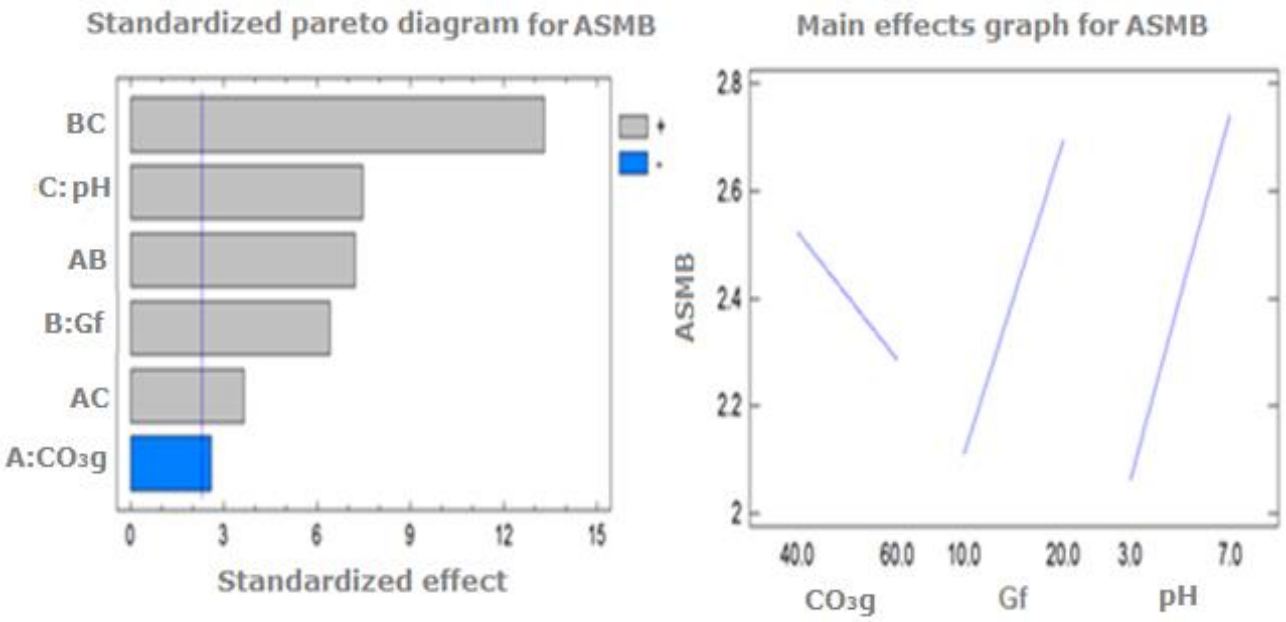

Figure 9. Standardized Pareto diagram and main effects graphic for ASMB.

In the reduction of turbidity and color, it is observed that the greatest effect is achieved with the decrease in pH and, to a lesser extent, with an increase in CO_3g and its interaction with the gas flow (AB) (Figure 10 and Figure 11).

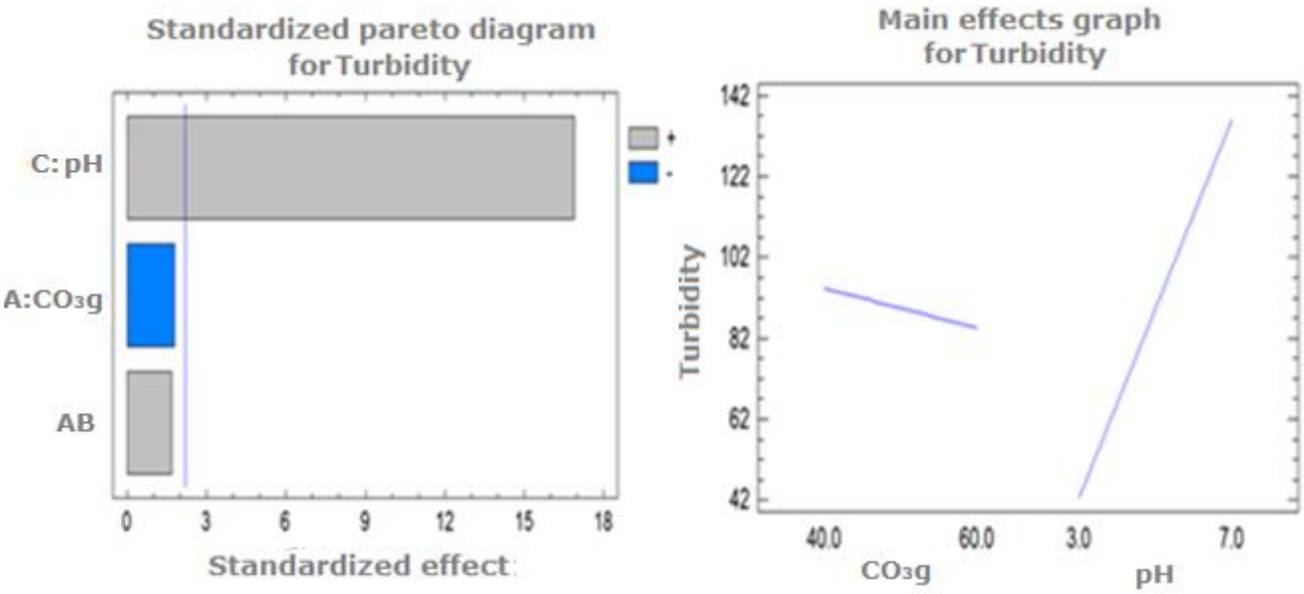

Figure 10. Standardized Pareto diagram and main effects graphic for turbidity.

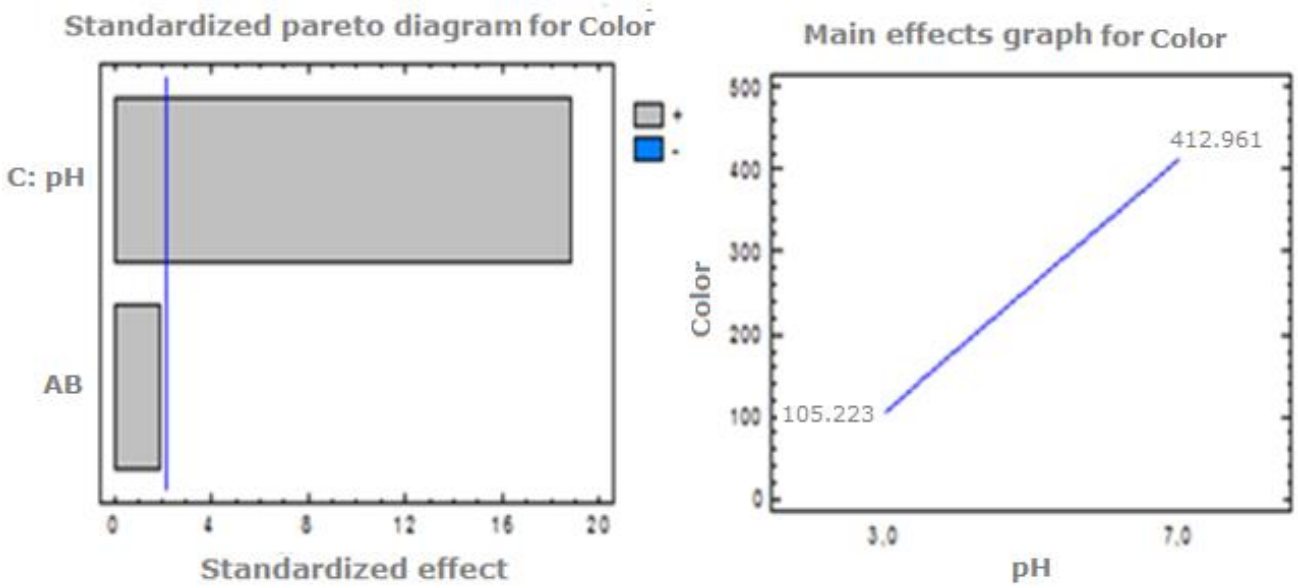

Figure 11. Standardized Pareto diagram and main effects graphic for color.

In the main effects, graphs for both parameters, the importance of reducing the pH in the ozonation process of the evaluated wastewater models can be observed.

Statistical models were obtained and predicted the variability of the evaluated pollution indicators based on the operating parameters used in future scaling of the ozonation process.

- COD (mgO_2/l) = 714.32 – 7.0462*CO_3g -18.381*Gf + 45.185*pH + 0.28743*$C(O_3)g$*Gf + 1.3210*Gf*pH

  R^2 = 99.67 %

- ASMB (mg/l) = 12.804 – 0.15166*CO_3g – 0.57256*Gf – 1.1528*pH + 0.006563*CO_3g*Gf+ 0.0082813*CO_3g*pH + 0.060563*Gf*pH

  R^2 = 97.74 %

- Turbidity (NTU) = 67.391 – 1.8951*CO_3g – 4.6713*Gf + 23.363*pH + 0.09343*CO_3g*Gf

  R^2 = 96.37 %

- Color (U Pt-Co) = 111.50 – 4.7417*CO_3g – 15.806*Gf + 76.935*pH + 0.31611*CO_3g*Gf

  R^2 = 96.8 %

Considering the trends obtained in the statistical analysis, it is proposed to use as operating parameters for the ozonation stage 60 mg/l of ozone concentration in the gas, 10 l/h of gas flow, and 30 min of ozonation time, which implies an applied dose of 500 mg/l.

Regarding the pH of the water to be treated, although the best results were obtained in an acid medium (pH 3), the implementation of

a flexible reagent dosing system is proposed for scaling at an industrial level, which also allows ozonation in an alkaline medium (pH ≥ 9) to carry out an advanced oxidation process if necessary, taking into account that the characteristics of wastewater to be treated may vary according to the drugs produced and/or different cleaning and disinfection products.

Gas-liquid transfer efficiency

Table 10 shows the average ozone doses applied and consumed and the gas-liquid transfer efficiency of the system for the experiments carried out at pH 3 and ozonation times of 5, 15, and 30 min. As can be seen, the highest transfer percentages are obtained after 5 minutes of ozonization and subsequently decrease and tend to stabilize. This may be because at acidic pH, the reactions of ozone with the pollutants present in the residual are rapid and are completed in the first minutes of treatment. Subsequently, there is a progressive increase in the concentration of residual ozone in the gas at the outlet of the ozonation column by reducing ozone consumption by chemical reaction with

compounds more refractory to oxidation by ozone, which causes a decrease in the efficiency of the gas-liquid transfer system.

Table 10. The average dose applied, consumed, and treatment efficiency in experiments at pH = 3, n = 3.

Ozonation time (min)	Gf (l/h)	CO_3 (in.) (mg/l)	CO_3 (out.) (mg/l)	AD (mg/l)	CD (mg/l)	TE (%)	COD (mg/l)
0	–	–	–	–	–	–	987.8 ± 31.6
5	10	40	15.2	55.3	34.3	62.0	
5	10	60	27.8	83.0	44.5	53.6	713.9
5	20	40	25.6	110.7	39.8	35.9	± 7.2
5	20	60	42.2	166.0	49.2	29.6	
15	10	40	25.5	166.7	60.4	36.2	
15	10	60	40.9	250.0	79.6	31.8	597.0
15	20	40	31.5	333.3	70.8	21.2	± 9.1
15	20	60	47.3	500.0	105.8	21.2	
30	10	40	29.2	333.3	90.0	27.0	556.1
30	10	60	46.1	500.0	115.8	23.2	± 12.4

30	20	40	33.5	666.7	108.3	16.2	
30	20	60	48.2	1000.0	196.7	19.7	

In the same way, it can be seen in Table 10 that the increase in the gas flow decreases the transfer efficiency because the superficial velocity of the gas increases, and the bubbles rise within the liquid more quickly. Therefore, the transfer time from gas to liquid decreases and a higher concentration of residual ozone is obtained in the gas at the exit of the column. Also, the greater the gas flow, the bubble size increases, which causes a decrease in the surface area of contact of the gas with the liquid, which affects the ozone mass transfer.

All the experiments were carried out at a similar temperature (≈ 25 ºC) to avoid the solubility effects of the gas in the liquid. It was impossible to measure the dissolved ozone concentration due to its low content in the treated water and due to the interference of the turbidity and the color of the samples in the measurement of this parameter by the Indigo colorimetric method.

Figure 12 shows the increase in the residual ozone concentration at the outlet of the ozonation column due to the increase in the gas flow (10-20 l/h) for the two applied ozone concentrations (40-60 mg/l).

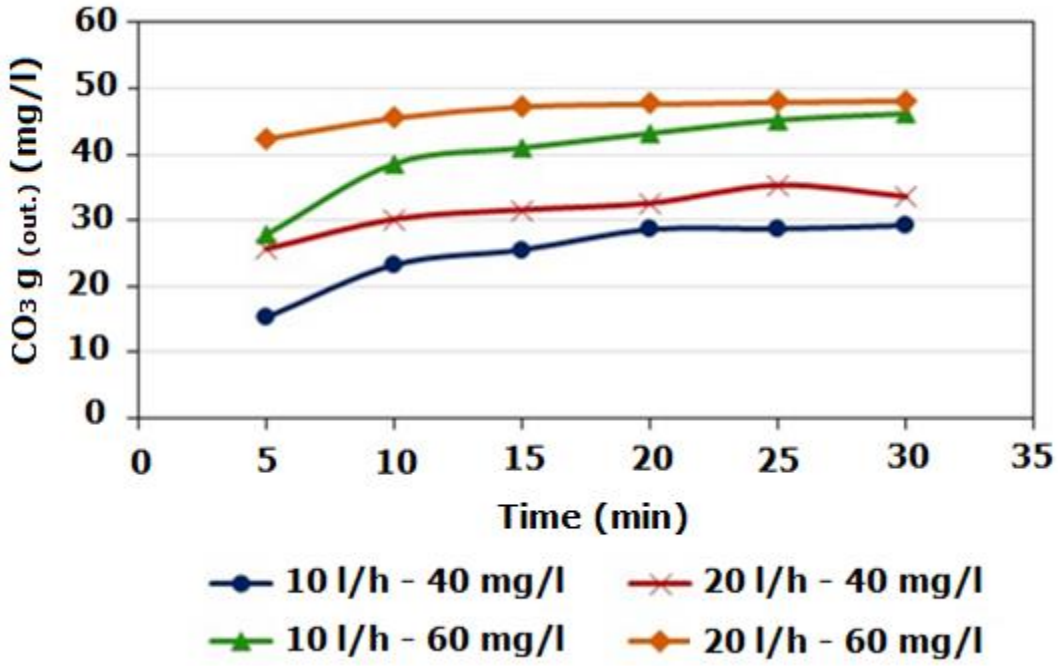

Figure 12. Variation of ozone concentration in the outlet gas with increasing gas flow.

The above confirms the trend obtained in the statistical analysis results on the positive influence of ozonation at gas flows of 10 l/h. Considering this gas flow value (0.01 m^3/h) and the cross-sectional area of the ozonation column (0.00125 m^2), a surface gas velocity value *Vs* = 8 m/h is calculated. This value is proposed as a design basis for scaling the ozonation column and calculating the gas flow for semi-continuous ozonation at larger scales. In the case of using a continuous ozonation scheme, it is necessary to complement studies of gas flow and liquid flow relationships (Q_g/Q_L) for an adequate mass transfer. Evaluations at

the pilot factory level, with hydrodynamic studies of the system operating continuously and economic cost analyzes, can provide important information for the scale-ups of industrial ozonation factories.

Evaluation of the proposed treatment scheme

Using the best-operating conditions obtained for each previously evaluated process (fat trap + primary sedimentation (HRT: 30 min) + ozonation (C (O_3) g = 60 mg/l, Gf = 10 l/h, pH = 3, time = 30 min), the model residuals were treated in a comprehensive manner, sampling at the beginning and end of the treatment scheme. The results and total efficiencies of the combination of treatments are shown in Table 11.

Table 11. Characterization of the residual models before and after the proposed treatment scheme

Parameters	Unit	Influent	Effluent*	Reduction (%)	NC 27:2012
Temperature	°C	54.9	26.1	52.6	< 50
pH	units	7.6	7.0	-	6-9

Conductivity	µS/cm	1752	1752	0	< 4000
COD	mg/l	1010.4	488.9	51.6	< 700
BOD_5	mg/l	519.0	183	64.7	< 300
Total solids	mg/l	1990	1571	21.1	-
Settleable solids	ml/l	4.0	0	100	< 10
fats and oils	mg/l	102.1	21.1	79.3	< 50
Detergents (ASMB)	mg/l	27.9	2.4	91.6	< 25
Total nitrogen	mg/l	95.2	66.5	30.1	-
Total phosphorus	mg/l	20.0	1.4	93.1	-
Turbidity	NTU	238.4	33.9	85.8	-
Color	U Pt-Co	776.9	76.9	90.1	-

* Effluent treated by fat trap + primary sedimentation + ozonation.

As seen in Table 11, the proposed treatment scheme achieves reduction efficiencies of the pollution indicators evaluated above 50 % in their majority. This makes it possible to comply with the safe discharge to the sewage system according to NC 27: 2012, for the temperature, COD, BOD5, fats, oils, and detergents exceeded their maximum permitted limits. In the cases of settling solids, total phosphorus, turbidity, and color, although they are not regulated for their discharge, a high reduction efficiency was achieved with values higher than 85 %.

According to the results achieved with the proposed treatment scheme for the treatment of pharmaceutical industrial wastewater, it is recommended to establish an HRT of 30 min for primary treatments as a design criterion for constructing the fat trap and the primary settler. The operating conditions selected for ozonation establish the design basis for scaling up this stage.

Conclusions

In the combination of treatments by fat trap and primary sedimentation, the best results were obtained with 30 min of HRT, which will be taken as a design criterion for its construction at larger scales.

The ozonation process was more effective at pH 3, possibly influenced by the denaturation of gelatin proteins in an acid medium and ozone oxidation by molecular means with the remaining dissolved pollutants.

An applied ozone dose of 500 mg/l is recommended (ozone concentration in gas: 60 mg/l, gas flow: 10 l/h, and treatment time: 30

min). The operating conditions and statistical models obtained will constitute the basis of the design for scaling up this treatment stage.

A treatment scheme is proposed with the combination of a fat trap, primary sedimentation, and ozonation, with a pH adjustment system that allows ozonation in acidic or basic conditions, depending on the type of wastewater treated or subsequent studies.

The present study achieved the total efficiency of reducing pollutant indicators evaluated between 21 and 100 %. These values guarantee the safe discharge to the city's sewage system according to the Cuban standard NC 27: 2012.

References

Abellán-Soler, M., Lardín-Mifsut, C., Morales-Cavero, E., Pastor-Alcañiz, L., Martínez-Muro, J. L., Santos-Asensi, J. M., Ibáñez-Martínez, M., & Hernández-Hernández, F. (2013). Eliminación de contaminantes emergentes en aguas residuales mediante oxidación avanzada con ozono y ultrasonidos. *Tecnoaqua*, 22-28. Recovered from https://core.ac.uk/download/pdf/61460705.pdf

Acero, J. L., Benítez, F. J., Real, F. J., & Teva, F. (2012). Coupling of adsorption, coagulation, and ultrafiltration processes for the removal of emerging contaminants in a secondary effluent. *Chemical Engineering Journal*, 210, 1-8. Recovered from https://doi.org/10.1016/j.cej.2012.08.043

Acero, J. L., Benítez, J., Teva, F., & Leal, A. I. (2010). Retention of emerging micropollutants from UP water and a municipal secondary effluent by ultrafiltration and nanofiltration. *Chemical Engineering Journal*, 163(3), 264-272. Recovered from https://doi.org/10.1016/j.cej.2010.07.060

Akhtar, J., Imran, M., Zahoor, M. K., & Amin, N. S. (2016). Granular activated carbon assisted ozonation of cephalexin antibiotic. *Journal of the Chemical Society of Pakistan*, 38(6), 1057-1063. Recovered from https://jcsp.org.pk/PublishedVersion/d12e13bb-2685-41cd-94c1-c8fe2b11104eManuscript no 2 Final Gally Proof of 10383 (Javaid Akhtar).pdf

Altmann, D., Schaar, H., Bartel, C., Schorkopf, D. L. P., Miller, I., & Kreuzinger, N. (2012). Impact of ozonation on ecotoxicity and endocrine activity of tertiary treated wastewater effluent. *Water Research*, 46(11), 3693-3702. Recovered from https://doi.org/10.1016/j.watres.2012.04.017

Alvares, A. B. C., Diaper, C., & Parsons, S. A. (2001). Partial oxidation by ozone to remove recalcitrance from wastewaters. A review. *Environmental Technology*, 22(4), 409-427. Recovered from https://doi.org/10.1080/09593332208618273

APHA, AWWA, & WEF, American Public Health Association, American Water Works Association & Water Environment Federation. (2005). *Standard methods for the examination of water and wastewater*. Recovered from https://beta-

static.fishersci.com/content/dam/fishersci/en_US/documents/programs/scientific/technical-documents/white-papers/apha-water-testing-standard-methods-introduction-white-paper.pdf

Baresel, C., Dahlgren, L., Lazic, A., Kerchove, A., Almemark, M., & Ek, M. (2015). Reuse of treated wastewater for non-potable use (ReUse). *IVL Swedish Environmental Research Institute*. Recovered from https://sjostad.ivl.se/download/18.7e136029152c7d48c2024c/1455548263429/B2219.pdf

Bataller, M., Veliz, E., Fernández, L. A., Fernández, I., & Espinosa, M.C. (2014). Effect of ozone on secondary effluent treatment for reuse in agriculture. *International Journal Environmental Engineering*, 6(1), 100-118. Recovered from https://www.inderscienceonline.com/doi/pdf/10.1504/IJEE.2014.057830

Beltrán, F. (2004). *Ozone reaction kinetics for water and wastewater systems*. Recovered from https://lib.ugent.be/catalog/rug01:001034738#reference-details

Beltran-Heredia, J. D. (2001). Kinetics of the reaction between ozone and phenolic acids in agro-industrial wastewaters. *Water Research*, 35(4), 1077-1085. Recovered from https://doi.org/10.1016/S0043-1354(00)00343-2

Benitez, F. J., Acero, J. L., Real, F. J., Roldán, G., & Rodríguez, E. (2013). The effectiveness of single oxidants and aops in the

degradation of emerging contaminants in waters: A comparison study. *Ozone: Science & Engineering*, 35, 263-272. Recovered from https://doi.org/10.1080/01919512.2013.794107

Blair, B. D., Crago, J. P., Hedman, C. J., & Klaper, R. D. (2013). Pharmaceuticals and personal care products found in the Great Lakes above concentrations of environmental concern. *Chemosphere*. Recovered from https://doi.org/10.1016/j.chemosphere.2013.07.057

Boyd, G. R., Reemtsma, H., Grimm, D. A., & Mitra, S. (2003). Pharmaceuticals and Personal Care Products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. *Science Total Environmental*, 311(1-3), 135-149. Recovered from https://doi.org/10.1016/S0048-9697(03)00138-4

Brian, J., & Fridrun, P. (2004). Pharmaceutical Capsules "The history of the medical capsule". *London Pharmaceutical*, 1-3. Recovered from https://www.pharmpress.com/product/9780857111654/pharmaceutical-capsules

Cabrera, A., Dueñas, J., Véliz, E., Díaz, M. A., Menéndez, C. L., Pereda, I., & Zaiat, M. (2016). Anaerobic digestion of vinasses by combining an upflow anaerobic filter reactor and ozonation process. *Brazilian Journal of Chemical Engineering*, 33(4), 753-762. Recovered from https://www.scielo.br/pdf/bjce/v33n4/0104-6632-bjce-33-04-0753.pdf

Carolina, A. (2010). *Validación del método de limpieza de la encapsuladora automática Boch luego de la producción de cápsulas de dicloxacilina en betapharma*. Riobamba, Ecuador: Facultad de Ciencias, Escuela de Bioquímica y Farmacia. Recovered from http://dspace.espoch.edu.ec/bitstream/123456789/704/1/56T00233.pdf

Chamorro, M., & Lorena, V. (2020). *Formulación de técnicas de control interno para la reducción de cargas contaminantes en los vertimientos industriales de una industria farmacéutica en la ciudad de Bogotá D.C.* Bogotá D.C., Colombia: Universidad de la Salle. Facultad de Ingeniería, Programa de Ingeniería Ambiental y Sanitaria. Recovered from https://ciencia.lasalle.edu.co/cgi/viewcontent.cgi?article=2876&context=ing_ambiental_sanitaria

Chang, R. (2015). Removal of animal antibiotics for potable water reclamation: A review. Los Angeles, USA: University of California. Recovered from https://escholarship.org/content/qt7nd7q428/qt7nd7q428.pdf

Chávez, A. M., Gimeno, O., Rey, A., Pliego, G., Oropesa, A. L., & Álvarez, P. M. (2019). Treatment of highly polluted industrial wastewater by means of sequential aerobic biological oxidation-ozone based AOPs. *Chemical Engineering Journal*, 361, 89-98. Recovered from https://doi.org/10.1016/j.cej.2018.12.064

Deblonde, T., Cossu-Leguille, C., & Hartemann, P. (2011). Emerging pollutants in wastewater: A review of the literature. *International Journal of Hygiene and Environmental Health,* 214, 442-448. Recovered from https://doi.org/10.1016/j.ijheh.2011.08.002

DICT-CNIC, Departamento de Información Científico-Técnica. Centro Nacional de Investigaciones Científicas .(2015). *Informe de estudio de patentes sobre tratamientos de aguas residuales de la producción de cápsulas blandas*. La Habana, Cuba: : Departamento de Información Científico-Técnica y Centro Nacional de Investigaciones Científicas.

Dougherty, J. A., Swarzenski, P. W., Dinicola, R. S., & Reinhard, M. (2010). Occurrence of herbicides and pharmaceutical and personal care products in surface water and groundwater around Liberty Bay, Puget Sound, Washington. *Journal of Environmental Quality*, 39, 1173-1180. Recovered from https://doi.org/10.2134/jeq2009.0189

Ebele, A. J., Abdallah, M. A-E., & Harrad, S. (2017). Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment. *Emerging Contaminants*, 3, 1-16. Recovered from https://doi.org/10.1016/j.emcon.2016.12.004

Fernández, L. A., Ledea, O., Véliz, E., Bataller, M., Ramos, Y., Hernández, C., Gutiérrez, C., & Fernández, I. (2020). Review of cytostatics wastewaters degradation by ozone and advanced oxidation processes: Results from Cuban studies. *Environmental*

Reviews, 28(1). Recovered from https://doi.org/10.1139/er-2018-0109

Fridrun, P. (2004). Pharmaceutical capsules "Technology to manufacture soft capsules". *London Pharmaceutical*, 195-196. Recovered from https://www.worldcat.org/title/pharmaceutical-capsules/oclc/644086994

Gerrity, D., Gamage, S., Holady, J. C., Mawhinney, D. B., Quiñones, O., & Trenholm, R. A. (2011). Pilot-scale evaluation of ozone and biological activated carbon for trace organic contaminant mitigation and disinfection. *Water Research*, 45, 2155-2165. Recovered from https://doi.org/10.1016/j.watres.2010.12.031

Gogoi, A., Mazumderb, P., Tyagi, V. K., Chaminda, G. G. T., An, A. K., & Kumar, M. (2018). Occurrence and fate of emerging contaminants in water environment: A review. *Groundwater for Sustainable Development*, 6, 169-180. Recovered from https://doi.org/10.1016/j.gsd.2017.12.009

Hernando, M. D., Mezcua, M., Fernández-Alba, A. R., & Barceló, D. (2006). Environmental risk assessment of pharmaceutical residues in wastewater effluents, surface waters and sediments. *Talanta*, 69, 334-342. Recovered from https://doi.org/10.1016/j.talanta.2005.09.037

Hogerzeil, H., Frank, G., Grundmann, N., Kettis, M., Knox, J., & Larsson, J. (2018*). Antimicrobial Resistance Benchmark 2018. Methodology Report*. Recovered from

https://accesstomedicinefoundation.org/media/atmf/2017-Methodology-for-2018-Antimicrobial-Resistance-Benchmark-final.pdf

Huber, M. M., Göbel, A., Joss, A., Hermann, N., Löffler, D., McArdell, C. Siegrist, H., Ternes, T. A., & von Gunten, U. (2005). Oxidation of pharmaceuticals during ozonation of municipal wastewater effluents: A pilot study. *Environmental Science & Technology*, 39(11), 4290-9. DOI: 10.1021/es048396s

Ikehata, K., & Gamal-El-Din, M. (2008). Ozonation and advanced oxidation treatment of emerging organic pollutants in water and wastewater. *Ozone: Science & Engineering*, 30(1), 21-26. Recovered from https://doi.org/10.1080/01919510701728970

Ikehata, K., & Gamal-El-Din, M. (2005). Aqueous pesticide degradation by ozonation and ozone-based advance oxidation processes. A review (Part I). *Ozone: Science & Engineering*, 27(2), 83-114. Recovered from https://doi.org/10.1080/01919510590925220

Ikehata, K., & Gamal-El-Din, M. (2004). Degradation of recalcitrant surfactants in wastewater by ozonation and advanced oxidation processe. A Review. *Ozone: Science & Engineering*, 26(4), 327-343. Recovered from https://doi.org/10.1080/01919510490482160

Ikehata, K., Jodeiri, N., & Gamal-El-Din, M. (2006). Degradation of aqueous pharmaceuticals by ozonation and advanced oxidation processes. A review. *Ozone: Science & Engineering*, 28(6), 353-

414. Recovered from https://doi.org/10.1080/01919510600985937

ISO 13964. (1998). (E). *Air quality — Determination of ozonein ambient air — Ultraviolet photometricmethod. First edition 1998-08-01*. Recovered from https://www.sis.se/api/document/preview/611423/

Jung, Y. J., Kim, W. G., Yoon, Y., Hwang, T. M., & Kang, J. W. (2012). pH effect on ozonation of ampicillin: Kinetic study and toxicity assessment. *Ozone: Science & Engineering*, 34(3), 156-162. Recovered from https://doi.org/10.1080/01919512.2012.662890

Kıdak, R., & Doğan, S. (2017). Medium-high frequency ultrasound and ozone based advanced oxidation for amoxicillin removal in water. *Ultrasonics Sonochemistry*. Recovered from http://dx.doi.org/10.1016/j.ultsonch.2017.01.033

Kolpin, D. W., Furlong, E. T., Meyer, M. T., Thurman, E. M., Zaugg, S. D., Barber, L. B., & Buxton, H. T. (2002). Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. Streams, 1999-2000. A National Reconnaissance. *Environmental Science & Technology*, 36(6), 1202-1211. Recovered from https://pubs.acs.org/doi/pdf/10.1021/es011055j

Leung, H. W., Jin, L., Wei, S., Tsui, M. M. P., Zhou, B., Jiao, L., Cheung, P. C., Chun, Y. K., Murphy, M. B., & Lam, P. K. S. (2013). Pharmaceuticals in tap water: Human health risk assessment and proposed monitoring framework in China. *Environmental Health*

Perspectives, 121(7), 839-846. Recovered from https://doi.org/10.1289/ehp.1206244

Luque, M. V. (2009). *Estructura y propiedades de las proteínas*. Recovered from http://www.uv.es/tunon/pdf_doc/proteinas_09.pdf

Manaia, C. M., Novo, A., Coelho, B., & Nunes, O. C. (2008). Ciprofloxacin resistance in domestic wastewater treatment plants. *Water, Air, & Soil Pollution*, 335-343. Recovered from https://www.researchgate.net/deref/http%3A%2F%2Fdx.doi.org%2F10.1007%2Fs11270-009-0171-0

Marcelino, R. B. P., Leao, M. M. D., Lago, R. M., & Amorim, C. C. (2017). Multistage ozone and biological treatment system for real wastewater containing antibiotics. *Journal of Enviromental Management*, 1-7. Recovered from https://doi.org/10.1016/j.jenvman.2016.04.041

Mariño, J. L., & Constanza, L. (2017). *Propuesta para la gestión de vertimientos industriales de Laboratorios Coaspharma S.A.S.* Bogotá D.C., Colombia: Fundación Universidad de América, Facultad de Ingeniería Química. Recovered from https://repository.uamerica.edu.co/bitstream/20.500.11839/6034/1/6112794-2017-1-IQ.pdf

Menéndez, C., & Pérez, J. M. (2007). *Procesos para el tratamiento biológico de aguas residuales industriales*. La Habana, Cuba: Universitaria. Recovered from

https://www.academia.edu/33133551/Procesos_para_el_tratamiento_biológico_de_aguas_residuales_industriales_Carlos_M_Gutiérrez

Miao, X. S., Bishay, F., Chen, M., & Metcalfe, C. D. (2004). Occurrence of antimicrobials in the final effluents of wastewater treatment plants in Canada. *Environmental Science & Technology*, 38(13), 3533-3541. DOI: 10.1021/es030653q

Mojgan, Z., Hamid, M., & Christian, M. (2007). Effects of concentration, temperature, and ph on chain mobility of gelatin during early stages of gelation. *Iranian Polymer Journal*, 16(12), 861-870. Recovered from https://www.researchgate.net/publication/228615392_Effects_of_Concentration_Temperature_and_pH_on_Chain_Mobility_of_Gelatin_during_Early_Stages_of_Gelation

Nasser, A. M. (2017). Inactivation of cryptosporidium by advanced oxidation processes. Applications of advanced oxidation processes (AOPs) in drinking water treatment. In: Barceló, D., & Kostianoy, A. G. (eds.). *The Handbook of Environmental Chemistry* (pp. 297-308). Recovered from https://link.springer.com/chapter/10.1007/698_2017_85

Nghiem, L. D., Schafer, A. I., & Elimelech, M. (2005). Pharmaceutical retention mechanisms by nanofiltration membranes. *Environmental Science & Technology*, 39(19), 7698-7705. Recovered from

https://era.ed.ac.uk/bitstream/handle/1842/4131/J41%20ERA.pdf;jsessionid=89AF63DE754845F2AFBDF84945939F18?sequence=1

Paul, E., & Debellefontaine, H. (2007). Reduction of excess sludge produced by biological treatment processes: Effect of ozonation on biomass and on sludge. *Ozone: Science & Engineering*, 29, 415-427. Recovered from https://doi.org/10.1080/01919510701593762

Pedreros-Calvo, C., Valderrama, K. V., Agudelo, R. N., Pérez, K., & Campo, C. E. (2021). Reducción de la concentración de DQO y COT en aguas residuales de la industria farmacéutica empleando ozono catalizado por Fe^{2+}. Estudio de caso a escala real. *Mutis*, 11(2) (en prensa). Recovered from https://revistas.utadeo.edu.co/index.php/mutis/article/view/1707/1739

Pineda, G. (2020). *Evaluación del sistema de tratamiento de aguas residuales de una industria farmacéutica de la ciudad de Quito*. Quito, Ecuador: Universidad Central del Ecuador, Facultad de Ingeniería en Geología, Minas, Petróleos y Ambiental, Carrera de Ingeniería Ambiental. Recovered from http://www.dspace.uce.edu.ec/bitstream/25000/20571/1/T-UCE-0012-FIG-177.pdf

Ramírez, N., Espinosa, M. C., Fernández, L. A., Véliz, E., & Ramos, Y. (2016). Tratamiento con ozono de agua residual con taninos de curtiduría al vegetal. *Tecnología y Ciencias del Agua*, 7(3), mayo-

junio, 53-73. Recovered from http://www.scielo.org.mx/pdf/tca/v7n3/2007-2422-tca-7-03-00053.pdf

Ramos, C., Pellón, A., Villafranca, D., Espinosa, M. C., Escobedo, R., & Yamilé-Alvarez, Y. (2005). Tecnología de tratamiento a las aguas residuales de un laboratorio farmacéutico de producción de semisólidos. *Revista CENIC Ciencias Biológicas*, 36(núm. especial). Recovered from https://www.redalyc.org/pdf/1812/181220525029.pdf

Reungoat, J., Escher, B. I., Macova, M., & Keller, J. (2011). Biofiltration of wastewater treatment plant effluent: Effective removal of pharmaceuticals and personal care products and reduction of toxicity. *Water Research*, 45(9), 2751-2762. Recovered from https://doi.org/10.1016/j.watres.2011.02.013

Rivera-Utrilla, J., Sánchez-Polo, M., Ferro-García, M. Á., Prados-Joya, G., & Ocampo-Pérez, R. (2013). Pharmaceuticals as emerging contaminants and their removal from water. A review. *Chemosphere*, 93(7), 1268-87. Recovered from https://www.academia.edu/25419212/Pharmaceuticals_as_emerging_contaminants_and_their_removal_from_water_A_review

Rodríguez-Narvaez, O. M., Peralta-Hernandez, J. M., Goonetilleke, A., & Bandalac, E. R. (2017). Treatment technologies for emerging contaminants in water: A review. *Chemical Engineering Journal*,

323, 361-380. Recovered from https://doi.org/10.1016/j.cej.2017.04.106

Rubio, D. I. C., Delgado, D. R., & Amaya, A. O. (2017). Normatividad ambiental dirigida a regular la presencia de los productos farmacéuticos residuales en ambientes acuáticos. *Revista Jurídica Piélagus*, 16(1), 121-130. Recovered from https://journalusco.edu.co/index.php/pielagus/article/view/1445/2563

Seo, G. T., Moon, B. H., & Lim, J. H. (2001). Ultrafiltration combined with ozone for domestic laundry wastewater reclamation and reuse. *Water Supply*, IWA Publishing, 1(5-6), 387-392. Recovered from https://doi.org/10.2166/ws.2001.0138

Sorensen, J., Lapworth, D. J., Nkhuwa, D. C. W., Stuart, M. E., Gooddy, D. C., Bell, R., Chirwa, M., Kabika, J., Liemisa, M., Chibesa, M., & Pedley, S. (2015). Emerging contaminants in urban groundwater sources in Africa. *Water Research*, 72, 51-63. Recovered from https://www.researchgate.net/publication/265176942_Emerging_contaminants_in_urban_groundwater_sources_in_Africa

Stackelberg, P. E., Furlong, E. T., Meyer, M. T., Zaugg, S. D., Henderson, A. K., & Reissman, D. B. (2004). Persistence of pharmaceutical compounds and other organic wastewater contaminants in a conventional drinking-water treatment plant. *Science of the Total Environment*, 329(1-3), 99-113. Recovered from

https://digitalcommons.unl.edu/cgi/viewcontent.cgi?referer=https://www.google.com/&httpsredir=1&article=1452&context=usgsstaffpub

Stuart, M., Lapworth, D., Crane, E., & Hart, A. (2012). Review of risk from potential emerging contaminants in UK groundwater. *Science of the Total Environment*, 416, 1-21. Recovered from https://core.ac.uk/reader/384302?utm_source=linkout

Ternes, T. A., Meisenheimer, M., McDowell, D., Sacher, F., Brauch, H. J., Gulde, B. H., Preuss, G., Wilme, U., & Seibert, N. Z. (2002). Removal of pharmaceuticals during drinking water treatment. *Environmental Science & Technology*, 36(17), 3855-3863. Recovered from https://doi.org/10.1021/es015757k

Vasquez, M. I., Lambrianides, A., Schneider, M., Kümmerer, K., & Fatta-Kassinos, D. (2014). Environmental side effects of pharmaceutical cocktails: What we know and what we should know. *Journal of Hazardous Materials*, 279, 169-189. Recovered from https://doi.org/10.1016/j.jhazmat.2014.06.069

Veliz, E., Bataller, M., Fernández, L. A., & Fernández, I. (2012). Chapter: Municipal wastewater treatment for reuse in agricultural irrigation. *Handbook of Environmental and Waste Management*, 347-381. Recovered from https://www.worldscientific.com/doi/abs/10.1142/9789814327701_0009

Veliz, E., Fernández, L. A., Llanes, J. G., & Bataller, M. (enero-febrero, 2016). Coagulación-floculación, filtración y ozonización de aguas residuales para reutilización en riego agrícola. *Tecnología y Ciencias del Agua*. 7(1), 17-34. Recovered from http://www.scielo.org.mx/pdf/tca/v7n1/2007-2422-tca-7-01-00017.pdf

O'Neill, J. (2016). *Tackling drug-resistant infections globally: Final report and recommendations. The review on antimicrobial resistance*. Recovered from https://www.biomerieuxconnection.com/wp-content/uploads/2018/04/Tackling-Drug-Resistant-Infections-Globally_-Final-Report-and-Recommendations.pdf

Wiegel, S., Aulinger, A., Brockmeyer, R., Harms, H., L€offler, J., Reincke, H., Schmidtc, R., Stachele, B., von Tümplingf, W., & Wankeg, A. (2004). Pharmaceuticals in the river Elbe and its tributaries. *Chemosphere*, 57(2), 107-126. Recovered from https://doi.org/10.1016/j.chemosphere.2004.05.017

Yasar, A., Ahmad, N., Chaudhry, M. N., Rehman, M. S. U., & Khan, A. A. A. (2007). Ozone for color and COD removal of raw and anaerobically biotreated combined industrial wastewater. *Polish Journal of Environmental Studies*, 16(2), 289-294. Recovered from http://www.pjoes.com/Ozone-for-Color-and-COD-Removal-of-Raw-and-Anaerobically-Biotreated-Combined-Industrial,87988,0,2.html