Overview of research on the treatment and reuse of effluents from the antibiotics industry

Panorama da pesquisa sobre tratamento e reúso de efluentes da indústria de antibióticos

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ABSTRACT This work carried out an integrative review of scientific articles indexed between 2007 and 2017 in different databases on treatment and reuse of effluents from the antibiotic industry. Thirty-one articles were found and only four addressed effluent reuse, and one used a full-scale treatment system. Most of these studies were conducted in Asia, with emphasis on China. In Brazil, which is one of the largest producers and consumers of drugs in the world, this type of research is still incipient. The most commonly found processes were oxidative advanced processes that showed greater efficiency in removing antibiotics, but may generate by-products, which might pose an even greater risk depending on the substance formed. Biological processes must first be acclimated to antibiotics in order not to be impacted, however, the release of these resistant microorganisms into the water bodies also presents an environmental risk. Biological integrated membrane systems were also very efficient, but attention should be given to the risk in the final destination of these membranes that were able to retain those compounds. Overall, further studies on this approach are needed to reduce the risks of developing multi-resistant microorganisms in the environment.

KEYWORDS Drug industry. Anti-bacterial agents. Industrial effluent treatment. Drug resistance, bacterial. Wastewater use.

RESUMO *Este trabalho realizou uma revisão integrativa de artigos científicos indexados entre 2007 e 2017 em diferentes bases de dados sobre o tratamento e o reúso de efluentes provenientes da indústria de antibióticos. Foram encontrados 31 artigos, sendo que somente 4 abordaram o reúso de efluente, e 1 utilizou um sistema de tratamento em escala real. A maior parte desses estudos foi realizado na Ásia, com destaque para a China. Observa-se que, no Brasil, que é um dos grandes produtores e consumidores de fármacos do mundo, esse tipo de pesquisa ainda é incipiente. Os processos mais encontrados foram os oxidativos avançados que mostraram maior eficiência na remoção de antibióticos, mas podem gerar subprodutos, o que pode representar um risco ainda maior dependendo da substância formada. Os processos biológicos devem ser primeiramente aclimatados aos antibióticos para não serem impactados, entretanto, a liberação desses*

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micro-organismos resistentes no corpo receptor também apresenta um risco ambiental. Os sistemas integrados de membranas ao biológico também foram bem eficientes, mas atenta-se ao risco na destinação final dessas membranas que foram capazes de reter esses compostos. No geral, são necessários mais estudos sobre essa abordagem para reduzir os riscos no desenvolvimento de micro-organismos multirresistentes no meio ambiente.

PALAVRAS-CHAVE *Indústria farmacêutica. Antibacterianos. Tratamento de efluentes industriais. Farmacorresistência bacteriana. Uso de águas residuárias.*

Introduction

In the modern concept, sanitation includes water supply, waste management (solid, liquid and/or gaseous), urban drainage, rational use of the soil and control of communicable diseases. Such actions are essential for the physical, mental and social well-being of the population[1]. Thus, the non-accomplishment of any of these actions may result in damage to human and environmental health. An important component with direct effects on human health is the collection and treatment of effluents. Brazil has alarming values in relation to this component: in 2017, the Country collected 74% of the sewage generated and treated only 46%, which totals 4.2 billion m³ of untreated domestic sewage being discarded in the different water sources[2].

The collection and treatment of domestic effluents is the responsibility of the public authorities, and may be granted to a private company, but supervised by the control agencies. A very critical type of effluent and that deserves attention is the industrial one, in which the responsibility for its collection and treatment lies with the generator. This effluent may be discharged into the public collection system or into receiving bodies as defined during the environmental licensing of the company[3]. It is noteworthy that effluents from the pharmaceutical industry may pose risks to human health[4-6]. The increased consumption of pharmaceutical products and the incentive to expand the pharmaceutical park lead to a greater generation of effluents with drug waste[7-9].

The Brazilian pharmaceutical industry presents financial profits superior to the other producing activities, having only the automobile industry ahead. The pharmaceutical sector obtained, in 2018, a 6.1% production growth compared to 2017[10]. Such a productive result is due to the fact that Brazil has recorded an accumulated increase of 10.8% in the consumption of pharmaceutical products between 2014 e 2018, with an estimated growth of 15% to 18% until 2023. This brings the Country from the seventh placing on the world drug market in 2018 to the fifth in the list of the 20 largest drug users in the world as shown in *chart 1*[11].

Chart 1. Ranking of the 20 countries with higher spending on medicines in relation to the United States of America showing Brazil's growth estimate from 2013 to 2023

2013		2018		2023	
Ranking	Country	Ranking	Country	Ranking	Country
1º	USA	1º	USA	1º	USA
2º	China	2º	China	2º	China
3º	Japan	3º	Japan	3º	Japan
4º	Germany	4º	Germany	4º	Germany
5º	France	5º	France	**5º**	**Brazil**
6º	Italy	6º	Italy	6º	Italy
7º	United Kingdom	**7º**	**Brazil**	7º	France
8º	**Brazil**	8º	United Kingdom	8º	United Kingdom
9º	Spain	9º	Spain	9º	India
10º	Canada	10º	Canada	10º	Spain
11º	India	11º	India	11º	Canada
12º	South Korea	12º	South Korea	12º	Russia
13º	Australia	13º	Russia	13º	South Korea
14º	Russia	14º	Australia	14º	Turkey
15º	Mexico	15º	Mexico	15º	Argentina
16º	Saudi Arabia	16º	Poland	16º	Australia
17º	Poland	17º	Turkey	17º	Mexico
18º	Belgium	18º	Saudi Arabia	18º	Poland
19º	Netherlands	19º	Argentina	19º	Saudi Arabia
20º	Switzerland	20º	Belgium	20º	Vietnam

Source: IQVIA, 2019[11].

Among the most commonly used drugs, antibiotics stand out. According to the World Health Organization (WHO) report, in 2016 alone the Brazilian population consumed 22.75 daily doses of antibiotics per thousand inhabitants[12]. The WHO also points out that among the 65 countries in the world, Brazil is ranked 19th in the antibiotic consumption ranking and the highest among the countries of the Americas[12].

The high consumption of antibiotics is due to the fact that this medicine has given the population a new hope against various diseases. However, microorganisms can adapt to environmental conditions, developing some resistance to antibiotics, requiring the development of new substances or their combined use[13-15]. There is also a warning about the development of multi-resistant microorganisms that has become a concern today. As a result, WHO has been searching for new antibiotics to prevent populations from dying again from previously controlled infections[16]. If nothing is done, it is estimated that 10 million people could die from a disease caused by multi-resistant microorganisms by 2050[17]. Environmental studies have been raising evidence of increased antimicrobial resistance by microorganisms found in rivers, seas and coastal areas that may have been developed by the presence of antibiotics from effluent disposal[18-20].

The effluent of the pharmaceutical industry is normally composed of wastewater from the production lines, waste from production and leftovers of substances removed from machinery and equipment. It has specific characteristics that can vary depending on the products that are manufactured by the industrial unit. The effluent generated by the production of antibiotics may carry residues of the active substance. In this way, this residue must first go through a process of inactivation or elimination of this active principle to prevent it from being carried into the environment.

Different processes may be used for the treatment of pharmaceutical industrial effluents. Among the most widespread and least expensive technologies, biological processes stand out[22], but the efficiency of these processes in degrading these compounds may be questionable. In some cases, it is necessary to use other processes combined with biological processes, such as physical and chemical processes. Chemical and physicochemical processes are more efficient than biological processes in the removal of refractory substances such as drugs[23]. Activated charcoal adsorption, acid or alkaline hydrolysis and ozone oxidation are examples of promising processes in the removal and/or degradation of drug wastes[24].

The level of treatment to be adopted by the industry is associated with the legal release requirements and the desired quality standard of the treated effluent[24]. In relation to the Brazilian regulation regarding the launch of drugs in the environment, there is a need for its suitability, mainly due to new evidences of effects on wild biota and men[25,26]. However, the countries of the European Union already have standardization for the subject[27-29].

Another important component in sanitation actions is water supply. Scarcity and low water availability represent the challenges of modern humanity. It is noteworthy that, among human activities, the industrial sector is considered the third largest consumer of water resources in the world[30].

In the pharmaceutical industry, water must have purity levels appropriate to its multiple uses. Water used in production, for example, must be treated at the level of purified water; while other support sectors, such as utility units, control laboratories, and research and development sectors, require different levels of water quality[30,31]. Therefore, the importance of water resources management in the pharmaceutical industry is highlighted.

Effective integrated water management (water consumed and effluent generated) in the industry can reduce the risk of environmental pollution and contribute to lower water consumption. One way to reduce water consumption in the industrial sector is to reuse treated effluents. While the petrochemical and food sectors are already doing a lot of work on this topic, little is known about this practice in the pharmaceutical industry[30]. On the other hand, the pharmaceutical industry must be aware of the risk of this reuse to public health and productive activity.

Reuse modalities may be adopted according to the need of the industry. Indirect reuse is the most common, in which treated effluents are thrown into rivers and lakes and, subsequently, captured, treated and used. Direct reuse is related to the use of effluents from one particular activity in another with lower requirements. In general, it is very common the reuse of industrial effluents in towers of cooling, gardening, washing of patios and sidewalks, water for toilets and in the activities of civil construction. For more specific uses of the industry, as in the manufacturing process itself, such effluents shall undergo treatment appropriate to the quality required for their application, observing the risks that this practice may have[32-34]. Therefore, effluent treatment efficiency should be evaluated for different types of reuse, especially those containing drug wastes[35].

In view of this, this article brings an integrative literature review on the studies performed in the treatment of effluents in the pharmaceutical industry of antibiotics and on the possibility of reuse of this treated effluent.

Methodology

This article was elaborated through an integrative literature review[36-38]. Inclusion criteria for this review were indexed articles written in Portuguese, English or Spanish, from 2007 to 2017, retrieved from the search for descriptors and keywords in the Science Direct, Scopus, Web of Science, PubMed and Virtual Health Library (VHL) databases through the website of the Journal of the Coordination for the Improvement of Higher Education Personnel (Capes).

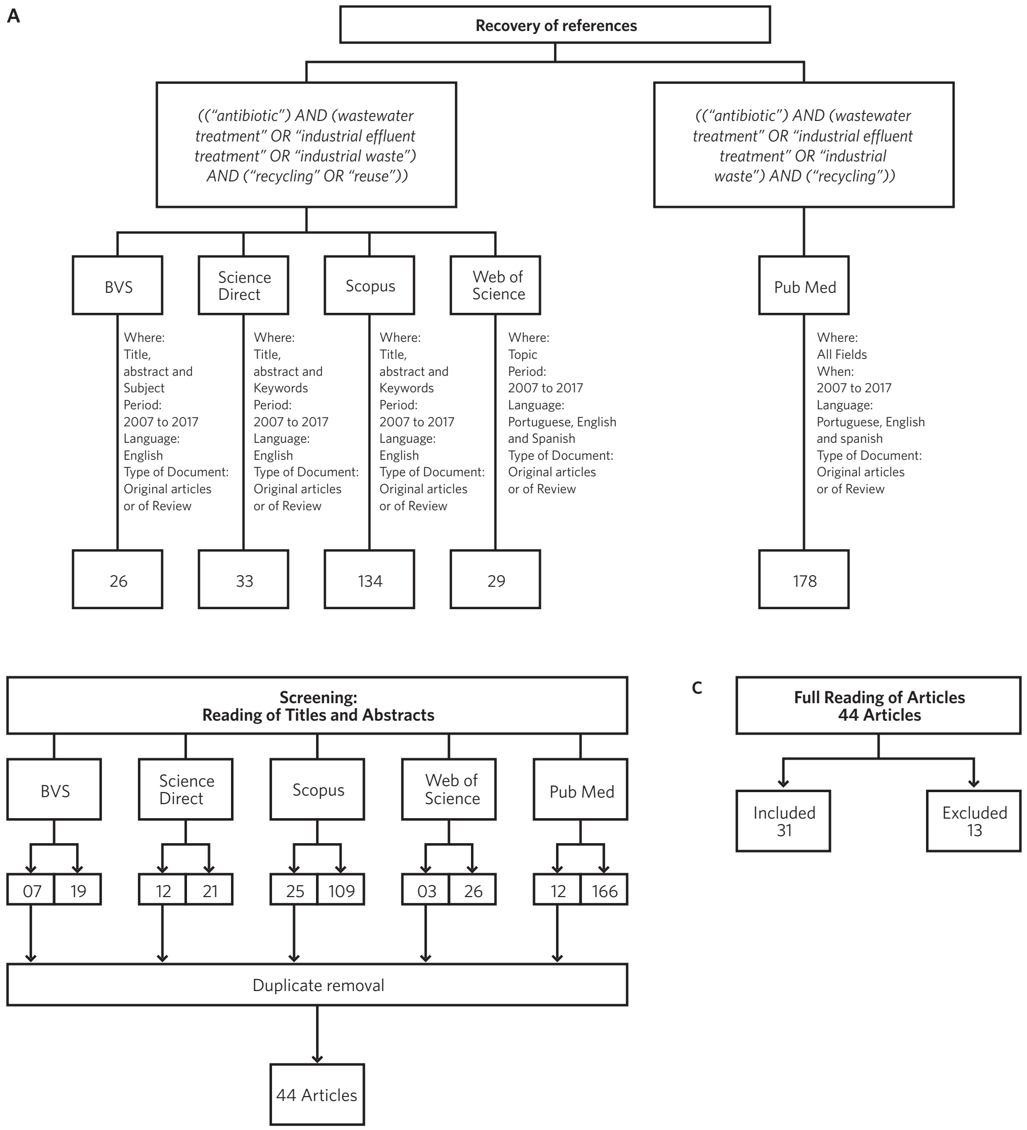
From the selection of descriptors and keywords, the retrieval of references in the indexed databases was performed by two forms of search. The first was composed of the terms *'antibiotic' AND 'wastewater treatment' OR 'industrial effluents treatment' OR 'industrial waste' AND 'recycling' OR 'reuse'* which are vocabularies controlled by DeCS and MeSH. These indices were used in all search bases except PubMed, where the term 'reuse' was excluded as it did not aggregate any results.

After the recovery of the publications, a screening process was performed from the reading of the title and the summary, adopting as inclusion criterion the presence of data on 'treatment of industrial effluents from the production of antibiotics'. Despite the use of the filters offered by the databases, books, opinion articles and patent were observed, which were also removed after detailed reading of the title and the summary. A second evaluation was performed with the help of the Zotero Program Standalone® for the exclusion of duplicate references. At the end of this screening, the articles were fully read, being excluded, restricted or paid access articles or, still, that presented divergent information to the object of this study.

Results

From the search criteria and the filters used in the databases, 400 references were cataloged as shown in *figure 1*. By reading the title and the summary of these articles, 341 articles that had divergent themes from the one proposed in this paper were excluded. Of the remaining 59, 15 were in duplicate and were excluded (*figure 1B*), thus, leaving 44 articles. Finally, with the full reading, only 31 articles were selected (*figure 1C*).

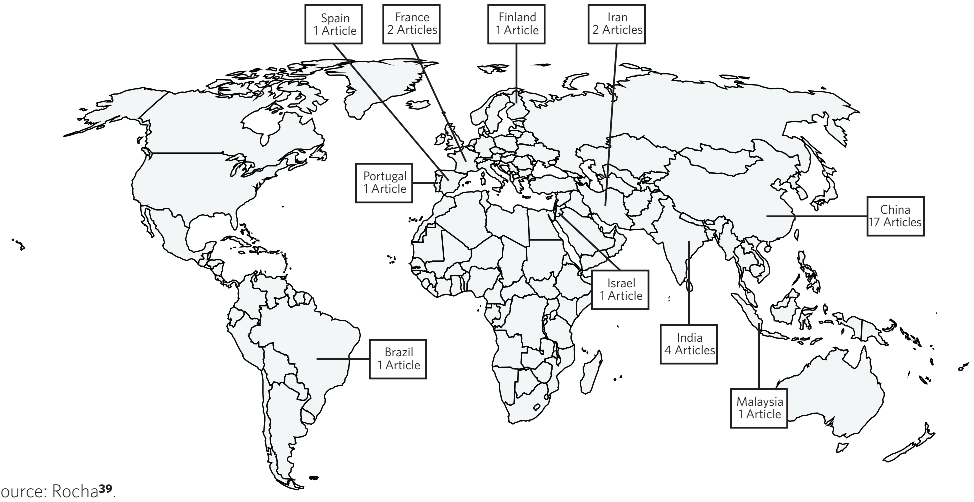
Figure 1. Path used for integrative review. (A) shows how was the recovery of articles based on descriptors using the VHL (Virtual Health Library) bases, Science Direct, Scopus, Web of Science and PubMed; (B) screening from the reading of the title and the abstract of the articles obtained as well as the removal of duplicate articles; (C) shows the exclusion from the full reading of the articles selected



Source: Rocha[39].

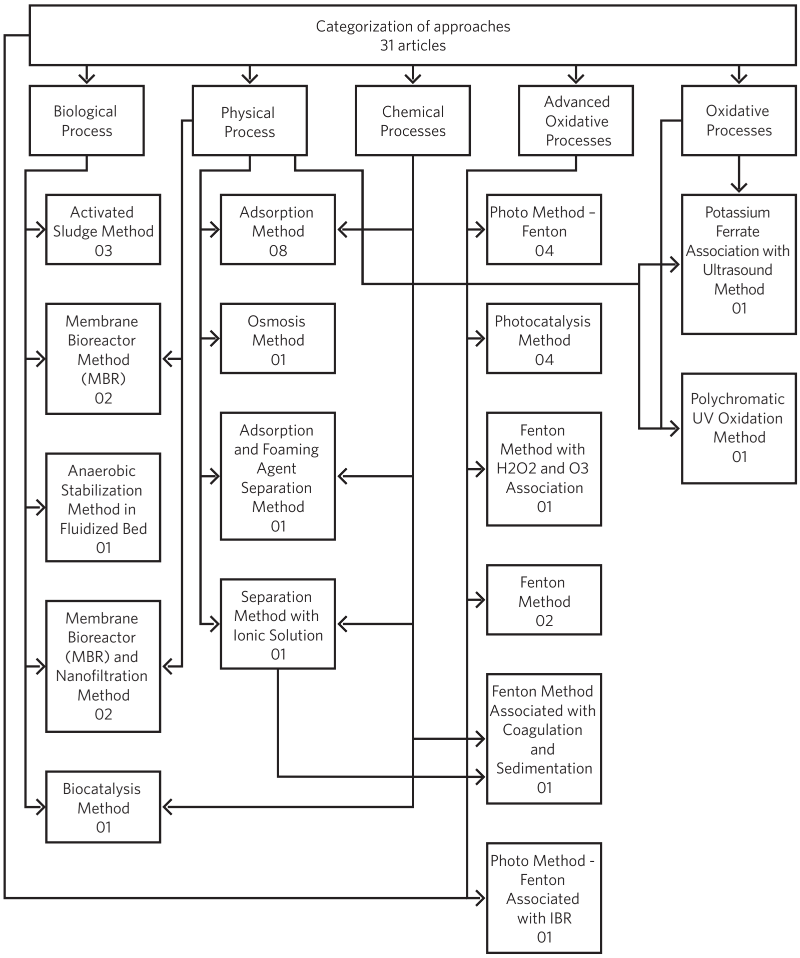
Of the works found on this subject, most were carried out in China (17 articles), followed by India (4), France and Iran (2 each); and Brazil, Spain, Finland, Israel, Malaysia and Portugal (1 each), as shown in *figure 2*. From the categorization of effluent treatment processes, 9 articles that addressed biological processes were found: where 4 referred to strictly biological processes – 3 for activated sludge and 1 for anaerobic reactors; 4 integrated the biological with the physical using membranes; and 1 associated the biological system with the chemical by biocatalysis, as shown in *figure 3*.

Figure 2. Geographical distribution of the 31 articles that were reviewed after the application of all screening tools



Source: Rocha[39].

Figure 3. Categorization according to the types of treatment systems applied in the article found by process: biological, physical, chemical, oxidative advanced and oxidative



Source: Rocha[39].

Of the other works, only 1 article used exclusively physical process by reverse osmosis, 10 articles used physicochemical processes, 8 of adsorption, 1 of separation by foaming agent and adsorption and 1 of separation using ionic solution. Of the articles found that used the oxidative processes, 1 was by the potassium ferrate oxidation method with ultrasound and 1 by the polychromatic UV oxidation. Among the 13 articles that tested Advanced Oxidative Processes (POA) in their work, 11 were exclusive to POA, of these, 2 by the Fenton method, 4 by photo-Fenton, 1 by hydrogen peroxide and 4 by photocatalysis. In addition, 2 articles used POA associated with other types of processes: one used Fenton associated with coagulation/sedimentation and the other applied photo-Fenton with immobilized biomass biological reactor.

It is also noteworthy that only four studies were obtained that addressed the possibility of reuse of these effluents. All of these studies found used POA as an alternative treatment.

Discussion

Most of the work on treating effluent from antibiotic production occurred in China. This result may express a marked economic expansion after its commercial opening, besides the need to adapt to patent laws that allowed the reproduction of various industrialized products, including drugs. This economic evolution covered the pharmaceutical sector, mainly in the field of active pharmaceutical production[40-42]. Other data that draw attention refer to the fact that 25 works were developed in Asia, 5 in Europe and only 1 in the Americas. Considering the level of production and consumption of drugs that has been reflected worldwide, there should be more studies on this approach, especially in Brazil and the United States. On the other hand, studies on the occurrence of drugs in surface water and drinking water in Europe and the United States have shown the importance of monitoring these residues[26]. In addition, rules and procedures reinforce the care these nations require to prevent their water resources from containing these types of waste[43,44]. However, even on this subject, there is little research in Brazil[26].

The POA, followed by membranes isolated or integrated to biological systems (Membrane Bioreactors – MBR), were the most cited in the articles found. The purely biological processes appeared in four works found. In fact, the most widely used treatment processes, whether for domestic or industrial wastewater, are biological ones. While the activated sludge system serves most of the Brazilian population, anaerobic reactors are the most used in the industrial sector. However, there is doubt as to whether the biological process is effective in removing/degrading antibiotics. Mechanisms for the elimination/removal of effluent antibiotic residues by biological processes may occur by incorporation of the compounds into the sludge biomass (sorption) or by biodegradation[45].

Abassi et al.[46] observed that the presence of ampicillin, amoxicillin and ciprofloxacin wastes in the industrial effluent caused a reduction in the concentration of microorganisms in the activated sludge process.

The acclimatization or prolonged exposure of antibiotic residues to microorganisms may increase their resistance to these compounds, improving their ability to degrade these substances, as compared to Industrial and Sanitary Effluent Treatment Plants containing fluoroquinolone-based antibiotics[45-47]. However, this procedure can be a risk, as these microorganisms present in this sludge can carry this resistance to the environment. It is also emphasized that this acclimatization is not a guarantee that these microorganisms can develop the biodegradability of these compounds. Saravanne and Sundararaman[48] used MBR with acclimatized biomass to treat cephalexin residues, and this resulted in the generation of 7 7-amino-3-desacetoxy cephalosporanic acid and phenylacetic acid metabolites. Another alternative tested in the MBR study was the addition of enzymes to favor the degradation of antibiotics. However, besides the high cost, this procedure may not be effective for a broad spectrum of antibiotics[45].

The degradation of drug wastes by biological processes presents better performance when associated with other processes, such as oxidative or physical. Sistori et al.[49] had an effective reduction in the concentration of nalidixic acid of the effluent using Immobilized Biomass Reactors associated with photo-Fenton. However, this process generated metabolites compounds with higher toxic potential and could be a risk to aquatic ecosystems. Wang et al.[50] used MBR with nanofiltration and observed a decrease in the concentration of spiramycin, being related to the mass transfer from the liquid phase to solid phase retained in the membrane, which also occurs in the osmosis treatment system. Despite the good efficiency observed by studies using membrane processes, a transfer of these wastes is observed, so, there is a demand for the proper treatment of these membranes[50-52].

Extraction processes adopting nonpolar or foam phases that favor the removal by liquid-liquid processes were also found in this search. Almeida et al.[53] analyzed the potential for removal of fluoroquinolones from the addition of an ionic solution to the effluent. The difference in polarity between these solutions (extractor and effluent) caused antibiotic residues to be removed from the effluent to the extractor solution. Kou et al.[54] used flotation coupled with adsorption separation for streptomycin removal (recovery). Other authors have also tested adsorption processes for the removal of antibiotic residues such as dioxicycline[55]; amoxicillin[56]; gatifloxacin[57]; cephalexin, cephradine[58], sulfamethoxazole[59]; tetracycline[60,61] and ciprofloxacin[62]. The environmental and financial cost of transferring phase contaminants can be extremely high due to the need for other processes that effectively degrade waste in these new matrices.

The phase transfer of the contaminant can also be observed in oxidation processes using medium support, such as in the application of photocatalysis in support medium for the removal of oxytetracycline[63], tetracycline[64] and deoxytetracycline[65]. This process did not present the complete elimination of antibiotics, however, photocatalysis without medium support has degraded 100% of antibiotic residues[65]. On the other hand, the protolithic oxidation requiring only the light source was not efficient for sulfamethoxazole, oxytetracycline and ciprofloxacina[66] elimination.

Oxidative processes may also be integrated with physical or chemical agents, such as the study by Zhang et al.[67] who tested potassium ferrate with ultrasound for the degradation of sulfadiazine, sulfamazine and sulfamethoxazole. However, this process was not as effective for the complete elimination of these compounds.

Many authors cite that POA are the most promising for drug waste degradation because they are capable of generating free radicals (●OH) that have high oxidative potential. However, many of the articles found in this search show that these processes and their associations did not achieve a 100% reduction in antibiotic concentration. The following methods were found: Fenton for removal of amoxicillin[56], cefpirome, latamofex, aztreonam, cefoperazone, cefatrizine, propylene glycol, ceftazidime[68] and sulfamethoxazole[69]; photo-Fenton associated with an iron and cerium heterogeneous catalyst in the presence of hydrogen peroxide under the irradiation of ultraviolet light for the removal of tetracycline in effluent[70]; and electro-photo-Fenton, electro-Fenton ultraviolet irradiation to degrade tetracycline[71]. It is also worth mentioning the application of Fenton associated with hydrogen peroxide and ozone that contributed to the complete degradation of sulfamethoxazole, sulfadimethoxine, sulfamethazine, erythromycin and tylosin tartrate[72]. All these processes, in addition to not completing the complete mineralization of antibiotics, cite the formation of other compounds (degradation by-products) that may have toxic characteristics or express similar resistance to the original compound[73].

Of the 31 articles recovered, only 2 presented techniques capable of completely eliminating the antibiotic residues tested[56,73], 27 demonstrated some level of removal and 2 were not efficient. The studies that carried out the association between the biological system by sludge activated with other processes presented good efficiency in the removal of antibiotics, which shows that this path can be quite promising.

One noteworthy observation is that only one article was performed in a full-scale treatment system, demonstrating that some of the methods tested by other studies may undergo considerable variations when submitted to larger scales.

From the analysis of these results, there is a need for urgent standardization measures for the release of effluents containing antibiotics. In addition, greater encouragement should be given to research and implementation of effective methods to reduce the risk of environmental contamination by these wastes in alignment with the emergency situation presented by WHO.

It is noteworthy that, in 2015, the WHO called on all countries to draw up National Action Plans to Contain Antimicrobial Resistance; and, in 2018, Brazil published its plan with the collaboration of the Ministry of Health and Welfare. It is emphasized that this plan is close to the current environmental demand of the implementation of reverse logistics for antibiotics, not addressing the problem of liquid effluent from industrial pharmaceutical production[74].

Of the 31 references retrieved by the integrative review, only 4 evaluated the possibility of reuse of treated effluents from antibiotic production. These studies used as a treatment method the Fenton/coagulation/sedimentation[68] association, photolysis[66] and MBR with nanofiltration[50,51]. Therefore, there are a small number of works seeking the reuse of effluents treated by the pharmaceutical industry. This fact may be related to the sanitary requirements for water use in this industrial typology[75]. However, other studies that apply the reuse of effluents in various industrial types are observed, being at the discretion of each manufacturing unit the best way to apply the reuse practice. Effluent reuse is reported in industrial activities that, due to quality criteria, are not incorporated into the product, and effluent reuse is more frequent after specific treatment in cooling towers and boilers[76-79.]

The plastic recycling industry is able to reuse 100% of the generated effluents. These effluents from the prewash and washing of plastics and sanitary sewage are directed to the wastewater treatment system, and the treated effluent is added to rainwater precipitated over the industry, which feeds the production process[80]. Likewise, the textile industry is also able to reuse its effluents from the effluent aftertreatment by advanced oxidative process[81]. Effluent reuse is already practiced even in the food production industry[82-84]. In addition to industrial processes, other segments also already perform the practice of reuse, as the International Airport of Rio de Janeiro, in which the treated effluents are directed to the cooling towers, reducing monthly consumption of up to 33 thousand m^3 of water. Therefore, further studies are needed on the reuse of effluents mainly treated in the pharmaceutical industry.

Final considerations

From this review, it can be concluded that, in these ten years of research, few studies have been found on treatment of effluents from the antibiotic industry, especially in countries with higher drug consumption and production. While China is emerging in research on this subject, Brazil, which rises in the ranking of pharmaceutical industries, generated little knowledge with this approach.

It is noteworthy that less than 5% of the studies found were developed in full-scale systems, which is a negative result since only in this way it is possible to understand the behavior of antibiotics in treatment systems already installed.

The most tested processes for antibiotic removal/degradation were the advanced oxidative processes (35%) followed by the physical-chemical processes (32%) and, lastly, the strictly biological ones (13%). It is noteworthy that many works used combined processes, including obtaining good efficiencies in relation to the isolated systems. The systems with the worst performance were strictly biological, while the advanced oxidative processes were the best. Few works used systems strictly of membranes (3%), but, yes, with the combination to the biological system (MBR) in which they had good removal efficiencies.

One of the problems for biological systems is the impact of these pollutants on sludge microfauna, because, once acclimatized, they can carry this resistance to antibiotics to the environment. When well adjusted, advanced oxidative processes promote good efficiency in the degradation of antibiotics, however, they can generate unknown byproducts or even with higher toxic potential than the original pollutant. Thus, an assessment of the toxicity and possible effects of these by-products on aquatic ecosystems is required. On the other hand, membrane systems are efficient in removing these compounds that are retained in the membrane; with this, a transfer of these pollutants is observed, which are then discarded as solid residues in the membranes. This same observation should be made to the processes of adsorption by activated carbon.

This review shows that research on the use of effluents in pharmaceutical industries is still in its infancy; especially on antibiotic producers. The 21st century will be marked by the challenge of water scarcity; and one of the ways to alleviate this problem is the reuse of water and effluent in producing activities such as industrial.

Finally, in Brazil, there are no legal limits for the release of effluents with antibiotic residues in the environment. However, this practice poses a risk to environmental health and may favor the development of multi-resistant bacteria.

Collaborators

Rock ACL (0000-0001-7243-7832)* contributed substantially to the design, planning, data analysis and interpretation, drafting and critical review of the content, as well as the approval of the final version of the manuscript. Kligerman DC (0000-0002-7455-7931)* contributed substantially to the design, planning, analysis and interpretation of the data and revision of the manuscript. Oliveira JLM (0000-0002-0361-3457)* contributed substantially to the design, planning, analysis and interpretation of the data and revision of the manuscript. ■

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