Wastewater Treatment and the Use of Nanoparticles, a Form of Circular Economy in the Pharmaceutical Industry

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Abstract. *People's health is the most valuable "quality" they can acquire, and sometimes it depends or not on their actions. The pharmaceutical industry is often responsible for people's health through the products it produces. However, the process of producing medicines can have significant effects on the environment. The good deeds of pharmaceutical companies also have consequences, and these ultimately end up being harmful to people as well. Based on the literature, this study aims to identify the possibility of implementing a circular economy at the level of the pharmaceutical industry, especially water consumption, which is perhaps the most exploited resource in pharmaceutical companies. The articles published between 2015 and 2024 from the Web of Science are used, which, with the VOSviewer software, are "transformed" into maps, thus representing the relationships between authors, the countries with the most publications, and the journals that published articles that address the research direction appropriate to the study. Also, methods for treating wastewater from the pharmaceutical industry have been identified, and it has been explained how drugs, more specifically antibiotics, can affect the environment and then humans and animals. In conclusion, the circular economy in the pharmaceutical industry is still a sufficiently unexplored topic to be applied with certainty, but it has potential, contributing to a reduction in environmental degradation caused by drug production. As research directions, the study can be expanded, the bibliographic analysis can be carried out in more detail, and even public data from companies operating in the pharmaceutical industry can be taken into account.*

Keywords: circular economy, pharmaceutical industry, wastewater, VOSviewer, antibiotic.

Introduction

The relationship between industry and the environment is becoming more complicated, and regrettably, it usually has a negative impact that is irreversible at a certain point (Pislaru et al., 2013). The pharmaceutical industry is one of the most important industries both economically and socially, as well as in terms of its level of environmental pollution. The significant consumption of resources required to obtain pharmaceutical products that play a vital role in health also draws the attention of those who are concerned with protecting the environment. It goes without saying that businesses impact the environment and that the environment influences their existence; as a result, the company's welfare is linked to the well-being of the society in which it operates (Pislaru & Trandabat, 2012). The process of obtaining pharmaceuticals is very complex, requiring impeccable attention, and also involves adhering to very strict work procedures and the continuous training of

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the personnel involved. The most commonly used resource in drug production is water, which is necessary at several stages of the process and is used with a certain degree of purity in the most stringent stages of the production flow.

According to Danner et al. (2019), “the global use of antibiotics exceeds 10k tons per year, and the discharge of these compounds directly into the environment is a major concern worldwide”.

To ensure the sustainability of water resources, industry should improve water efficiency in a value chain and maximize possibilities for safe reuse of various water qualities. For extremely contaminated water, new treatment solutions are presently being researched. For the treatment of industrial wastewater, the literature contains reviews of chemical, biological, advanced chemical, or advanced oxidation technologies, as well as hybrid technologies. There have been a lot of new technologies that have been proposed, but the main idea is to remove all chemicals from pharmaceutical wastewater by using hybrid methods that combine multiple “treatment mechanisms”.(Strade et al., 2020).

The pharmaceutical industry is constantly developing, which can create problems for water resource management. Inadequate wastewater discharge leads to the release of pharmaceutical substances into the environment. This endangers water quality and can have a harmful effect on aquatic ecosystems and on human health (Larsson, 2014).

To meet regulatory requirements, “many pharmaceutical processes require highly pure water that meets strict quality standards” (Strade et al., 2020). However, wastewater can be highly polluted and toxic, requiring complex and expensive multi-stage treatment to meet the requirements. The production of human and veterinary drugs requires high-purity water, but the pharmaceutical industry is one of the main polluters of local water resources (Larsson, 2014). In the pharmaceutical industry, strict regulations and safety concerns hinder the implementation of circular water management. “However, there is evidence that it is possible to reduce water consumption by up to 50% in some sectors” (Andrews et al., 2011).

To analyze the difficulties faced by the pharmaceutical industry in terms of water consumption and wastewater quantity, it is necessary to go through several stages such as water sources, conditions regarding the standard of water utilized in industry, processes by which water used in production units is prepared or pretreated, “water consumption, wastewater production processes (including generation, composition, flow rates, and treatment), and methods of water and wastewater reuse” (Strade et al., 2020).

The research aims to deepen the possibility of implementing circular management in the pharmaceutical industry, given that the rigor in this field reaches high standards that cannot be easily modified. It also takes into account the degree of environmental pollution in pharmaceutical companies, resource consumption, and adaptability in terms of addressing sustainable manufacturing methods.

Implementing circular management in a pharmaceutical company regarding water consumption could involve: the reuse of untreated wastewater as a secondary means of biological wastewater treatment, the recovery of substances from concentrated wastewater, the chances of wastewater reuse after applying various treatment methods, but also the restrictions on their use.

In what follows, the paper has a literature review section, followed by the research methodology, results and discussions, and finally conclusions.

Literature review

We divide wastewater treatment methods into three categories: physical, chemical, and biological processes. Biological wastewater treatment is the most commonly used term when talking about the removal of organic contaminants from wastewater, which can be carried out in conjunction with mechanical operations.

First off, recirculation is nearly impossible in biological wastewater treatment, a popular end-of-pipe waste treatment method. However, it is not always appropriate in the case of technological wastewater with a high organic content due to operational limits (Tóth et al., 2023).

Reducing, reusing, and recycling are the cornerstones of the circular economy. This economic approach does not produce waste and encourages the constant use of resources (Miraute & Pislaru, 2024).

In pharmaceutical production, different grades of water are used as raw material, ingredients, and solvents to produce active pharmaceutical ingredients, processes, and final dosage forms for humans or animals. Strade et al., (2020) state that the formulation and method of administration of a pharmaceutical product, as well as the phases of the manufacturing process in which water is used, have a significant impact on the quality of the water used. Prior to the last phases of isolation and purification, drinking water can be utilized for the chemical production of all active ingredient intermediates. Regarding water efficiency, the preparation of high-quality pharmaceutical water requires significant water losses. Strade et al. (2020) argue that, due to the high purity requirements of purified water, up to half of the feed water in a production facility is discharged as waste. “However, this water is still good enough to be reused as an alternative water source on-site in facilities where pharmaceutical products do not come into direct contact, such as cooling systems”(Strade et al., 2020).

In their study, Singh et al. (2021) consider nanostructured materials as an economical and effective approach to pollution caused by waste from pharmaceuticals. These nanoscale materials, or nanoparticles, have tremendous potential for the mineralization of pharmaceutical compounds in aqueous solutions. They are cheap, easy to handle, and perform very well. Furthermore, nanoparticles can absorb pharmaceutical by-products and waste at minimal cost, which can be easily recycled.

In treating pharmaceutical wastewater, physicochemical methods, such as the coagulation method and air flotation method (Wen et al., 2024), adsorption method, and electrolytic method (Abdelwahab, 2023), are frequently used as pretreatment or as a more advanced treatment. Chemical methods include the oxidation of pollutants into easily degradable intermediates or final products. These methods include a variety of advanced oxidation technologies and iron-carbon microelectrolysis. This technology has been very advanced in wastewater treatment for pharmaceuticals, as it has been used for ozone oxidation, phenone oxidation, electrochemical oxidation (Tóth et al., 2023), photocatalysis, ultrasound irradiation, and humid air oxidation.

Since VOSviewer allows for the visualization of bibliometric maps, a co-occurrence analysis of the keywords of the articles was conducted to identify study groups and highlight research trends, an approach also taken by Abdelwahab et al. (2023) in their study. Each article uses keywords to represent the main ideas and developments of the subject under study. Since keywords indicate the growth of a research topic and the actual content of an article, a co-occurrence network of keywords is beneficial for mapping knowledge (Abdelwahab et al., 2023). VOSviewer finds the author's keywords from the literature database for co-occurrence frequencies.

Methodology

This paper conducts an analysis based on information from the literature with the aim of researching ways to improve sustainability in the pharmaceutical industry. The primary focus is on how pharmaceutical companies manage water consumption as well as the methods used for treating wastewater resulting from manufacturing processes. The aim is to find works that emphasize the adoption of a circular economy in the pharmaceutical industry so that water consumption can be reduced and the level of recovery/recycling as well as the decontamination of wastewater can be increased. Articles addressing the topic of interest are extracted from the Web of Science database, so the search engine includes the keywords: circular economy in the pharmaceutical industry, wastewater in the pharmaceutical industry, and treatment of wastewater from pharmaceutical companies. The search filters are selected so that the search is conducted only for articles published between 2015 and 2024, which have open access for readers. A total of 213 articles were identified, which were then analyzed using the VOSViewer tool. In bibliometric studies, VOSviewer is becoming increasingly popular, "this bibliometric analysis helps us to follow the evolution of the concept" (Miraute & Pislaru, 2024). Van Eck and Waltman (2010) created the program to help with the creation and presentation of accessible bibliometric maps. It performs a remarkable job of gathering pertinent information, identifying patterns across publications that fit the same criteria, and identifying the broad topic that pertains to the works it has chosen (Wen et al., 2024). Bibliometric mapping examines the impact and advantages of regulations for particular article attributes. The co-occurrence weight of the article and the total strength of the laws are used for this. Bibliographic coupling, co-citation analysis, co-authorship analysis, co-word analysis (keywords), and citation analysis are some of the methods that are combined in this approach. (Abdelwahab et al., 2023). VOSviewer provides a complex visualization of bibliometric data, creating networks that can contain multiple elements that, together, offer a perspective on the structure and evolution of the analyzed field. Each node represents an entity in the dataset, which can be an author, an institution, a document, or even a research topic, depending on how the analysis was configured. The size of a node reflects its importance—usually, this is related to the number of publications, the number of citations, or another measure of impact. A larger node indicates that the respective entity plays a central role in the network. This paper uses bibliometric methods to conduct a comprehensive analysis of the current research situation on pharmaceutical wastewater and future trends . The paper is more of a literature review looking for papers that focus on how pharmaceutical companies manage water consumption and wastewater treatment methods. VOSViewer helps us identify authors who have the same research direction and find articles relevant to this study.

Tabel 1. Top 10 countries with the most publications, citations and total link strength

No.	Country	No. of publication	Citations	Total link strength
1	Portugal	45	968	11664
2	Spain	36	841	12951
3	Italy	29	1280	12846
4	Brazil	18	213	2101
5	England	14	677	3203
6	India	14	261	3176
7	China	14	266	4975
8	Germany	10	174	8311
9	Mexico	9	316	3049
10	Romania	8	159	262

Source : own research by VOSviewer.

In Table 1, the top 10 countries with the most publications in the field of interest (circular economy in the pharmaceutical industry and wastewater management) are listed, according to the results obtained with the VOSviewer application, based on data exported from the "Web of Science". The number of citations for each country and the total link strength are also specified. At the top is Portugal with the most published articles, 45, followed by Spain with 36 works, and in third place is Italy with 29 works but with the highest number of citations, 1280 citations. The following countries in the ranking are Brazil (18 publications), England, India, and China, each with 14 publications; Germany (10 articles); Mexico (9 articles); and Romania (8 articles).

Results and discussions

Using the VOSviewer tool, Figure 1 shows a network that highlights the relationships between authors based on the number of published papers, the number of citations, and the years in which they were most prominent through those links and nodes. Thus, the thickness or intensity of a link indicates the strength of the relationship—for example, how many times two authors have collaborated or how often they appear together within the same research topic. Warmer shades (e.g., red or orange) indicate that authors have relatively recent publications, suggesting current or emerging research activity. Cooler shades (e.g., blue or green) signal that authors have been active in a more distant period, indicating a historical presence or an interest that was focused in the past. Nodes that are more closely connected to each other often group together in "clusters" or communities. These clusters may represent research subfields, collaborative networks, or similar thematic themes. The positioning of nodes in space is determined by how closely they are connected to each other. Close nodes indicate strong relationships or similarities, while distant nodes have weaker ties or less frequent relationships.

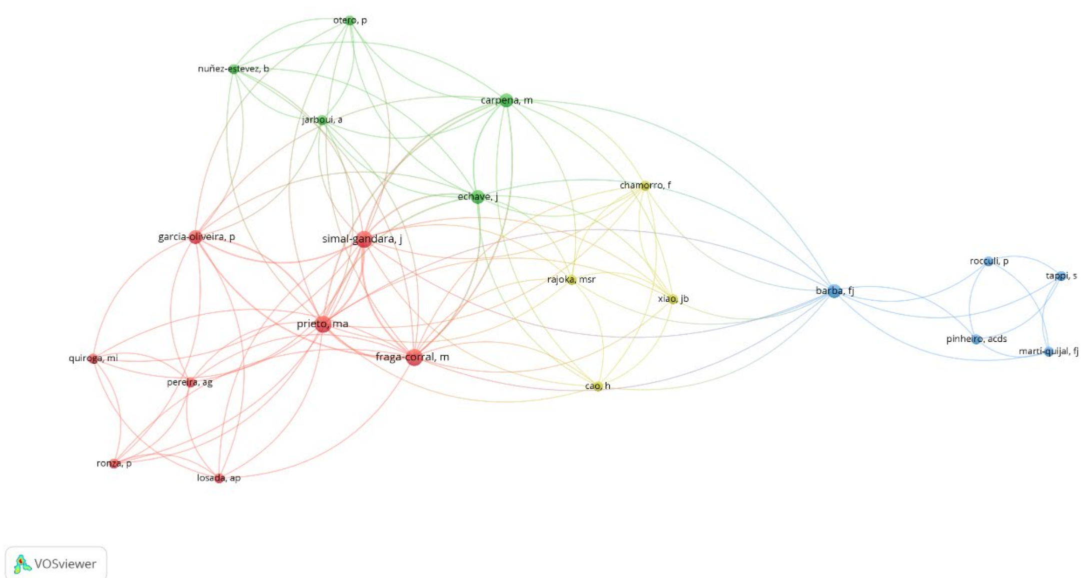

Figure 1. Co-authorship analysis network

Source: VOSviewer.

In the analysis conducted using the VOSviewer tool, a map was obtained showing the countries (Figure 2) that stand out in terms of the number of publications adopting the studied research field. The connections between countries are represented here in different colors and nodes of various sizes depending on the level of publication in each. A total of 63 countries were grouped into 7 clusters, the largest of which consists of 16 countries (Brazil, England, Romania, Argentina, Colombia, Costa Rica, Croatia, Iran, Ireland, Malaysia, Netherlands, Pakistan, Philippines, South Africa, Thailand, Uruguay). The second cluster consists of 12 countries (Greece, Poland, Slovenia, Indonesia, Latvia, Lithuania, Norway, Sweden, Turkey, Bosnia & Herzegovina, Estonia, Finland). The third cluster is composed of 11 countries (USA, Australia, Canada, France, South Korea, Singapore, Bangladesh, Chile, Cyprus, Greenland, and Israel). The fourth cluster is made up of 7 countries (China, Mexico, Saudi Arabia, Angola, Egypt, Taiwan, North Ireland). The fifth cluster contains 7 countries, including those with the most publications (Portugal, Spain, and Italy, followed by Germany, Austria, Tunisia, and Belgium). The sixth cluster consists of 6 countries (India, Japan, Algeria, Scotland, Serbia, and Wales). The last cluster, the seventh, is made up of 3 countries (Czech Republic, Hungary, and Denmark).

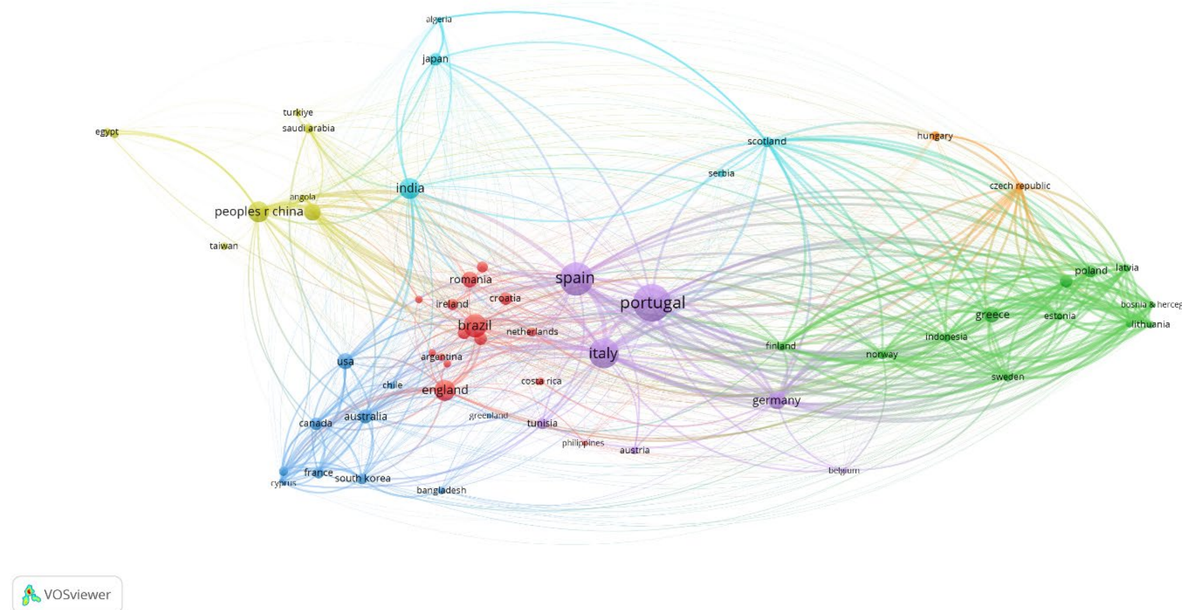

Figure 2. Bibliographic analysis of countries according to the number of publications

Source : VOSviewer.

Also through VOSviewer, a map of the journals (publication sources) where works addressing the research direction necessary for this study were published was created and can be seen in Figure 2. Thus, 4 clusters were obtained, grouping a total of 181 publication sources. Among the most cited are "Bioresource Technology Journal" with 565 citations and a 9.7 impact factor, "Food Chemistry Journal" with 553 citations and an 8.5 impact factor, "Journal of Cleaner Production" with 441 citations and a 9.8 impact factor, "Molecules Journal" with 406 citations and a 4.2 impact factor, and "Journal of Agricultural and Food Chemistry" with 305 citations and a 5.7 impact factor.

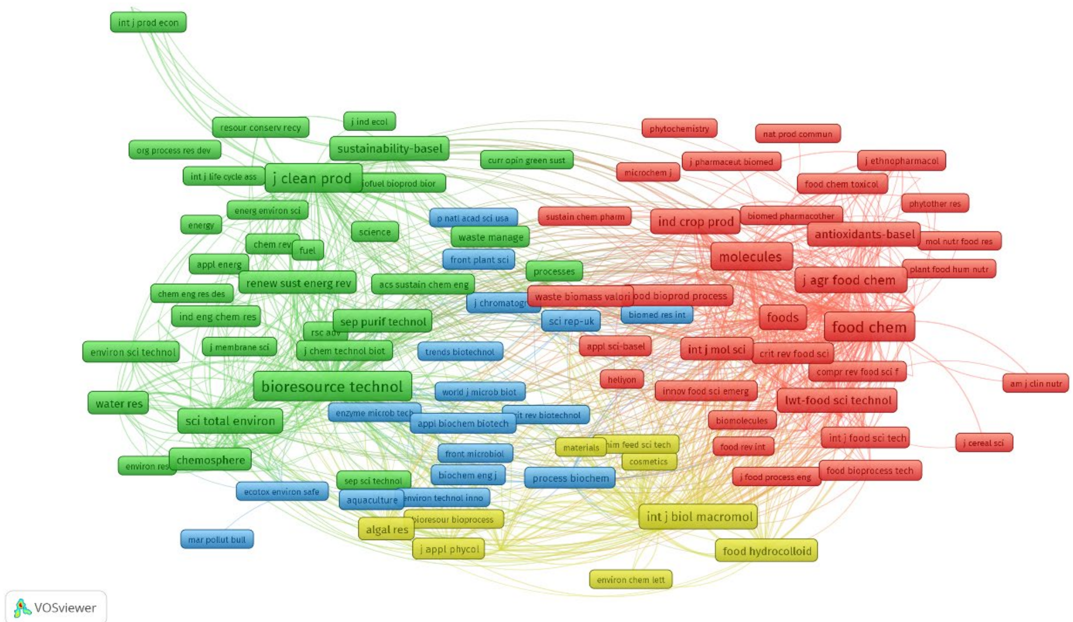

Figure 3. Visualization of the connections between publication journals in the field of circular economy in the pharmaceutical industry

Source: VOSviewer.

Among the medications produced by pharmaceutical companies, a significant class is represented by antibiotics, which can have a broad spectrum of action against viruses/bacteria but which, if not administered and managed with care and consideration for the environment, can ultimately lead to the development of resistance in microorganisms to this class of drugs, making it more difficult to combat various conditions caused by viruses or bacteria.

Both antibiotics used for treating human ailments and those for animals have an equally significant impact on the environment and ultimately on the lives of humans and non-human animals. It is a cycle of action for these medications, initially aimed at healing and treating certain conditions, but later, if not managed properly, they can become harmful. In Figure 4, based on the findings in the literature, the action cycle of antibiotics on the environment is presented, with a direct effect on humans and animals.

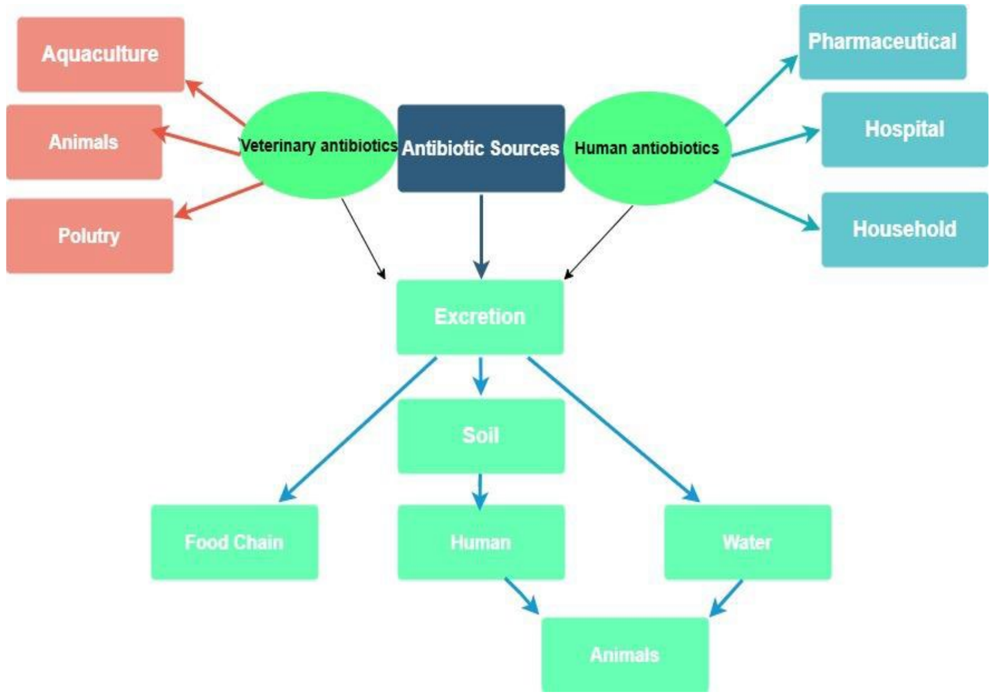

Figure 4. Sources of antibiotics and their action on the environment

Source: own research.

Since there is currently no technological process that generates only the desired final product, it can be said that the chemical industry and all industrial activities, in general, generate inevitable waste. Regarding environmental protection, Wen et al. (2024) believe that technological changes occurring in the chemical industry can be divided into two categories: the modernization of existing facilities and the construction of new facilities that include basic environmental protection technologies. In general, it is better to consider waste reduction principles when it is being designed and constructed a new facility than to modernize existing technology.

In their research, Tóth et al. (2023), propose a series of wastewater treatment methods from the pharmaceutical industry, these being of three types: mechanical, biological, and physicochemical, which can be seen in Figure 5.

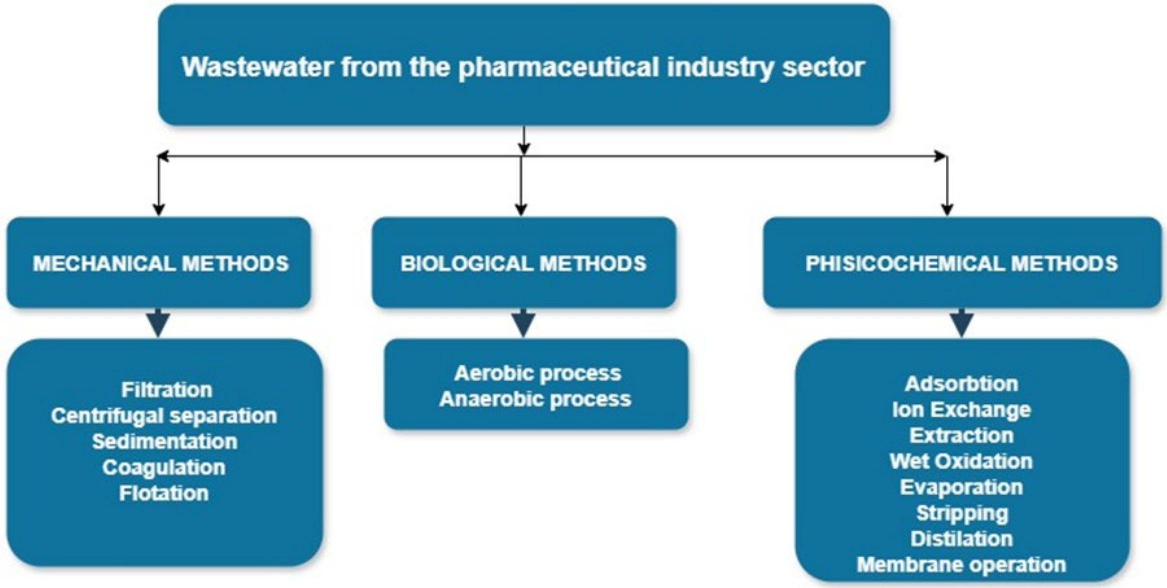

Figure 5. Wastewater treatment methods from the pharmaceutical industry

Source: Tóth et al. (2023) research.

Due to its low cost, ease of preparation, and strong regeneration capacity, the most widely utilized adsorbent in methods of adsorption is activated carbon.; however, it also has certain limitations. An efficient method for treating pharmaceutical wastewater is photocatalysis, which works well for contaminants in wastewater from pharmaceuticals that are hard to biodegrade. Due to its high photostability, low cost, and non-toxicity,"TiO_2 is one of the most widely used photocatalysts and is often employed to decompose pharmaceuticals and endocrine disruptors in wastewater "(Garcia-Segura and Brillas, 2017). A series of studies have demonstrated that MBR technology is one of the best technologies for treating pharmaceutical wastewater currently available and is remarkably efficient in removing pollutants found in pharmaceutical wastewater (Wen et al., 2024). However, membrane fouling hinders the progress of the MBR (Membrane Bioreactor) process, this combines biological processes of pollutant degradation with membrane filtration. Research and the development of effective membrane contamination mitigation methods are essential for the implementation of the MBR process. Moreover, understanding how pollutants are bound to pharmaceutical wastewater by microorganisms is essential for the safe treatment of wastewater from pharmaceuticals. Since the pollutants in pharmaceutical wastewater are both so different and so complex, current technology cannot completely treat these pollutants. In addition, the pollutants associated with pharmaceutical waste will migrate into the environment upon discharge. Therefore, it is essential to pay special attention to characteristic pollutants and to develop methods for their identification and analysis (Wang et al., 2023).

When it comes to existing manufacturing processes, as well as new ones, environmental concerns and wastewater reduction are becoming increasingly important. It is important to specify that such development is driven by increasingly strict environmental regulations. An essential component of the pharmaceutical industry is environmental protection. Many industrial and scientific advancements have been made to reduce the use of raw materials and energy, as well as to recover and recycle the polluting secondary products of wastewater. The developments and research in the environmental and technical chemical industry have contributed to its orientation towards a more ecological variant while also reducing waste.

On the other hand, the most powerful photocatalytic nanomaterials are nanoparticles. Due to their small size, they have unique chemical and physical properties, such as a high surface area-to-volume ratio, increased reactivity, and the ability to interact effectively with various substances. Nanoparticles can help treat wastewater resulting from processes in the pharmaceutical industry through multiple mechanisms. For the adsorption and removal of pollutants, iron oxide nanoparticles are used, which have the ability to adsorb heavy metals and hazardous organic compounds. Additionally, carbon nanotubes have a large surface area and can efficiently adsorb antibiotics, dyes, and other toxic substances. Their use in the treatment of wastewater resulting from the antibiotic manufacturing process is becoming increasingly widespread, considering the significance of photocatalytic activity in a range of applications and its influence on the worldwide waste and emissions crisis. "The most powerful photocatalytic nanomaterials are semiconductors due to their unique photocatalytic activity and overall capability in measurable environments" (Tahir et al., 2020). Titanium dioxide nanoparticles are used to decompose organic compounds under UV light; silver nanoparticles have antimicrobial properties and can help destroy antibiotic-resistant bacteria. For filtration and separation, membranes with nanomaterials (nanocellulose or graphene) are used, which have the ability to retain pollutant particles from water, providing efficient filtration (Tóth, 2023). The recovery of pollutants is achieved with magnetic nanoparticles that have the ability to capture pollutants from water, and these can be removed with the help of a magnetic field, thus reducing costs and material waste.

Although all nanostructured materials can be used, metal oxides are known to have exceptional photostability, which is why several photocatalysts have been created to remove antibiotics (Singh et al., 2021).

Therefore, the advantages of using nanoparticles in wastewater treatment are high efficiency in pollutant removal, reduction in the use of environmentally harmful chemicals, the possibility of being reused after water treatment, and compatibility with conventional water purification methods.

As a novelty in research, the use of the VOSviewer program allows for the exploration of various research topics and their presentation in the form of maps that can be read and interpreted. The variety of results can be very large depending on the parameters entered into the program before the map is generated. Therefore, articles can be extracted from various databases over different periods, and depending on the search engine, the results can vary (number of articles, period, keywords, number of citations, etc.). Therefore, each map represented using VOSviewer can generate different results and can bring an added novelty to the conducted study.

Conclusion

In conclusion, the circular economy can be applied to some extent in pharmaceutical companies, but it largely depends on the manufacturing stage. Referring strictly to the recirculation of water or its treatment for reuse, we touch on a delicate subject in the pharmaceutical industry, as water consumption is significant, but water quality cannot be neglected either. Therefore, there are stages in the drug manufacturing process where the water purity level must be very high or even sterile water is required, which might not be achievable through a recirculation process, or the costs to meet certain quality parameters could be higher than producing the water itself. In conclusion, the circular economy can be applied to some extent in pharmaceutical companies, but it largely depends on the manufacturing stage In this research, information found in the literature was taken into account, and works from the period 2015-2024, published in the “Web of Science” database, were analyzed. The results obtained and exported from the “Web of Science” were projected using VOSviewer software in the form of "readable maps," thus highlighting the connections between authors, the countries with the most publications in the sought research field, and the journals that stood out in this list of published articles. Thus, a ranking of the top 10 countries with significant publication numbers was created, with Portugal in the first place with 45 articles and Romania in the tenth place with 8 articles. The most frequently encountered journal is "Bioresource Technology Journal" with 565 citations and an impact factor of 9.7. In practice, an initial bibliometric analysis was conducted on several aspects that confirm that the chosen research direction has been and continues to be addressed by a number of authors, but answers and solutions regarding circular economy methods in the pharmaceutical industry are still being sought. The literature review has contributed to the identification of some water treatment methods that can be used in the pharmaceutical industry and are ultimately considered a form of circular economy. It has also it is described the effect that antibiotics have on the environment regardless of their source. Practically, it is not only the water consumption in the pharmaceutical industry that impacts the environment, but the totality of medicines, particularly antibiotics, which can cause significant degradation if not managed properly.

To cope with increasingly strict environmental rules are getting progressively more significant to discover appropriate methods for treating wastewater in the pharmaceutical industry sector. However, physicochemical methods increasingly rely on the recycling and reuse of pollutants, which opens up fresh viewpoints on the circular economy and technologies that make it possible to discharge liquids with zero emissions.

Also, the use of nanoparticles in the treatment of wastewater from the pharmaceutical industry represents a promising solution for the elimination of hazardous pollutants, contributing to the protection of the environment and human health.

Therefore, the chosen research direction is still insufficiently analyzed in the literature, has potential for new research topics, and can be extended to more detailed bibliometric analysis or to concrete information within pharmaceutical companies where this is permitted.

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