CHEMICAL ENGINEERING TRANSACTIONS
VOL. 114, 2024
A publication of AIDIC
The Italian Association of Chemical Engineering
Online at www.cetjournal.it
Guest Editors: Petar S. Varbanov, Min Zeng, Yee Van Fan, Xuechao Wang

ISBN 979-12-81206-12-0; **ISSN** 2283-9216
DOI: 10.3303/CET24114115

The Processing of Biological Waste from the Pharmaceutical Industry

Aleksandra Petrovič*, Klemen Rola, Sven Gruber, Neža Šantl, Saša Sankovič, Lidija Čuček, Darko Goričanec, Danijela Urbancl

Faculty of Chemistry and Chemical Engineering, University of Maribor, Maribor, Slovenia
aleksandra.petrovic@um.si

The pharmaceutical industry produces waste that can pose significant environmental and health risks if not handled properly. The aim of this research is to investigate the microfiltration (MF) method for the treatment of pharmaceutical waste mycelia (fermentation residue) and to test different operating conditions (different permeate flows, operating pressures, and treatment times) to identify and determine the optimum setting conditions. The products resulting from the best operating conditions permeate and retentate and were then subjected to further chemical characterisation.
The results showed that the operation of the MF pilot plant, consisting of 4 sequentially coupled 0.1 µm ceramic ZrO_2 membranes with a total membrane area of 56 m^2, was optimal at a permeate flow of 1.2 m^3/h (pressure of 2 bar, temperature of 60 °C) with a permeate flux of 21.4 L/(m^2×h). Two different operating times (3.5 and 8 h) were tested under these conditions without any clogging of the membranes being detected, neither in the long nor in the short time of operation. The chemical analysis showed that MF is highly efficient in removing chemical oxygen demand (COD), which decreased by 67 %, although the removal of other small micropollutants was less efficient.

1. Introduction

The waste generated by the pharmaceutical industry can pose a serious threat to the environment and human health if it is not properly treated and disposed of (Adeoye et al., 2024). Pharmaceutical waste comes mainly from pharmaceutical production, which can be divided into the production of active pharmaceutical ingredients (APIs) and the production of final pharmaceutical products (FPP). The main problem with waste streams from the pharmaceutical industry is the transfer of antibiotic resistance genes into the food chain, which can lead to bacteria becoming immune to antibiotics, which is why appropriate treatment is required (Kotwani et al., 2021). Besides, another threat to human health and freshwater reserves is the rising of emerging contaminants in the water and environment, such as pharmaceutical drugs (Alfonso-Muniozguren et al., 2021).
One of the ways of producing pharmaceutical ingredients is through fermentation, which also generates huge amounts of biological waste consisting of the fermentation medium, metabolites, amino acids and other components, including cell residues, nutrients, minerals and traces of APIs (Jaseem et al., 2017). It is estimated that the production of 1 t of API produces between 8 and 10 t of fermentation waste (Hui et al., 2023).
The method chosen for the processing and disposal of pharmaceutical waste depends primarily on its composition. However, from a circular economy and sustainability perspective, the waste streams could be used to recover nutrients or to produce other value-added products. In general, fermentation waste (mycelium) is classified as non-hazardous and is suitable for various biological treatment methods, such as aerobic or anaerobic degradation with bacteria or biological treatment with fungi (Gong et al., 2020). As it contains large amounts of water (less than 8 % dry matter), its treatment and disposal are associated with high costs. In addition to fermentation residues, other waste streams are also produced in the pharmaceutical industry, including wastewater, which can contain various organic pollutants, suspended and dissolved solids, chlorides, sulfides, oils and heavy metals (Kumar et al., 2024). Their presence in the environment causes concern, as they are not biodegradable, are often carcinogenic, and can easily accumulate and cause damage to organs in the

Paper Received: 30 May 2024; Revised: 20 August 2024; Accepted: 6 December 2024
Please cite this article as: Petrovič A., Rola K., Gruber S., Šantl N., Sankovič S., Čuček L., Goričanec D., Urbancl D., 2024, The Processing of Biological Waste from the Pharmaceutical Industry, Chemical Engineering Transactions, 114, 685-690 DOI:10.3303/CET24114115

human body (Okeke et al., 2022). Various studies were dedicated to treatment of pharmaceutical waste, with the most investigated processes being biological like anaerobic digestion (Yang et al., 2024), physico-chemical treatment like membrane filtration (Kumar et al., 2024), photocatalytic degradation (Bhattacharjee and Ahmaruzzaman, 2024), and thermal treatment, such as pyrolysis (Mgharbel et al., 2023) and hydrothermal carbonisation (Javid et al., 2021). Despite many studies, several questions regarding the treatment of such waste remain unsolved, and their complex composition requires the treatment of each waste separately.
The aim of this study was to investigate the MF of waste mycelium (fermentation residue) from the pharmaceutical industry and to find the optimal way of processing it, depending on its physico-chemical properties. Different operating conditions were tested, and the products, permeate and retentate, obtained from the experiment with the most optimal operating conditions were characterised using different chemical methods. They were subjected to analyses such as COD, total phosphorus (TP), total nitrogen (TN) and others. Based on the results of the analyses, the optimal operating conditions for the treatment of a real sample of waste mycelium were proposed. The study's distinctive contribution lies in its comprehensive approach to address the treatment of specific pharmaceutical waste mycelium sample. This is achieved through the utilisation of a pilot-scale MF unit and the optimisation of specific operational parameters.

2. Materials and methods

2.1 Feedstock

The waste mycelium resulting from the production of an API for one of the commonly used antibiotics was collected in one of the Slovenian pharmaceutical companies and treated by membrane filtration. The waste mycelium was not pretreated with any other method prior to membrane filtration.

2.2 Treatment of mycelium

The raw mycelium was treated by pilot MF equipment, which consists of a mycelium-fed buffer vessel equipped with a mixer. A pump is installed under the vessel, which pumps the fluid (mycelium) to the MF unit. The unit consists of 4 sequential stages, with 0.1 µm ceramic ZrO_2 membranes with a net area of 56 m^2, set in a Cr-Ni-Mo steel casing. Each stage is composed of multiple parallel modules. In the first three stages, three parallel modules are installed at each stage and in the last stage, two parallel modules are installed. Modules in each stage are of the same capacity, where the first stage has the highest, and the last stage has the lowest capacity. The second and third stages have the same intermediate capacity. Before each stage, pumps raise the pressure to the appropriate value and simultaneously produce the heat, raising the feedstock temperature. To counteract this, a tube heat exchanger is installed at each stage, providing water cooling. Two tubular heat exchangers are installed at the outlet of retentate and permeate, which are collected as products of membrane filtration to cool each outlet. For MF, filtration pressure, temperature (average across stages) and permeate flowrate at each MF stage, i.e. MF unit, can be set. The volume flowrates of permeate and feed are measured with magnetic-inductive flowmeters. Diaphragm pressure sensors are used to measure the pressure, and temperature is measured using temperature sensors with Pt100 transducers. The data is measured on-line at each stage and sent to the equipment display, where it is updated regularly.
During the experiment, temperatures, inlet and outlet membrane pressures of the retentate side, and flowrates of permeate were recorded by taking a snapshot of the display every 0,5 h during operation. The MF was performed under the next set of conditions: feed mycelium flowrate of 3.0 m^3/h, temperature of 60 °C and pressure of 2 bar. The operating time varies depending on the experiment. Three different permeate flowrates were tested: 1.0, 1.2 and 1.7 m^3/h. More specifically, for the experiment at flowrate, 1.2 m^3/h, the flowrates of permeate were set to 0.5, 0.3, 0.3, and 0.1 m3/h at stages 1, 2, 3, and 4, considering the capacity difference between the stages. The flowrates were lower in each subsequent stage, with stages 2 and 3 allowing the same permeate flow rates. The experiments at the highest permeate flow rate (1.7 m^3/h) were conducted at two different pressures (2 and 2.5 bar), while at a permeate flow rate of 1.2 m^3/h the two different operating times were tested (3.5 and 8 h). When MF was operated for 8 h, a semi-stationary state was achieved around 1 h of filtration. The permeate and retentate samples collected in the experiment with the optimal operating conditions were further chemically characterised. The samples were taken from the last stage of MF after 8 h of operation before the columns were switched to the washing sequence.

2.3 Measurement of chemical parameters

The mycelium raw waste stream, permeate and retentate were collected immediately after MF tests and then stored at 4 °C in the fridge until further chemical analyses. The samples were analysed for COD, TN, ammonia nitrogen ($N\text{-}NH_4^+$), TP and phosphate (PO_4^{3-}) using appropriate standard methods. In addition, the pH value was measured using the pH sensor of the Pasco producer.

3. Results and discussion

3.1 The results of microfiltration tests

The results of MF experiments are shown in Figure 1. At the highest permeate flowrate and the highest pressure tested (1.7 m^3/h, 62.5 °C, 2 h, 2.5 bar), the MF was stopped after ~1.5 h of operation because the pressures at the membrane outlets increased above 3.5 bar, even though the pressure was set to 2.5 bar. This is inferred to be due to a very dense i.e., viscous concentrate. Despite the increase in pressure, the concentrate and permeate flows remained constant, and there were no noticeable changes in the opening of the permeate valves. The permeate flux, calculated by the equation proposed by Pan et al. (2015), was 30.4 L/(m^2×h).

In the second experiment that was conducted at the same permeate flow and temperature (1.7 m^3/h, 62.5 °C) but lower operating pressure (2 bar), the impact of operating pressure on the MF process was studied. Despite the lower operating pressure, the pressure for the individual membrane filtration columns still increased with operating time duration, although the increase was slightly lower. The outlet pressure of all membranes was similar, while the inlet pressure significantly differed. The highest pressure was observed in the case of the first membrane stage and the lowest at the third stage. The other two stages (2 and 4) were within the pressures of stages 1 and 3 and exhibited more equal pressures to each other. However, after 2 h of the operation, the experiment was stopped as an increase in pressure was observed. This indicated that the permeate flow was too high. Therefore, in the next experiment, the permeate flow of 1.0 m^3/h was tested.

The experiment at a permeate flow of 1.0 m^3/h (60° C, 2 bar) runs 3.5 h, wherein the calculated permeate flux was 17.9 L/(m^2×h). During the operation, except at the beginning of the experiment, no significant pressure increase was observed in any of the membrane stages, and no clogging was detected. Regarding the operating temperature, the measurements revealed the highest temperature in the last stage (stage 4), followed by stages 3, 2 and 1. This indicated that during the MF, the temperature of the feedstock increased due to several reasons. The fluctuation of the temperature at each MF stage can be attributed to the nature of regulation. Each pump, besides raising the pressure, also introduces heat into each stage feed, raising its temperature. During MF, it is likely that the temperature also increases due to the friction. As mentioned in section 2.2, the cooling for each stage is provided as a result. It is thought that in the first and second stages, the temperature cannot reach 60 °C since not enough heat is introduced to the feed. This then allows the temperature of the third and last stages to reach higher values to balance lower stage 1 and 2 temperatures. As a result, it is thought that the first two stages do not cool much. This can also be noticed in all the diagrams, where the first two stages have significantly more uniform curves compared to the last two stages. Significant fluctuations could be attributed mostly to the regulation's natural slow response of temperature-regulated systems and to the allowed set temperature interval of ±2 °C, allowing the fluctuation between 58 °C and 62 °C.

Due to the encouraging results obtained at a permeate flow of 1.0 m^3/h, in the next experiment, the permeate flow was increased to 1.2 m^3/h. Similar results were obtained in the case of lower permeate flow. In addition, the temperature and the pressure were relatively constant, and no significant changes were noticed during 3.5 h of operating. In all four stages, a temperature rise was observed at the start of operation due to start-up to reach the temperature setpoint. The permeate flux in this experiment was higher because of the higher permeate flow and was equal to 21.4 L/(m^2×h).

To investigate the impact of operating time on the MF, the previously mentioned experiment at permeate flow of 1.2 m3/h was repeated at the longer operating time (8 h). The temperatures varied between 50 and 73 °C, depending on the MF stage, with an average value of 60 °C for all four stages together. Modules 3 and 4 exhibited higher temperature increases than the other two stages, where the temperature was more constant. A slight increase in the pressure was also observed in the stages, first after 1.5 h of operation and the second near 4.5 h of operation, which was again followed by a slight decrease. The changes in pressure are most likely also related to the temperature. It is thought that the drop in temperature causes the viscosity to rise and density to increase, making it harder to achieve the specified permeate flowrate, causing the pressure to increase. This can be clearly seen when looking at the segment between 1 h and 4 h of operating time. In the next time section, however, an increase in pressure is noticed at the same time as the temperature is increased, which undermines the dependence on operating pressures. It is also possible that some time lag is present since the change in pressure won't take effect immediately after the temperature change. To prove this, the MF would need to be operated multiple times at longer periods of time. Nevertheless, the valves that regulate the flowrate of permeate were opened to the same extent during the whole time of operation, and clearly, no drop in permeate flowrate was observed because of this. However, as the operation was stable most of the time, the permeate flow of 1.2 m^3/h was adopted as the most optimal among the tested flows.

The literature review revealed that membrane filtration processes are also considered highly efficient for the treatment of pharmaceutical waste streams in other studies. For example, hybrid membrane filtration and

advanced oxidation processes were found to be highly effective in the treatment of pharmaceutical wastewater (Rosman et al., 2018). Nanofiltration alone and its combination with electrodialysis with bipolar membranes was also successfully used to recover nutrients from a microbial fermentation effluent (Knežević et al., 2022), and a biological system coupled with membranes, e.g. a membrane bioreactor, was efficient in the removal of pharmaceuticals from water (Alfonso-Muniozguren et al., 2021).

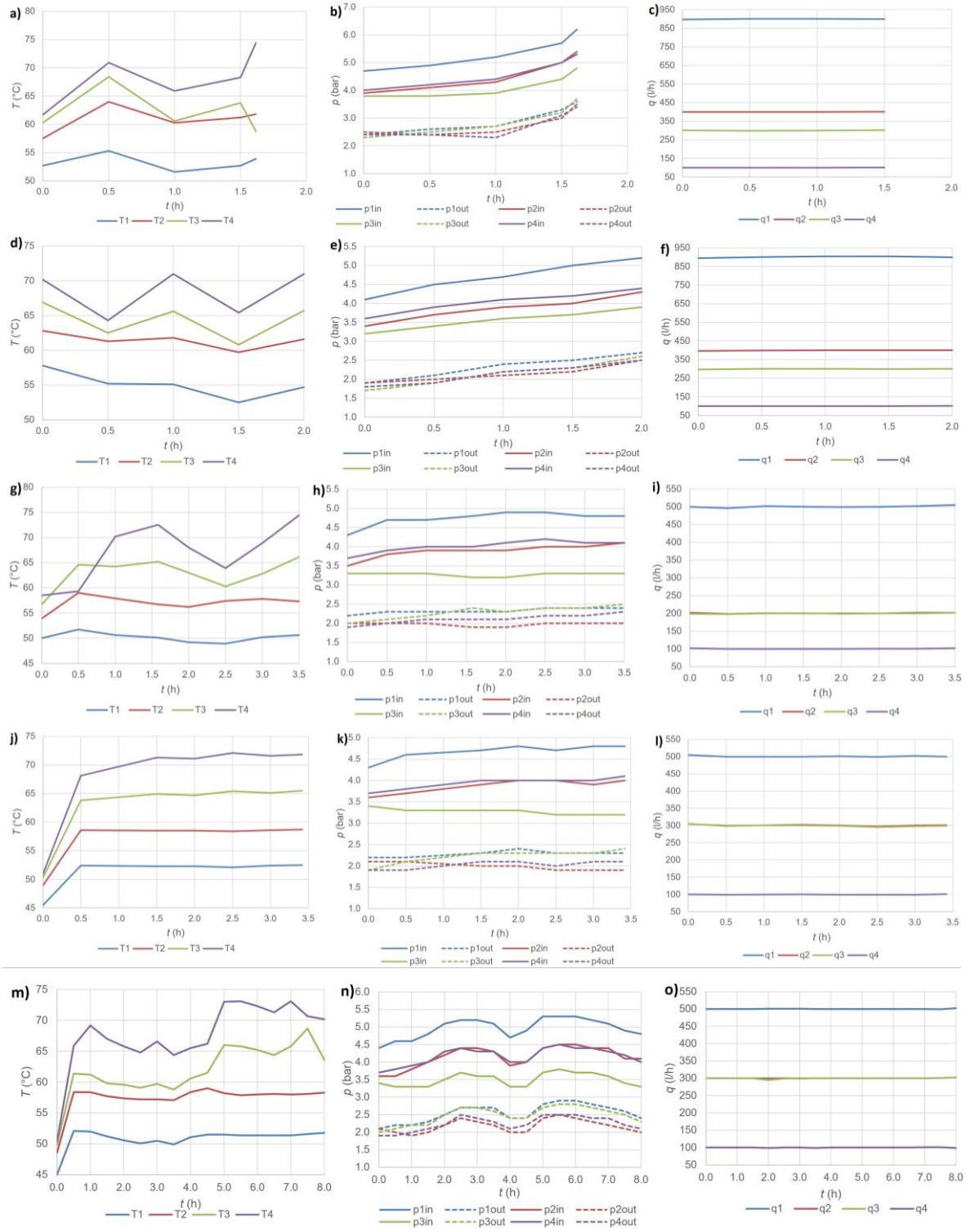

Figure 1: The temperatures, pressures and permeate flow rates in the MF columns during the experiments performed at permeate flow of: 1.7 m^3/h and 2.5 bar (a, b, c), 1.7 m^3/h and 2 bar (d, e, f), 1.0 m^3/h and 2 bar (g, h, i), 1.2 m^3/h at shorter operating time (j, k, l) and 1.2 m^3/h at longer operating time (m, n, o)

3.2 Chemical characteristics of mycelium and products of microfiltration

The chemical properties of raw mycelium, the retentate and the permeate obtained by MF at 1.2 m^3/h are shown in Figure 2. Raw mycelium contains 81.7 g/L COD, 4,460 mg/L TN and 640 mg/L TP. The content of all parameters, including TN, ammonium nitrogen, TP and phosphate in the permeate decreased compared to the raw mycelium. The removal efficiency of TP was higher (57 %) than that of TN (24 %). Microfiltration and ultrafiltration membranes are primarily used to remove relatively large particulate matter, macromolecules and sub-molecular organic groups, proteins and some higher ions, while smaller organic and inorganic micropollutants and ions can only be removed by nanofiltration or reverse osmosis (Gupta et al., 2022). The pH of the raw mycelium was acidic (around 5.2), as was that of the permeate (6.1).
The COD, which reflects the oxygen consumption due to the chemical oxidation of organic substances, decreased by 67 % in the permeate and increased by 19.5 % in the retentate. Compared to the results of this study, nanofiltration of spent fermentation broth in one of the previous studies removed between 78 and 85 % of dissolved organic carbon (DOC), while the combination of nanofiltration with electrodialysis with bipolar membranes was an even more promising treatment, as it removed 95–98 % DOC, but on the other hand consumed more energy (Knežević et al., 2022). Reverse osmosis filtration of oxytetracycline wastewater reduces the COD content from 10,000 mg/L to less than 200 mg/L, and the additional treatment by ultrafiltration recovers more than 60 % of the oxytetracycline (Li et al., 2004).

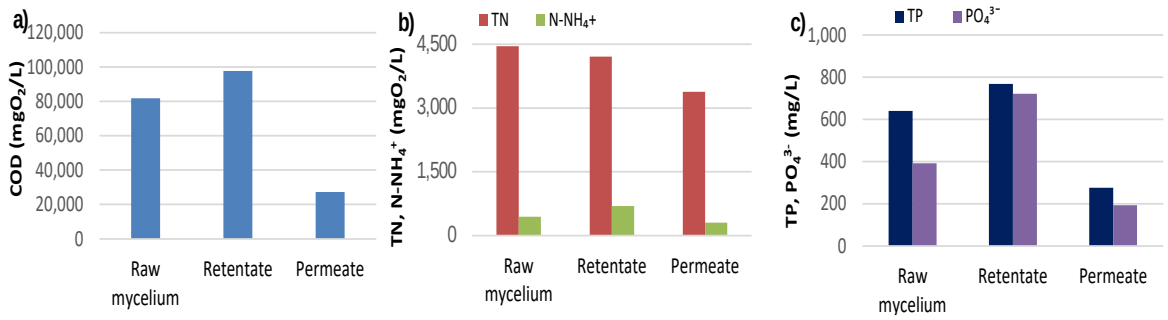

Figure 2: The content of a) COD, b) TN and N-NH_4^+, and c) TP and PO_4^{3-} in raw mycelium, retentate and permeate

4. Conclusions

The MF of mycelium from the pharmaceutical industry was investigated with a pilot MF unit under different operating conditions (permeate flow, operating time and pressure) and the optimum operating conditions for the treatment of the mycelium waste sample were determined. The problem with mycelium is its high viscosity, which leads to clogging of the membranes and an increase in operating pressure, so the optimal conditions should be determined individually for each type of mycelium. The chemical analyses showed that MF with the pilot MF unit tested was very efficient in reducing the COD in the permeate and less efficient in removing nitrogen and phosphorus. However, the MF system reduces the amount of mycelium that needs to be further treated with other methods, which can translate into lower treatment costs and is in line with the sustainable approach and environmental protection. The main outcome is the determination of optimal operating parameters for the given membranes and the specific mycelium sample. The permeate obtained could be further treated in a biological wastewater treatment plant. Further studies could aim to investigate the combination of ultrafiltration with other advanced treatment processes, such as reverse osmosis, to increase treatment efficiency and recover nutrients from the waste mycelium, such as nitrogen or phosphorus.

References

Adeoye J.B., Tan Y.H., Lau S.Y., Tan Y.Y., Chiong T., Mubarak N.M., Khalid M., 2024, Advanced oxidation and biological integrated processes for pharmaceutical wastewater treatment: A review. J Environ Manage, 353, 120170.

Alfonso-Muniozguren P., Serna-Galvis E.A., Bussemaker M., Torres-Palma R.A., Lee J., 2021, A review on pharmaceuticals removal from waters by single and combined biological, membrane filtration and ultrasound systems. Ultrasonics Sonochemistry, 76, 105656.

Bhattacharjee B., Ahmaruzzaman M., 2024, Photocatalytic degradation of pharmaceuticals: Insights into biochar modification and degradation mechanism. Next Materials, 5, 100238.

Gong P., Liu H., Xin Y., Wang G., Dai X., Yao J., 2020, Composting of oxytetracycline fermentation residue in combination with hydrothermal pretreatment for reducing antibiotic resistance genes enrichment. Bioresource Technology, 318, 124271.

Gupta S., Singh A., Sharma T., Kaur R., Khandelwal V., Rawat K.D., Pathak S., Sharma M.K., Singh J., Shah M.P., Chauhan S.C., Parashar D., Shankar P., Kashyap V.K., 2022, Chapter 2 - Applications of ultrafiltration, nanofiltration, and reverse osmosis in pharmaceutical wastewater treatment. In: Shah M.P., Rodriguez-Couto S. (Eds.), Development in Wastewater Treatment Research and Processes, Elsevier, Oxford, United Kingdom, 33-49.

Hui X., Fang W., Wang G., Liu H., Dai X., 2023, Waste recycling of antibiotic mycelial residue: The feasible harmless treatment and source control of antibiotic resistance. Journal of Cleaner Production, 401, 136786.

Jaseem M., Kumar P., John R., 2017, An overview of waste management in pharmaceutical industry. The Pharma Innovation Journal, 6, 158-161.

Javid F., Ang T.N., Hanning S., Svirskis D., Burrell R., Taylor M., Wright L.J., Baroutian S., 2021, Hydrothermal deconstruction of local anesthetics (bupivacaine and lignocaine) in pharmaceutical waste. Journal of Environmental Chemical Engineering, 9(5), 106273.

Knežević K., Rastädter K., Quehenberger J., Spadiut O., Krampe J., Kreuzinger N., 2022, Circular production – Evaluation of membrane technologies for nutrient recycling from a microbial fermentation effluent. Journal of Cleaner Production, 377, 134436.

Kotwani A., Joshi J., Kaloni D., 2021, Pharmaceutical effluent: a critical link in the interconnected ecosystem promoting antimicrobial resistance. Environmental Science and Pollution Research, 28(25), 32111-32124.

Kumar R., Awino E., Njeri D.W., Basu A., Chattaraj S., Nayak J., Roy S., Khan G.A., Jeon B.H., Ghosh A.K., Pal S., Banerjee S., Rout P., Chakrabortty S., Tripathy S.K., 2024, Advancing pharmaceutical wastewater treatment: A comprehensive review on application of catalytic membrane reactor-based hybrid approaches. Journal of Water Process Engineering, 58, 104838.

Li S.-Z., Li X.-Y., Wang D.-Z., 2004, Membrane (RO-UF) filtration for antibiotic wastewater treatment and recovery of antibiotics. Separation and Purification Technology, 34(1), 109-114.

Mgharbel M., Halawy L., Milane A., Zeaiter J., Saad W., 2023, Pyrolysis of pharmaceuticals as a novel means of disposal and material recovery from waste for a circular economy. Journal of Analytical and Applied Pyrolysis, 172, 106014.

Okeke E.S., Ezeorba T.P.C., Okoye C.O., Chen Y., Mao G., Feng W., Wu X., 2022, Environmental and health impact of unrecovered API from pharmaceutical manufacturing wastes: A review of contemporary treatment, recycling and management strategies. Sustainable Chemistry and Pharmacy, 30, 100865.

Pan S.F., Zhu M.P., Chen J.P., Yuan Z.H., Zhong L.B., Zheng Y.M., 2015, Separation of tetracycline from wastewater using forward osmosis process with thin film composite membrane – Implications for antibiotics recovery. Separation and Purification Technology, 153, 76-83.

Rosman N., Salleh W.N.W., Mohamed M.A., Jaafar J., Ismail A.F., Harun Z., 2018, Hybrid membrane filtration-advanced oxidation processes for removal of pharmaceutical residue. Journal of Colloid and Interface Science, 532, 236-260.

Yang G., Xu Y., Wang J., 2024, Antibiotic fermentation residue for biohydrogen production: Inhibitory mechanisms of the inherent antibiotic. Science of the Total Environment, 944, 173986.