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Study of cyclophosphamide removal by using sodium hypochlorite: A case study on hospitals sewage

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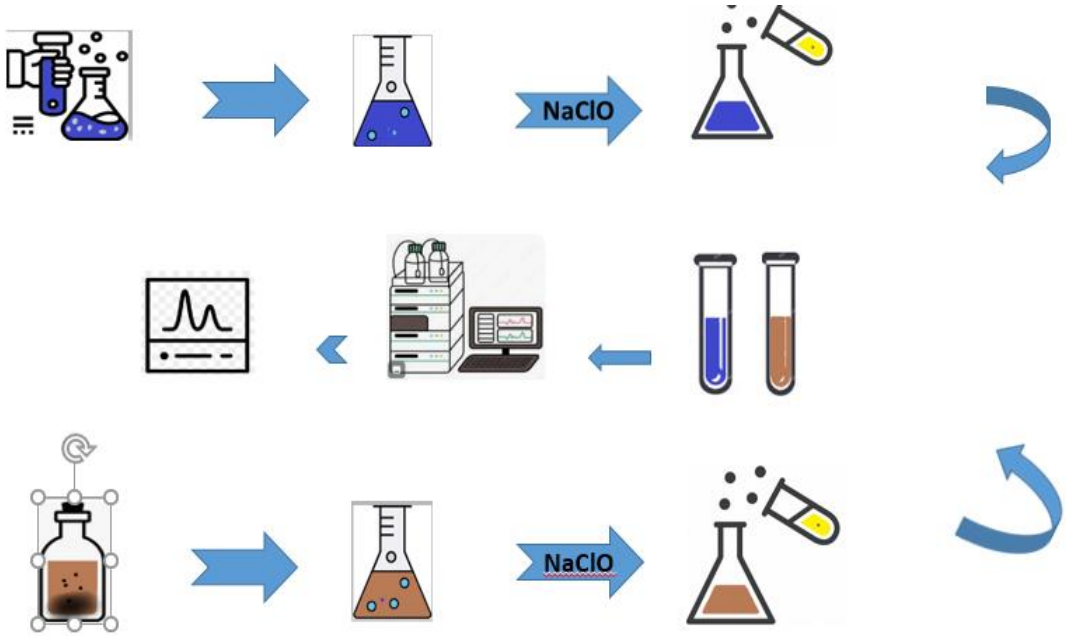
GRAPHICAL ABSTRACT



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ABSTRACT

Due to the increasing incidence of cancer, the consumption of anti-cancer or neoplastic drugs has increased significantly. These compounds are not removed during wastewater treatment with sufficient efficiency, they could be found in the groundwater. Oxidation is an efficient method for removing neoplastic drugs such as cyclophosphamide. The previous researchers could make use of a wide range of oxidants because of compiling the health protocols for the lowest risk of drug hazards. The purpose of this research is to remove cyclophosphamide residue in vomit contents, urine, or feces of patients through toilet sewage that merges with household sewage or municipal sewage. In this study, all experiments were done by the oxidation method of cyclophosphamide 10 mg/L with sodium hypochlorite and considering of effectiveness of pH changes and reaction time. It was shown that cyclophosphamide degradation has increased with increased concentration of sodium hypochlorite and reaction time at pH=9.8. The destructive 94.8% of cyclophosphamide was optimized by the concentration of 0.02 % sodium hypochlorite, pH=9.8, and a reaction time of 5 min. Also, the comparative results of drug removal in hospital wastewater with optimal concentration, pH, and time showed increasing of 4% reduction in cyclophosphamide drug removal (98.02%) compared to the test sample. The result of the research can be effective in removing cyclophosphamide by installing a dosing pump in the flush tank or toilet siphon of the oncology department.

1. Introduction

The important goals in waste disposal management systems are preventing infectious, carcinogenic diseases, removing pathogens, and eliminating disease factors in hospital wastes. Since the biomedical waste of cytotoxic is extremely hazardous to human health and the environment owing to its mutagenic or carcinogenic properties, cytotoxic drugs have become a great environmental threat. Today growing up of cancer diseases are on the rise, and as a result, the number of therapeutics administered for chemotherapy is increasing

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and consumption of antineoplastic drugs has increased significantly, that is conventional wastewater treatment systems are not able to remove all these substances from the wastewater and some of the remaining drugs are observed in surface and running waters, which can be a serious threat to the environment and health for human and living things (Ohe *et al*., 2004, Rowney *et al*., 2009, Jureczk and Kalka, 2020,Saab *et al.*, 2021). Initial research on the side effects and environmental consequences of anticancer and cytotoxic drugs, such as cyclophosphamide (CP), was made in the 80s. The studies have been categorized according to different bases. The primary research was about the cytotoxic safety of the hospital staff and healthcare workers involved in the drugs. This research has been practiced on more than hundreds or thousands of people and sometimes lasted for years (Mohseni *et al*., 2001, Turci *et al*., 2003, Arul, 2016, Asefa *et al*., 2021). The results of the findings led to the formation of protocols, and standardized health guidelines during work which finally ended in the reduction of potential health risks for hospital personnel. Another part of the studies was related to investigating cytotoxic drug dispersal and the residual of anti-cancer drugs in the hospital effluent which continuously enters the municipal sewage and was considered the main source of water pollution. So it was recommended to properly manage and inactivate the disposal of cytotoxic drugs in medical health care centers before discharging them into the municipal sewage system and strongly should never be landfilled or discharged to the sewage system (Capoor and Bhowmik, 2017, Dugheri *et al*., 2018, Ahmad Khan *et al*., 2019). Cytotoxic drugs have a wide range of chemical structures or formulas. Currently, there is no known common agent to inactivate all cytotoxic drugs, but oxidation has been suggested as a suitable method to destroy cytotoxic compounds (Hansel *et al.,* 1997). Also in some research that investigated, some chemical solutions were used as oxidants that could be suitable alternatives to incineration of cytotoxic medicinal wastes. For example, oxidizing substances such as alcohols, detergents, sodium thiosulfate, sodium hypochlorite, and hydrogen peroxide were used instead of incinerators (Hansel *et al*., 1997, Hon *et a*l., 2013, Gohma *et al*., 2014, Anastasi *et al*., 2015, Cox *et al*., 2015, Sewel, 2016, Federici *et al.,* 2019, Soubieux *et al*., 2019, Stasny *et al.,* 2019, Kumar Trpathi *et al.,* 2020, Simon *et al*., 2020, Jureczk and Kalka, 2020). Also, other sources of contamination cytotoxic drugs come out from the left-over drugs, returned drugs, syringes, or vials as well as cytotoxic waste which is in urine, feces, and vomit from outpatients that are genotoxic for 48 h to 1 week after the drug administration (Capoor and Bhowmik, 2017). This study was purposed to investigate the instability and neutralization of cyclophosphamide in the contents of outpatients (urine, feces...) that enter hospital sewage before mixing with other hospital effluents and transferring to municipal sewage. Cyclophosphamide (CP) is one of the alkylating agents of antineoplastic drugs (Ads) that prevents cell division and RNA and protein synthesis. Cyclophosphamide with the trade names Cytoxan, Neosar, or Cytophosphan is one of the most widely prescribed cancer patients for treatment. The current study is purposed to inactivate and neutralize Cyclophosphamide and as an object of desire make a comparison of degradation CP between toilet wastewater of the oncology department of the hospital and test sample. The whole experiments of degradation Cyclophosphamide were done by a chemical oxidation reaction and sodium hypochlorite as oxidant agent (the main variable) used for the removal of CP. To optimize of oxidation reaction, some experiments were carried out on the effectiveness of reaction time and pH (secondary variables). All experiments were performed by classical chemical and instrumental methods. The oxidation reaction between Cyclophosphamide and sodium hypochlorite was directly carried out in aqueous media in vials and quantitative of the remaining drug was measured by LC_MS chromatography in LC-MS Department of Institute of Chemistry and Chemical Engineering.

2. Materials and methods

2.1. Experimental design

2.1.1. Materials

Materials used for experiments were: Cyclophosphamide (CAS# 6055-19-2, Lot no. 217B032), chemical formula $C_7H_{15}CL_2N_2O_2P.H_2O$, made by Solarbio Co. (China), purchased from Mehr Arman Gostaran Sadid (Tehran, Iran); Sodium Hypochlorite (Lot No. 225.08.18-L14.21), NaClO (13% v/v), made by and purchased from Dr. Majalli Chemical Industries Complex Co. (Tehran, Iran); 0.1N Hydrochloric Acid (HCl) and 0.1 N soda (NaOH) available in Institute of Chemistry and Chemical Engineering Lab. All chemicals were obtained in the highest available analytical quality.

2.1.2. Analytical procedure

Residual contamination was measured by applying liquid chromatography with a tandem mass spectrometry detection method developed and validated specifically to estimate surface contamination by the tested contaminants in the LC-MS-MS Department of the Institute of Chemistry and Chemical Engineering (Tehran). All experiments were performed chemically in the liquid phase and at ambient temperature.

2.1.3. Preparation of stock cyclophosphamide solution

All experiments were performed with stock CP solution, 10,000 mg/mL, or 10 mg/L cyclophosphamide. At first, for optimizing the liquid chromatography device, 420 mg/L standard solution was made up by adding 8.4 mg of cyclophosphamide to methanol in a 20 mL flask. Standard stock solutions were prepared by diluting standard solutions in distilled water and stored in the refrigerator.

2.1.4. Preparation of sodium hypochlorite solutions

Sodium hypochlorite does not have a stock solution because it becomes unstable by releasing chlorine ions. For this purpose, in each stage of the experiments, sodium hypochlorite solution with desired concentrations was freshly prepared.

2.2. Test steps

Removal of cyclophosphamide (CP) was evaluated for the effectiveness of four stages in aqueous media. All reactions were carried out in 10 mL glass vials.

Step 1: Removal of cyclophosphamide with sodium hypochlorite (the main variable)

Step 2: a study of the effect of pH changes on the reactivity and degradation of cyclophosphamide with sodium hypochlorite in alkaline and acidic media.

Step 3: a study of the effect of reaction time (min) on the destruction of cyclophosphamide. Then the optimized condition will be defined.

Step 4: a comparison reaction of sodium hypochlorite and the cyclophosphamide sewage of the hospital with sample test under optimized conditions.

2.2.1. Step 1: Removal of cyclophosphamide with sodium hypochlorite

The destruction reaction of CP is a direct combination of CP and sodium hypochlorite in 10 mL vials. So, taking off, 2 mL of stock CP solution (10 mg/L cyclophosphamide) with equal volume (2 mL) of 0.01 to 6.0% sodium hypochlorite was directly reacted. In addition, a control sample (10 mg/L CP solution) was prepared for the calculation of removal efficiency (%). After mixing, decontamination was carried out. Then the content of the solution of the vials was transferred to the vial of the chromatography machine. Residual CP was measured with a validated liquid chromatography with a tandem mass spectrometry detection method. The residual of CP was computed by the device. CP was significantly different from one solution to the next for single vials from 93.84% to 99.86% respectively. The results were also significant for drug destruction. Generally, the destruction efficiency % has is proportional to more concentration of sodium hypochlorite.

2.2.2. Step 2: study of the effect of pH changes on the decontamination of CP with NaOCl

Cyclophosphamide is soluble in water and usually has a pH of about 6.2 to 6.8. Since CP solution is very sensitive to pH, changes in pH could play a role in the instability of its chemical structure. A study aimed to effect pH changes on the removal reaction in the range of pH= 2. 4, 10, and 12 were determined. Measuring of pH was carried out with the digital pH meter in the Analysis Lab of the Research Institute of Chemistry and Chemical Engineering (Tehran) and made by Metro Ohm (Germany). After calibration of the pH meter (with buffers 4, 7, and 10), washed and bubbled the burette, filled with acid or alkali (in every 2 steps), adjusted stand, added drop by drop acid/ alkali into the beaker containing stock CP solution. Then, read on the pH monitor at each added drop. After reaching to desired pH, taking amount of solution into vials, and reacted samples with sodium hypochlorite for evaluation of residuals CP. Eventually, samples were analyzed by LC-MS chromatography. Considering alkalinized CP solution, was added 0.1N alkali, and for acidification, was added 0.1N HCl. Decontamination was carried out with four different solutions; stock CP solutions (10 mg/L) with pH= 2.5, 4.2, 9.8, and 12.4. Destruction of CP started with adding

the first drop of acid or alkali in stock CP solutions. The observation showed that adding the first drops of acid or alkali caused pH changes from pH=6 to pH=4.2 and 9.8 respectively. However, adding more and more drops of acid/soda does not change of pH. The study revealed that CP solutions with pH= 4.2 and 9.8 were a buffer behavior in which dropping of acid/alkali did not cause any pH changes. Since all tests had to be performed in a fixed concentration of stock CP solution (10 mg/L), then because of volumetric increase, CP solution with pH= 2.5 and 12.4 were not fixed concentration and could not be the correct set point. In one step, CP solutions with specific pHs were measured without any adding sodium hypochlorite (investigation of the effect of pH changes). In the other step, 2 mL from CP solutions with pH= 4.2, 9.8, mixed with 2 mL 0.02% sodium hypochlorite in vials, and CP solutions were measured by applying liquid chromatography. A concentration of 0.02% sodium hypochlorite was selected to mix with CP because other concentrations would upset the pH fixed in the stock CP solutions.

2.2.3 Step 3: Study of the effect of reaction time on the destruction of CP

Sodium hypochlorite is a strong oxidizer. The reaction time of sodium hypochlorite with Cyclophosphamide is very short. The step aimed to determine how the CP destruction could be affected by reaction time. Moreover, the CP destruction was carried out in three periods of time, including 5, 10, and 15 min. The experiments were made up of a stock CP solution of pH=9.8 and two concentrations of 0.02% and 4% sodium hyposulfite. The degradation of CP was performed with two concentrations of NaOCl, at three periods of time simultaneously. At the same time, 2 mL stock CP solution was mixed with 2 mL 0.02% and 4% sodium hypochlorite in 6 vials, respectively paired off, mixed, and adjusted pH. After a measured time of 5 min, the content of 2 vials of 0.02% and 4% sodium hypochlorite was transferred to LC vials, analysed CP concentration by applying liquid chromatography. In the same way, after 10 min. and finally after 15 min. respectively process was done again. Also, there was a control sample besides all test samples for calculating destructive efficiency (%). The study found that reaction time has wildly impacted CP degradation efficiency (%). As reaction time increased, CP degradation efficiency increased. The results have shown that the time could be more effective in the lowest concentration. CP degradation efficiency (%) with 0.02% NaOCl went up from 93.91% (at 5 min.) to 98.56% (at 15 min) which was the same degradation efficiency with 4% NaOCl (at 5 min.)

2.3. Calculation method

Residual contamination was measured with validated liquid chromatography in tandem Mass spectrometry detection method. Decontamination efficiency (in %) was computed as follows:

$$\text{Decontamination efficiency (\%)} = \left(1 - \frac{Cs}{C0}\right) \quad (1)$$

The residual of cyclophosphamide after oxidation reaction was calculated as follows:

$$R = \frac{cs}{c0} \times 100 \quad (2)$$

Quantity before decontamination has to do with 10 mg/L cyclophosphamide that is measured as a control sample and quantity after decontamination is related to 10 mg/L cyclophosphamide after oxidation reaction measurements.

2.4. Optimizing factors for removal of cyclophosphamide drug

It created, optimized, and validated an innovative monitoring protocol for the removal of cyclophosphamide (CP) from hospital toilet wastewater. There are currently no occupational exposure limits for CP or other anti-cancer drugs in any hospital toilet sewage. The excellent sensitivity of the analytical methods along with innovative methods make this protocol useful. Samples were prepared and collected in vials. The stock cyclophosphamide solution, 10 mg/L, was reacted with 0.01% to 5.5% sodium hypochlorite, desired pH = 2, 4, 9.5, 12, and periodic time of 5, 10, 15 min. According to the results of the study, the removal reaction was optimized. The optimal factors included; 0.02 % sodium hypochlorite, 5 min' reaction time, and pH=9.8 which were applied for carrying out of comparative test with a hospital wastewater sample.

3. Results and discussion

3.1 The effect of sodium hypochlorite concentration

Sodium hypochlorite can easily oxidize cyclophosphamide by releasing chlorine ions and neutralizing it in terms of nontoxic risks. In the current study, it was shown that the combination of cyclophosphamide (10 mg/L) with sodium hypochlorite rapidly caused degradation of CP. The degradation of CP was directly proportional to the concentration of sodium hypochlorite. It was observed that with increasing the concentration of sodium hypochlorite (0.01% to 5.0%), the CP degradation efficiency (%) increased (93.84% to 99.86%) and consequently the residual of CP was decreased, moreover, there was no practically formed any CP chromatogram curve with 5.5% and 6.0% sodium hypochlorite and cyclophosphamide were completely degraded. Considering the result of 93.84% destruction of CP with 0.01% NaClO and under restrictions of sodium hypochlorite directive, the study suggested 0.01 or 0.02% sodium hypochlorite to degrading of CP. Fig. 1 and 2 show that with increasing concentrations of sodium hypochlorite (%), the residual of CP was decreased and the degradation efficiency was increased.

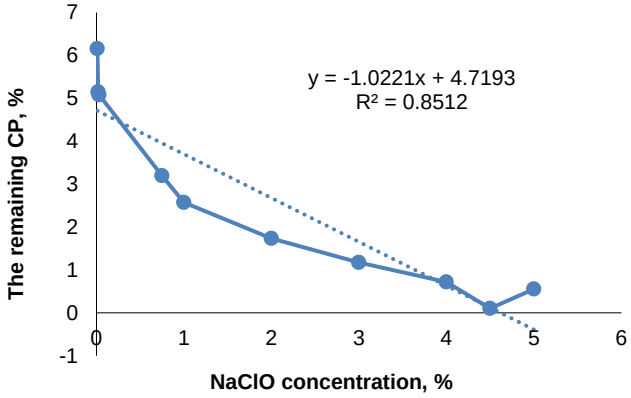

Fig. 1. The remaining amounts of CP versus sodium hypochlorite amounts.

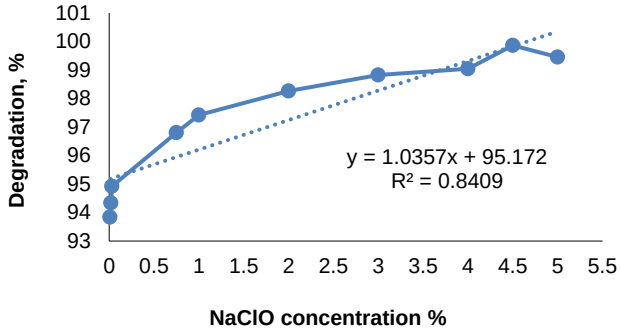

Fig. 2. CP degradation efficiency relative to sodium hypochlorite (%).

3.2 Effect of pH

The present study showed that cyclophosphamide solutions at pH = 9.8 and 4.2 behave like a buffer and the pH does not change easily by adding acid/alkali. Due to the disruption of the fixed concentration of CP solution (10 mg/L) and volumetric increase of stock CP solutions pH=2.5 and 12.4, these pHs do not merit further consideration and are put aside from the study. Fig. 3 shows the result of the residual cyclophosphamide (%) without any addition or reaction with sodium hypochlorite. Supposing the CP solution within pH= 4.2, 9.8 had the constant concentration (10 mg/L), the proposed study pointed to continued experiments followed by adding sodium hypochlorite.

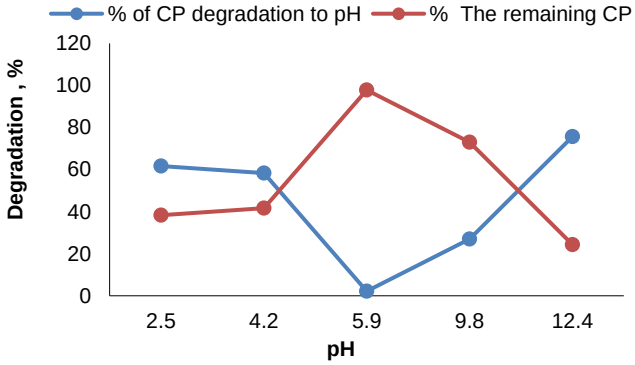

Fig. 3. The effect of pH changes on residual CP (%) and CP degradation (%), without with reaction of sodium hypochlorite.

The degradation efficiency (%) of cyclophosphamide with/ without addition and reaction to sodium hypochlorite at pH= 4.2 and 9.8 was shown in Fig. 4.

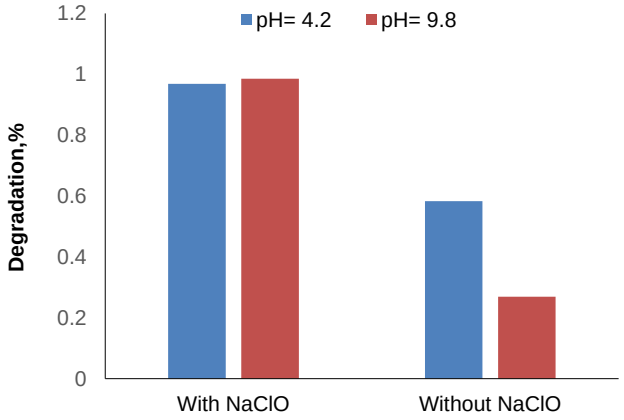

Fig. 4. Comparison of degradation drug with and without NaClO at pH = 4.2, 9.8.

Also, Fig. 4 compares the degradation efficiency (%) of CP with/ without adding sodium hypochlorite. The Fig. shows how sodium hypochlorite as a destructive agent could develop the degradation efficiency of pH=9.8 CP solution and oxidize cyclophosphamide. There is another comparison of the degradation efficiency of CP with/ without sodium hypochlorite with adding more sodium hydroxide for fixing pH=9.8 solution as shown in Fig. 5. As the graph displays, the most degrading efficiency of CP is related to 0.02% sodium hypochlorite with adding more 2 drops of sodium hydroxide to fixing at pH=9.8. Note: to the sensitivity of cyclophosphamide in alkali or acidify media, adjusting of exact pH= 9.8 is not easy, the pH during experiments had a range of pH= (9.2 to 9.8), but it assumed that it was pH fixed at 9.8.

3.3. Effect of reaction time

Sodium hypochlorite is a strong oxidizer. By adding sodium hypochlorite to stock CP solution, oxidation and destruction of cyclophosphamide is happened. The reaction time as a side variable was investigated in the direct reaction of cyclophosphamide. This step was performed with two concentrations of 0.02 and 4.0% sodium hypochlorite, the fixed pH=9.8, and periods of 5, 10, and 15 min. to clarify the effectiveness of time. The obtained results in Fig. 6 showed that the destructive of cyclophosphamide pH = 9.8 with 4% sodium hypochlorite, has increased from 99.048% (at 5 min) to 99.972% (at 15 min). Also, the degradation of cyclophosphamide (%) with 0.02% sodium hypochlorite has increased from 93.911% (at 5 min) to 98.561% (at 15 min). So this step indicated the reaction time could be effective in the CP destruction process. The destructive rate with 0.02% sodium hypochlorite is significant compared to higher concentrations. Because, after 15 min, it could be comparable with destructive efficiency (%) with 4% sodium hypochlorite in 5 min.

Considering of emphasis keep limiting exposure to sodium hypochlorite, the concentration of 0.02% NaClO and reaction time of 5 min. picked as one of the optimized variable factors.

3.4. Study and comparison of destructive efficiency (%) of CP in wastewater of hospital

This step is to study and compare of destructive efficiency (%) of CP in wastewater of hospitals and sample tests by using optimized variable factors. The factors optimized contains 0.02 % sodium hypochlorite, pH= 9.8, and time= 5 min. Also, the hospital wastewater sample was obtained from the toilet of the oncology department of one of the hospitals where cancer patients were hospitalized. At first, it was necessary to filter and centrifuge wastewater to remove turbidity to have a clear solution. Then the clear wastewater solution was studied for recognition of cyclophosphamide by analyzer LC-mass chromatography. For this purpose, 2 mL wastewater and 2 mL stock cyclophosphamide solution (control sample; 10 mg/L) were poured separately into the 2 vials and analyzed by the device. Analyzing of the wastewater sample showed that the wastewater sample is free of cyclophosphamide and there was not any formation of the chromatogram.

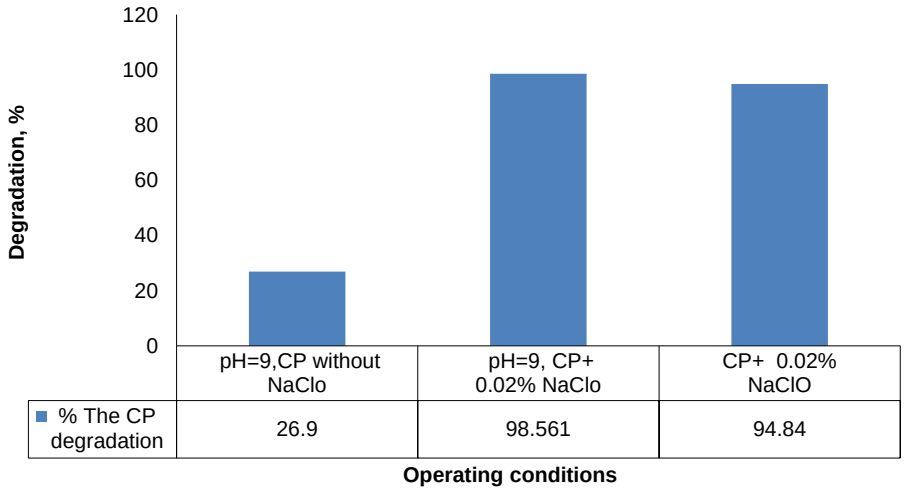

Fig. 5. A comparison of degrading efficiency of CP with/ without sodium hypochlorite and adding NaOH for fixing pH= 9.8.

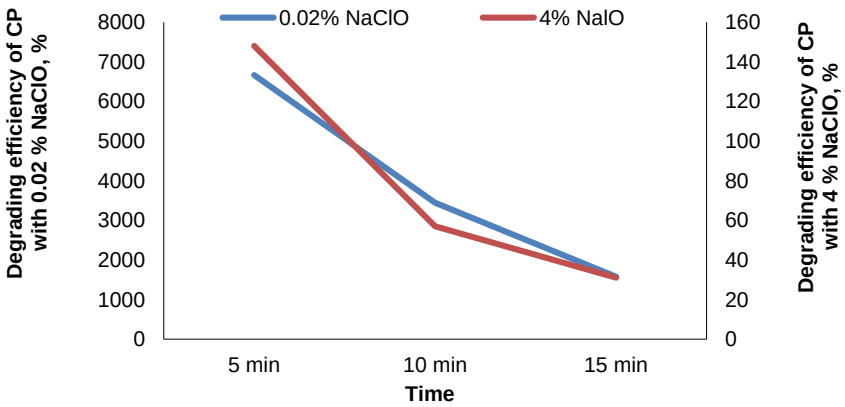

Fig. 6. comparison of degrading efficiency of CP with 0.02% and 4% sodium hypochlorite.

Then, a comparative test with the wastewater media needed a wastewater sample containing 10 mg/L cyclophosphamide. So, for the preparation wastewater sample, taking 0.84 cc off from 420 mg/L standard solution of cyclophosphamide was reached in a 50 flask with wastewater. It required consideration of optimized factors such as 0.02 % sodium hypochlorite, pH=9.8, and reaction time of 5 min to comply with the test sample and wastewater sample to get competitive results. At the same time, 2 mL of wastewater containing 10 mg/L cyclophosphamide was poured into two sample vials, one for sampling and the other as a control sample. Also, in two other sample vials, poured from 10 mg/L cyclophosphamide solution, one for sampling, another for the control sample. Adding 2 mL of 0.02% sodium hypochlorite just only to test samples vials, mixing, transferring of content to device vials, and finally analyzing by LC- Mass after 5 min.

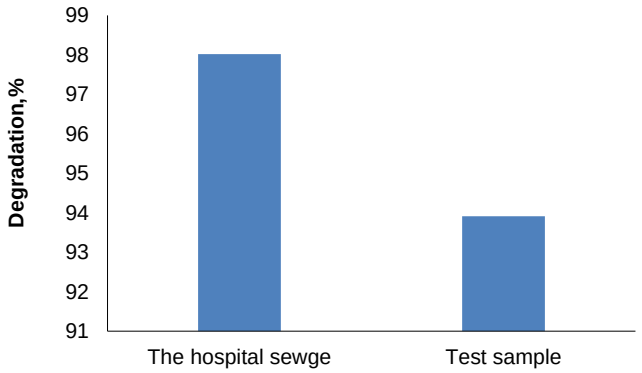

Fig. 7. Comparison of the degradation of CP in the test sample and hospital wastewater under the same conditions (0.02% sodium hypochlorite, time 5 min, and pH = 9.8.

The results have shown that the efficiency of CP degradation in sewage effluent is higher and seems that sodium hypochlorite is a better performance on the destructive of CP in sewage effluent media than in test samples. As Fig. 7 displays, the CP degradation efficiency in the sewage sample (98.02%) was more than the CP degradation efficiency in test samples (93.91%). The residual of CP% in sewage effluent is 1.980% and in the test sample is 6.088%. It seems that the compatibility with the microbial environment of wastewater and the physic-chemical properties of wastewater could cause better destruction of CP in wastewater. The study found that the higher degradation of CP took place in the microbial context of sewage effluent. Since the wastewater environment and aquatic organisms in sewage areas vary widely and depend on microbial composition and biotic of sewages, the obtained results cannot be generalized to other hospitals. Also, regional wastewaters have different microbial contexts that include single fungal species or different microbial protozoa which are affected by geography areas that could be effective in degrading or purifying CP or other chemotherapy drugs (Ads). Previous research showed that the degradation of cyclophosphamide in regional and geographical wastewater is very different. For example, the highest degradation efficiency has been observed in Spain and Switzerland, and the lowest removal efficiency has been observed in China and Slovenia (15). Also, there are great attempts to apply the biological methods for the decomposition of antineoplastic drugs that are safe and stable by fungal and bacterial protozoa to chemical and oxidation methods. Moreover, some methods integrate biological and non-biological methods which can remove anticancer medicinal products.

4. Conclusions

Cytotoxic medicinal products are classified as “hazardous waste” in the sections regarding “wastes from human health care” and “municipal wastes” separately. This classification of anticancer medicinal products triggers specific obligations under the Waste Framework Directive to protect employees from accidental contact with low levels. Contamination of cytotoxic drugs such as cyclophosphamide can occur through inhalation of airborne particles, absorption through the skin and body fluids of patients undergoing chemotherapy, or transfer to the desk, work surfaces, walls, handles, and also during the preparation, administration, and injection of anti-cancer drugs. That is all the reason why for more than thirty years, most researchers have focused on monitoring of contamination cytotoxic from surfaces. Besides there is not taking any action on the degradation of cytotoxic wastes of outpatients including urine, feces, and vomit contents in the toilets of the oncology department of hospitals that sequentially get through to municipal wastewater. So this study aimed to assess and specify a method for the degradation of cytotoxic (as cyclophosphamide) in hospital sewages and decrease residual cytotoxic drugs in wastewater. In previous research, sodium hypochlorite was also one of the cleaners for the decontamination of surfaces that were removed cyclophosphamide by "wiping" method which dragged a napkin on plates for monitoring of contaminated drugs on the surfaces, and measured residual drugs by liquid chromatography. Due to the reaction with sodium hypochlorite, chlorine ions release and cause to formation of a Hypochlorous ion. These by-products could have made seriously a potential risk of lung and respiratory problems, moreover, it is strongly able to destroy cyclophosphamide or other Ads. The safety precautions of sodium hypochlorite caused the researchers to use other cleaners besides sodium hypochlorite for the removal of drugs on surfaces. This study represented a considerable achievement in showing that a CP removal efficiency of 94.84% resulted from a low concentration of 0.02% Sodium hypochlorite. As well as, it was shown that for CP removal not only 0.02% sodium hypochlorite, other variables of reaction time and pH could be effective in removal efficiency. According to the experimental data obtained, a comparison experiment with a hospital sewage sample was performed. It showed that removal efficiency (%) in sewage hospitals was improved by about 4% than the test sample. It could be related to the kind of microbial contexture or single cells that exist in the sewage effluent. The findings of this study can be reduced residuals of cyclophosphamide or other alkylated agents in the hospital toilet sewage and consequently minimized risk of exposure to these hazardous drugs in hospital effluent. The study suggests a simple and cost-effective procedure for removing CP in a hospital toilet, with the installation of a dosing pump connected to the siphon or flush tank and injecting 0.02% sodium hypochlorite into the toilet bowl. In this case, the toilet wastewater could be neutralized and get rid of cyclophosphamide or others. Considering how the experimental design and the findings of the CP removal method, it is believed that this method can also be applied to other alkylated agents such as FU-5 and Cisplatin that reduce the burden of drugs before entering the municipal sewage. Therefore, the chemical-physical process and energy needed to treat wastewater plants would be reduced. Afterward, destructive effects of cytotoxic drugs as a mutation in the environment or any environmental threat would be left off.

Author Contribution

Elham Asrari: Corresponding Author, Supervisor, review and control of results, finalization of the article.
Afsaneh Saemian: Method designing, calculations, analysis, interpretation of information and results, sampling, testing, and data collecting.

Data Availability Statement

Corresponding author will permit using the datasets used on request.

Conflict of Interest

There is no conflict of interest between the authors.

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References

Ahmed Khan, B. *et al.* (2019) ‘Healthcare waste management in Asian developing countries’, *Waste Management & Research*: *The Journal of International Solid Waste and Public Cleansing Association,* 37(9), pp. 863–875*.* doi: https://doi.org/10.1177/0734242X19857470

Anastasi, M. *et al*. (2015) ‘Efficacy of two cleaning solutions for the decontamination of 10 antineoplastic agents in the biosafety cabinets of a hospital pharmacy’, The *Annals of Occupational Hygiene,* 59(7), pp. 895-908. doi: https://doi.org/10.1093/annhyg/mev031

Arul, P. (2016) ‘A study to assess the effectiveness of structured teaching program for nurses administering intravenous chemotherapy, in PSG Hospital, Coimbatore, India. MA Dissertation. The Tamil Nadu Dr. M G R Medical UniversityBoddu, V. M. *et al.* (2016) 'Gray water recycle: effect of pretreatment technologies on low-pressure reverse osmosis treatment', *Journal of Environmental Chemical Engineering,* 4, pp. 4435-4443. doi: https://doi.org/10.1016/j.jece.2016.09.031

Asefa. S., Dinegde, N., and Demie, T. (2021) 'Knowledge and practices on the safe handling of cytotoxic drugs among Oncology Nurses Working at Tertiary Teaching Hospitals in Addis Ababa, Ethiopia', *Dove Press Journal: Drug, Healthcare and Patient Safety,* 13, pp. 71-80. doi: https://doi.org/10.2147/DHPS.S289025

Capoor, M., and Bhowmik, K. (2017) 'Cytotoxic drug disposal, cytotoxic safety, cytotoxic waste management, India', *Indian Journal of Medical and Paediatric Oncology,* 38(2), pp. 190-197. doi: https://doi.org/10.4103/ijmpo.ijmpo_174_16

Carmignani, S., and Raymand, J. 1997 'Safe handling of cytotoxic drugs in the physician's office: A procedure manual Model', *Oncology Nursing Forum,* 24, PP. 41-48. PMID: 9010864

Cox, J., Speed, V., and O'Neal, S. (2015) 'Development and evaluation of a novel product to remove surface contamination of hazardous drugs', *Journal Oncology Pharmacy Practice*, 23(2), pp. 1-13. doi: https://doi.org/10.1177/1078155215621151

Dugheri, S. *et al.* (2018) 'A new approach to assessing occupational exposure to antineoplastic drugs in hospital environments', University of Florence, Italy, *Arh Hig Rada Toksikol*, 69, pp.226-237. doi: https://doi.org/10.2478/aiht-2018-69-3125

Federici, M. et al. (2019) 'Efficacy of four cleaning solutions for the decontamination of selected cytotoxic drugs on the different surfaces of an automated compounding system', *Journal of Occupational Environmental Hygiene,* 16(1), pp. 6-15. doi: https://doi.org/10.1080/15459624.2018.1526384

Gohma, H., Inoue, Y., and Asano, M. (2014) 'Testing the degradation effects of three reagents on various antineoplastic compounds', *Journal of Oncology Pharmacy Practice,* 21(4), pp. 268-273. doi: https://doi.org/10.1177/1078155214530175

Hansel, S. *et al.* (1997) 'Chemical degradation of wastes of antineoplastic agents; Cyclophosphamide, Ifosfamide, and Melphalan', *Archives of Occupational Environmental Health,* 69(2), pp.109-14. doi: https://doi.org/10.1007/s004200050124

Hon, C. *et al.* (2013) 'Examining factors that influence the effectiveness of cleaning antineoplastic drugs from drug preparation surfaces', *Journal of Oncology Pharmacy Practice,* 20(3), pp. 210–216. doi: https://doi.org/10.1177/1078155213497070

Jureczko, M., and Kalka, J. (2020) 'Cytostatic pharmaceuticals as water contaminants', *European Journal of Pharmacology,* doi: https://doi.org/10.1016/j.ejphar.2019.172816

Kumar Tripathi, A. et al. (2020) 'Environmental remediation of antineoplastic drugs: Present Status, Challenges, and Future Directions', *Processes*, *8*(7), pp. 747, doi: https://doi.org/10.3390/pr8070747

Minh Mai Le, L., and Jolivot, P. (2013) 'Effectiveness of cleaning of workplace cytotoxic surface', *International Archives of Occupational and Environmental Health,* 86(3), 333-341. doi: https://doi.org/10.1007/s00420-012-0769-1

Mohseni, A. *et al.* (2001) 'Evaluation of collection, transfer, and disposal of hospital solids waste government and private hospitals in Mazandaran Province in 2001', *Journal of Mazandaran University Medical Science,* 11 (32), pp. 45-52. Available at: https://www.sid.ir/paper/45370/en (Accessed: 20 February 2022).

Ohe, T., Watanabe, T., and Wakabayashi, K. (2004) 'Mutagens in Surface Waters', *Mutation Research,* 567 (2–3), pp. 109-149. doi: https://doi.org/10.1016/j.mrrev.2004.08.003

Rowney, N., Johnson, A., Williams, R. (2009) 'Cytotoxic drugs in drinking water: a prediction and risk assessment exercise for the Thames catchment in the United Kingdom', *Environmental Toxicology and Chemistry,* 28(12), pp. 2733-2743. doi: https://doi.org/10.1897/09-067.1

Saab, Y., Nakad, Z., and Rahme, R. (2021) 'Chemotherapeutic drugs in Lebanese surface waters: Estimation of population exposure and identification of high-risk drugs', *Sustainable Environment Research*, 31, pp. 1-10. doi: https://doi.org/10.1186/s42834-021-00105-8

Sewell, G.J. (2016) 'Detergents and disinfectants currently used in hospital pharmacies', Abilities for removing and degrading cytotoxic drugs. Kingston University and Plymouth Hospitals Trust, UK, 15 November 2010. Available at: https://www.gerpac.eu/en (Accessed: 8 October 2021).

Simon, S. *et al.* (2020) 'Efficiency of four solutions in removing 23 conventional antineoplastic drugs from contaminated surfaces', *PLOS ONE,* 15(6), e0235131. doi: https://doi.org/10.1371/journal.pone.0235131

Soubieux, A., Palamini, M., and Tanguay, C. (2019) 'Evaluation of decontamination strategies for cyclophosphamide', *Journal Oncology Pharmacy Practice*, 26(2), pp. 413-422. doi: https://doi.org/10.1177/1078155219865931

Stasny, M. *et al.* (2019) 'Removal of anthracycline cytostatics from the aquatic environment: Comparison of nanocrystalline titanium dioxide and decontamination agents', *PLoS One*, 14(10), e0223117. doi: https://doi.org/10.1371/journal.pone.0223117

Turci, R. *et al.* (2003) 'Biological and environmental monitoring of hospital personnel exposed to antineoplastic agents', *Journal of Chromatography B,* 789 (2), pp. 169–209. doi: https://doi.org/10.1016/s1570-0232(03)00100-4