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Removal Methods of Antibiotic Compounds from Aqueous Environments– A Review

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ABSTRACT

Introduction: Antibiotics as a type of pharmaceutical compounds are widely used in modern medicine and veterinary industries. They enter the environment in different ways, including agricultural runoff, direct discharge of urban wastewater treatment or human waste, direct disposal of medical, veterinary industrial waste and to name but a few. Antibiotics have been able to influence the microbial population. Their continuous presence in the environment can lead to bacterial resistance and in recent years, the issue has caused serious concerns in the scientific community.
Materials and Methods: Unfortunately, in spite of the extensive investigations, there is still a considerable lack of integrated and classified information to assess the environmental risks of antibiotics. Therefore, in the current study, the removal of these compounds from aqueous solutions was studied. This study was carried out on the basis of surveys accomplished in recent decades and also the ones published in databases such as Google Scholar, PubMed, Elsevier, Scopus, Springer, Magiran and SID using anti-bacterial agents, antibiotic, wastewater and removal methods as the keywords.
Results: Advanced treatment processes such as ozonation, advanced oxidation, activated carbon, Nano filtration and reverse osmosis can remove higher levels of antibiotics.
Conclusion: Generally, the biological and chemical processes alone are not effective for antibiotics' removal from aquatic environments while combination of advanced oxidation and biological treatment processes can effectively reduce the amount of antibiotic.

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Introduction

The amount of drug consumption suggests that there is a high interaction between the human and microorganisms in the modern medicine and biological health [1-3]. According to the statistics published by the Food and Drug Administration (FDA) and the Ministry of Health and Medical Education (MOHME), by the end of February of 2014, 31363314674 drugs had been sold, among which at least 33% of patients' prescriptions contained a kind of synthetic antibiotics [4-6]. Antibiotics can be mentioned as pharmaceutical compounds widely used in the modern medicine and veterinary industries. As a matter of fact, they enter the environment via different ways, including agricultural runoff, direct discharge from refineries of urban and hospital wastewater, human waste, direct disposal of medical, veterinary as well as industrial waste to name but a few. [7-9]. Exposure to low-doses that causes the development of antibiotic resistance is raised as a major concern [10, 11]. Indeed, during the last years, much attention has been paid to the studies related to the reduction of such micro-pollutants; furthermore, notable researches have been carried out regarding the antibiotics removal from aqueous environments. In spite of the extensive investigations, there is still a considerable lack of integrated and classified information to assess the environmental risks of antibiotics [8, 12]. Antibiotics enter the surface and groundwater resources in different ways. The issue can lead to serious concerns over human drinking water, which doubles the necessity of identifying and removing the compounds from aqueous solutions. Some reports suggest that the compounds are resistant to conventional (water and wastewater) treatment and purification methods. As a result, some concentrations of the drug combinations may be observed in the people's drinking water, which were not able to be removed by our refineries [13, 14]. On the other hand, the resistant microorganisms can be transmitted to the human beings through the food chain or through contact with animals. Antibiotic resistance can be considered as a food security problem, that is to say, reduction of unnecessary antibiotic consumption as a dietary supplement in animals can exert less pressure on the micro-organisms and as a result, it lowers the possibility of bacteria's resistance [15, 16]. There is much concern over the issue that the World Health Organization (WHO) puts up the year 2011 as the year of global campaign against antimicrobial resistance. Today, a serious problem exists in regard with finding new antibiotics to deal with old diseases;there is also a serious problem in regard with finding new antibiotics to combat the new-emerging diseases [17].

Introducing the Antibiotics

Today, any substances with anti-bacterial, anti-fungal or anti-parasitic activities are called antibiotic, which scientifically refers to any agent with biological activity against the living organisms. Antibiotics have no toxicity effect on their host and are used to treat infectious diseases in humans, animals and plants. In other words, all the compounds with natural origin, which can affect the cell life, are called antibiotic. Generally, antibiotics affect four major components and functions of cells:

1-Cell wall;
2-Cell membrane;
3-Protein synthesis;
4-DNA replication and its transcription [18-20].

The Entry Ways of Antibiotics to the Environment

Many studies have been conducted on the presence of antibiotics in the environment and their effects on the nature thus far. Researchers through their examination of hospital wastewater found that certain substances such as anti-tumor agents, antibiotics and organ halogenated compounds are often removed from the wastewater refinery entrance without any analysis. As a consequence, the mentioned chemical compounds can cause natural environment pollution due to the biological imbalances they can cause. Emanuel et al. proposed that hospital wastewater and municipal wastewater had the highest and lowest concentration, respectively [13, 21, 22].

Generally, there are two main ways for antibiotics to enter the environment:

1-Through the excretion and the entrance to the sewage network and eventually surface water or groundwater or soil. In fact, after taking various drugs, different percentages of them excrete from the body without any changes. The amounts of any antibiotic's metabolism in the human body depend on its chemical structure and also its operation in the body.

2- Through the discard of expired and unused antibiotics which may be carried through the health services, sewage or household waste. In such cases, the antibiotics are carried to landfill through the discard of waste. In fact, the amounts of discarded drug all depend on the patient's habit and also the amount of drugs prescribed by the physicians. The main sources of antibiotics entrance to environment is shown in figure 1.

Generally, these sources can be categorized into several groups:

Natural sources

Some different antibiotics such as beta lactams, streptomycin, amino glycosides etc. are produced by bacteria in soil. For example, actinomycete group is produced by some soil bacteria like streptomycin.

Pharmaceutical industry

During the past decades, the effluence from the manufacture of pharmaceutical compounds was less considered; nonetheless, recently in some Asian countries, the high concentration (up to several milligrams per liter) of pharmaceutical compounds has been reported for the outputs of such industries. Even in the developed countries, antibiotics manufacturing industries have a significant effect on the total concentration of mentioned compounds, distributed in the wastewater treatment plant's output [12, 23, 24].

Antibiotics' consumption

Antibiotics are widely used in human societies to prevent and treat bacterial infections. Obviously, the habit of their consumption would be different in different countries. In general, per capita consumption of antibiotics for human use and the prescribed dose of these compounds vary significantly from one country to another. As the compounds will not completely have metabolized in human body, they would excrete from body and eventually enter the environment [12, 26, 27].

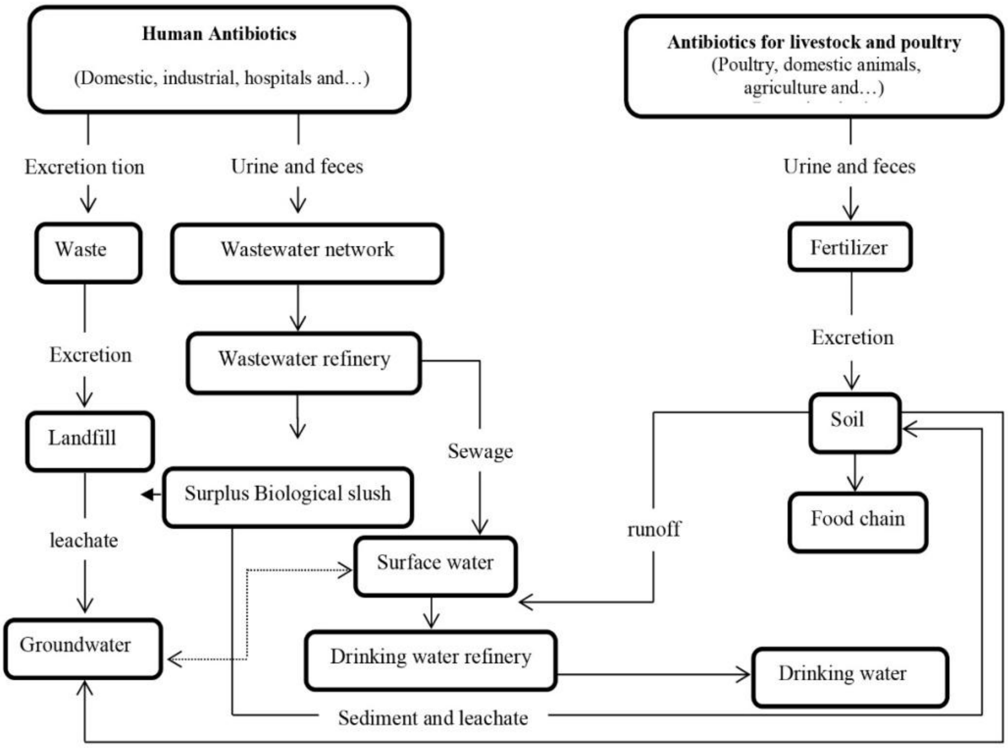

Figure 1: The main routes and sources of contamination of human and animal antibiotics [20, 25]

Sewage from hospitals and health centers

In general, the wastewater from hospitals and health centers are qualitatively almost the same as city wastewater; nevertheless, they may endanger the health of environment, the employees of the health and treatment centers and the whole society because they contain potential toxic or infectious substances and compounds. As in developed and some developing countries, the amount of water consumption in hospitals is high and wastewater is diluted. As a result, the wastewater from hospitals and health centers, in these countries, will be treating in municipal wastewater treatment plants without the need for additional treatment and would not cause any specific health and environmental risk. In countries where there is no network to collect the swage, the evacuation of wastewater, untreated or partially treated, from hospitals and health centers can inevitably endanger the health of society. It must be said that during the process of treatment, the chemical substances of wastewater from hospitals and health centers can have a toxic effect on bacteria and active microorganisms. In fact, this is another risk which is associated with the hospitals and health centers' wastewater [24, 28, 29].

Veterinary

Animal antibiotics are used in different ways in order to prevent or treat the animal diseases. They would be taken as an animal feed or growth supplement. Indeed, in some countries, small amounts of antibiotics would be used in animal feed in order to improve the product quality and produce a meat with low fat and high amounts of protein [30].

The production of herbal products

Since World War II, antibiotics had been used in order to control and threat certain bacterial diseases and also for producing many fruits, vegetables and decorative plants. Antibiotics should have the fallowing features in order to be suitable for control of plant diseases:

1-Being active both on the surface and inside of the plant,

2-Being resistant to oxidation, ultraviolet radiation (UV), rain and high temperatures.

Having the mentioned features play a crucial role in environmental problems occurrence. The antibiotics used in agricultural and fishery products can aggregate or settle in soil and provoke the infection and environmental pollution [8, 12, 31].

Aquaculture

In aquaculture also the antibiotics would be used for therapeutic purposes or as a preventive agent. The antibiotics used in aquaculture include: Sulfonamides, erythromycin and oxitetracycline [19, 32].

The Effect of Antibiotics on the Environment

The human body cells react to antibiotics in very low systemic levels. As a result, their existence in drinking water or food can increase the levels of these compounds in body. These compounds can reach the body tissues and cause different responses from body. It can be said that there is still insufficient information available about the possible effect of small amounts or low concentrations of antibiotics on human body. Nonetheless, even low concentrations can act as a vaccine for bacteria and make them resistant to the antibiotics used in the treatment of diseases. The bacteria resistance can happen due to the existence of antibiotics in hospitals and health centers wastewater, swage, soil etc. Moreover, on barren fields, the wastewater containing antibiotic, bacteria and resistant bacteria would be used for irrigation and also the excess sludge is used as fertilizer. As a result, the resistant bacteria directly enter the food chain. The concentrations less than the required rate for diseases treatment have a significant role in bacteria resistance, which can even transmit to the bacteria genetics. Studies have shown that the chronic effects of antibiotics are more than their acute effects [23, 30, 33].

The Effect of Antibiotics on the Wastewater Treatment System

Antibiotics have the ability of affecting bacteria colony existing in wastewater networks. Moreover, in the presence of antibiotics in the sewage treatment systems, bacteria activities would be inhibited and this can seriously affect the decomposition of organic matter [34, 35].

The Effect of Antibiotics on Surface Water

Antibiotics that have been removed partially from wastewater in treatment systems can enter the surface water resources and affect the different organisms of food chain. Algae have abundance sensitivity to different types of antibiotics. Algae are the basis of food chain. Therefore, even a slight decrease in the population of algae can affect the balance of water system. Although the concentration of related compounds in water is very low (ng or µg), their aggregation in poultry, livestock and plants can cause a disease in human and in animals, as well [26, 36, 37].

The Effect of Antibiotics on Sediments

Antibiotics can qualitatively and quantitatively affect the bacteria colonies existing in sediments, which can seriously affect the decomposition of organic matter. The aggregation and concentration of antibiotic compounds in sediments can reduce the growth and activity of sulfate reducing bacteria and consequently affect the sulfate reduction process. Indeed, due to the aggregation and high concentration of such anti-bacterial compounds in sediments located in the bottom of fish farming sites, it is essential to consider the effect of antibiotics on sediments [38].

The Reasons and Necessity of Treating Aqueous Solutions Containing Antimicrobial Compounds

Among the proposed reasons about the necessity of treating aqueous solutions containing antimicrobial compounds, we can mention the following:

- The production and consumption of large quantities of a variety of human and animal antibiotics around the world;
- Arrival of large quantities of antibiotic compounds and metabolites into the environment through feces and urine;
- Disposal of antibiotics with no expiration date, which can pollute the ecosystem;
- The possible increase of contiguity with antibiotic residues can accumulate in food chain or drinking water;
- increased risk of unwanted effects on the ecosystem;
- Lack of sufficient information on the presence and persistence of antibiotics in the environment and its risks to ecosystems and humans [12, 37-39].

Materials and Methods

So far, many studies had been done about the presence of antibiotics in the environment. Unfortunately, in spite of the extensive investigations, there is still a considerable lack of integrated and classified information to assess the environmental risks of antibiotics. Therefore, in the current study, the removal of these compounds from aqueous solutions was studied. This study was carried out on the basis of surveys accomplished in recent decades and also the ones published in databases such as Google Scholar, PubMed, Elsevier, Scopus, Springer, Magiran and SID using Anti-bacterial agents, antibiotic, wastewater, removal methods as the keywords.

Results

Examining the Methods of Removing Antibiotics from Aqueous Solutions

Biodegradation

Biodegradation is a process during which microorganisms would be used to convert and degrade pollutants to final stable and safe products. Studies in laboratory scale and full-scale have shown that some antibiotics in soil and sediments are quite resistant to biodegradation. On the other hand, there are some other components that are not degrading well under anaerobic biodegradation. Ingerslev and Halling [32] found that there are 12 different sulfonamide components, which were not biodegraded during the process of active sludge in sewage treatment. Indeed, the amounts of biodegrading for most of studied components in laboratory scale were low. Generally, it must be said that biodegradation processes are not effective in removing antibiotics [37, 39, 40].

Absorption

The process is widely used to remove organic industrial pollutants in a medium that molecules of liquid phase tend to be a solid phase. In fact, accessing the absorption of antibiotic on absorbent requires knowing their physical and chemical features. Studies have shown that antibiotics' absorption behaviors could be very complex. On the other hand, deployment and generalization of data from experiments with unknown matrices such as soil to another, such as sewage sludge, is not possible. Although the use of an adsorption filtration method by adsorbents such as activated carbon is suitable for removing high doses of many antibiotic compounds, the efficiency of antibiotics absorption could be affected by several factors such as the type of activated carbon, the initial concentration of target compounds, pH, temperature and concentration of dissolved organic carbon [8]. *Kim* et al. studied the adsorption characteristics of antibiotics Trimethoprim (TMP) in continuous and batch conditions and achieved the removal efficiency greater than 90%. The document published by the United States Environmental Protection Agency (USEPA) announced that the best available technology for filtering pollutants and also sweeteners disrupting the endocrine is granular activated carbon process [12, 41- 43].

Membrane processes

The removal of chemical pollutants will be determined by means of high pressure membranes such as nanofiltration (NF) and reverse osmosis (RO) and the help of complex interaction of physical and electrostatic forces between pollutants, aqueous solution (water, sewage, etc.) and membrane. The processes are increasingly used for separation while the method is not able to remove or decompose the pollutants and only enters them into a new dense phase. *Gholami* et al. in their study on antibiotics ampicillin and amoxicillin removal by means of reverse osmosis membrane stated that the flux flow and also the amount of antibiotic removal is affected by any factors of leading flux, pH and temperature [44]. The limitations to predict the chemical behaviors of treatment systems in full-scale, membrane fouling due to chemical deposits or microbial growth and thus the need to increase the pressure to maintain leadership flux, changing the physicochemical properties of membrane surface are considered as the disadvantages of using this method [42, 43]. Indeed, due to the wide range of their application and also in order to facilitate the understanding and application of membranes, there would be different classifications. Fallowing, some of the classifications are mentioned:

- classification of membrane processes based on the mechanism governing the separation;
- classification of membrane processes based on membrane type;
- classification of membrane processes based on the geometric shape of the membrane;
- classification of membrane processes based on membrane structure;

The main separation processes include microfiltration, ultrafiltration, nanofiltration, reverse osmosis, electrodialyze, gas separation and evaporative leak each of which are used in many different areas [45, 46].

Reverse Osmosis

Reverse osmosis process is able to remove dissolved solid particles, bacteria, virus and microbial agents in water. Reverse osmosis is basically a penetrating membrane process that works on the basis of compression driving force. The process is mainly used to desalinate seawater. The prominent features of reverse osmosis are the absence of phase change and its low energy consumption. In the reverse osmosis, the mean antibiotics separation rate changes from 90.2% for distilled water to 90.3% for river water. Considering the calculated rates, it can be said that using two or three consecutive reverse osmosis units, 99 and 99.9% rate can be achieved, respectively. Using reverse osmosis in municipal water treatment systems is not usually economic. Although the method is often used in particular refinery units, in general, it could be an appropriate method to remove the above mentioned antibiotic compounds from drinking water [47- 49].

Nanofiltration

Nanofiltration is a kind of filtration which uses the membranes in order to segregate the fluids or ions of different sorts. It is regarded as more gentle reverse osmosis due to the fact that it contains bigger membranous holes in comparison with reverse osmosis membranes. Owing to the fact that these membranes are operated in very low pressures and transmit some minerals, nanofiltration can be regarded to be useful in conditions in which high removal of organic material and average removal of minerals are vital and warranted. The advantage of this method (nanofiltration) over the reverse osmosis is that nanofiltration is usually useful in higher recycles;

as a result, there would be more chances of saving total used water, which in turn is due to the flow rate with lower density. Nonetheless, this method is not effective concerning with organic compounds with low molecular weight like methanol. In respect of energy costs, ions disposal and hole dimensions, nanofiltration has provided more optimum condition than other methods[50, 51].

UltraFiltration

Ultrafiltration (UF) is partly dependent on factors such as load and particle size. This method is not so effective in segregation of organic streams. UF membranes are capable of maintaining species, which have the molecular weight running the gamut from 300 to 500000 Dalton, and the size of holes ranging from 10 to 1000 angstrom [49, 52].

Microfiltration

Microfiltration is a process in which the size of the holes is between 1 and 10 microns. Microorganisms are unable to transmit those holes. This process is utilized for separation of substances with colloidal size in which screening mechanism is used for retaining the substances larger than the holes' diameter [52, 53].

Membranous Biological Reactor

This reactor contains a chamber in which segregation of biological mass is done by a membrane, namely, micro filter, with size around 1_10 micrometers. These reactors have been found to be useful in wastewater filtration in aerobic and anaerobic conditions. In these reactors, filtered wastewaters have quality the same as the output of the secondary sewage deposits and microfiltration unit output. These reactors are useful for urban and industrial wastewater treatment and wastewater reuse schemes [3, 54].

The process of coagulation, flocculation and sedimentation

The processes of coagulation, flocculation, and sedimentation are methods of chemical and physical filtration in which they increase the amount of sediments and segregation of solids. In this method, the flocculation and consequently sediment are used [55].

Ultrasonic Radiation

The word ultrasonic means beyond the sound. Ultra sonic waves are classified as those types of mechanical waves in which frequency fluctuation is beyond the range of human hearing (20HZ-20KHZ). Having idiosyncratic properties, these waves perform various and interesting functions. Therefore, as other types of waves, ultrasonic waves have properties of deflection, reflection, permeability and diffraction. There are different ways of producing these waves. One of the features of this method versus filtration is the probability of effect on organic material with low solubility or high volatility and also there is a possibility of being effective for pharmaceutical Micro-pollutants. After all, there is possibility effect of many factors on its efficiency such as frequency, ultra sound density, type and nature of pollutant, water temperature and water matrix [46, 50, 56-59].

Advance Oxidation Process

Advance oxidation process usually involves producing and using free radicals, hydroxyl, as a powerful oxidizer for purposes such as destruction of compounds in which they do not oxidize completely with prevailing oxidizers such as chlorine. Hydroxyl radical reacts with soluble compounds, which results in oxidization reactions so that it leads to doing away with the component in mind. These treatment processes are considered as suitable methods for purification of pollutants in groundwater resources, waters at the surface level of ground, industrial wastewaters containing biological non-biodegradable pollutants. Hydroxyl radicals are very reactive; as a result, they react to the most of organic compounds. For the time being, in advanced oxidation processes, there are many technologies for producing hydroxyl radicals. These processes have been categorized differently in different sources and texts based on ultraviolet ray, processes based on hydrogen oxidation and processes based on ozonation [60, 61]. They studied the decomposition of β-Lactam antibiotic. Using this method, they found that although they reach at high removal efficiency, it is low. And all authors studied the effect of pH in this process and found that there was an increase in decomposition rate as pH increased [60].

- *Ozonation*

During the treatment process by ozonation, oxidative decomposition of organic compounds is occurred by direct reaction of ozone molecules, and or indirectly by hydroxyl radicals. Ozone or hydroxyl radicals produced in this process, attacks the active pharmaceutical ingredients, and thus their anti-bacterial properties will be inactive. Different studies have shown that the ozonation could be effective in regard with removing antibiotics from water and wastewater. Several studies have been carried out on using ozone to treat the contaminated water via antibiotics and indicate that ozonation process requires a greater amount of oxidizing agent in comparison with the other oxidation methods to treat the similar pollution. Moreover, the findings of other studies revealed that although the degradation efficiency of this method is high, mineralization and detoxification of wastewater seem to be low. In fact, this process depends on pH changes and requires cost, equipments and high energy, which is not regarded appropriate for treatment of environments contaminated by pharmaceuticals [62-65].

- *Fenton Oxidation Process*

In Fenton oxidation process, the toxic or biologically non-biodegradable chain structure can transmute to less toxic or biologically oxidable substances. These reactions are progeny, which result in foam and gas emission. This process is easily used in the treatment of small contaminants due to the capability for mineralization of main portion of contamination, creation of less toxic wastewater, ease of final biological treatment, easier utilization and control, and thus, adjustment of the work conditions. This process not only helps to remove organic carbon, heavy metals and phosphorus, but also deactivates the bacteria. Nevertheless, it is necessary to consider the adjustment of environment pH and retrieval of the soluble ions from the treated wastewater [66- 68].

- *Photo-Fenton*

Generally, the presence of UV light in the Fenton process (Photo-Fenton) seems to improve the performance of treatment. However, the process of Photo-Fenton is regarded inapplicable for wastewater with high amount of organic matter (high concentration of COD such as wastewater of antibiotic factories, hospitals and urban wastewater), since the turbidity prevents the penetration of UV rays. Although the Fenton process can cause less efficiency of removal and mineralization, it is regarded more applicable for treatment of this kind of wastewater. The Fenton process in low concentration of COD is applicable while water with high concentrations of ions (such as seawater) cannot be treated with this method since the chlorine- nitrate- carbonate ions and bicarbonate are captors of hydroxyl ion (pH) [69- 71].

- *Oxidation of Electrochemical*

In this method of treatment, the efficiency would be increased by H_2O_2 usage. Effective parameters on performance consist of used electrodes, type of electrolyte, electricity use, and initial concentration of organic substances. In fact, applying NaCl increases a concern regarding formation of oregano-chlorine compounds as a byproduct. The need to adjust the pH of wastewater can be stated as another limitation of this method [66]. *Dirany* et al. [72] examined the reduction of antibiotic sulfamethoxazole by the electrochemical process of water anddemonstrated that the sulfamethoxazole under the experimental conditions was quickly destroyed. However, the elimination of all organic carbon was obtained only in boron-doped diamond (BDD) anode/carbon felt cell [7, 72].

- ***Semiconductors Photocatalysts***

Photo catalysts are substances that destroy the contaminants of water and wastewater, and convert them into harmless substances such as water and carbon dioxide. Photo catalyst is a substance that can induce a chemical reaction by the light exposure while it would not be subject to any changes. In deed; they are not directly involved in oxidation and reduction processes, and only provide the required conditions for the reaction. Some substances that can be used as a Photo catalyst entail: titanium dioxide (TiO_2), zinc oxide (ZnO), iron oxide (Fe_2O_3), tungsten oxide (WO_3). Titanium dioxide is regarded more popular than the other catalysts due to low cost, no need for high energy, high efficiency, and lack of contamination.

Generally, semiconductor photo catalyst mechanism is performed in five main steps:

1) Transmission of the reactant in the liquid phase to the surface;

2) Absorption of the reactant;

3) Reaction in the adsorbed phase;

4) Desorption of products;

5) Removal products from the intermediate zone. Several researchers used this method to remove different antibiotics and have reported a high efficiency for this method [12, 73].

- *Chlorination (Cl_2)*

Due to the low cost of chlorine or hypochlorite, these oxidizer materials are usually used in disinfection unit of water and wastewater refineries. In addition, it is used as a next filtration unit in order to maintain some disinfecting agents in distribution system of drinking water. This method is used more than biological methods to treat water containing pharmaceuticals in order to oxidate the contaminants [2, 74]. By chlorination, there is a possibility of oxidation of target antibiotics to non-active small molecules. Nevertheless, the need to high concentration of free chlorine (3.5-3.8 mg/L) for removing more than 90% of antibiotics such as Sulfamethoxazole (SMX) with 24 hours of contact time, need to adjust the pH, and the possibility of creating the byproducts, even more harmful than initial compounds, can be mentioned as the limitations of this method. Although some studies have examined wastewater treatment by chemical oxidation using a variety of chlorinated substances, this method is less employed in treatment of water containing medicinal material before applying the biological treatment in regard with more biodegradation and less toxic compounds. The chlorination method was done with a dose of nearly 1 mg per liter in the both distilled and river water. Based on the results of this research, the studied antibiotics are removed at a rate of 50-90% of what was expected. The chemical oxidation of organic compounds by organic chlorine as an oxidizing could lead to byproducts production [74, 75].

- *Ion Exchange*

The ion exchange phenomenon was first reported in 1850 following observing the agricultural soil ability in the exchange of some ions such as ammonium with calcium and magnesium ions existing in their structures. The ion exchange is a process in which cations or anions in a liquid environment are exchanged with zinc anions and cations on a solid adsorbent. In this process, cations exchange with cations and anions exchange with anions, as well. Moreover, chemical reactions between ions within the phase are liquid and the phase ions are solid. Some particular ions are preferably absorbed by solid ion exchangers in the liquid. Since electrical inactive state must be established, the solid exchanger releases some ions into the liquid in order to present an alternative to the absorbed ions. The ion exchange process is mainly used to soften water, remove minerals, desalination, and denitrification [43, 76, 77]. *Choi*et et al. (2007) widely investigated the ion exchange system in removal of pharmaceutical compounds, and was reported that this method has some disadvantages such as a need to inverse washing, reducing and obstruction [78].

- *Photolysis*

Photolysis is the disintegration of chemical composition by natural or artificial light consisting of direct and indirect photolysis. In direct photolysis process, the organic compounds absorb UV rays whereas in indirect Photolysis, the disintegration of light is done by photosensitizers such as oxygen and hydroxyl, or peroxide radicals [11, 79, 80]. If the organic compounds are sensitive to light, optical dispersion would be the main removal process. The photolysis process widely occurs in surface water, which plays an important role as an extra phase of removal in surface water or wastewater treatment.

Photochemical decomposition depends on the intensity and frequency of light. Moreover, the effect of frequency is based on absorption spectrum of combination. Therefore, the photolysis process will not occur, if the surface of river or lake is covered by shade of trees or other factors, or existence of given contaminant in the soil. All combinations have not the ability of light decomposition. Several studies examined optical disintegration of tetracycline (a group of antibiotics that are very sensitive to light), and found that their removal efficiency was about 80%, and the removal efficiency of TOC was approximately 14%, which represented the production of intermediate compounds. They concluded that the treated wastewater is more toxic than input wastewater. In comparison with other methods, this process is nearly inefficient and is only usable for wastewaters with light-sensitive combinations as well as water with low concentrations of COD [81]. In the case of antibiotics, the amounts of direct and indirect photolysis in water environments for various compounds are different. *Baron* et al. (2006) in their examination on the removal of sulfamethoxazole and sulfadiazine antibiotics with initial 1.0 mM concentration from synthetic wastewater through the 365 nm TiO_2/UV photo catalytic process, concluded that using this treatment method leads to removal of all considered pharmaceutical compounds after 180-300 minutes from reaction time. In addition, they reported that mediatory produced compounds have more biological degradability and less toxicity than initial compounds [82].

- *Ultraviolet (UV) Radiation*

UV radiation in completely random manner was discovered by color changing and darkening of silver solutes against direct sunlight. German scientist, *Johann Wilhelm Ritter* (1801), based on his observations, discovered that UV radiations, which are invisible, are the main factor in the darkness of paper sheets impregnated with silver chloride. He then called it "chemical rays". UV radiation is the electromagnetic energy that has short wave length and high energy that is invisible, and locates X-rays and visible light in the electromagnetic spectrum. This ray has a wavelength between 0.0144 to 0.39 micrometers. Irradiation with UV could be employed to decompose the organic compounds in water. In this process, the decomposition is resulted from energy absorption and load of UV quantum by combining. The concentration of dissolved organic carbon (DOC), UV dose, and contact time are regarded as the important factors in order to achieve the removal efficiency. The results of different studies revealed that in the dose range of 30 to 80 mj/cm^2 of UV radiation, antibiotics' slight removal from secondary wastewater treatment of WWTP occurs, and for achieving high efficiency (more than 90%) in removing some antibiotics such as Sulfamethoxazole and Nourphloxazine, a high dose of UV (about 3000 mj/cm^2) is needed [8]. The amount of ultraviolet rays to disinfect water is about 30 mj/cm^2 while the radiation dose was 3000 mj/cm^2 in a research conducted on disinfecting the studied antibiotics, in which obtained percentages of the removal was only between 50% and 80%. It is obvious that the applying ultraviolet rays with a wavelength of 254 nm and conventional intensity used in water disinfection for removing the given compounds are ineffective [26].

In the figure 2 and 3, distribution and frequency of studied antibiotic, and the methods using to remove these substances from environment are displayed.

Discussion

With development of cities and increasing population and expansion of industries, the importance of environmental pollution is increasing day by day. Sewages and industrial pollution are the result of human activities that varies depending on the source of the quality and content of organic and inorganic, dissolved and suspended matter. Natural cleansing action to reduce and remove contaminants in the environment always occurs; nonrtheless, it takes during very long period of the processes and reactions that may take several years to remove a contaminant from the nature 21, 83. In general, the most important goals include providing water treatment and wastewater sanitary conditions suitable for life, preserve the environment and prevent pollution in sewage acceptor with the advancement of science in relation to environmental engineering.

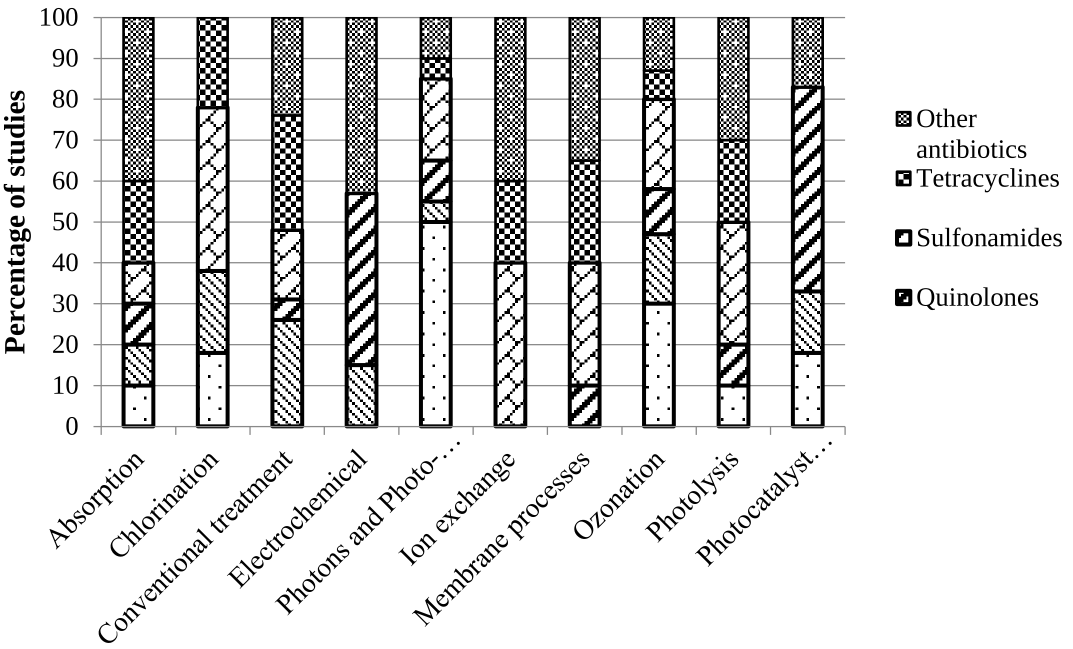

Figure 2: Distribution and frequency of various processes of removing antibiotics from aquatic environment

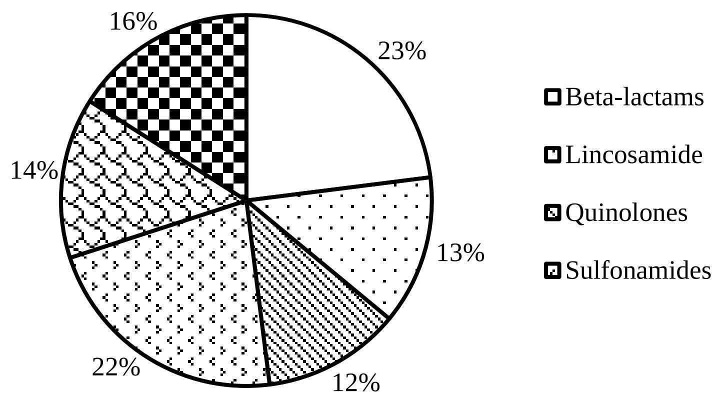

Figure 3: Distribution and frequency of antibiotics

Today, we can refine different types of wastewater treatment plants with different characteristics in order to maintain the required standards.

Environmental pollution is a serious problem with which human is faced and due to the population growth, the importance of environmental pollution control and its exponential growth prevention is needed more than ever. Problems caused by the presence of persistent pollutants in the environment such as amoxicillin require investigation to identify various strategies to reduce or remove them. Various processes for the removal of environmental pollutants in water, wastewater and air are used that there is not suitable efficiency. In recent years, biological technologies for pollutants removal from the environment has played an important role in the use of these technologies for the removal of environmental pollutants as one of the newest and best pollutant removal practices in the world.

Toxicology is the study of the effects of harmful chemical compounds in natural environments. This category includes the harmful effects on people although the main aim is to understand the effects on individuals and how to change the community and ecosystem levels (the natural environment). Persistent organic pollutants, which are sufficiently long half-life in the body of living creatures, move along the food chain and can increase their life to reach higher trophic levels. Lower trophic levels can bioaccumulate in biological concentrations while at higher levels easily metabolized by vertebrates. Biological increase during drought in the food chain is owing to bioaccumulation, food pollutants is the main source of most of the pollutants. In some cases, major possible route of pollutants emission is the air in contact with contaminated surfaces or drinking water. The cause of bioaccumulation is a chemical combination like following factors:

Biological increase along the food chain, as a result of condensed water, can be biological as well as bioaccumulation. Aquatic Vertebrate and invertebrate can attract the surrounding water organisms that live in the lower levels of sediment contaminants and which can enter their body. Biodoping agent is a chemical compound that is absorbed directly from the water, which is defined as follow:

One of the challenges, during reviewing biological increase in the food chain, is proving their bioaccumulation importance in opposition to doping. To increase the biological processes that lead to the development of stable, predictable patterns of synthetic pollutants are being studied. When living organisms are continually exposed to contaminants in food or wastewater and the amount is almost constant, concentration of pollutants in the tissues increases with time until:

1- Reach the lethal concentrations in which the organism will die.

2- A constant state arises where pollutants entering the living body are equal to the ones lost.

Bio-concentration factor or bioaccumulation factor in the steady state is of prime importance because:

1- It is the highest possible value, and therefore, represents the maximum risk;

2- Does not depend on time;

3- The speed of input and loss of pollutants are equal, and thus the rate of constants becomes easier.

Measuring the concentration of biological and environmental factors before reaching a steady state concentration has a very little value, because they depend on how long an organism is exposed to the chemical composition and an increase in temperature may be less than what is calculated. This issue will be corrected in consideration of the fact that long-term exposure to the organism has not come to steady state. The overall position of the relative importance of entry and loss in different livings is shown by counting system in the positive scale. Some differences have been observed in each group of living organisms in regard with the importance of various mechanisms between the compounds, for instance, some differences have been detected with respect to different biological polarities and degradability. The most important concepts are listed as follows:

1-Entering and missing (loss) from exchange spread of water. The surrounding environment is of great importance for aquatic organisms, but not for land creatures.

2-Metabolism of major mechanism of pollutants' loss is in terrestrial vertebrates, though it is of less importance in aquatic organisms that pollutants can be eliminated via spreading to the surrounding water.

3-Most aquatic invertebrates demonstrate very little capacity for the metabolism, which this issue is especially true in the case of mollusks. Crustaceans such as round crabs and elongated crabs have a greater metabolic capacity compared to mollusks. The balance between competitive mechanisms of pollutants' loss in a living organism depends on the composition and the studied species. For example, within aquatics, some of the compounds that serve as good substrate for monooxygenases, hydrolases, etc. can be metabolized fairly quickly, though even the fishes, as a group, have a low metabolic capacity. Thus, in such metabolic cases as emissions of pollutants, the amount of pollutants' loss is taken as an important factor into consideration. On the contrary, since many multi-halogenated compounds by fish are metabolized too slowly, metabolism does not contribute significantly to remove the pollutants and in fact, the loss of pollutants via the diffusion method is regarded as the major mechanisms of digestion. However, the emergence of slow burning organic pollutants, which has integrated the high toxicity and high lipophilicity, indicate the restrictions of detoxification systems. Soil particles can be introduced as complex interfaces between living organisms and mineral particles. Decomposing the organic remains of the microorganisms produces complex organic polymers ("Humic substances" or simply "soil organic matter"), that join the mineral particles together and form clumps that give the soil a special structure.

Soil organic matter and clay minerals make up the soil colloids. Small size and larger surface than its volume possess a large capacity in order to absorb soil- contaminating organic pollutants. Air and water ducts in the soil freely groove it and then ground water moves near to the surface and eventually exits. Chemical compositions are differently distributed to three phases of water, soil, and air depending on their physical properties. Lipophilic compounds are strongly attracted to soil colloids and thus are static and durable. Due to low solubility in water and slow burning nature of these compounds, the major mechanism of loss in various soils is performed by volatility.

Metabolism is limited by two factors:

1- Tight connection, these compounds are not freely available to the enzymes of soil organisms as they can be broken.

2- At the best state, they can be metabolized as slowly as the enzyme systems.

Due to strong absorption and low solubility in water, they are often washed in a small quantity by water from the soil surface and penetrate into the underlying layers.

The degree of absorption and thus the strength and mobility depend on the type of soil. Heavy soils involving high amount of clay or organic matter absorb hydrophobic compounds with more force, compared to light sandy soils possessing lower amount of organic materials. Lipophilic compounds seem to be more resistant in the heavy soils. In high contrast with hydrophobic compounds, more polar compounds are absorbed in a less quantity and get a relatively higher concentration in the soil water.

It was thought for a long time that organic contaminants demonstrate a low tendency to move from soil into the fields of water (water drainage, sewerage). In fact, the same can be expected from the undisturbed soils. Hydrophobic compounds get rejected by adsorption since the water-soluble compounds are decomposed by soil living organisms. In heavy soils, Then if it rains, contaminants that are dissolved or have been absorbed in the form of movable colloids can be washed into the fissures and appear in the adjacent ponds and streams.

In assessing environmental risks, the purpose is to prove the possibility of a compound or chemical compounds that make toxicity in their natural biological environment. The analysis was based on comparing environmental toxicities data of laboratory experiments to the data obtained or estimated in the natural environment. Posing questions in regard with the quality of the population level or above mentioned issues can be related to that the consequences of such toxicity has not been taken into account. Toxic effects on each individual in the environment can be established in various ways and quantitatively estimated. In the case of cytotoxic effects, a simple approach is that after applying chemical compounds, the bodies are collected and counted, such as the tests carried out on the effects of modern insecticides in natural environments.

However, it is a non-precise approach since many kinds of sacrifices; especially stirring varieties such as birds flee from poisoning. Such data can be used to assess the effects of chemical compounds on the rate of population killing in the natural environment, and then they can be placed in the form of population patterns.

Biological response criteria seem to have greater ability in order to control the effects of chemical compounds on living organisms in the natural environment. In this regard, the side effects can be calculated and measured using biological response criteria. To obtain the desired result, they should be nondestructive, so if the sampling could be performed on individual organisms in each groups. The position of population can be illustrated by numbers (population density and population density) or genetic combining components (population genetics). Early in the history of evolution, "natural" xenobiotic toxicity has exerted a selective pressure imposed on the living organisms. Much evidence of chemical compounds produced by plants and animals exist that are toxic to species other than their own and have been used as chemical warfare agents. Preparing chemical compounds produced by human is regarded as an extremely new event. In truth, selective pressure on natural populations, and thus the emergence of resistant strains has recently been started. To put it more generally, mechanisms of resistance are of two sorts:

1- Mechanisms that depend on the synthetic factors of toxin such as decreased entering, increased metabolism or increased storage.

2- Mechanisms that rely on dynamic factors of toxin, mainly a shift in action positions leads to reduce the sensitivity.

Resistance mechanisms associated with changes in toxins synthetics, largely belong to metabolic detoxification cases. Metabolic resistance may be resulted from incidence of a new gene in the resistant varieties that are absent in the other members of the population. Furthermore, it may be related to multiple copies of a gene in different races or communities.

According to the aforementioned adverse effects resulting from exposure to the little concentrations of pharmaceutical compounds in the long run, making an effort to identify the status of surface water, groundwater, as well as drinking water in the cities of Iran should be considerate. In this regard, studying and identifying effective methods on the removal of discussed compounds from drinking water need to be illuminated further. The results of studies that have been published indicated that unfortunately common methods mainly used for purification of drinking water in our country seem to be ineffective for the removal of hormone and antibiotic compounds, except for several exceptional cases. Within mostly influential methods in removal of hormonal compounds and antibiotics as well as other pharmaceutical compounds based on some evidence, such advanced methods can be mentioned as absorption by activated carbon, reverse osmosis and nanofiltration as well as oxidation by chlorine and ozone.

Although ozonation presents many benefits, it needs great cost, energy and equipment, while mineralization rate is unchanged or even lower after reduced long treatment duration and toxicity of treated wastewater demonstrating production of metabolites which are more toxic compared to the primary compounds. In spite of the fact that combined methods are not regarded as normal methods, they are recognized as one of the powerful processes to remove antibiotics from the environment.

In a study, analyses with grid solar photo-fenton process and biological treatment were investigated by *Sirtori* et al. [84]. The overall efficiency of dissolved organic carbon removal was 95% of which 33% and 62% belonged to solar photo-fenton and biologic treatment, respectively. In this study, analysis of all antibiotics with 90% mineralization was attainable. Applying photo-fenton as a preliminary method resulted in increased capacity of biological wastewater treatment.

Assessing the Technologies of Toxicity Removal or Reduction:

Technologies of toxicity removal or reduction are being used in order to remove contaminants from the aquatic environment and to protect human and ecosystem health. Absorption is also one of the approaches that have been used. Although the method does not have broad application, in all studies, it has been very effective (more than 80%

removal). However, the main disadvantage of absorption is producing a new residual. Moreover, in most studies, the active carbon is being used, that is very expensive. On the other hand, most researchers believe that using cheap and economic absorbents is not very efficient. While advanced oxidation processes with biological treatment or membrane or even with absorption process are frequently effective and reduce the production of toxic metabolites, the methods are impractical due to their complexity, operational costs and the required time.

Although antibiotics are invaluable compounds with broad application in modern societies, releasing them in wastewater despite some problems in the biological treatment, they disrupt filtration operations; with accumulate different organisms on filters and cancause pathogens resistance. Absorption, biotic and abiotic transformations are among main processes that affect antibiotics in natural or engineered aquatic environments. Some antibiotics may be removed through the absorption or decomposition process while others would not completely remove. Indeed, there are many different physical, chemical and biological methods to remove antibiotics which their selection depends on chemical and physical properties of the desired material. Biological methods usually have less negative effects on the environment and produce fewer byproducts. Nonetheless, in many cases, they lack efficiency due to their low availability and also their resistance to biodegradation. On the other hand, chemical methods will be selected to increase pharmaceuticals degradability due to the chemical structure of the drug substance and also the number of aromatic rings in it. Among chemical methods, ozonation, oxidation with Fenton, TiO_2 photocatalysis etc. are being used as a pretreatment to increase degradability of noted pharmaceuticals. Advanced treatment processes such as ozonation, advanced oxidation, active carbon, nanofiltration and reverse osmosis can cause higher removal rates.

Generally, chemical and biological processes by themselves are not effective in biodegrading and antibiotic removal through water or wastewater treatment while the combination of chemical and biological processes can lead to more effective antibiotics removal.

Ozonation, Fenton- Photo- Fenton and semiconductor photo-catalyzers have been considered as the most used technologies in order to remove pharmaceutical compounds from aqueous solutions.

Conclusion

Over the past years, the presence of antibiotics in the environment has been of particular interest to scientists since they can have harmful effects on land and sea ecosystems. As a result, several removal and analysis processes have been studied to solve this problem. Most conventional treatment processes in regard to removal of these compounds in the refinery were unsuccessful consist of coagulation, flocculation, sedimentation and filtration. Due to the nature of the antibiotic-containing waste, utilizing advanced oxidation process has been taken into consideration as an option. In general, ozonation and oxidation by fenton involve the most experimented methods. Although ozonation has advantages, it suffers from some disadvantages as high costs, the need for advanced equipment, high required energy and the need for backwashing. Several studies have reported that these methods are effective for the removal of certain antibiotics, whereas mine building is really low even during long periods. Furthermore, toxicity of treated wastewater has remained unchanged, or even more toxic due to compared to the primary compounds. All these methods are not applied due to their complexity as well as high operating cost, though combined processes can be introduced as the best solution for antibiotic-containing wastewater treatment.

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Conflict of interest

We have no competing interests.

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