



Review Article

Developed Sustainable Green Nanoadsorbents for the Removal of Antibiotics: A Comprehensive Review

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ABSTRACT

Antibiotics as the most widely prescribed medicinal compounds are considered now as a main emerging environmental contaminant all over the world because their existence in environmental matrices not only endanger the health of human and other living organisms but also can cause serious environmental issues. The statistical studies estimate the amount of utilized antibiotics is 1×10^5 to 2×10^5 tons globally in each year. In this respect, antibiotics removal is of great importance and this review study was devoted to a comprehensive and critical look at the adsorption-based methods for the removal of antibiotics (from different chemical families) and the effects of various parameters that can influence the removal capacity such as adsorbent dosage, temperature, initial concentration, solution pH, and etc. were discussed in details. Besides, some important suggestions that can enhance the removal percentage of antibiotics in the future studies were also proposed and discussed.

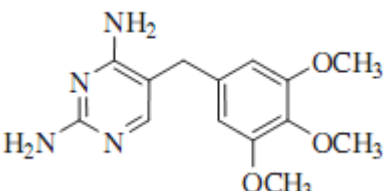
Keywords: Adsorption, Antibiotics, Green nanostructures, Emerging contaminants, Removal

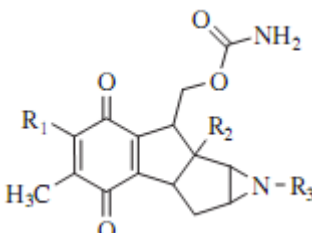
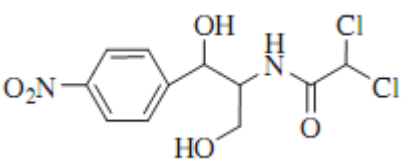
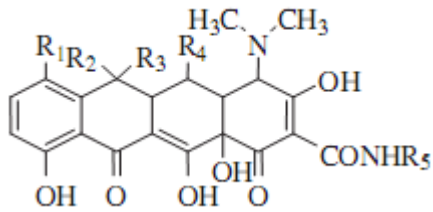
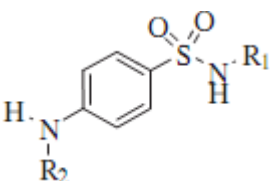
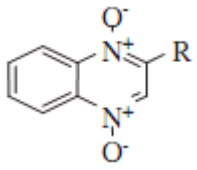
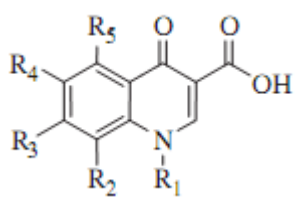
Introduction

Antibiotics as the most widely prescribed medicinal compounds are considered now as a main emerging environmental contaminant all over the world because their existence in environmental matrices not only endanger the health of human and other living organisms but also can cause serious environmental issues [1]. Since the discovery of penicillin by Alexander Fleming in 1942, more than 250 antimicrobial agents were synthesized and introduced in the pharmaceutical market for the treatment of different bacterial infections in human and animals [2]. Moreover, antibiotics are also utilized as food additives for promoting the growth of livestock animals. The statistical studies estimate the amount of utilized antibiotics is 1×10^5 to 2×10^5 tons globally in each year [3]. Most of the antibiotics are not metabolized in the body and excreted as the primitive form through urine and feces to the environment [4]. The next subject that accentuates the matter of antibiotic existence in the environment is their high solubility, non-volatile nature and durable stability in the water [5]. The inappropriate discharge of pharmaceutical companies' sewages and improper disposal of unused or expired medicines are other sources that contribute to the occurrence of antibiotics in the water sources and soils in the ecosystem [6]. The physicochemical traits of each antibacterial agent including molecular structure, shape, size, solubility, hydrophobicity and also their consumption level will determine the manner of their distribution in water, soil and consequently the food chain [7]. The occurrence of antibiotics in the environment has been detected since four decades ago but their presence as emerging environmental contaminants has become a concern in mid-1990s [8]. The first report about the observation of antibiotics in environmental waters was published by Watts et al. in 1982 in England [8]. They detected different pharmaceutical compounds from three kinds of antibiotics including tetracyclines, sulphonamides, and macrolides in a river at the concentration of 1 ppb [9]. Former studies showed prolonged exposure to low levels of antibiotics may lead to adverse toxic effects like hypersensitive allergic reactions and malfunction of digestive system organs. In addition, antibiotics residues in environmental matrices can induce antibiotic resistant genes in microbes which contributes to severe infections in living organisms that are highly resistant to the available antibiotics. On the basis of their origin antibiotics are divided to three groups: natural, synthetic and semi-synthetic compounds [10]. On the other hand, from the chemical structure point of view antibiotics are divided to 19 different classifications which are explained in details in Table 1 [11]. In this respect, development of an economic, rapid, and highly efficient method for the removal of antibiotics from environmental matrices is of great importance [11]. To date, different techniques have been reported for the removal of antibiotics from waste waters including biological treatment, membrane filtration, electrochemical destruction, photocatalysis, advanced oxidation, reversed osmosis, ozonation and disinfection [12]. However, the aforementioned techniques suffer from various disadvantages such as high cost, limited removal capacity, harsh reaction mediums, being time-consuming, expensive, and complicated and in some cases, in their procedures, several by-products that are potential environmental contaminants themselves are produced [13]. However, adsorption is an ideal alternative for the

above-mentioned techniques because of its simplicity, low-cost, versatility in the chemical and physical features of adsorbents, high efficiency, insensitivity towards hazardous materials, rapidness, flexibility and easy operability [14]. Among the various adsorbents that were employed in the field of adsorptive removal of emerging environmental contaminants nanostructures and nanoparticles have exhibited significant potentials. However, one of the main subjects that has been ignored widely by nanoresearchers is the toxicity and biocompatibility of the developed nanostructures and environmental aspects of their synthesis process [15]. In other words, in environmental research our utilized methodology must not create an environmental problem itself. In this respect, the used nanostructures for this purpose should be non-toxic themselves and in their synthesis procedure the usage of toxic reagents must be confined as much as it is possible. Most of the employed techniques for the synthesis of nanostructures requires aggressive chemical reducing agents like sodium borohydride, hydrazine, volatile organic solvents like chloroform and toluene and may also a capping agent. Unfortunately, information about health adverse effects that are related to the nanostructure's exposure are too limited and more researches should have been done in this field and some practical regulations should be set for their synthesis in large scales, especially in developing countries [16]. The toxicity of a nanostructure depends on its physicochemical properties including specific surface area, surface charge, size effect, hydrophobicity, structure (shape), etc. It seems nanoparticles with lower sizes and higher specific surface area are more chemically reactive than the ones with larger sizes and consequently are associated with more toxicity [17]. Moreover, the clearance of smaller nanoparticles from the body of living organisms is very harder than the ones with larger size. In this respect, the adsorptive removal of antibiotics by green and sustainable nanostructures is the main subject of this review. The reported green nanoadsorbents are divided to different groups on the basis of their chemical nature and their capability as a potential adsorbent are scrutinized. Besides, all of the factors that can influence the removal capacity are discussed in details and some important suggestions have been proposed for the upcoming studies in this subject at future.

Table 1. Antibiotics classification on the basis of their chemical structures

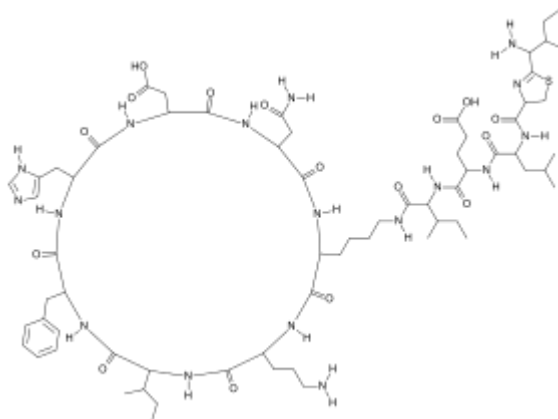
Class	Core structure
Trimethoprim	<p>It is a diaminopyrimidine, a structural analogue of the pteridine moiety of folic acid</p> 

Mitomycins	<p>They have a unique chemical structure, in which 3 different functional groups e aziridine, carbamate and quinone are arranged around a pyrro[1,2-a]indole nucleus.</p> 
Chloramphenicol	<p>It contains a nitrobenzene moiety connected to a propanol group as well as an amino group binding a derivative of dichloroacetic acid.</p> 
Tetracyclines	<p>These antibiotics contain an octrahydronaphtacene ring skeleton, consisting of 4 fused rings.</p> 
Sulfonamides	<p>They are characterized by sulfonyl group connected to an amine group.</p> 
Quinoxaline derivative	<p>Their structure contains a benzene ring and a pyrazine derivative ring.</p> 
Quinolones	<p>Their structure contains 2 fused rings with a carboxylic acid and a ketone group. If R4=F, then it is a fluoroquinolone</p> 

Polypeptides

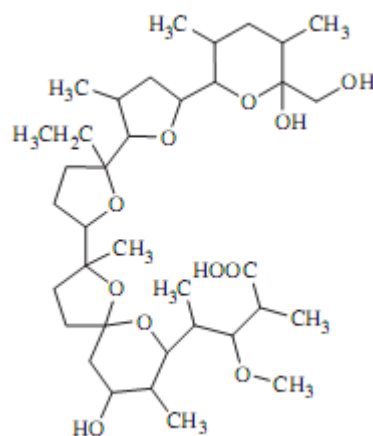
compound.

They are polymers formed from the linkage of α -amino acids.



Polyethers

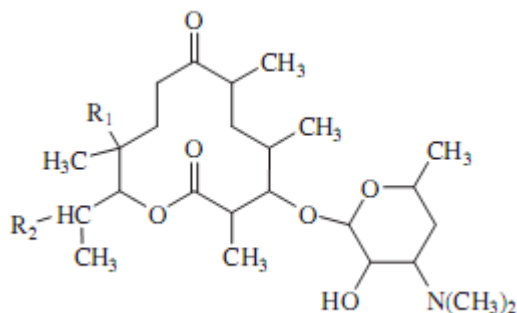
They are characterized by multiple tetrahydrofuran and tetrahydropyran rings connected by aliphatic bridges, direct C-C linkages, or spiro linkages.



Macrolides

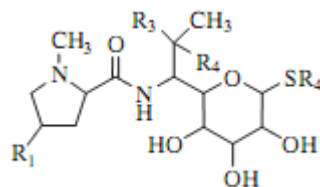
They are highly substituted monocyclic lactone with 1 or more saccharides glycosidically

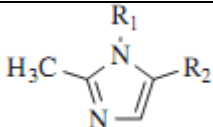
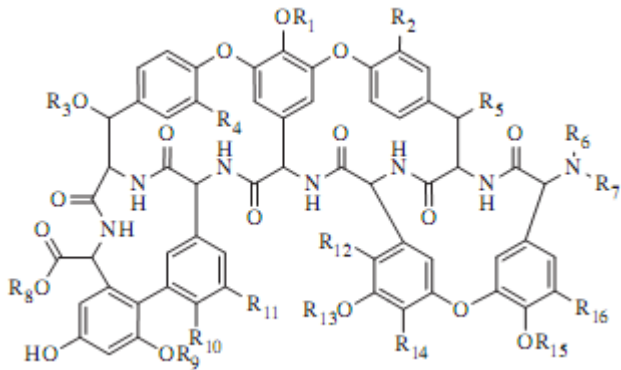
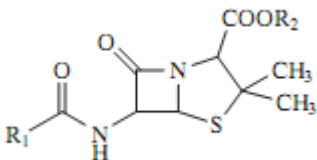
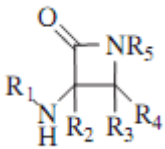
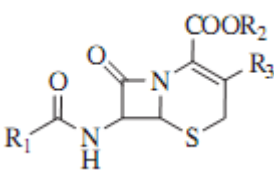
attached to hydroxyl groups.

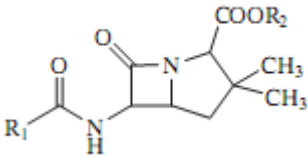
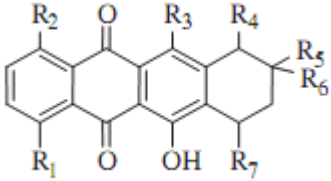
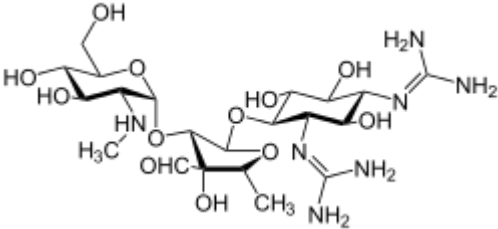


Lincosamides

They are a small family of antibiotics that have carbohydrate-type structures.



Imidazoles	<p>They are heterocyclic compounds of 5 member</p> <p>di-unsaturated ring structure with 2 nitrogen atoms at nonadjacent positions. If R₂=NO₂ than it is a nitroimidazole compound.</p>	
Glycopeptides	<p>They are composed for carbohydrate moieties (glycans) covalently attached to the side chains of an amino acid.</p>	
Penicillins	<p>Consists of a thiazolidine ring connected to a b-lactam ring, to which a side chain is attached.</p>	
Monobactams	<p>In these compounds, the b-lactam ring is alone and not fused to another ring.</p>	
Cephalosporins	<p>They possess a cephem nucleus to which 2 side chains are linked: one esterifies the carbamate group (R1) and the other is linked to the nucleus (R3).</p>	

Carbapenems	They are structurally very similar to the penicillins, but the sulphur atom of the structure has been replaced by a carbon atom.	
Anthracyclines	They are structurally glycosylated tetracyclines.	
Aminoglycosides	Consists of 2 or more amino sugars joined by a glycoside linkage to a hexose nucleus of the drug.	

Basics and Mechanisms of Antibiotics Adsorption

Adsorption is a surface event that generally happens in the interface of two different phases including solid-liquid, solid-gas, liquid-liquid, and liquid-gas [18]. From the thermodynamic feasibility and interaction natures points of views adsorption process can be categorized in two chemisorption and physisorption classes. In chemisorption, a strong interaction exists among adsorbent and the adsorbate and generally chemical bonds are formed between them. Chemisorption happens in a vast range of temperatures and its efficiency improves with increasing of temperature [19]. However, in physisorption, weak interactions including hydrogen bonding, van der waals forces, and π - π interactions contributes to the adsorption of adsorbate on the surface of adsorbent and no chemical bonds created between them. Physisorption is usually a multi-layer process and has better efficiency in lower temperatures. The adsorption enthalpy changes (ΔH_{ad}) for chemisorption and physisorption processes are in the ranges of 40-400 and 20-40 kJ/mol respectively. Various methods are available for investigating the adsorption mechanism such as density functional theory calculations, Fourier transform infrared spectrometry (FTIR), and X-ray photoelectron spectroscopy (XPS). As an example, Gu et al. [20] used a magnetic biochar for the removal of oxytetracycline. In their study, the adsorption mechanism was scrutinized by comparing the FTIR and XPS spectrums of the adsorbate before and after adsorption of oxytetracycline. In fact, after adsorption of oxytetracycline on the surface of magnetic biochar new peaks have emerged in the spectrums and most of the primitive peaks

experienced a tangible shift both findings indicated a chemisorption process. In other research [3], the performance of a biochar-Fe/Ce nanocomposite for the ampicillin removal was checked out and the adsorption mechanism was scrutinized by calculating thermodynamic parameters the results showed ΔH_{ad} is -33.12 kJ/mol that indicated ampicillin interaction with the adsorbent surface is carried out through a physisorption process. In another study by Afzal et al. [13] a composite of chitosan and biochar hydrogel beads was employed for the adsorptive removal of ciprofloxacin. Their kinetic results with FTIR data suggested the adsorption mechanism is simultaneously involved by physisorption and chemisorption and three different pathways including hydrogen bonding, π - π and hydrophobic interactions contribute to the adsorption process.

Parameters Influencing Adsorption Efficiency

In the adsorption technique, several factors including pH, temperature, adsorbent dosage, and initial concentration can play a key role in increasing the removal percentage of antibiotics. To develop novel adsorbents with relatively higher adsorption capacity for antibiotics removal, it is helpful to look more precisely into the mechanisms by which experimental variables affected their removal efficiency. In this respect, the effects of important factors influencing the antibiotics removal percentage will be discussed in the following [21].

Solution pH

pH is the most important factor that can highly influence the removal capacity of an adsorptive system because the surface charge of the employed adsorbent and also the speciation of the purposed antibiotic are related to it. The adsorption process efficiency is directly contingent on the surface chemistry of adsorbent and contaminants. On the one hand, antibiotics are generally organic compounds with several ionizable functional groups in their molecular structures and as a consequence, they can exist in various forms such as anions, cations, zwitterions and neutral molecules depending on the solution pH. On the other hand, the surface charge and the degree of dissociation of the available functional groups on the active sites of the adsorbent are also pertinent to it [1].

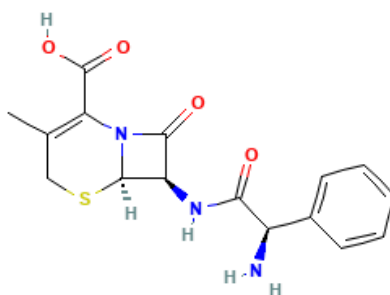


Fig. 2. Chemical structure of cefalexin

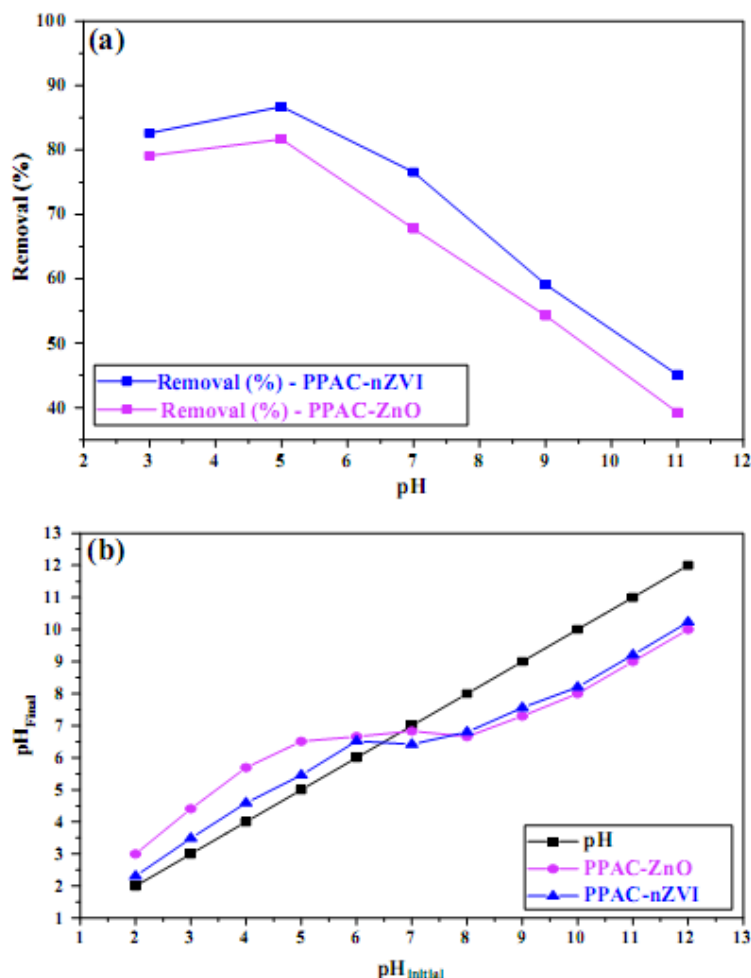


Fig. 3. The effect of solution pH on the CEX removal by PPAC-ZnO and PPAC-nZVI (initial concentration = 50 mg L⁻¹, dose = 0.75 g L⁻¹, and contact time = 30 min) (a) and pH_{Hpzc} of PPAC-ZnO and PPAC-nZVI (b). [40]

In other words, pH can mainly influence the efficiency of an adsorptive removal system via electrostatic interactions. As an example, Rashtbari et al. [2] synthesized two adsorbents including activated carbon coated with zinc oxide derived from pomegranate peel (PPAC-ZnO) and activated carbon coated with NZVI (nanoscale zero valent iron) nanoparticles derived from pomegranate peel (PPAC-nZVI) for the removal of cefalexin (Fig.2.). The influence of pH on removal efficiency in their study is shown in Fig.3. As can be seen, both adsorbents exhibited the highest removal percentage at pH= 5 with 86.73% and 81.64% efficiencies for PPAC-nZVI and PPAC-ZnO respectively. The increase in pH to 11 causes reduction in removal efficiency to 45.08% and 39.25% for PPAC-nZVI and PPAC-ZnO respectively. Thus, the lowest and the highest removal were documented for pH values equal to 11 and 5. The pH_{Hpzc} values were equal to 6.83 and 6.42 for PPAC-ZnO and PPAC-nZVI, respectively. Cefalexin (Fig. 2.) possesses an amine group in its side chain as well as a carboxyl group. Cefalexin features two $PKa_1 = 2.56$

and $PK_{a2} = 6.88$ that are in anion form in $pH = 6.88$ and in cation form in pH values below 2.56 and they are in molecular or charge-free forms in pH values between PK_{a1} and PK_{a2} amounts for the reason that the protons of the functional groups are lost. In basic pH values, cefalexin molecules are dissolved in their anion forms. In addition, pH_{pzc} of the adsorbent's surface is surrounded by the carboxylic factors containing proton and H^+ ion and such conditions cause an increase in positive charge of the composite surface. In pH values higher than pH_{pzc} , the functional groups on the composite surface lose proton in the presence of OH^- ions hence they will have more negative charges as a result of which in pH values lower than pH_{pzc} , the majority of dominant cefalexin species feature negative charges and a little positive charge in the solution; whereas, in this pH domain, the adsorbent's surface takes positive charges. So, the electrostatic attraction between the negatively charged cephalixin molecules and positive adsorbent surface causes an increase in the adsorption output following which the adsorbent's surface will be negatively charged due to the high concentration of OH^- ions when the pH of the solution is increased upon reaching values about 11 hence the efficiency of adsorption process is subsequently reduced.

Temperature

Temperature plays a crucial role in the adsorption rate and dye equilibrium uptake. The effect of temperature on the adsorption efficiency depends on the thermodynamic properties of the system. In the case of endothermic systems, the removal percentage enhances significantly by increasing the temperature because the required energy or heat for the implementation of the process will be supplied from the environmental heat more conveniently at higher temperatures. For exothermic systems, on the other hand, the adsorption process is more favorable at lower temperatures because the heat resulting from the interaction of antibiotic with the adsorbent is hardly conveyed to the environment at high temperatures. As an example, Abdelfatah et al [3]. synthesized a green composite of reduced graphene oxide and nZVI for the adsorptive removal of doxycycline. They scrutinized the thermodynamic of the adsorption process and the negative values of enthalpy changes (ΔH) indicated the exothermic nature of doxycycline interaction with the proposed adsorbent. They also investigated the influence of temperature on the removal efficiency and the obtained results are shown in Fig. 4a. As can be seen and also was expected by increasing of temperature the removal percentage declined significantly. In another study by Shafaati et al. [5] a composite of chitosan and magnetic graphene oxide was synthesized and its performance for removal of rifampicin was investigated. Their thermodynamic studies showed the adsorption process is endothermic due to the obtained positive values of ΔH . The impact of temperature on the removal capacity at different time intervals were also checked out and the archived results are exhibited in Fig. 4b. As it is clear by temperature rising the removal efficiency enhances remarkably. It should be noted that adsorbents with high removal efficiencies at the room temperature and low impressment from temperature are more desirable because of the repeatability and simplicity of the work.

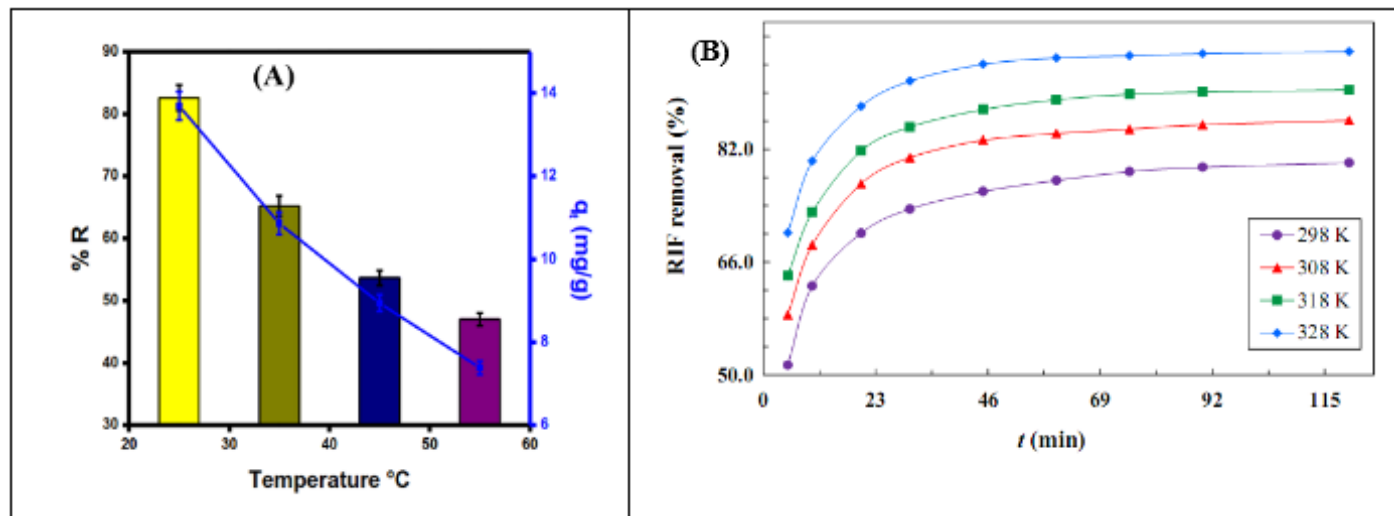


Fig 4. The effect of temperature on the removal efficiency of doxycycline (A) and rifampicin (B)

Adsorbent Dosage and Initial Concentration

One of the factors that play a key role in the removal efficiency is the amount of utilized adsorbent. Generally, removal percentages enhanced tangibly by increasing the amount of adsorbent because more binding sites for the adsorption of adsorbate are available at higher doses of adsorbent [4]. However, using large amounts of adsorbent is not preferable because of economic aspects. In this respect, developing adsorbents with higher binding sites, specific surface area, porosity, and consequently better adsorption capacity is of great importance. A similar trend is also observed in the case of initial concentration of antibiotics. Generally, the removal percentage was reported to decrease proportionally with increased amounts of adsorbed antibiotic by increasing the initial concentration [15]. This phenomenon is usually observed because the adsorbent has finite binding sites on its surface for the antibiotic adsorption and the binding sites will be occupied rapidly by the adsorbate molecules with increasing the antibiotic concentration. Hence there is no further place for interacting with other adsorbate molecules. Moreover, the selectivity of the adsorbent is also important because the matrix of industrial, municipal and hospital wastewaters are very complicated and is composed of various species. Thus, if the adsorbent has no selectivity, other molecules can also occupy the binding sites and consequently, the adsorbent performance will be very poor in the effluents [19]. In this respect, adsorbents with higher adsorption capacity and selectivity have better performance in specimens with higher antibiotic concentrations in the presence of other species [21].

Future Perspectives

Generally, the selection of a natural based adsorbent that is not harmful itself for the environment and its production in large scale has a great reproducibility and also high selectivity is highly recommended.

Conclusions

Antibiotics are one of the most commonly prescribed medicinal compounds worldwide. However, their widespread use has led to their emergence as a major environmental contaminant. The presence of antibiotics in environmental matrices poses a threat not only to human health but also to other living organisms and the environment as a whole. It is estimated that the amount of antibiotics utilized globally each year is between 1×10^5 to 2×10^5 tons. The removal of antibiotics from the environment is of utmost importance. This review study aims to provide a comprehensive and critical look at the adsorption-based methods for the removal of antibiotics from different chemical families. Furthermore, this study discusses the effects of various parameters that can influence the removal capacity, such as adsorbent dosage, temperature, initial concentration, solution pH, and more. Adsorption-based methods involve the use of an adsorbent material to remove antibiotics from a solution. The adsorbent material can be in the form of activated carbon, zeolites, or other materials. The adsorption process is based on the principle that the adsorbent material has a high affinity for the target antibiotic compound. As a result, the antibiotic molecule is attracted to and binds with the adsorbent material, thus removing it from the solution. The adsorption capacity of an adsorbent material depends on various factors, including its surface area, pore size distribution, and functional groups. In addition, the removal efficiency of antibiotics can be influenced by several parameters such as adsorbent dosage, temperature, initial concentration, solution pH, and contact time. Adsorbent dosage refers to the amount of adsorbent material used for a specific volume of solution. An increase in adsorbent dosage leads to an increase in the removal efficiency of antibiotics. However, excessive adsorbent dosage can lead to a decrease in the removal efficiency due to competition for adsorption sites. Temperature also plays a crucial role in the adsorption process. An increase in temperature leads to an increase in the rate of adsorption due to enhanced molecular motion. However, excessively high temperatures can lead to desorption of the adsorbed antibiotic molecules. The initial concentration of antibiotics in a solution also influences the removal efficiency. A higher initial concentration of antibiotics leads to a decrease in removal efficiency due to saturation of the adsorption sites. Solution pH is another crucial parameter that influences the removal efficiency of antibiotics. The optimal pH range for adsorption varies depending on the type of antibiotic and adsorbent material used. In general, acidic conditions favor the adsorption of antibiotics with basic functional groups, while basic conditions favor the adsorption of antibiotics with acidic functional groups. In conclusion, adsorption-based methods are effective for the removal of antibiotics from environmental matrices. The removal efficiency can be influenced by various parameters such as adsorbent dosage, temperature, initial concentration, solution pH, and contact time. Therefore, it is crucial to optimize these parameters for each specific case to achieve maximum removal efficiency. Furthermore, future studies should focus on developing new adsorbent materials with higher adsorption capacity and selectivity to enhance the removal percentage of antibiotics from environmental matrices.

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