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Nanotechnologies - A Modern Approach against the Development of Bacterial Resistance

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Introduction

Antibiotics play an essential role both in human medicine (being used both for treating bacterial infections and prophylactically in case of different surgical interventions) and veterinary sector, to treat infections and maintain health and productivity. Huge amounts of antibiotics have been also used as growth promoters in zootechny and aquaculture [1-3]. With the introduction of penicillin as an efficient drug in the treatment of bacterial infections, the 1940-1962 period is recognized as the "golden age of antibiotics". Over the years, the effectiveness of the first commercially available antibiotics has been weakened first by the native capability of microbes to evolve and adapt so that they can survive in the presence of antibiotics and secondly by the enhancement of this natural phenomenon, triggered by the misuse and overuse of antibiotics both in human and veterinary sectors [4]. Unfortunately, Antimicrobial Resistance (AMR) was not a matter of concern as new generations of antibiotics were discovered and developed, either by synthesizing new ones or by modifying existing ones. Unfortunately, the public health sector has now reached a critical juncture, confronting these days with a major threats [5-7]. Precisely, US Centre of Disease Control and Prevention estimated that more than 2.8 million infections are antibiotic-resistant causing more than 35,000 deaths each year in USA, while in EU/EEA approximately 33.000 deaths are associated with infections caused by antibiotic-resistant bacteria [8,9]. The antibiotic therapies lose their effectiveness leading to persistent infections and increased risks of infection spread, as well as high morbidity and mortality rates [10]. Considering the severity of the issue, World Health Organization (WHO) declared AMR as one of the three major threats to human health [11].

Until recently, drugs were not considered pollutants, even though the first studies of their presence in aquatic environment were reported since longtime [5]. The antibiotics release in the environment has influenced over the years

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the quality of ground, surface and drinking water as well as that of sediments. As described by WHO, AMR is selected when microorganisms are being exposed to low levels of antimicrobial drugs, as it is the case when antimicrobials or their metabolites are reaching the water bodies. The ignorance of considering antibiotics as contaminants has therefore had a major contribution to what seems to be now a one health problem, a clear relationship between AMR and the occurrence of pharmaceuticals in the environment being clearly established [6].

A key factor in the fight against AMR is the recognition of the factors and sources responsible for the occurrence, selection and accumulation of resistance determinants and bacteria.

Sources and factors contributing to AMR

As we mentioned before antibiotic resistance occurs naturally over time, but is also accelerated by the incorrect and excessive use of antibiotics in human medicine and animal treatment, the transfer of resistant bacteria from animals to humans through direct contact or through the food chain, the release of antimicrobial substances in the environment, improper disposal of unused drugs and lack of development of new antibiotics [4].

It is estimated that only pharmaceuticals for human use number up to over 3000 different species, including antibiotics, analgesics, contraceptives and steroids, most of which being detected over time in the environment, with emphasize on sulphonamides, fluoroquinolones, macrolides, and tetracycline as the most detected antibiotic drug in the aquatic environment [12-15]. An analysis conducted to estimate the global antibiotic consumption showed that the intake rate increased by 36% between 2000 and 2010, the most prescribed and administered being broad-spectrum penicillins and cephalosporins [16].

Another source of AMR is represented by animal farms and aquaculture where antibiotics are used both as curative and preventive treatments, but also, in the past, to enhance the growth rate of animals. Antibiotics given in animal foods were also identified in municipal groundwater systems or in the soil.

Studies related to quality of wastewater generated from hospitals have shown that this sector is characterized by serious concerns related to the quality of the discharged effluents. Pathogenic bacteria as well as chemical species such as phenols, heavy metals or antibiotics are present in trace level concentrations (ng/L or μg/L), but sufficient to select for AMR [14]. For example, in the hospital effluents in Spain there have been detected 10 to 30 ng/L trimethoprim and erythromycin [17]. More recently, in Turkey, Aydin et al*.* reported a total concentration of antibiotics ranging from 21.2 to 4886 ng/L in summer and from 497 to 322.7 ng/L in winter, with azithromycin, clarithromycin, and ciprofloxacin accounting the majority [18].

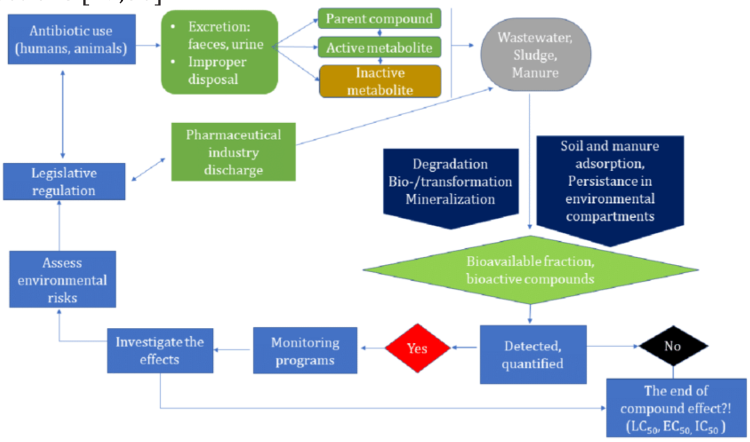
Also, the fact that urban or rural Wastewater Treatment Plants (WWTPs) are the main sources of antibiotics released in the environment is already a well-documented topic. Urban WWTPs have high loads of antibiotics, accumulating both effluents from residential areas and effluents from hospitals and industries. In Slovakia for example, one WWTP showed significant higher concentrations in February, also explained by another key factor in developing AMR, i.e., the misuse of antibiotics in viral infections [19]. Rodriguez-Mozaz et al*.* [20] recently published a study to quantify the presence of 53 antibiotics, from 10 different classes, in 13 urban WWTPs from 7 European countries. 17 out of 53 monitored antibiotics were at least once detected in effluents from WWTPs, with ciprofloxacin, azithromycin and cephalexin having the highest concentration. After the treatment in WWTPs, rivers or lakes receive the effluents so becoming the water source for the entire population. Studies in China demonstrated that rivers and lakes receive the legally treated effluent with massive loads of antibiotics [21]. Hundreds of ng/L of sulfamethoxazole, trimethoprim and erythromycin were also detected in European rivers [22].

Ecotoxicity

The presence of antibiotics and antibiotic residues in the environment can cause ecotoxicological effects by endangering the balance of ecosystems and human health [23]. The main ways in which antibiotics are released into the environment are animal, human, and manufacturing waste (from human and veterinary medicine, animal husbandry and aquaculture, industrial production, and the production of agricultural and ornamental plants) [24,25]. Due to incomplete absorption, 30-90% of administered antibiotics can be released into the environment in active form through urine and faeces having a negative impact on terrestrial and aquatic ecosystems [23,24,26]. Once in the environment, microorganisms exposed even at low concentrations of antibiotics, can acquire or be enriched in AMR [2], becoming a threat to both human and animal health. Both short-term and long-term antibiotic exposure has been shown to result in enhanced tolerance to antibiotics due to the selection of antibiotic-resistant bacteria [26]. The presence of antibiotics, such as ciprofloxacin and sulfamethoxazole, in soil and surface waters, contributes to the development and spread of resistant bacteria, fungi and biofilms in natural environments [27]. Bacteria and fungi found in soil and water are essential for accomplishing important ecological functions. Antibiotics can affect the structure and function of the ecosystem causing indirect effects on animals, higher plants and fungi through competitive interference with trophic interactions [26]. For example, the presence of antibiotics in soil has changed microbial structure, thus, reducing microbial activity (respiration, nitrification, and denitrification). In aquatic environments, antibiotics can inhibit ecosystem functions and affect organisms throughout their life cycle [28].

Different environmental conditions, such as type of soil and organism, pH, water content *etc*., have an important influence on the biological activity of antibiotics [23].

The human population may be exposed to antibiotics directly (by oral or injectable administration) or indirectly (from the environment or from accidental consumption of contaminated foods and/or water) [27]. They could cause drug hypersensitivity, irritable bowel syndrome, human growth promotion etc. [31]. The presence of antibiotic residues in the environment, by changing the microbiota structure, could have serious consequences on human health, as resistant pathogenic bacteria from soils, treatment plants, hospital effluents, municipal sewage, wastewater etc. could cause foodborne, waterborne and hospital infections [29,30].



Scheme 1: The impact of antibiotics on the environment and key steps for their monitoring and assessing/reassessing environmental risk [23].

Antibiotic residues are found in different environmental niches as mixtures, rarely in individual form. For example, compared to individual parent compounds, binary mixtures of antibiotics have a risk of environmental toxicity of 50 to 200% [23].

Consequently, the impact of antibiotics on ecosystems (Scheme 1) will cause serious pollution, modifying the ecological balance and also human health [11]. Therefore it is necessary to reduce the use of antibiotics by implementing legislative measures, targeting specific high-risk environments, such as sewage treatment plants, hospitals, *etc*. [23]. It is also necessary a solid risk assessment and continuous development of ecological chemistry and new monitoring strategies considering the benefit-risk ratio. O'Flynn, D. *et al.* recommend the implementation of more substantial drug delivery systems by improving existing legislation and increasing consumer involvement in the proper use, disposal and responsible management of antibiotics [8] and Ben, Y. *et al.* [13] proposed the establishment of a standardized guide for monitoring antibiotic residues and antibiotic resistant microorganisms in the environment, as well as a dose-response relationship between antibiotic-resistant pathogenic bacteria and various infectious diseases.

Although drug discovery should remain a priority to strengthen last-lines of defense, efforts to promote rational use of antibiotics, to put in place infection control practices, and to improve hygiene should be high on the international agenda [16]. Addressing loss of antibiotic efficiency only through new drugs discovery is an unsustainable strategy because new antibiotics are increasingly difficult and expensive to discover, and the AMR could occur very easily.

Advanced technologies for drug removal

The objective of any WWTP implies transforming wastewaters into useful aqueous systems, which can further be reused. Traditional technologies used for wastewater treatments include biological, chemical, and physical methods. Biological treatments usually use bacteria, or other organisms to transform biodegradable organic pollutants from wastewaters, into simple substances and supplementary biomass. Examples of biological methods include anaerobic digestion, aerated lagoons, activated sludge, fungal treatment, trickling filters, and stabilization [32]. Chemical treatments are an important type of technology that uses chemical substances to treat contaminants from wastewaters. Such chemical processes are catalysis, electrolysis, ion exchange, neutralization, oxidation, and reduction [33]. Physical methods on the other side do not modify the chemical structure of substances and are based on naturally occurring facts like van der Waals forces, electrical attraction, or gravity. Nevertheless, in some cases a physical state change of the substance may appear, causing agglomerates to occur. Sedimentation, coagulation, membrane treatment, adsorption, distillation, and filtration are the most known physical treatments [34].

Anyway, the previously mentioned technologies, currently used in most of the WWTPs are not effective when it comes to antibiotic removal from effluents. These being said, further treatments need to be carried out in order to remove antibiotics contaminants from wastewaters [35,36]. At present, numerous techniques are investigated for the removal of organic pollutants from wastewater, such as reduction, co-precipitation, UV photolysis/ photocatalysis, membrane filtration, ion exchange and adsorption [37].

Therefore, the following section will present several advanced technologies and their performances in antibiotics wastewater treatments.

Advanced biological treatment

When it comes to biological treatments for contaminants removal, it is mandatory to evaluate the biodegradability of the substance. To this end, it is important to first determine the biodegradability of antibiotics, before employing biological treatment, because, usually, non-biodegradable antibiotics are normally less effectively removed by biological treatments [32]. Usually, microorganisms used in the biological process are in two forms, such as suspended activated sludge and biofilms. Biofilms can be defined as the aggregates of microorganisms growing adhered on a solid material. Compared to suspended sludge, biofilms have shown considerable advantages for treating wastewaters polluted with organics, including antibiotics [38]. A comparative study investigating the biological treatment of non-antibiotic pharmaceutical ibuprofen with activated sludge and biofilms, showed that the biofilm reactor presented a higher degree of ibuprofen biodegradation (64-70 %) in comparison to the activated sludge (57-60 %) [32,39].

All these findings have shown that the highest antibiotics removal efficiency can be achieved through the combination of conventional biological processes and other water treatment technologies, which can clarify the pathway for further studies in wastewater treatments. Such technologies include biofilm-covered granular, and powder-activated carbons, which combine the benefits of both adsorption and biodegradation methods. The hard surface of granular activated carbon offers an excellent substratum for the microbial colonization and at the same time, its adsorption capacity diminishes the concentration of pollutants. Meanwhile, the attached microorganisms onto the granular activated carbons could continuously degrade the organic compounds [40,41]. Studies revealed that biofilm-covered granular activated carbon and powder activated carbon can remove a wide-ranging variety of antibiotic pollutants from wastewaters, with high efficiency and the release of organics from granular activated carbon to biofilm strengthen the biodegradation capability of the biofilm-covered granular activated carbon [42,43].

Advanced oxidation process (AOP)

Advanced oxidation processes usually imply the formation and use of the hydroxyl-free (HO•) radicals to destroy complex non-biodegradable organic pollutants from wastewaters, by oxidation. Except for the conventional oxidants, such as oxygen, ozone, and chlorine, other reagents able to produce HO• include UV-H_2O_2, Fenton's reagent, and ultrasounds. These processes require the generation of free radicals *via* chemical, photochemical, electrochemical, and photocatalytic reactions [40]. Consequently, many studies regarding photocatalytic degradation of antibiotics under UV light presented a high removal rate from wastewaters. For example, photocatalysts such as TiO_2 and ZnO are more photoactive in UV light, due to the wider bandgap, reasons for using them in antibiotics degradation under UV irradiation [32]. It has been reported that combined advanced oxidation processes are more effective when a mixture of individual agents is used. Until recently, advanced oxidation processes were not used in wastewater treatment processes, due to their high cost, but the latest studies have shown that oxidation improves the biodegradability of antibiotic wastewater. Advanced oxidation processes are advantageous to other methods of treatment because the compound that is found in wastewaters is degraded in safer compounds, rather than transferred into diffused phase or concentrated. Therefore, it prevents the production and disposal of secondary waste material [32,40].

Nanofiltration

Nanofiltration (NF) proved to be an effective method used for removal of low molecular weight organics in wastewater treatments. The mechanism of action can be roughly classified in two types of nanofiltration: adsorption of contaminants with strong hydrogen-bonding characteristics to the membrane or steady-state rejection due to electrostatic forces, steric effects *etc*. [44]. Koyuncu *et al.* investigated the removal of antibiotics and hormones using hydrophilic NF membranes (MWCO = 200-300 Da) with emphasis both on the effects of solution chemistry, salinity, or organic loadings and how each drug class influence the removal of the other one. Tetracycline showed the highest adsorption affinity compared to sulphonamides or hormones. Also, hormones rejection significantly increased when antibiotics were added in the test solution. Overall removal efficiency increased with the molecular weight of the drug, reaching a maximum of 95% for drugs with molecular weights larger than 300 Da [45].

Adsorption

Among the aforementioned wastewater treatment technologies, researchers have focused also on finding alternative and potentially more effective methods for antibiotics removal. One of the most promising technique is adsorption, that is based on the porosity of adsorbents to remove organic contaminants from aqueous media [46]. Adsorption is the process that involves the accumulation of matter from a gas or liquid phase to the surface of an adsorbent, which could include physical and/or chemical adsorption. The most extensively used adsorbents for antibiotic removal include activated carbons, carbon nanotubes, bentonite, ion exchange resins, and biochar [47]. Other adsorbent materials have been used for the removal of antibiotics from aqueous systems. It was found that mesoporous and nonporous silica (SiO_2) and alumina (Al_2O_3) were used as adsorbents for the removal of ofloxacin antibiotics. Other studies investigated the adsorption of enrofloxacin on natural zeolite and it was found that the process was highly pH-dependent [48,49]. By evaluating different adsorbents, it was demonstrated that chitosan is a potential adsorbent for different organic pollutants, having a higher adsorptive capacity and combining it to photocatalysts form a hybrid or membrane structure used in wastewater treatment [32,50].

Based on the literature data, highly porous adsorbents, such as zeolites, carbon-based materials, metal-organic frameworks (MOFs), *etc*. have been investigated and proven to successfully remove antibiotics from wastewaters [51-53].

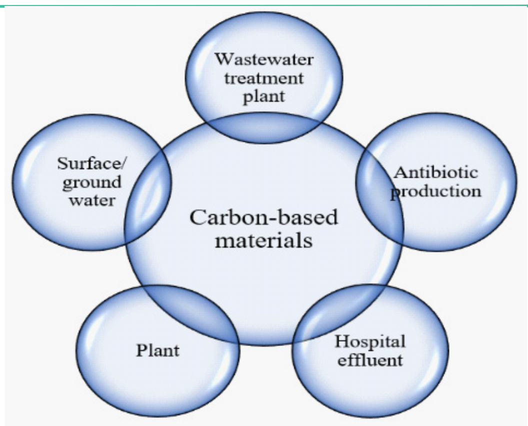
Metal-organic frameworks (MOFs)

MOFs are crystalline porous materials that contain metal ions that are bound together by organic linkers. This novel class of materials have exceptionally large surface area, are highly porous and can be easily tuneable, these characteristics making them suitable and highly efficient for adsorption of specific antibiotics from water even if their costs are still very high while the accessibility is very limited [54].

Gadipelly *et al.* [55] recently reported the adsorptive removal of ciprofloxacin hydrochloride (CIP) using an efficient adsorbent (MOF-5). Compared to adsorption capacity of charcoal (65 mg/g), MOF-5 revealed a maximum adsorption property of 98 mg/g, attributed to the electrostatic interactions between MOF-5 surface and CIP. Moreover, the adsorption of CIP was investigated using simulated pharmaceutical wastewater, and the obtained results showed a maximum adsorption capacity of 88.95 mg/g for MOF-5. The removal efficiency of CIP was of 71.6%. DeFuria and coll. [56] developed a new perfluorinated In-derived MOF (YCM-101) synthesized from $InCl_3$ and tetrafluoroterephthalic acid, and demonstrated its ability to remove tetracycline (TEC) from aqueous solution *via* π-π stacking interactions. A recent study used UiO-66 (a MOF that consists of $Zr_6O_4(OH)_4$ metal clusters and 1,4-benzenedicarboxylate organic linkers) to remove doxycycline (DOX) from aqueous environments. The results indicated that UiO-66 was able to remove nearly 90% of the initial concentration of DOX, Langmuir model being best suited. This study also investigated the possibility of recycling UiO-66 using gamma radiation, heat and/or heating under low pressure. Findings suggest that UiO-66 can be a promising cost-effective material for wastewater treatment of antibiotics [46].

Carbon-based materials

Another important class that has been widely used as highly effective adsorbents for the removal of organic pollutants from aqueous solution is represented by carbon-based materials (Scheme 2). These materials have unique properties, such as large specific surface area, high porosity, and high reaction activity [57].



Scheme 2: Adsorption of antibiotics in the environment using carbon-based materials [57].

The adsorption efficiency of aluminium-based MOF/graphite oxide (Al-MOF/GO) granule was investigated for the removal of oxytetracycline (OTC) and chlortetracycline (CTC). Al-MOF/GO granule was characterized and compared to Al-MOF/GO powder. Al-MOF/GO granule showed better stability in a wide pH range and an improved adsorption capacity of 224.60 and 240.13 $mg \cdot L^{-1}$ for OTC and CTC respectively, compared to the parent powder sample. Also, the regeneration experiment was carrying out and the findings showed that after five cycles, the adsorption capacities decreased to 24.11% and 22.31%, for OTC and CTC, respectively. These novel granules showed great water stability, high reusability, and adsorption efficiency, indicating that they can be a potential adsorbent for the removal of OTC and CTC from aqueous solutions [58]. Indherjith et al. [59] prepared polymeric nanocomposites using GO and polysulfone (GO-Psf and RGO-Psf) and evaluated the adsorption properties for the removal of CIP from aqueous solutions. The characterisation data showed superior properties for GO-PSF, because of the enhanced hydrogen bonding between GO-Psf and CIP. Compared to RGO-Psf, the maximum adsorption capacity for CIP is 82.781 mg/g for GO-Psf and 21.486 mg/g for RGO-Psf. The GO form a uniform sheet onto the polymer surface, enhancing the adsorption properties. The removal of amoxicillin (AMO) from aqueous solution was studied using natural single walled carbon nanotubes (SWCNTs) as effective adsorbents. By varying different parameters such as adsorbent dosage, initial AMO concentration, contact time and temperature, it has been demonstrated that the adsorption of AMO was strongly dependent on these parameters. The maximum adsorption data was 99.1% after 45 minutes, adsorbent dosage of 0.3 g/l, initial AMO concentration of 200 mg/l and temperature of 323 K. The Langmuir isotherm was best suited to the AMO adsorption [60].

Zeolites

Due to their worldwide abundance, natural zeolites have been widely studied as adsorbents for wastewater pollutants removal. They exhibit also the advantages of being low-cost materials and having unique ion-exchange and molecular sieving capacity [61]. Clinoptilolite (CLI) (the most abundant natural zeolite), has a 3D structure consisting of two interconnected micropore channels that have the property of exchanging cations and water molecules. This natural zeolite rich in calcium, along with magnetite-coated CLI (MAG-CLI) have been studied for their adsorption capacities towards CIP at different temperatures and at a pH of 5. Electrostatic interactions and ion-exchange reactions took place between the cationic form of CIP and negatively charged aluminosilicate lattice. The magnetite coverage (approx. 12 wt.%) acts as a protection, preventing CIP from leaching. Moreover, the antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* was investigated and the results showed strong antibacterial properties of the CIP-containing adsorbents [62]. CLI was also examined for the sorption of two tetracyclines (oxytetracycline and chlortetracycline) and two fluoroquinolones (ofloxacin and enrofloxacin) at environmentally relevant pHs, with the presence of NOM at pH 7. The results revealed that in acidic pH conditions, the maximum sorption capacities are between 7.7 (for enrofloxacin) and 11.8 mg/g (for ofloxacin). With the increase of pH, the sorption capacities decreased to 4.7, 7.8, 8.4, and 5.4 mg/g for chlortetracycline, oxytetracycline, ofloxacin, and enrofloxacin, respectively. Because at pH 9, the negatively charged species are dominant, the maximum sorption activity decreased significantly. When NOM was added, adsorption of oxytetracycline decreased, but in the case of chlortetracycline, oxytetracycline, and enrofloxacin, the adsorption effect increased. This is due to the formation of ion complexes between antibiotics and NOM. All these results demonstrated that natural zeolites can be an economically feasible means of antibiotics removal [63].

The adsorption of TEC onto zeolite (a micro-porous, aluminosilicate mineral) adsorbent was studied at 25°C in different pH values (from 2 to 9). The sorption kinetics were studied with Langmuir and Freundlich isotherm to understand the aspects of the process. Thus, the results demonstrated that when pH was increased from 2.0 to 5.0, the adsorption capacity of TEC onto zeolite increased, and after pH 5, the adsorption effect decreased significantly. Also, 90% of TEC was adsorbed in the first 45 minutes, and the adsorption equilibrium was reached in about 3 h. These results showed that adsorption of TEC onto zeolite is pH dependent [64].

Metal oxides

Although, metal oxides are a class of typical adsorbents, they continue to play a very important role in this area and attract widespread attention, due to their attractive properties, high chemical stability, adjustable shape and size and abundant surface sites [65]. Along with the absorption capacity, both TiO_2 (anatase form) and ZnO can play an important photocatalytic activity and thus, multifunctionality is assured.

Titanium dioxide (TiO_2)

Because of its excellent photocatalytic character, titanium dioxide (TiO_2), can be used as adsorbent for pollutant removal from wastewater. It has been studied for the removal of TC, and the results showed that the removal rate decreased with an increase in drug concentrations from 93.706 to 60.227%. Also, different factors like pH, adsorbent dose, the condensation of the pollutant and the temperature play an important role, influencing the adsorption rate. The best results were obtained at pH 6, where 92.853% of TC was eliminated [66]. To improve the adsorption performance of TiO_2, Wang et al. [67] designed a composite adsorbent consisting of ultralong titanium dioxide/carbon nanotubes. Three different categories of antibiotics were used in this study: TC, ofloxacin (OFO) and norfloxacin (NFO). Compared with single TiO_2, the adsorption capacities of TiO_2/carbon nanotubes have been greatly enhanced reaching 240 mg/g for TC, 232 mg/g for OFO, and 190 mg/g for NFO, respectively). TiO_2 nanotube/reduced graphene oxide (rGO-TON) hydrogel was synthesized by Zhuang et al. [68] in order to demonstrate the enhanced adsorption and regeneration activity towards CIP. Neat rGO and P25 nanotube/rGO hydrogel were used for comparison. The obtained values for adsorption of CIP were 178.6 mg/g, 181.8 mg/g, and 108.7 mg/g for rGO, rGO-TON, and rGO-P25, respectively. For the regeneration study, after five cycles, the adsorption capacity of rGO-TON and rGO-P25 has little reduced, compared to rGO where the adsorption of CIP decreases to below 100 mg/g.

Zinc oxide (ZnO)

Pistachio shell powder coated with ZnO nanoparticles (CPS) was analysed for simultaneous adsorption of TEC, AMO, and CIP. Functionalization of pistachio shell with ZnO improved surface and structural characteristics of CPS. The Fruendlich model was better suited for the adsorption of TEC and CIP, but the Langmuir model produced a better fit to the AMO adsorption. The maximum adsorption capacities of CPS were of 132.240 mg/g for AMO, 98.717 mg/g for TEC and 92.450 mg/g for CIP. These results showed that CPS can be a highly efficient adsorbents for wastewater antibiotics [69].

Conclusion

AMR is a current threat which affects many countries and regions, including EU countries, US but also Asian and African countries. The drug resistance index is directly related to the degree of well-being, but also with the habits and lifestyle. Antibiotics misuse and abuse are considered determinant factors for AMR emergence and spread and regulatory measures need to be taken as soon as possible. Supplementary, solutions related to the removal of agents generating or contributing to the development of AMR are starting to be developed and some of them include nanotechnology. The nanotechnological approaches involve pure adsorption, degradation, or their mixture. Different materials are already used in antibiotics removal. A major factor affecting the efficiency is related to the surface and thus nanomaterials are remarkable candidates able to assure high specific surface area and among these materials TiO2, ZnO, C-based materials, zeolites, MOFs are just some of the most promising of them. If several materials, such as zeolites, which are natural materials and are available in large quantities and are cheap, other types of materials are difficult to be obtained and more expensive, as is the case of different MOFs. Certainly, considering the urge of implementing regulations regarding antibiotics removal, new improvements are expected by combining different mechanisms of removal – absorption and/or degradation.

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