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Carbon-Based Materials (CBMs) for Determination and Remediation of Antimicrobials in Different Substrates: Wastewater and Infant Foods as Examples

Ahmed El-Gendy, Ahmed S. El-Shafie, Ahmed Issa, Saeed Al-Meer, Khalid Al-Saad and Marwa El-Azazy

Abstract

The widespread use of antimicrobials within either a therapeutic or a veterinary rehearsal has resulted in a crisis on the long run. New strains of antimicrobial-resistant microorganisms have appeared. Contamination of water with pharmaceutically active materials is becoming a fact! and efficacy of wastewater treatment plants is a question. Adsorption is a promising technique for wastewater treatment. Carbon-based materials are among the most commonly used adsorbents for remediation purposes. Food production and commercialization are posing rigorous regulations. In this concern, almost all authoritarian societies are setting up standards for the maximum residue levels permissible in raw and processed food. Among these products is infant foods. The current trend is to use carbon-based and recycled from agricultural wastes, which can selectively remove target antimicrobials. Nanoparticles are among the most commonly used materials. With the enormous amount of data generated from an analytical process, there is a need for a powerful data processing technique. Factorial designs play an important role in not only minimizing the number of experimental runs, and hence saving chemicals, resources, and reducing waste but also, they serve to improve the sensitivity and selectivity, the most important analytical outcomes.

Keywords: pharmaceutically active materials (PhAMs), wastewater treatment, adsorption, carbon-based materials (CBMs), infant food, detection, factorial designs

1. Introduction

Drugs and pharmaceutically active materials (PhAMs) represent an enormous category of chemicals that include all materials with therapeutic effects (e.g., drugs that can be further classified according to their chemical structures, biological activities, and mechanism of action), cosmetics, supplementary and dietary products, personal care products (PCPs), X-rays contrast media, etc. Daily use of PhAMs is then becoming a fact. As per the Organization for Economic Co-operation

and Development (OECD) report, in 2017, the expenditure on retail pharmaceuticals per capita was the highest in USA and averaged 564 \$/person among the OECD countries [1].

It is noteworthy to mention that 75% of this amount was devoted to prescription drugs. With the increased awareness with health and health standards, the consumption of PhAMs is also escalating. As per FDA's (USA Food and Drug Administration) Center for Drug Evaluation and Research's (CDER) annual report, 59 novel drugs were approved in 2018, compared to 48 drugs in 2019. Of course, these approvals are associated with many new formulations being available for the consumer in the market [2, 3].

Representing a significant category of aquatic pollutants, PhAMs are usually released into the aquatic systems from different sources, including but not limited to: the effluents of the manufacturing sites and hospitals, illegal disposal, veterinary applications, and landfill leachate. The daily use by humans and the subsequent conversion of PhAMs into various metabolites with variable chemical structures is also a major source. The fate of these metabolites, and probably their parent drug compound, is usually the wastewater [4–8].

Antimicrobials (antibiotics, antifungals, antiseptics, antivirals, etc.) are also an enormous category of pharmaceuticals used mainly in the treatment and control of infectious diseases. Having unquestionable benefits for human and animal health, their use is becoming indispensable. However, *nothing is absolute!* The pervasive use of antimicrobials within either a therapeutic or a veterinary rehearsal (mainly antibiotics) especially in developing countries where medicine is usually dispensed as OTC (over the counter, non-prescription) drug has resulted in a crisis in the long run. Moreover, the excessive release of antibiotics into the surface and wastewater with ubiquitous concentrations reflects the magnitude of the problem [9]. New strains of antimicrobial-resistant microorganisms have appeared. These breeds are no longer responding to any medication, an issue that exaggerates the problem especially with the sluggish development of new drugs and therapeutics [10–13].

Figure 1 shows a schematic representation of the subcategories of antibiotics and their fate in the environment.

Antimicrobials can be further classified according to their chemical structures into subcategories; for example, antibiotics can be classified into subclasses such

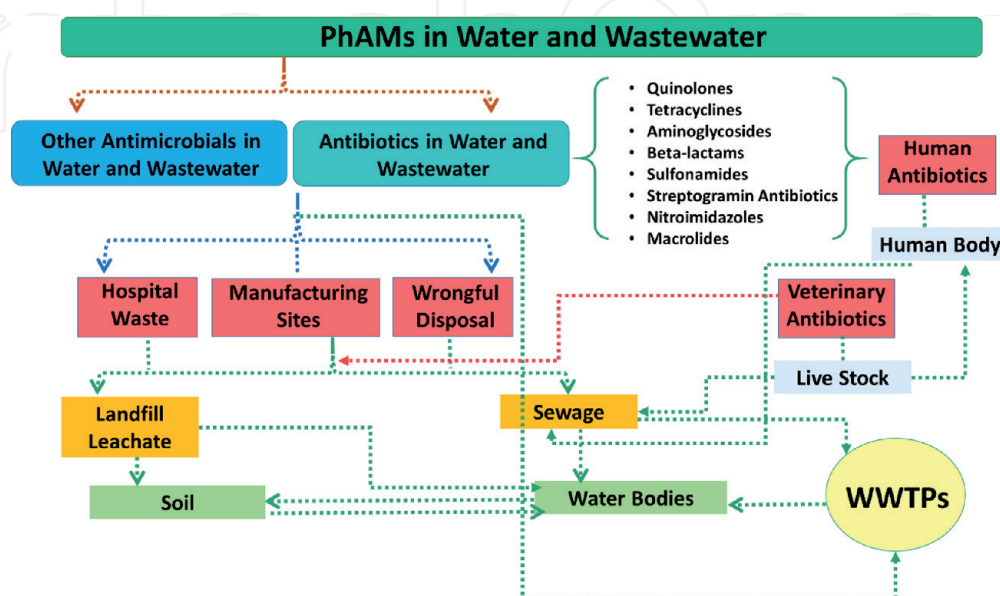


Figure 1.
Schematic representation of categories of antibiotics and their routes in the environment.

as quinolones and fluoroquinolones, tetracyclines, aminoglycosides, β -lactams, sulfonamides, streptogramin antibiotics, nitroimidazoles, and macrolides [14]. Due to this variable chemical structure, removal of this category of pollutants is an intricate task. Several approaches exist in literature for the remediation of wastewater samples from antimicrobials and their metabolites. Similarly, many techniques were described to detect anti-infective agents in foods and dietary supplements.

2. Chapter taxonomy

Throughout the following subsections, the discussion will be focused on applications of carbon-based materials (CBMs) for the detection of antimicrobials in food products, especially baby foods, as well as the remediation of wastewaters from antimicrobials. Though the aim is to survey the use of CBMs in the literature as a removal approach, a comparison between CBMs and other materials/techniques used will be useful in terms of evaluating their removal efficiency. Special attention will be paid to the methods conducted via the use of factorial designs and response surface methodological approaches.

3. Pharmaceutically active materials (PhAMs) in water and wastewater: frequency, fate, health risks, regulatory concerns, and removal

3.1 Occurrences and fate

As previously mentioned, PhAMs intimidate the water systems from different sources. Contaminated water bodies included wastewater as well as drinking water. Reported concentrations were in the range of parts-per-trillion (*ppt*) up to parts-per-billion (*ppb*), and included locations all over the world [15–21]. Higher concentrations, up to $\mu\text{g/L}$, were also reported for more than 160 drug species and PhAMs [9, 22]. In a comprehensive review prepared by Verlicchi et al. [16], the risk quotient (RQ) of 51 PhAMs was screened and assessed. Out of the investigated PhAMs, it was found that 14 compounds represent a high risk to the environment. The list included seven antibiotics from different subclasses (erythromycin, azithromycin, clarithromycin, tetracycline, ofloxacin, amoxicillin, and sulfamethoxazole), representing 50% of the high-risk PhAMs. The reminder of the list included antipsychotics, lipid-regulating, and anti-inflammatory drugs. Yet, 19 PhAMs were of a medium risk, and this time the list included eight antimicrobials (penicillin G, sulfadiazine, cefotaxime, enoxacin, trimethoprim, doxycycline, roxithromycin, and metronidazole), representing around 42% of the reported list. For antimicrobials, concentrations ranged between 0.001 and 32 $\mu\text{g/L}$, with the highest absolute and highest average concentrations being reported for ofloxacin and sulfadiazine/ofloxacin, respectively. Antifungals also had their share and clotrimazole was reported with a concentration of 0.029 $\mu\text{g/L}$ [16].

The presence of these concentrations in wastewater as well as drinking water is raising several apprehensions about the competency of wastewater treatment plants (WWTPs) and the implemented remediation techniques. These concerns might be resolved when it is comprehended that residues of undegradable PhAMs reach the WWTPs through the urban wastewater compilation structures. The positive point is that some of these compounds might be completely degradable and can be effectually removed; however, others, possessing variable chemical structures with different physical, biological, and chemical properties, may not.

These compounds being widely variable in terms of hydrophobicity, polarity, solubility, volatility, absorbability, and binding abilities, as well as biodegradability can get through to the WWTPs even at very low concentrations [23–26]. The intricate task in removing PhAMs, therefore, stems from their properties. The majority of these materials possess acidic/basic functional groups, are of high polarity with high solubility, and cannot be easily degraded, or hydrolyzed. Yet, and in comparison to other contaminants (e.g., dyes/pigments, pesticides), PhAMs could be classified as *persistent* [27, 28].

Figure 1 shows a representation of the presence of antibiotics (human and veterinary) in the environment, and their routes until they reach the aquatic environments and WWTPs.

3.2 Health risks

The consequences of the existence of the PhAMs either in waste and drinking water or even in WWTPs is still indistinct. However, what is well understood is that the impact in the long run extends to human's and animal's health, the aquatic environment, and eventually the ecosystem. This effect is greatly dependent on the released dose of the PhAMs as well as their pharmacological effects. The issue becomes of concern when we know that the metabolites might be of a higher risk compared to the parent drug compound.

These effects and upon protracted exposure to PhAMs above the permissible limits include for example intoxication in human beings (e.g., the inundated enzyme-substrate relationship following long-term exposure to analgesics might result in elevated plasma concentrations and hence toxicity). Other adverse effects include somatic abnormalities, allergies, lung diseases, and hormonal disruption (e.g., in case of hormones, the adverse effects might instigate cancer following the destruction of DNA) [24, 29–31].

Moreover, the toxicity of the aquatic environment indirectly influences the human health. At the aquatic level, the metabolic mechanisms of aquatic microorganisms are affected. At the microbial level, microorganisms, upon prolonged exposure to anti-infectives, for example, become more tolerant and new strains, which cannot be cured using the conventional antimicrobials, are now in the scene. Influences include impaired reproduction, adversative effects on movement, and metabolism in mussels. Since PhAMs are not the only species released into the receiving aquatic bodies, adverse synergetic interactions between PhAMs and other contaminants should be expected [32–34].

3.3 Regulations and roles of regulatory bodies

The following few paragraphs will focus on the regulatory measures taken by the regulatory bodies and some countries to control the release of PhAMs, especially human drugs, in aquatic environments. Many countries have executed the environmental risk assessment (ERA) measures for the regulation of human PhAMs. Taking USA as an example, the National Environmental Policy Act of 1969 (NEPA) 21 C.F.R. 25.15, 40 C.F.R. 1508, necessitates all concerned organizations, for example, the U.S. EPA (Environmental Protection Agency) and the U.S. FDA, to implement the following measures:

- Assess the environmental influences of their actions,
- Perform an environmental assessment (EA),

- Create an environmental impact statement (EIS).

Consequently, any application to file a new drug to the US FDA requires the applicant to submit an EA or requires an entitlement for categorical exclusion. The latter would be approved in case the filed substance will not increase the concentration of an “active moiety”; or it will increase the concentration of this moiety, but the estimated concentration of this moiety as it reaches the aquatic body (entrance point) is below 1 ppb; or the filed material will neither change the distribution of the substance, nor its metabolites or degradation products [35]. In Canada, however, a priority substance list (PSL) has been founded and priority is given to the assessment of the toxicity of the PhAMs [36–38].

As per US FDA guidelines, and in order to estimate the expected introduction concentration (EIC) of a substance at the point of entry to the aquatic body, the following equation should be used:

$$\text{EIC-Aquatic (ppb)} = A * B * C * D \tag{1}$$

where,

A is the amount produced of the PhAM annually—as an active moiety—in kilograms and designated for direct use;

B is the L^{-1}/day entering the publicly owned treatment works (POTWs);

C is the conversion factor (1 year/365 days); and

D is the conversion factor ($10^9 \mu\text{g}/\text{kg}$)

This equation was established assuming the following:

- No metabolism is taking place,
- All PhAMs manufactured annually are consumed and enter the POTWs,
- The use of the produced PhAMs happens thru the US and depends on the population and quantity of wastewater produced.

The European Union (EU), and on the other hand, has created two lists: one is a priority list, which includes 45 PhAMs where the environmental quality standards (EQS) have to be held in the highest regard for the disposal of these materials into the aquatic environments. The other list is a “watch-list” that compromises eight PhAMs, for which the risk to the aquatic environment needs to be investigated and verified [39]. The second list included antimicrobials, mainly antibiotics (azithromycin). Two other antibiotics, amoxicillin and ciprofloxacin, were also included in the same list but with different justifications. As per the commission, new “eco-toxicological” data were obtained for clarithromycin and azithromycin. **Table 1** shows the antimicrobials included in the watch-list, their analytical method of detection, and the maximum acceptable method detection limit (ng/L).

3.4 Water and wastewater treatment approaches

3.4.1 Classification of remediation approaches

Surveying the literature shows that different approaches have been reported for remediation of water and wastewater from PhAMs [24]. In general, wastewater treatment technologies can be categorized into *chemical* (e.g., ion exchange,

Name of the antimicrobial [*]	Indicative analytical method ^{**,***}	Maximum acceptable method detection limit (ng/L)
Macrolide antibiotics <ul style="list-style-type: none">• Erythromycin• Clarithromycin• Azithromycin	SPE—LC-MS-MS	19
Metaflumizone	LLE—LC-MS-MS or SPE—LC-MS-MS	65
Amoxicillin	SPE—LC-MS-MS	78
Ciprofloxacin	SPE—LC-MS-MS	89

^{*}CAS (Chemical Abstracts Service) and EU (European Union) numbers can be obtained from Ref. [30].
^{**}Extraction methods: LLE—liquid-liquid extraction; SPE—solid-phase extraction.
^{***}Analytical methods: GC-MS—Gas chromatography-mass spectrometry; LC-MS-MS—Liquid chromatography (tandem) triple quadrupole mass spectrometry.

Table 1.
Some of the antimicrobials included in the watch-list of substances for Union-wide monitoring as set out in Article 8b of Directive 2008/105/EC.

chlorination, coagulation, ozonation, photo- and chemical oxidation); *physical* (e.g., membrane separation, and adsorption); and *biological* (e.g., biodegradation, membrane bioreactor, and enzyme bioreactor) approaches. Sometimes, combinational approaches are used as a series of treatment steps [24, 38–45]. Each of these approaches has its pros and cons. For example, chemical and physical approaches, unless being coupled to experimental design and response surface methodological approaches, would result in the generation of toxic byproducts, and the consumption of chemicals and solvents as well as time and resources. Overall, these techniques will not be green or ecofriendly. **Figure 2** shows a classification of the commonly used approaches in wastewater treatment.

3.4.2 Adsorption as a remediation approach

As previously mentioned, removal of PhAMs in WWTPs might be inadequate and occurs partially. Implementing the traditional remediation techniques, the removal of antibiotics was incomplete (e.g., removal of β -lactams was achieved with 17–43% efficiency, macrolides with 40–46% efficiency, sulfonamides with 66–90% efficiency, and tetracyclines with 66–90% efficiency) [46]. Adsorption as a physical/chemical remediation methodology is a versatile technique that has been extensively used in water and wastewater treatment from almost all types of contaminants (dyes, heavy metals, PhAMs, etc.) [6–8, 41, 43, 46–51].

As an approach, adsorption offers several advantages, mainly the availability of candidate adsorbents at almost no cost, easy application on the large scale with no toxic byproducts being generated, and most importantly, reasonable competency. Moreover, adsorption can be used as a removal approach following biological or chemical treatments in WWTPs. Several materials have been reported in literature as adsorbents. These adsorbents might be naturally occurring (e.g., carbon adsorbents recycled from agricultural waste products) [47–51], or synthetic (e.g., microporous and mesoporous carbons synthesized using Y zeolite and synthesized mesoporous silica as hard templates) [52]. Various adsorbents were reported in literature for the removal of antibiotics [53]; for example, carbonaceous materials [54], polymeric resins [55], chitosan [56], mesoporous materials [52], and molecularly imprinted polymers (MIPs) [57]. In the following subsections, the focus will

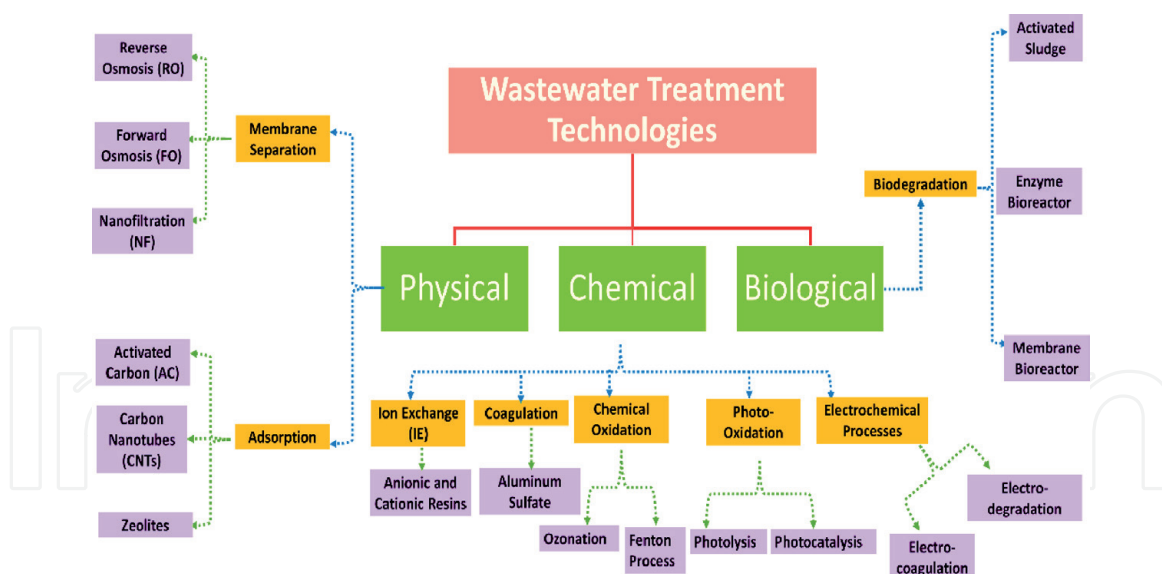


Figure 2.
Classification of wastewater treatment technologies.

be on carbon-based materials and their subcategories that are commonly used in the removal of antimicrobials.

3.4.3 Carbon-based materials (CBMs) for water and wastewater treatment

Possessing high surface area, pore size distribution, and pore volume, surface properties that enable strong interaction with the adsorbate, carbonaceous materials are among the most widely used and investigated adsorbents. In the following subsections, application of activated carbons (AC), graphene, carbon xerogels, and carbon nanotubes (CNTs), see **Figure 2**, in the treatment of water and wastewater from contaminants will be thoroughly discussed.

3.4.3.1 Activated carbons (ACs)

Activated carbon (AC) is generally a porous solid material with high surface area. With a high extent of microporosity, AC is a contemporaneous adsorbent that is widely used in water treatment on a large scale. According to the IUPAC classification, three types of materials can be recognized depending on the pore diameter: (1) microporous (pores < 2 nm diameter), (2) mesoporous (pores 2–50 nm diameter), and (3) macroporous (pores > 50 nm diameter) [58]. Activated carbon is an example of mesoporous materials, which is basically composed of a non-constant carbon framework. In reality, both micro- and mesopores exist in AC depending on the synthetic conditions.

As mentioned, AC can be obtained from agro-waste, carbonization at low temperature, and activation (physical “PA” or chemical “CA” depending on the temperature at which the activation/carbonization was conducted, and the experimental conditions where PA is usually conducted at anaerobic conditions compared to the use of inert gas in case of CA) [47–51, 53]. Adsorption capacity and efficiency are greatly dependent on the activation procedure followed and the nature of the raw material. Though CA takes place over a short period of time compared to PA, due to the usage of chemicals, CA might not be an ecofriendly approach [59, 60].

Treatment of AC using different approaches and with the purpose of increasing its adsorption efficiency for antimicrobials or even using it without activation has been the subject of lots of investigations. Treatment procedures included loading of

magnetite nanoparticles, where for example, powdered date pits (DPs) were treated with a mixture of ferric and ferrous with a ratio of 2:1, followed by stirring at 60°C for 3 h, then neutralization using 4 M NaOH till pH 12. The mixture was washed with water several times, with methanol four times and then left to evaporate. **Figure 3** shows a picture for DPs before and after magnetization. Prepared AC was used for the removal of enrofloxacin and difloxacin from water samples. Other activation techniques included treatment with NaOH for the removal of tetracycline [61], H₃PO₄ and H₄P₂O₇-AC for the removal of ciprofloxacin [62], composites for the removal of tetracycline [63], and sulfamethoxazole [64]. Untreated AC was also applied for the removal of antibiotics; for example, non-AC produced by pyrolysis of primary paper mill sludge was used for the removal of sulfamethoxazole [65] and tetracyclines [66].

3.4.3.2 Carbon nanotubes (CNTs)

First discovered in 1991, CNTs have become a target of hundreds of investigations. Representing an enormous transition in the field of nano-products, CNTs have seen an escalating interest in applications as well as investment. With extraordinary physicochemical properties, and feasibility of surface modification, CNTs are a *trap* for many environmental pollutants. Compared to the discrete structure of ACs, CNTs possess a more compact and well-defined structure. Three types of CNTs are now known: single-walled carbon nanotubes (SWCNTs), double-walled carbon nanotubes (DWCNTs), and multi-walled carbon nanotubes (MWCNTs). As their name implies, MWCNTs, unlike SWCNTs, are basically formed of cylinders arranged coaxially with the graphitic shells being alienated at a space of 0.34 nm, and a diameter of 1 nm. Therefore, the aspect ratio of the cylinder usually surpasses 10⁵ and the CNTs are usually said to be highly directionally dependent or anisotropic. This feature, in addition to the noticeable chirality of the carbon atoms and their possible variable arrangements around the perimeter of the cylinder, the hollow structure with multiple adsorption sites, represents that of an *ideal* adsorbent [67–70]. **Figure 4** shows the possible adsorption sites in a CNT:

1. The external sites: located on the outside surface of each CNT;
2. The internal sites: the interior of individual CNT;

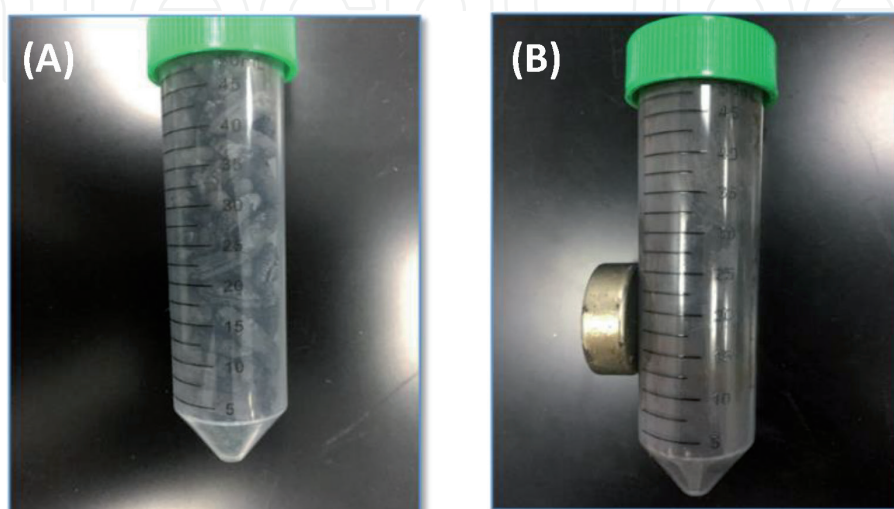


Figure 3. Date pits (DPs) (A) before and (B) after loading of magnetite. Picture was taken in our laboratory at Qatar University.

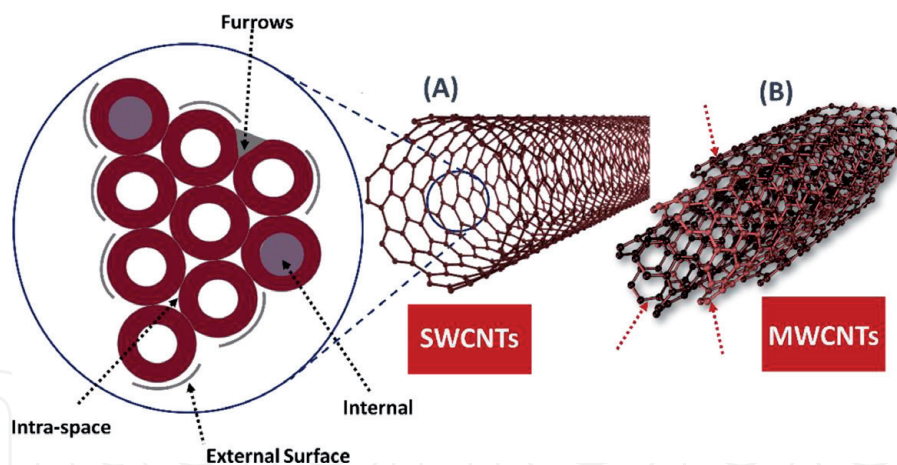


Figure 4.
(A) SWCNTs and (B) MWCNTs. The inset shows the possible adsorption sites.

3. The interstitial sites: located between the nanotubes;
4. The furrows: located across the peripheral intersection of two adjacent CNTs.

Applications of CNTs in the removal of antimicrobials has seen a major progress in the past few years. Untreated SWCNTs were used to remove tetracycline, sulfamethoxazole, and ciprofloxacin, oxytetracycline [71–74]. SWCNTs refluxed with 70% HNO_3 were used for the removal of triclosan [75]. Pristine MWCNTs were used for the removal of roxarsone [76]. Functionalization with carboxylic and hydroxyl moieties facilitated the removal of sulfapyridine [77].

3.4.3.3 Graphene-based materials

Graphene, graphene oxide (GO), and reduced graphene oxides (rGOs) are attracting a great deal of attention nowadays. Graphene is a 2D sheet in which the sp^2 -hybridized carbon atoms are arranged as a monolayer. With a large surface area, graphene can adsorb aquatic PhAMs via van der Waals or π - π electronic interactions [46, 78]. Since majority of antibiotics possess one or more cyclic component, they can be feasibly adsorbed by graphene via π - π interaction. Ciprofloxacin is among the antibiotics that have been removed using GS (graphene-soy gel) bio-composites [79]. GO was used to remove levofloxacin from aqueous solutions [80]. rGOs were similarly applied to remove sulfapyridine and sulfathiazole [81].

4. PhAMs in infant food: occurrence, health risks, regulations, and determination

4.1 Occurrence, health risks, and regulatory issues

Three categories of infant foods can be recognized: (1) infant formulas (0–6 months), (2) follow-on formulas (6–12 months), and (3) growth formulas (different ages after baby's first year and dependent on child's age). The composition of these formulas is variable and is dependent on the infant's age and nutritional needs of this age. Source of these formulas is therefore variable. Bovine milk is a major source for these formulas. Therefore, it is indispensable to ensure that these formulas are veterinary-drugs free!

The increasing understanding of the assembly of the food chain and the probability of infection of human with these resilient microorganisms either

directly or via the food chain has explained largely the spread of these species. Therefore, the process of food production and commercialization is posing more rigorous regulations nowadays. In this regard, different societies, for example Food and Drug Administration (US FDA), European Union (EU), World Health Organization (WHO) in collaboration with Food and Agriculture Organization of the United Nations (FAO) creating the FAO/WHO Codex Alimentarius Commission (CAC), are setting up standards for the maximum residue levels (MRLs) permissible in raw and processed food products of animal or poultry origin. Yet, any food product that would conform to these criteria and the preceding risk assessments cannot be banned by countries of the World Trade Organization (WTO) [82–86].

Infant foods, in specific, should be monitored with a kind of scrupulousness either statutory or non-statutory. The main apprehension is that this food is to be offered to an age group that is the most susceptible for microbial infections and the chance of spread of resistant microorganisms becomes more likely. As per EU council regulation No. 2377/90, the MRL extends to include not only the intact drugs, but their degradation products as well as their metabolites. While the MRLs are well defined for a variety of baby foods, the situation is different for meat-, milk-, poultry-based infant foods, where the EU council is implementing the zero-tolerance policy; that is, the presence of such drugs in the said foods is totally banned. Existence of such a policy necessitates the presence of a sensitive analytical technique that can determine suspected drugs at even minute concentrations [86, 87].

4.2 Determination of antimicrobials in infant foods

Few methods exist in literature for the determination of antimicrobials in infant foods with major attention being directed to fluoroquinolones and tetracyclines, few antifungals, antiseptics, and antivirals. Techniques used ranged from pressurized liquid extraction followed by solid phase extraction (SPE) and LC-fluorescence detector analysis to ultra-high-performance liquid chromatography hyphenated to tandem mass spectrometry (UHPLC-MS/MS) and salting-out assisted liquid-liquid extraction (LLE) coupled to UHPLC-MS/MS [88–92].

With the progression in analytical method development, the current trend is to use miniaturized materials, which can selectively remove the target antimicrobial. Nanoparticles (NPs) either functionalized or non-functionalized, MWCNTs, molecularly imprinted polymers (MIPs), and graphene are among the most commonly used materials. Magnetic nanoparticles (MNPs) in particular and with their large surface area, and hence the swiftness of sorption, offer a great advantage in sample treatment [93, 94]. Surveying the literature shows that applications of CBMs in sample treatment are almost absent. In one of the investigations [95], the Zr-Fe-CMNPs composites were studied for sample pretreatment. It was shown that coating of the Zr-Fe MNPs with carbon increased elution efficiency of the studied fluoroquinolones, and therefore was used for the determination of fleroxacin, norfloxacin, and ofloxacin in meat-based baby food samples.

5. Multivariate analysis

Several parameters affect the adsorption of PhAMs either from wastewater or from foods. For example, parameters such as pH, contact time, adsorbent dose, initial adsorbate concentration, and ionic strength can affect adsorption efficiency of studied adsorbents [47–51].

Yet, very few of the techniques reported in literature implemented chemometrics or factorial designs as an approach and the regular one-variable-at-time (OVAT) approach is still used. In such an approach, only one variable is investigated at a time, with almost no idea about factorial interactions and no idea on how to deal with multiple-response variables concurrently. With the enormous amount of data generated from an analytical process, the need for a powerful data processing technique is needed. Chemometrics plays an important role not only in minimalizing the number of experimental runs, and hence saving chemicals, resources, and reducing waste but also in serving to improve the sensitivity and selectivity of the methods, the most important analytical outcomes [47–51, 96–99].

As a vision, Green Analytical Chemistry (GAC) adopts 12 principles that serve to compromise between the quality of an analytical process and the conservation of environment. Achieving such a settlement is an intricate task! Using chemometrics is one aspect of such an arrangement and ensuring a sustenance of the highest safety standards—both in water and wastewater remediation and in the production of infant foods—is another aspect.

Design of Experiments (DoE) as a multivariate approach is used to screen and then optimize the experimental conditions. The design usually entails two phases: screening (where all variables that might affect the process are investigated at wider levels), then optimization (where variables that were proved to be statistically significant from phase I are re-tested at narrower levels). Both phases are accompanied by statistical analysis using analysis of variance (ANOVA) [99].

In one of the investigations, a method based on pressurized liquid (PLE) and LC with fluorescence detection (LC-FLD) was used for the determination of residues of fluoroquinolones in baby foods. Factorial design was implemented in two phases. In the screening rehearsal, a fractional-factorial design was adopted to screen the impact of four parameters on the extraction process. Statistically significant variables as per ANOVA were further optimized using the face-centered central composite design [89, 100]. Applications of other designs were also reported [101].

6. Conclusions

The literature is rich with hundreds of articles that investigate the removal of antimicrobials from water and wastewater samples. Investigations that entail the usage of CBMs such as ACs, CNTs, and the graphene family, which possess unique physicochemical properties and most importantly a high surface area, are the most prevailing. Yet, and on the other hand, very few investigations on the determination of antimicrobials in baby foods, an important concern, are available in literature. Usage of CBMs in such a rehearsal is almost absent. All in all, removal of antimicrobials from wastewater and their determination in baby foods are usually affected by a number of variables. The common approach found in literature is the one based on the investigation of one-factor-at-a-time (OFAT). Application of chemometrics is still not as expected.

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Conflict of interest

The authors declare no conflict of interest.

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