Migration and transformation routes of pharmaceutical substances in the aquatic environment

M A Kozlova¹ and N M Shchegolkova¹,²
¹ Water Problems Institute, Russian Academy of Sciences, Moscow, Russia
² Faculty of Soil Science, Lomonosov Moscow State University, Moscow, Russia

mblshok@mail.ru*, nshegolkova@mail.ru

Abstract. The paper considers the ways of migration and transformation of pharmaceutical substances in the aquatic environment. It is shown that the main source of pollution is insufficiently treated domestic wastewater. The occurrence of pharmaceutical substances is characterized by spatial and temporal variability. Some correlations in the distribution of certain groups of pharmaceuticals in water, sediments and suspensions are presented.

1. Introduction
Modern studies have significantly expanded the possibilities to determine pharmaceutical pollution in water bodies. This results primarily from the success and active development of analytical chemistry which enabled us to measure lower concentrations of pollutants in highly contaminated matrices [1].

Currently, medicine and veterinary medicine use approximately 4000 pharmaceutically active compounds which are present in many environmental objects due to their wide and long-term use [2]. The worldwide annual consumption of antibiotics is estimated at 100-200 thousand tons. Moreover, their use is increasing in all countries, including the developing ones [3]. For instance, in 2020, Russian pharmaceutical market reached the volume of 2,005 billion rubles, which is 6.1% higher than for the previous year [4].

To date, the works on the detection of pharmaceuticals (mainly antibiotics, sex hormones, non-steroidal anti-inflammatory drugs, as well as antiepileptics and antidepressants) in the environment, particularly in surface and waste waters, have been carried out in many countries, including the UK, Germany, Spain, China, Norway, Slovenia, USA, Thailand, South Korea, Japan, etc. [5].

For example, the antibiotic lincomycin was found in hospital and livestock effluents in the United States (2-6.6 mg/l). Fluoroquinolones were revealed in hospital wastewater in the USA and Portugal (2-11 mg/l), in the influent (90-1000 ng/l) and effluent from wastewater treatment plants in the USA, Portugal, and Sweden (<6-310 ng/l), as well as in surface waters, namely the Lambro river in Italy (14.36 ng/l) and the Mondego river in Portugal (79.6-119.2 ng/l). The hormone 17-estradiol was detected in rivers of different countries at concentrations of 0.6-100 ng/l, as well as in the treatment plant effluents at concentrations of 0.3 - 85 ng/l. Diclofenac (a non-steroidal anti-inflammatory drug) was found in the wastewater from treatment plants in Switzerland and Belgium at a maximum concentration of 2.4 and 1.42 mg/l, respectively, as well as in groundwater in Germany (590 ng/L), in hospital wastewater in Spain (1.9 mg/l) and Taiwan (328 ng/l), in the rivers of Luxembourg (19 ng/l), China (147 ng/l), Germany (67 ng/l), etc. [6].
Since 30 - 90% of pharmaceuticals are excreted with waste products, mainly in non-metabolized form, domestic wastewater and wastewater from agricultural enterprises (livestock, poultry and fish farms) are the main sources of pharmaceutical substances ending up in the aquatic environment. Moreover, the most common treatment facilities with activated sludge cannot sufficiently remove these compounds [7]. In addition to pharmaceutical substances used in medicine, veterinary medicines are environmentally hazardous as their active agents and decomposition products can directly enter the environment avoiding any water treatment system [8].

Knowing the concentrations of various pharmaceutical substances in the environment is essential to understand their distribution and potential environmental risks (figure 1).

**Figure 1.** The life cycle of pharmaceuticals in the environment [9].

However, there are still insufficient studies devoted to the distribution of pharmaceutical substances in the aquatic environment, bottom sediments, suspensions, etc. Additionally, under certain conditions bottom sediments may cause secondary pollution. Currently, this issue is addressed only in a few scientific works which aim to determine the correlations between multi-factor processes, such as properties of the aquatic environment (temperature, salinity, water pH, etc.), properties of bottom sediments (structure, composition, density, etc.), chemical properties of pharmaceutical substances themselves, etc. The aim of this study was to analyse the existing correlations of migration and transformation of pharmaceutical substances in the aquatic environment and to assess the role of suspended solids and bottom sediments in the distribution of these compounds.
2. Materials and methods
The research materials were scientific publications in high-ranking journals included in the Elsevier and Springer Nature databases. The articles were found with keyword searching. One of the criteria for article selection was the novelty - the publication date no later than 2010. The access to the Elsevier and Springer Nature databases was obtained within the framework of the National subscription to electronic publications and scientific information resources.

3. Results and discussion
Let us consider several major factors that can affect migration of pharmaceutical substances in water, bottom sediments and suspension.

3.1. Dilution and concentration due to spatial and temporal variability
Siedlewicz et al. [8] show that the occurrence of various antibiotics is characterized by spatial and temporal variability. The concentration of substances can increase in the autumn-winter and spring periods, i.e. during epidemiologically unfavourable months, as well as in some summer months (during the dry period), when the dilution of inadequately treated wastewater in a water body decreases naturally. The opposite situation is observed during flash floods: large water masses can significantly reduce the content of pharmaceutical substances in water bodies due to dilution. Thus, in this study, the hydrological factor of zones with a pronounced flash flood was designated as one of the basic factors changing the concentration of pharmaceuticals in water bodies.

The work by Zhou et al. [10] is also devoted to the study of hydrological factors and sorption processes. The authors considered the accumulation process of pharmaceutical substances in bottom sediments above, below and at the very discharge of domestic wastewater in the River Medway (Kent, UK). The samples were taken regularly from December 2009 to December 2010 to determine the content of 9 pharmaceuticals (propranolol, sulfamethoxazole, mebeverin, thioridazine, carbamazepine, tamoxifen, indomethacin, diclofenac and meclofenamic acid). It was noted that all compounds except sulfamethoxazole, showed 100% detection, indicating a widespread presence of such compounds in water and bottom sediment in the study area and their potential persistence. The discharge zone was found to have the highest concentrations in the water column, which is aligned with the fact that they are a point source. In addition, diclofenac, carbamazepine and meclofenamic acid proved to be the most common substances. In surface sediments, the highest concentrations were observed at the wastewater discharge site, with the exception of February 2010, when the downstream area was the most saturated with pharmaceuticals. This was caused by the high flow rate during that period, indicating the transport of pharmaceutical substances in water and their relatively slow accumulation [10].

3.2. pH and chemical composition of the aquatic environment and bottom sediments
Liang et al. [11], who analysed the samples from the mouth of the Pearl River (South China), revealed that antibiotic concentrations had large seasonal fluctuations in the water column, and not in the bottom sediments. The total organic carbon (TOC) of sediment and water pH were found to be the most important factors affecting the dynamic distribution of norfloxacin and erythromycin in water and sediment, respectively. Thus, the authors demonstrated that estuarine sediments could be a potential secondary source of pollution under changing environmental conditions.

Moreover, it was noted that hydrophobic compounds were more attracted to bottom sediments, especially those with a high content of organic carbon. Furthermore, the more suspended solids there were in the water, the more pharmaceuticals deposited and accumulated in the surface layer of the sediment [10].

3.3. Physical factors
An interesting effect was analysed by Liao et al. [12]: the effect of wind-wave disturbances on adsorption and desorption of tetracycline and sulfadimidine in water - sediment systems. During wind
waves, sediment particles are frequently dispersed in the near-surface layer of water, which contributes to adsorption and desorption of pollutants in the aquatic ecosystems. The research used microcosms including sediments and water from Lake Taihu (China) to study the adsorption and desorption of substances under various wind-wave disturbances in the shallow lake environment.

The analysis of the adsorption process showed that the concentration of tetracycline in the near-surface layer of water was rapidly decreasing, while the concentration of sulfadimidine remained almost constant. The experiments on substance desorption from bottom sediments have revealed that sulfadimidine is released better than tetracycline. These results demonstrated that the sediment particles strongly adsorb tetracycline but weakly adsorb sulfadimidine. Compared to background conditions (calm), strong wind waves led to higher concentrations of tetracycline and sulfadimidine in sediments and facilitated their migration into deeper layers of bottom sediments during adsorption. Consequently, this encouraged a greater release of analytes from sediment particles into water during desorption.

3.4. Chemical structure and properties of pharmaceutical substances
Ferreira da Silva B. et al. [13] investigated the distribution of 43 pharmaceuticals in surface waters, suspended solids and sediments in the Ebro River Basin in Northeastern Spain. The measured concentrations of suspended matter were generally higher than in the sediment samples. In terms of the distribution of pharmaceuticals, approximately 70% of the 43 measured pharmaceutical compounds were found to have been determined primarily in the aqueous phase, while the remaining 30% was found only on suspended solids and sediments.

Typically, the sorption of organic pollutants by solids (sediments, soil and suspended particles) is regulated by several processes, such as hydrophobic separation, ion exchange, complexation, and hydrogen bonding. In the case of polar and ionic pharmaceuticals, the sorption properties cannot be estimated using the traditional octanol-water partition coefficients (Kow) and organic carbon content (Koc) of the compound. It has been found that distribution can be affected by other properties, such as constant values of conjugate acids (pKa). It has been observed that compounds with base characteristics (pKa>7), such as famotidine, timolol and nadolol, show a higher tendency to bind to suspended solids. High pKa values indicate that these compounds have a positive charge at the pH of river water. Accordingly, they participate in other interactions (cations interactions, complexation, hydrogen bonds), which can affect the distribution of these compounds. In any case, sorption depends on both the properties of pharmaceuticals and suspended solids. Since a significant amount of pharmaceuticals were not detected in surface water samples, but were found associated with solid particles in suspension, the analysis of a water sample (filtration included) may not take into sufficient account the data on the presence of pharmaceuticals in the aquatic environment [13].

3.5. Photodegradation of pharmaceuticals in the aquatic environment
Photochemical degradation is likely to be an important mechanism for the degradation of many pharmaceuticals in surface waters. However, the environmental persistence of almost all of these compounds is currently unknown. There are several indications [14] that photochemical degradation may be a central factor to determine the environmental fate of pharmaceuticals and personal care products. Many of these compounds contain aromatic rings, heteroatoms, and other functional groups that can either absorb solar radiation or react with photogenerated temporary particles in natural waters (e.g. reactive oxygen species and photoexcited natural organic matter). However, some compounds also contain phenolic, nitro- and naphthoxyl groups, similar to those found in pesticides. For example, pesticides carbaryl and napropamide are known to be readily degraded by photodegradation [15] and to contain naphthoxyl chromophore which can also be found in pharmaceuticals as propranolol, naproxen, and nabumetone.

In natural waters, for some pharmaceutical substances (e.g. triclosan and diclofenac), photolysis proved to be the dominant degradation process, especially in summer. Since many pharmaceutical substances entered surface waters after active biodegradation during wastewater treatment, it can be
expected that photochemical processes in sunlit waters will play a more considerable role than biodegradation. However, some compounds can avoid photochemical degradation due to sorption by suspended particles, especially for compounds with high affinity for surfaces (e.g. tetracyclines) [14].

3.6. Bioaccumulation

As a rule, the study of pharmaceuticals is restricted to their occurrence in the aquatic environment. However, they can accumulate in aquatic organisms and plants. Wilkinson J.L. et al. [16] studied the accumulation and spatial distribution of thirteen pharmaceutical and other priority pollutants in bottom sediments, periphyton (biofilm), plants Callitriche sp. and Potamogeton sp., as well as in crustaceans amphipods (Gammarus pulex) and water snails (Bithynia tentaculata). All samples (65 pieces) were collected from the Hogsmill, Blackwater and Bourne rivers in the south of England. The remains of the studied substances were found in all bottom sediments and biota. The concentration of pollutants in biota was generally higher than in sediments. Pollutants appear to bioaccumulate differently in various biota species, which requires the development of a species-specific classification system for the dependence of bioconcentration and biota-sediment accumulation factors (BCF/BSAF).

Liu J. et al. [17] demonstrated that ten investigated pharmaceutical substances accumulated in fish tissues were in the following order: kidney > brain > liver > gills > muscles. Based on the actually dissolved concentrations of compounds in water, the bioaccumulation factors in fish tissues ranged from 3.7 to 2727.3 with sertraline mainly accumulating in the liver.

The work by Koba O. et al. [18] confirms that many compounds, except sertraline (bioaccumulation factor (BAF) is 6200), are not bioaccumulative in fish liver.

At the same time, risk assessments have shown that erythromycin can cause the most hazardous adverse health effects of the most sensitive group of algae, based on the data on acute and chronic diseases. In addition, the values of the hazard ratio of diclofenac in relation to some fishes were higher than 1 [17].

These results indicate that pharmaceuticals may pose a potential risk to aquatic organisms, especially under chronic exposure.

4. Conclusion

The issue of pharmaceutical pollution of the environment is still relevant and requires further research. Meanwhile, to assess environmental risks, it is necessary to know not only the content of pharmaceuticals in water, but also their fate (migration routes, transformation processes, possibility of natural degradation, etc.). Undoubtedly, abiotic factors strongly affect the behaviour of substances in the environment, i.e. promoting adsorption, desorption, photodegradation, etc. The nature of pharmaceuticals and their physicochemical properties frequently allow us to predict their distribution in the environment. It can be concluded that in order to obtain a comprehensive view of the distribution of these poorly studied potentially hazardous pollutants, it is necessary to classify pharmaceuticals by their sorption capacity, as well as by their ability to degrade under different conditions: aerobic and anaerobic, in dissolved or sorbed form, in the presence/absence of certain bacterial groups. Thus, to elucidate these correlations, specific laboratory studies and a publicly available special database to collect and classify these correlations are required.

It is certain that understanding such processes is of great practical importance. This type of knowledge will make it possible to recommend various techniques to treat domestic and agricultural wastewater without neglecting the actual natural and anthropogenic conditions in wastewater receivers.

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