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MINI-REVIEW

Environmental Transformation of Pharmaceutical Formulations: A Scientific Review

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Abstract

Environmental pollution caused by pharmaceuticals and their transformation products (TPs) has become an increasingly important concern, due to the increased use of pharmaceutical formulations exposed to environmental change. Considerable concerns have been raised regarding potential toxic effects of the transformation products of pharmaceutical formulations on human health. Environmental risk assessments are mostly based on one active component, which causes different ecotoxicological effects, albeit the particular component is present in the environment as a part of a multicomponent mixture with different pharmaceuticals and excipients. The purpose of this review was to present the insight and new knowledge recently obtained by studies on the risk of pharmaceutical formulations, including all contained excipients, pharmaceuticals, and their transformation products exposed to the environment. Numerous studies have shown that the level of pharmaceuticals in the environment is below toxic concentration; however, long exposure to very low concentrations can still lead to harmful concentrations in biota. Accordingly, the findings of this study are expected to highlight the existing issues of the effect of pharmaceutical formulations to the environment, including TPs, and help to determine future research directions towards accumulating the data and improving ecological risk assessment.

Environmental pollution involves the release of pharmaceuticals into water supplies, the atmosphere, and the soil causing detrimental effects on the environment. Recently, the environmental pollution caused by pharmaceuticals and their transformation products (TPs) has become a global concern, due to the continual rise in human population and the increasing use of pharmaceutical formulations. Pharmaceuticals may have long half-lives in the environment, so they can accumulate, and adversely affect human health and the environment due to their properties and toxicity even at very low concentrations. Considerable concerns have been raised regarding potential effects of the transformation of pharmaceutical formulations on human health. It has been discovered that not only active drug components are significant in terms of evaluation of ecological risk but also those compounds created as a consequence of their TPs and mixture of different excipients contained in the pharmaceutical formulation. Many studies have reviewed that pharmaceutical products and their TPs in nature can lead to various undesired consequences, with toxicological effects on human health and ecosystems (Bartrons and Penuelas 2017; Daughton 2016; Snyder and Benotti 2010). Despite the rapidly growing number of studies and reports on the presence of pharmaceuticals in the environment, the number of studies on identification, quantification, and characterisation of TPs of pharmaceuticals and excipients is still low. Advanced analytical methods have a significant role in the analysis of environmental samples with the goal of confirming their degree of pollution. Advantage is given to quick, simple, and economically profitable methods that allow for obtaining reliable results of a greater number of samples, offering a quick estimate of exposure of population to pharmaceuticals and their TPs (Gracia-Lor et al. 2010; Negreira et al. 2015). Many studies of toxicity have shown that some pharmaceuticals are found in the environment at concentrations well

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below their NOEL (No Observed Effect Level). The NOEL can be observed, but the same compounds may have the potential to cause serious adverse effects when form toxic transformation products or in mixture with excipients composed in drugs.

The European Medicines Agency requires that new pharmaceuticals undergo an environmental risk assessment during the pharmaceutical formulations development stage. Exposure assessment is conducted through the calculation of the predicted environmental concentration (PEC) if the PEC of pharmaceuticals in environment is above 0.01 µg/L (*Guideline on the Environmental Risk Assessment of Medicinal Drugs for Human Use*, 2006). In this phase of the assessment, the PEC/PNEC ratio also is calculated, where PNEC is the predicted no effect concentration. If the PEC/PNEC ratio is < 1, then it is assumed that the substance poses little environmental risk. If the PEC/PNEC ratio is > 1, then a risk is assumed and a refined risk assessment is usually performed. Some studies assess risk by comparing PECs to predicted no-effect concentrations (PNECs). A recent study showed that PEC/PNEC ratio was higher than 1 for 12 pharmaceuticals, indicating a risk to all three trophic levels of aquatic organisms (algae, invertebrate, fish). This study suggested that future environmental risk assessment should incorporate a risk–benefit analysis, an important risk-management step (Pereira et al. 2017). Second phase of the risk assessment consists of a basic investigation of potential environmental effects of the pharmaceuticals, including their TPs information pertaining to the biodegradability, photolysis, hydrolysis, and aerobic and anaerobic transformation potentials. However, it is not yet possible to assess the hazards of all TPs, including mixture interactions of pharmaceuticals and excipients in the environment due to the lack of ecotoxicity data. Ecotoxicological data on the toxicity of transformation products with a mechanism of action different from the parent compound is yet to be assessed. In addition, excipients are nonpharmacologically active but may have toxic effects on the environment.

The purpose of this review was to present the insight and new knowledge recently obtained by studies on the risk of pharmaceuticals, excipients, and their TPs posed to the environment, as well as to give recommendations in terms of research needs pertaining to these problems and improving ecological risk assessment.

Ways Pharmaceuticals Enter the Environment

In many monitoring studies around the world, the main sources and pathways of pharmaceuticals to the environment have been measured. The major pathways of these pollutants to the environment occur after excretion as a consequence of patient use, by means of waste generated from expired household pharmaceuticals, and via sewage treatment plant (Gomes et al. 2017). After excretion, pharmaceuticals are excreted into the environment in an unchanged form or as metabolites (Subedi et al. 2017; Wilkinson et al. 2017). Excreted metabolites that undergo sewage treatment lead to some inactive pharmaceuticals becoming active again (Daughton and Ternes 1999; Heberer 2002). A significant amount of pharmaceuticals in the environment comes from improper handling of unused pharmaceuticals (Evgenidou et al. 2015). Expired household pharmaceuticals often end up in wastewaters or municipal wastes. In accordance with the EU regulations, disposing of unused pharmaceuticals has been forbidden since 1994 (European Council Directive 94/67/EC). Yet, it has been established that a third of all sold pharmaceuticals in Germany, as well as approximately 25% of those sold in Austria, are disposed of with other household waste or end up in wastewaters (Vogler and de Rooij 2018). A survey showed that 17.7% of respondents dispose of expired and surplus pharmaceuticals by flushing them down the toilet. More than half of the respondents of the U.S.-made study threw medicines into wastewater, whereas only 23% of the respondents returned pharmaceuticals to the pharmacist (Bashaar et al. 2017). Research conducted in other countries has shown that unused pharmaceuticals are mostly stored in households and that they most often are thrown into municipal waste or spilled into wastewater (Tong et al. 2011; Kümmerer et al. 2009). Pharmaceuticals contained in soil and sludge can contaminate surface waters, accumulate in sediments, and/or be taken up into plant and animal tissues, and eventually the human body. Some studies indicate that several common pharmaceuticals were present in the final effluent in concentrations high enough potentially to affect ecosystems (UK Water Industry Research 2014). For example, Magdaleno et al. (2014) investigated toxicity and genotoxicity of wastewaters from the public hospital of Buenos Aires (Argentina). Toxicity assay showed that 55% of the samples were toxic (green algae *Pseudokirchneriella subcapitata*) and 40% of the samples were genotoxic (*Allium cepa* test) (Magdaleno et al. 2014). Moreover, there are many evidences on the occurrence of approximately 160 pharmaceuticals in wastewater, ground water, and soil, and some active components of pharmaceutical products also have been detected in drinking water (Jones et al. 2005; Luo et al. 2014a, b; Mompelat et al. 2009). Pharmaceutical substances can be transformed in the environment and in wastewater treatment plants by different chemical and biological mechanisms. Mechanisms of degradation/transformation of pharmaceutical formulations (active pharmaceuticals ingredients and many excipients) into the environment depend on their physical and chemical

properties. Due to the continuous presence of these substances, pharmaceuticals that accumulate in the ground and water may have an unfavourable impact on ecosystems (Daughton 2016).

Effect of Pharmaceuticals Identified in the Environment

Intensive analyses of environmental pollution by pharmaceuticals remnants have been performed in the past 10 years. The greatest attention so far has been paid to antibiotics and steroid medicines, considering that antibiotics may lead to resistance in such an environment. For steroids, an induction of oestrogen response can occur, as well as changes in reproduction and foetus development (Corcoran et al. 2010; Isidori et al. 2006; Todini 2007). In 2013, for the first time, the European Committee included the following three pharmaceuticals: an anti-inflammatory analgesic medicine (diclofenac), as well as two hormones (17 alpha-ethinyl estradiol and 17 beta estradiol) on a watch list of newly discovered pollutants that could be added to the priority list of chemicals that are known to pose a risk to ground water safety (Environmental Quality Standards Directive 2013/39/EU of the European Parliament). The lack of relevant data on the toxicity of most pharmaceuticals to aquatic organisms as well as of data pertaining to environmental concentrations of these substances logically prevents the calculation of risk quotients based on actual measurements.

Although the detected concentrations of pharmaceuticals in the environment were mostly on the level of traces (ng/L to low values of µg/L), many studies show that even such low concentrations were sufficient to cause a toxic effect (Daughton 2016; Heberer 2002; Ternes et al. 2015; Tiwari et al. 2017). The most often detected pharmaceuticals in the environment are the anti-epileptic carbamazepine, the antibiotics sulfamethoxazole, erythromycin, and trimethoprim, as well as the analgesic antipyretics ibuprofen, diclofenac, acetylsalicylic acid, and paracetamol (Heberer 2002; Yang et al. 2018). Contrary to the developed countries that have a significant amount of data on pharmaceuticals, the data on the occurrence and presence of these compounds in developing countries is rare and unsystematic. Although the effects are analysed through safety and toxicological studies, the potential impact of pharmaceuticals and their TPs on the environment, from production to use, is less known and has become a significant topic of research interest.

Degradation and Transformation of Pharmaceuticals in the Environment

In the environment, pharmaceuticals undergo numerous reactions that lead to complete or partial transformation and/or degradation of the initial compound. These changes of pharmaceuticals in the environment depend on chemical traits of the active substance and their stability under the influence of various factors, such as temperature, pH, light, humidity, interaction with other substances, etc. For example, during the oxidative water treatment or disinfection of drinking water via ozone or chlorine, pharmaceuticals can transform into toxic products. The reaction of diazepam and related benzodiazepines with chlorine produces three different products; these transformation products could be more toxic and mutagenic than the precursor drug (Carpinteiro et al. 2017). Also, during chlorine disinfection, chlorinated derivatives of triclosan might further form toxic polychlordibenzo-p-dioxin under natural sunlight (Buth et al. 2011). Several studies showed that during water chloranation, pharmaceuticals with the amino group (ranitidin, enalapril, fluoxetine, diclofenac, sumatriptan) form N-nitrosodimethylamine, which is known as a semivolatile organic chemical that is highly toxic and is a suspected human carcinogen (Shen and Andrews 2013). All of this adds to the complexity of the degradation ways of pharmaceuticals in nature. The goal of the degradation process is to remove the parent compounds only, but novel degradation processes must consider the posibilitty of TPs forming and go one step further by removing all of the potential pollutants.

Phototransformation of Pharmaceuticals

In the environment, an active substance can be degraded and transformed by means of abiotic and biotic processes. Abiotic transformations commonly are carried out via hydrolysis and photolysis (Tixier et al. 2003). The most significant way of abiotic degradation of pharmaceuticals in ground waters is direct and indirect photolysis.

Degradation/transformation under natural light is one of the most important processes in terms of defining the fate of pharmaceuticals in the environment because of the very fact that many pharmaceuticals, due to their aromatic structure, the presence of heteroatoms and other chromophores can either absorb the sunrays or react with generated reactive species in the environment. Efficiency of photochemical degradation processes of pharmaceuticals in ground and waters depends on many factors, such as pH, turbidity, quantity, intensity, and wavelength of solar radiation, latitude, and weather conditions. The presence of pharmaceuticals in the environment confirms that they pass intact through intensive conditions of biodegradation in sludge processing. Thus, it is expected that photochemical processes under the effect of sunlight play a significant role during the transformation of pharmaceuticals in the environment. As a result of this, processes are forming transformation products (Fatta-Kassinos et al. 2011). Many research has shown that phototransformation

products are more toxic than initial substances (Table 1). Such is propranolol, which by phototransformation, transforms into more hydrophilic and more polar products. This leads to acute toxicity. For example, the phototransformaton product of phenazone, aniline, and 1, 5-dimethyl-4-((1-methyl-2-phenylhydrazinyl)methoxy)-2-phenyl-1H-pyrazolone showed more toxic than the initial structure (Miao et al. 2015). For instance, an increase in toxicity was reported after phototransformation of sulfamethoxazole. Nine more toxic TPs were identified after 30 h of irradiation than the initial substance (Trovo et al. 2009). The analysis of these transformation products is a demanding task for scientists, due to both phototransformation mechanism complexity and difficulties in isolation and identification of very small quantities of these products.

Biotic Degradation/Transformation

Bacteria and fungi play a great role in pharmaceuticals degradation in the environment, which is a part of biotic decomposition. Biodegradation is an important pathway for the removal of pharmaceuticals and potential pollutants from the environment (Im et al. 2016), but it may lead to the formation of transformation products. The biodegradation ability may differ significantly with different pharmaceuticals. For example, 90% ibuprofen is biologically transformed into hydroxyl and carboxyl derivatives, whereas carbamazepine and ciprofloxacine are more resistant to biodegradation (Ji et al. 2014). Funke et al. (2016) investigated biodegradation of abacavir, emtricitabine, ganciclovir, lamivudine, and zidovudine in wastewater, in which case three TPs were detected in finished drinking water (Funke et al. 2016). Additionally, the results of these studies suggest that indigenous microbial

Table 1 Phototransformation toxicological effect of pharmaceuticals

Pharmaceuticals	Phototransformation toxicological effect	Organism tested	References
Prednisolone Dexamethasone	More toxic transformation products	Rotifer *Brachionus calyciflorus*, crustaceans *Thamnocephalus platyurus*, *Daphnia magna*	DellaGreca et al. (2004) and Isidori et al. (2006)
Naproxen	Acute and chronic toxicity of transformation products	Algae, rotifers, and microcrustaceans	Isidori et al. (2006)
Furosemide	Mutagenic potential	Bacteria, algae, rotifers, and microcrustaceans	Isidori et al. (2006)
Tamoxifen	Induced mainly chronic effects without significant differences	*Brachionus calyciflorus*, *Thamnocephalus platyurus*, *Daphnia magna* and *Ceriodaphnia dubia*	DellaGreca et al. (2007)
Fibrates	Genotoxic and mutagenic effects were especially found for the Gemfibrozil photoproducts	Bacteria, algae, rotifers, and microcrustaceans, SOS Chromotest, and Ames test	Isidori et al. (2006)
Triclosan	More toxic transformation products	Fish, crustaceans, and algae	Bedoux et al. (2012)
Ranitidine	Genotoxic and mutagenic effect	Rotifers, SOS Chromotest, and Ames test	Isidori et al. (2009)
Sulfamethoxazole	More toxic transformation products	*Vibrio fischeriand* Daphnia magna	Trovo et al. (2009)
Tramadol Ranitidine	Toxicity was detected for the resulting mixture of the photolytic transformation products of tramadol	Bacterial growth inhibition test (EN ISO 10712)	Bergheim et al. (2012)
Carbamazepine	More toxic transformation products	Bacteria, algae, and crustaceans	Donner et al. (2013)
Ciprofloxacin	Transformation products responsible for the biological activity	*Escherichia coli* strain indicate that the antimicrobial potency	Haddad and Kummerer (2014)
Ibuprofen	More toxic transformation products	*Elenastrum capricornium*	Quero-Pastor et al. (2014)
Vancomycin.	More toxic transformation products	*Daphnia magna*, *Pseudokirchneriella subcapitata*, and *Ceriodaphnia dubia*	Lofrano et al. (2014)
Phenazone	More toxic transformation products	Daphnia magna, Oral rat	Miao et al. (2015)
Propranolol	115 newly formed transformation products with cytotoxic and mutagenic activities	*Salmonella typhimurium*, *S. typhimurium*, CHO-K1 cell line	Menz et al. (2017)
Atenolol Metoprolol	Several transformation products were present a greater hazard than parent	Daphnia magna	Koba et al. (2016)

communities may be altered through adaptation to pharmaceuticals and thereby alter the microbial transformation of these compounds.

Excipients in the Environment

Pharmaceutical formulations contain a variety of excipients. Still most of the ecotoxicity studies focused only on pharmaceuticals, although excipients also can pose a risk to nontarget organisms. Excipients should be subjected to the same testing procedures and intake limits as proposed for active components. The growing concern over the release of all components of drug formulation into the environment has prompted the introduction of risk assessment guidelines. However, while in the United States and the European Union all pharmaceuticals need an environmental risk assessment for registration, there is no such requirement for excipients. Environmental risk assessments are mostly based on one active component, albeit it is present in the environment as a multicomponent mixture with different pharmaceuticals and excipients, which may cause different ecotoxicological effect (Altenburger et al. 2013; Backhaus 2014). The safety profiles of excipients need to be evaluated systematically for potential risk to the environment. The examples of excipients as potential toxicants at high doses are diethylene glycol (renal failure and death), cyclodextrins (epithelial toxicity, nephrotoxic), dextrans (renal toxicity), mannitol (osmotic diarrhea), propylene glycol (cardio toxicity), etc. (Valeur et al. 2018; Yang et al. 2018). In some cases, excipients do not interact chemically but contribute to the transformations of other pharmaceuticals (Pifferi and Restani 2003). For example, primary amines can react with lactose, glucose, and maltose to form glycosylamines (Wirth et al. 1998). Excipients also should be evaluated for their degradation/transformation processes and potential interactions with pharmaceuticals and other substances from nature.

Toxicity of Pharmaceutical Formulations

Unlike single-compound toxicity, the joint-toxic effects between excipients mainly lead to synergistic or antagonistic interactions. Thus, more studies on ecotoxicological effects of excipients and mixtures of excipients and active components are required to assess the risk that they may pose to the environment. As previously discussed, there are currently no standardised regulatory risk measures to assess the mixtures of excipients with active components and TPs as pollutants. TPs of excipients are even of higher concentration than their active compounds in the environment; however, their toxicity is still undetermined.

Silva et al. (2014) proved the ecotoxicity of five medicines (3 generic formulations and 3 brand labels) containing the same active substance (fluoxetine hydrochloride), which was tested to evaluate whether excipients can influence their ecotoxicity. This study showed that excipients may bear ecotoxic potential, and there is a need for identification and quantification of excipients in the environment (Silva et al. 2014). A similar study investigated the toxicities of the three distinct pharmaceutical formulations with the same active ingredient, which had different toxicity (Jacob et al. 2016). These results highlight the toxicological potential of drug excipients in the environment. Further studies are needed to investigate this phenomenon.

However, the potential effects of long-term exposures or exposures to excipients in mixtures with pharmaceutical active substances in the environment have not been studied. Therefore, it is somewhat difficult to determine whether the safety level is adequate for all excipients and their combinations with pharmaceuticals based on the results presented, particularly those that are likely to be present in the environment. However, the study was beneficial in highlighting the issues with a basic arithmetic summation approach to assessing mixture effects. This enhanced the knowledge and understanding of predictive mixture experimental designs and supported the development of an improved mixture study necessary for investigating the effects of mixtures on a more complex biological endpoint in a higher organism.

Conclusions

According to scientific resources, it is apparent that pharmaceuticals pose a grave danger to the environment, as well as human health, as indicated by numerous studies that have proven the presence of various pharmaceuticals in the nature in levels above allowed concentrations, especially in water. Although there are numerous studies on the presence of pharmaceuticals in the environment, the number of studies on ecotoxicological characterisation of pharmaceutical's transformation products and excipients remains insufficient. Based on the previously mentioned research, great attention should be paid to transformation products of pharmaceuticals that are created under the influence of various environmental factors, because they can demonstrate a more toxic effect than the initial compounds. Pharmaceutical preparations may contain a variety of excipients, although excipients also can pose a risk to nontarget organisms. It is important that we begin to understand the potential impacts of these substances on the environment and their mixtures, given their wide applications.

Pharmaceuticals ranked as low risk individually may become high risk when present in mixture with their transformation products and excipients contained in

pharmaceutical products. It is necessary to determine the toxicity of mixtures of pharmaceuticals, their transformation products together with excipients on the environment, and include these data when determining NOEL and EC. This would require an ecological risk assessment of each unique mixture. Therefore, researchers are facing great challenges, ranging from foreseeing the ways of transformation of pharmaceuticals, excipients and their mixture in the environment, their identification, quantification, and specification to means of their removal in an already endangered environment. More effort should be invested into the development of sensitive analytical methods for better identification and quantification of TPs pollutants. It is necessary to educate, adjust the attitude, and raise the awareness on the harmfulness of improper disposal of pharmaceuticals. Due to the possibility of pharmaceuticals entering the food chain, a strict control of use and storage of pharmaceuticals is necessary, as well as the development of methods that would lead to the removal of pharmaceuticals already present in the environment.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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