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Sorption of active pharmaceutical ingredients in untreated wastewater effluent and effect of dilution in freshwater: Implications for an "impact zone" environmental risk assessment approach

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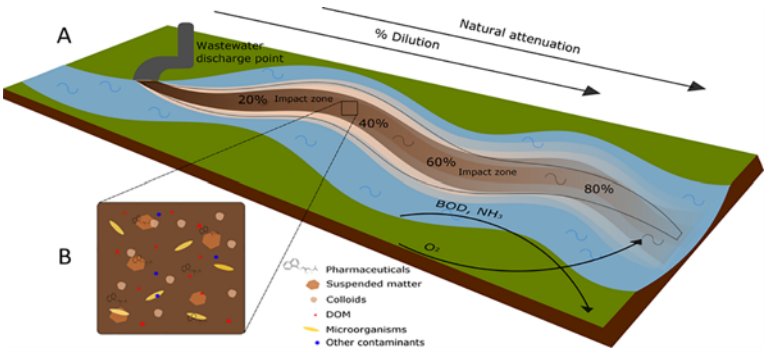
HIGHLIGHTS

- Pharmaceutical risk assessment for wastewater impact zones of developing countries
- Dilution effect of untreated wastewater on distribution of pharmaceuticals
- Lipophilicity correlation to desorption of pharmaceuticals from wastewater solids
- Dissolved organic matter contribution to sorption as a natural attenuation process

GRAPHICAL ABSTRACT



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ABSTRACT

Evidence of ecotoxicological effects of active pharmaceuticals ingredients (APIs) has increased research into their environmental fate. In low and low-middle income countries (LLMICs) the main source of APIs to surface waters is from discharge of untreated wastewater. Consequently, concentrations of APIs can be relatively high in the "impact zone" downstream of a discharge point. Little is known about the fate of APIs in these impact zones. In this laboratory scale investigation, the effect of successive dilution of synthetic untreated wastewater (dilution factor 1 to 10) on the distribution of APIs was studied. The sorption was consistent with the chemical properties of each compound: charge, lipophilicity, and structure. Dilution increased desorption of the basic and neutral APIs (up to 27.7%) and correlated with their lipophilicity ($R^2 > 0.980$); the positive charge was of secondary importance. Anions did not significantly desorb (<10% loss). Increased concentrations of dissolved organic matter at dilutions of 8 and 10 times that of untreated wastewater coincided with lower dissolved API concentrations. The data showed a clear trend in the desorption process of APIs that may lead to higher exposure risk than anticipated. Therefore, it is suggested that these aspects should be accounted for in the development of dedicated environmental risk assessment approach for APIs in riverine impact zones of LLMICs countries.

Abbreviations: APIs, active pharmaceutical ingredients; LLMICs, low and low-middle income countries; DUW, direct discharge of untreated wastewater; DF, dilution factor; CBZ, carbamazepine; ACT, acetaminophen; NVR, nevirapine; DCF, diclofenac; VLS, valsartan; ACE, acebutolol; AMI, amitriptyline; SW, synthetic wastewater.

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1. Introduction

The increasing consumption and production of active pharmaceutical ingredients (APIs) in low and low-middle income countries (LLMICs) is growing environmental concern owing to the awareness of possible ecotoxicological effects (Kookana et al., 2014). This is related to the diffused practice of direct discharge of untreated wastewater (DUW), the main source of APIs to the environment, which creates a heavily polluted area downstream from the discharge point, named the "impact zone" (A.I.S.E./CESIO, 1995; Finnegan et al., 2009; Kookana et al., 2014; Malik et al., 2015; Nansubuga et al., 2016; Thebo et al., 2017).

Little is known about the environmental fate of APIs in the "impact zone" created by the DUW. Nevertheless, a few available measured environmental concentrations (MECs) of APIs in impact zones of LLMICs show higher concentrations than for high-income countries with developed wastewater treatment infrastructure (Madikizela et al., 2017). For instance, in the Nairobi River basin, Kenya, APIs were detected at concentrations ranging from ng L^{-1} to 160 μg L^{-1} (K'oreje et al., 2016, 2012; Ngumba et al., 2016), in Nigeria were reported individual concentrations above 50 μg L^{-1} (Olatunde et al., 2014), and again, in South Africa were detected concentrations of atenolol and ibuprofen up to 30 and 85 μg L^{-1} respectively (Agunbiade and Moodley, 2014, 2016; Matongo et al., 2015), and antiretroviral were quantified at concentrations up to hundreds of ng L^{-1} (Wood et al., 2015). Pharmaceutical factories wastewater was thought to be the source of APIs concentrations up to mg L^{-1} in Pakistan (Ashfaq et al., 2017) and India (Larsson, 2014); and in tropical Asia, sulphonamides antibiotics in surface waters were found to be at higher concentrations than in high-income countries (Shimizu et al., 2013). In one reported case, the environmental risk assessment showed a potential for risk, and pharmaceutical manufactory wastewater contribution was deemed as important, as also evidenced by other investigations (Ashfaq et al., 2017; Larsson, 2014; Ngumba et al., 2016). Although API manufacturing sites would be expected to be identified as high risk, it should also be noted that in high income countries direct discharge of untreated wastewater from such factories is illegal. The reported data for LLMIC countries therefore highlights the environmental concerns and need for carefully considered risk assessment.

As demonstrated above, globally there are common occurrences of API concentrations in "impact zones" which exceed 0.01 μg L^{-1} for any individual compound. Under the existing risk assessment process, if predicted, such a PEC would trigger Phase II of the environmental risk assessment (ERA) (EMA, 2006), which consists of a two-step tiered protocol to evaluation of the risk. Tier A is an initial environmental fate and effects analysis that, if resulting in a risk, should be followed by Tier B, an extended environmental fate and effects analysis (EMA, 2006). The latter is a refinement of the predicted environmental concentration (PEC) in the surface water using a distribution coefficient, which considers the moiety adsorbed to sewage sorbents as being retained in the wastewater treatment sludge (OECD, 2000). Eq. 1 is used for PEC refinement in tier B of the ERA:

$$PEC_{surface\ water} = \frac{Elocal_{water} * F_{stp\ water}}{WASTEW_{inhab} * CAPACITY_{stp} * FACTOR * DILUTION} \quad (1)$$

where $PEC_{surface\ water}$ is the output of the local surface water concentration (μg L^{-1}); $Elocal_{water}$ is the local emission to wastewater of the relevant residue (μg L^{-1}); $F_{stp\ water}$ is the fraction of emission directed to wastewater (μg L^{-1}); $WASTEW_{inhab}$ is the amount of wastewater per inhabitant per day (L d^{-1}); $CAPACITY_{stp}$ is the capacity of the local wastewater treatment plant (l); *FACTOR* accounts for adsorption to suspended matter; and *DILUTION* is the DF, with a default value of 10 (EMA, 2006).

Where untreated wastewater is discharged there is little or no retention of sludge, the entire crude sewage is input to the "impact zone" scenario. Consequently, the sorbents loaded with APIs are discharged and diluted with the receiving freshwater, and possible redistribution processes might cause imprecise calculation of PECs and the associated risk quotient.

Engineering protocols recommended a ratio of river flow to untreated wastewater flow of 40 (DF) (Keller et al., 2014) to allow dilution and dispersion of pollution. A DF of 10, assuming previous wastewater treatment, is used as the default value for environmental risk assessment (EMA, 2006; European Comission Joint Research Centre, 2003).

Although risk assessments are inherently designed to be conservative, reported data suggests that this level of dilution may not always occur. In at least 14 countries worldwide, the local predicted DF median observations show a value below 10, the majority being in North Africa and the Middle East, with Belgium as the only European country (Keller et al., 2014). The number increases to 53 countries worldwide if data of observations falling in the 5 and 25 percentiles are considered (Table S2 in the additional information of Keller et al., 2014). The APIs sorption processes to wastewater sorbents control the exposure to biota (Agunbiade and Moodley, 2016; Carmosini and Lee, 2009; Hernandez-Ruiz et al., 2012; Hudson et al., 2007; Lahti and Oikari, 2011; OECD, 2000; Peng et al., 2014; Svahn and Bjorklund, 2015; Wang et al., 2016; Zhou et al., 2007), and since DUW occurs at dilutions that can cause significant desorption of APIs (Hajj-Mohamad et al., 2017; Yang et al., 2011) such exposure might be underestimated with simple dilution calculations.

The aim of this study was to assess the partitioning of APIs to wastewater sorbents, and to quantify the potential dilution-induced desorption in receiving freshwaters using a standardised synthetic untreated wastewater diluted across a range of DFs. This approach was designed to assess the effect of the major constituents present in untreated wastewater (particularly the presence of high concentrations of organic carbon, potentially capable of 'stabilising' APIs in the dissolved phase) on the environmental fate of APIs. Outcomes of the study could then be used to inform the development of an improved exposure assessment approach for a range of contaminants in the impact zone generated by the DUW in freshwaters.

2. Materials and methods

2.1. Active pharmaceutical ingredients

The APIs were selected to reflect consumption patterns of LLMICs where the DUW occurs more commonly. Compound structure and chemical functionality were also fundamental selection criteria due to their fundamental impact on partitioning processes. The selected compounds are the neutral carbamazepine (CBZ), acetaminophen (ACT), and nevirapine (NVR), the acidic diclofenac (DCF) and valsartan (VLS), and the basic acebutolol (ACE), and amitriptyline (AMI) (Table S1 of the Supporting Information). The compounds were obtained at the highest purity available, either from Sigma-Aldrich (acebutolol hydrochloride, amitriptyline hydrochloride, nevirapine, valsartan, acetaminophen) or Fisher Scientific (carbamazepine, diclofenac sodium salt).

2.2. Synthetic wastewater

Wastewater composition is highly variable both within and between wastewater treatment works (WwTW) particularly in LLMIC countries (Tchobanoglous et al., 2003). It is impossible to replicate any given natural matrix within a laboratory setting owing to this inherent variability. The choice of using 'natural' versus synthetic wastewater is an interesting debate with benefits and drawbacks associated with each approach (O'Flaherty and Gray, 2013). The purpose of these experiments was to generate a surrogate untreated wastewater with which to assess the partitioning behaviour of APIs. Consequently, to ensure a consistent, reproducible and stable starting matrix for testing, a synthetic wastewater (SW) formulation was used (Boeije et al., 1999). The keys aspects of the starting 'crude' sewage matrix were appropriate suspended solids and