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Environmental risk assessment for excipients from galenical pharmaceutical production in wastewater and receiving water

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ABSTRACT

Many different excipients are used in galenical pharmaceutical production, in addition to the active pharmaceutical ingredients. Excipients are little investigated regarding their environmental fate and impact, even though some of them are used in appreciable quantities. For 35 excipients used in galenical production at Roche Basle and Roche Kaiseraugst, both in Switzerland, in the years 2013 and 2014, the environmentally relevant properties were collated. A predicted environmental concentration (PEC) was calculated for the wastewater treatment plants (WWTPs) and the receiving water, the River Rhine for both sites, based on maximum daily losses of the single excipients to wastewater, derived by mass balance, and the site-specific dilution factor. Predicted no effect concentrations (PNECs) were derived for the WWTPs and the River Rhine. PECs and PNECs were compared for the WWTPs and the receiving water, in an environmental risk assessment. Additionally, to simulate a worst case scenario, certain galenical productions where given excipients are used in the highest amounts were assumed to take place in parallel on the same day, resulting in theoretical maximum excipient losses to wastewater. All PEC/PNEC risk characterisation ratios for the excipients currently used by Roche in Switzerland are well below 1 throughout. Together with the fact that based on biodegradability data many excipients will be removed in the WWTP, this indicates that the excipients currently used do not present a risk to the environment.

1. Introduction

Galenical production of medicines needs excipients for various purposes, e.g., to stabilise the active pharmaceutical ingredient (API), lend bulk and colour to tablets, assist in breaking these up in the stomach, control the time course of API release from the formulation, disguise a bitter taste of the pure API, or other functions (Swarbrick, 2015). The United States Pharmacopeia and National Formulary (United States Pharmacopeia, 2014) lists 48 functional categories for excipients, from Adhesive over Antimicrobial Preservative, Bulking Agent and many others, to Wetting/Solubilizing Agent. While in the USA and the European Union (EU), new APIs need an environmental risk assessment (ERA) for registration, there is no such requirement for excipients (even though an older EU ERA draft did mention excipients (Straub, 2002)). Excipients are being investigated regarding toxicological endpoints and quality standards (Kemsley, 2014), but not for environmental risks. Only one publication so far, by Silva et al. (2014), comparing algal toxicities of fluoxetine in drug products of differing compositions, i.e., containing varying excipients, suggested excipients to be responsible for manifestly different toxicities. However, some excipients are being used in comparatively high amounts in galenical production of medicines. Therefore, we collated data and performed a site-specific ERA for the wastewater treatment plants (WWTPs) and receiving water for the excipients used in two galenical production sites of F. Hoffmann-La Roche Ltd (Roche) in Switzerland. To our knowledge, the present contribution is the first to investigate the potential environmental risks arising from losses of excipients from galenical production to wastewater.

Abbreviations: API, Active pharmaceutical ingredient; BOD_5, Biochemical oxygen demand in 5 days; EC_{50}, 50% effect concentration; ERA, Environmental risk assessment; EU, European Union; NA, Not available; NOEC, No observed effect concentration; NRT, New Roche test; OECD, Organisation for Economic Co-operation and Development; PEC, Predicted environmental concentration; PNEC, Predicted no effect concentration; Q347, Minimum residual (5th percentile) river flow; QSAR, Quantitative structure–activity relationship; RA, Read-across; TOC, Total organic carbon; WWTP, Wastewater treatment plant

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2. Materials and methods

2.1. Excipient use amounts

An initial list of excipients was prepared by collating excipient information from current or former, solid or liquid Roche drug products worldwide, based on unpublished company-internal documentation. Galenical production records at Roche Basle and Kaiseraugst for the year 2013 and the first six months of 2014 were then consulted to identify those excipients actually being used at those two sites. Maximum theoretical losses to wastewater were calculated by mass balances for the single productions as described by Hoerger et al. (2009). In brief, the final products and all documented losses were substracted from the total of active ingredients plus excipients, to result in worst-case losses, all of which were assumed to be drained to wastewater in the first approximation.

Roche has two galenical production sites in Switzerland, viz. Roche Basle and Roche Kaiseraugst, both situated on the River Rhine, with Kaiseraugst approximately 13 km upriver from Basle. Production of solid medicinal products ('solida'; coated or uncoated tablets, capsules, dry granulates (Hoerger et al., 2009)) in general needs more excipients than the formulation of liquid drugs ('parenteralia'), e.g., due to the necessity for bulking or disintegrating agents, colourants and lacquers. In contrast, solida may be produced at up to 1000 kg per batch, with no or only little liquid (water or alcohol) added for technical reasons. Solida are mixed in large mixing units, in which at the end of the process a thin layer of caked mixture of APIs and excipients may remain (see Hoerger et al. (2009)). For cleaning, this cake is normally scraped out manually and disposed of as special waste by incineration, while the subsequent aqueous rinses from cleaning are discharged to the WWTP. In some special cases, due to high ecotoxicity of the API or in case of the API being categorized as 'high-potency' based on toxicological or pharmacological reasons, the first rinse (containing most of the active substance remaining in the mixer) will be separated and incinerated as well. Also, samples for quality control, air filters, tablet breakage or mixtures and products not meeting specifications will be incinerated. Substracting all those categories disposed of by incineration from the total of APIs and excipients weighed in, results in the worst case estimate of losses to wastewater from solida production (Hoerger et al., 2009).

Parenteralia for Roche nearly exclusively means biologics, i.e., monoclonal antibodies and other biotechnologically produced protein APIs, usually of very high molecular mass $>$ 50,000 Da. As doses are low, galenical batch sizes are comparatively small, up to 100 L per batch for the two sites, moreover, most of the total consists of ultrapure water for formulation. Excipients are mainly organic buffers (e.g., arginine, glutamine, glycine, histidine), often with a sugar (e.g., sucrose, trehalose) and a detergent (e.g., polysorbate 80); as an example, see the SDS for MabThera SC (Safety Data Sheet for MabThera SC, 2014). Parenteralia are mostly filled into glass vials, which are then sealed, or into syringes. These containers are inspected visually for cloudiness (signifying either undissolved solids or microbial growth) and all units not passing are collected for incineration; the same holds for the bags with residuals of ready mixed solutions or mixtures not meeting specifications. Only liquid losses during the mixing or the filling process, including possible breakages, are discharged to wastewater. Substracting the incinerated and produced amounts from the initial total results in the worst-case estimate of losses from parenteralia production.

2.2. WWTP and receiving water data, predicted environmental concentrations

Basic data for daily wastewater fluxes and treatment for the two WWTPs serving Roche Kaiseraugst and Basle were searched for as well as flow data for the receiving water, which for both WWTPs is the River Rhine. Predicted environmental concentrations (PECs) for the WWTPs were calculated by dividing the worst-case loss of excipients in grams per day by the average total wastewater treated daily in the respective WWTP. Worst-case PECs for the River Rhine were calculated by dividing the loss in g/d by the minimum residual flow or Q347 in Swiss terminology (the long-term lower 5th percentile flow (Swiss Federal Office for the Environment (BAFU), 2015c)) of the River Rhine in a day, i.e., without factoring in removal in the WWTPs through biodegradation or adsorption, hence in this first approximation the WWTPs do not influence the surface water PEC. In addition, as a worst-case scenario, it was assumed that those productions with the highest amounts of the same excipients would take place on the same day, which leads to an inordinately high PEC for those substances.

Roche Kaiseraugst discharges the wastewater from galenical production to WWTP Rhein in Pratteln, which treats approximately 15,800 m^3 wastewater per day with an overall removal efficiency of 98% regarding biochemical oxygen demand in 5 days (BOD_5) and of 90% regarding total organic carbon (TOC) (WWTP Rhein, 2015). Basle galenical production discharges to WWTP Basle, which treats approximately 93,100 m^3/d with a removal efficiency of 92.9% regarding BOD_5 and 93.0% regarding TOC [data for 2013, Ref. Pro Rheno Betriebs AG, 2013].

The River Rhine is the receiving water for both WWTP effluents. It has a long-term (1891–2013) average flow at the measuring station Rheinhalle Basle of 1051 m^3/s (Swiss Federal Office for the Environment (BAFU), 2014) and a minimum residual Q347 flow of 459 m^3/s (Swiss Federal Office for the Environment (BAFU), 2014). The only two significant surface water inflows into the Rhine between the two WWTP effluents are the smaller River Birs, which has an average flow of 14.6 m^3/s and a monthly minimum of 8.0 m^3/s (Swiss Federal Office for the Environment (BAFU), 2015a), and the River Wiese with an average of 9.6 m^3/s and a monthly minimum of 4.9 m^3/s (Swiss Federal Office for the Environment (BAFU), 2015b). In a low-flow situation for the River Rhine, also the tributaries will carry little water; hence, the contributions from the Birs and Wiese do not significantly change the Rhine flow and will be disregarded for upstream (WWTP Rhein effluent) surface water PEC derivation.

2.3. Environmental data for excipients

Environmentally relevant substance data for these substances were researched in company-internal documentation Roche Safety Data Sheets (SDS) database and supplier SDS collection; older hardcopy collections like Verschueren (1996)) as well as in online databases and sources ChemIDPlus, Ref. ChemIDPlus database, 2015; Detergents Ingredients Database, 2014; European Chemicals Agency (ECHA), 2015; Hazardous Substances Data Base (HSDB), 2015; ECOTOX Database, 2015; Environmental Fate Data Base (EFDB), 2015 and on Scholar, 2015. The excipients were usually identified by their Chemical Abstracts Services (CAS) numbers, which was used for further data search. Search criteria included molecular mass, physico-chemical data, ready (OECD 301) (Organisation for Economic Co-Operation and Development (OECD), 2015) or inherent (OECD 302) or model WWTP (OECD 303) biodegradability, algal growth inhibition (OECD 201 test or equivalent), acute (OECD 202) or chronic (OECD 211) daphnid toxicity, acute (OECD 203) or subchronic (OECD 210) to chronic fish toxicity and activated sludge respiration inhibition (OECD 209) (Organisation for Economic Co-Operation and Development (OECD), 2015), where available. In the first step of the ERA, only experimental biological data were used to fill, as completely as possible, a spreadsheet with the relevant informations on the excipients.