Journal of Hazardous Materials xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Primary degradation of antidiabetic drugs

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HIGHLIGHTS

- Primary biodegradation of antidiabetic drugs and one transformation product were examined.
- Complete primary degradation of metformin, acarbose, glibenclamide and glimepiride was found.
- On the contrary gliclazide seems to be transformed to minor extent being a first indication of possible persistence.

ARTICLE INFO

Article history:
Received 21 April 2016
Received in revised form 5 October 2016
Accepted 2 November 2016
Available online xxx

Keywords:
Primary biodegradation
Pharmaceuticals
Antidiabetic drugs
Sulphonamides
Environmental fate

ABSTRACT

Type 2 diabetes is a chronic disease affecting a large portion of the world population and is treated by orally administered drugs. Since these drugs are often taken in high doses and are excreted unchanged or partially metabolised many of them are nowadays detected in surface waters or wastewater treatment plants effluents. Unmetabolised antidiabetics or some of their transformation products retain their pharmacological activity, therefore their presence in the environment is highly undesired. One of the main routes of elimination from wastewaters or surface waters is biodegradation. Within this work we tested primary biodegradation of: metformin and its metabolite guanylurea, acarbose, glibenclamide, gliclazide and glimepiride. We also inspected what might be the extent of the degradation by examining the products formed during the degradation using liquid chromatography coupled to tandem mass spectrometry. Transformation of diabetes staple drug metformin to dead-end product guanylurea was generally confirmed. An alternative, though rather minor pathway leading to complete mineralisation was also found. Complete primary degradation was observed for acarbose, glibenclamide and glimepiride whereas gliclazide was shown to be resistant to biodegradation. These results allow a preliminary assessment of environmental persistency of a very important group of pharmaceuticals and show need for implementing monitoring programs.

1. Introduction

1.1. Pharmaceuticals in the environment

Diabetes mellitus is a chronic disease affecting the metabolism of carbohydrates. It was estimated to affect approximately 6.4% of world population in 2010, yet the prevalence is predicted to increase to 7.7% by 2030 [1]. Type 2–insulin independent – diabetes comprises approximately 90% of all diabetes cases in United States and Europe and almost 100% in Asia. More than half of patients are treated by orally administered drugs [2]. The first line of therapy is usually metformin followed by other oral antidiabetics such as glibenclamide, repaglinide, glimepiride, gliclazide, and acarbose (Table 1) [3,4].

As these compounds are not completely metabolized in the human body [4], a portion of them is excreted unchanged and therefore released into the environment via wastewaters. There are several reasons why the presence of pharmaceuticals or their degradation products in the environment is a cause for concern. Pharmaceuticals or some of their transformation products retain the pharmacological activity, which means they can still affect living organisms including humans. The effect they might have on

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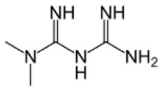
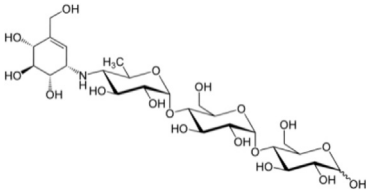
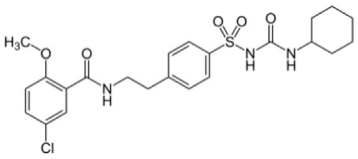
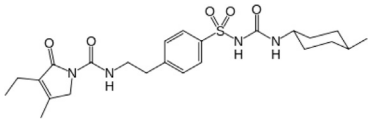
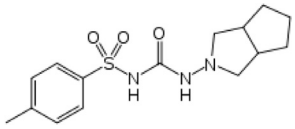
http://dx.doi.org/10.1016/j.jhazmat.2016.11.008
0304-3894/

Table 1
Chemical structure, selected physico-chemical properties, yearly consumption in US, the extent of human metabolism and pharmacological activity of metabolites of the investigated pharmaceuticals.

Name (abbreviation) MW MIM log K_{ow}[a]	Chemical structure	Consumption in US [t year^{-1}][b]	Human metabolism and pharmacological activity of metabolites[c]
Metformin (MET) MW = 129.16 g mol^{-1} MIM = 129.101 log K_{ow} = -2.64		12 913 313	not metabolised, excreted as active parent compound
Acarbose (ACB) MW = 645.60 g mol^{-1} MIM = 645.248 log K_{ow} = -8.08		4 095	metabolised extensively by gastrointestinal flora[d]
Glibenclamide (GLB) MW = 494.00 g mol^{-1} MIM = 493.144 log K_{ow} = 4.79		10 533	extensively metabolised with limited activity of metabolites
Glimepiride (GMP) MW = 490.62 g mol^{-1} MIM = 490.225 log K_{ow} = 4.70		5 877	extensively metabolised, some metabolites are active
Gliclazide (GLZ) MW = 323.41 g mol^{-1} MIM = 323.130 log K_{ow} = 2.12		no data	extensively metabolised to inactive compounds

Abbreviations: MW – molecular weight, MIM – monoisotopic mass, K_{ow} – octanol-water partition coefficient.
[a] K_{ow} value predicted using EPI Suite™ KOAWIN v1.68.
[b] Value obtained by multiplying number of patients prescribed the drug in 2012 according to [7] by maximum recommended daily dose [mg kg^{-1} of body weight per day] assuming average adult weight of 60 kg [8,9].
[c] Source [4,10].
[d] Source [4].

no-target organisms cannot be predicted easily and it is possible that the transformation products will be more potent or toxic than the parent compound (e.g. metabolites of anticancer drug tamoxifen are hundred times more potent than the parent compound) [5]. For that reason in most countries pharmaceuticals before entering the market are subjected to some kind of evaluation and authorisation procedure to exclude potential negative effects. These procedures are based, at the very least, on the assessment of aquatic toxicity and susceptibility to degradation. Nevertheless to this date ecotoxicological data are available for less than 10% of the currently prescribed drugs [6].

Very often oral antidiabetic drugs are at the top of the list of pharmaceuticals found in the environment. Therefore, the objective of our investigation was to obtain an insight into potential environmental impacts of these pharmaceuticals. Herby we present the account of biotic transformation – where we chose to examine primary biodegradation levels of five antidiabetics. The fact that chemical undergoes primary degradation means that it is transformed to another compound. The extent of this transformation is not known from the primary degradation test itself. The transformation might indeed be limited to e.g. an addition of one hydroxyl group. If any of the examined compounds showed low biodegradability it would be a reason to red-flag it as potentially persistent. Nevertheless, high level of primary degradation does not mean that the chemical is fully mineralised to simple compounds. To shed more light on how much of the molecule was still left we used direct MS or LC–MS to look for possible transformation products. We did not optimised the method for a full structure elucidation therefore transformation products suggested should be treated as a starting point to a more in depth investigation of transformation pathways and metabolites. Additionally and assessment of ultimate degradation as well as ecotoxicity of said pharmaceuticals is needed to give a more comprehensive picture.

1.2. Antidiabetics – occurrence, degradability and environmental impact

Metformin (MET) is by far the most often prescribed antidiabetic drug worldwide. More than 1200 t of this drug were consumed by patients in Germany (in 2010) and over 205 t in United Kingdom (in 2000) [11–13]. It is also especially important in the environmental context as in addition to being a staple antidiabetic it is usually taken in relatively high doses of 0.5–2 g/day and is mostly excreted unchanged [4]. As a result metformin is a drug with one of the highest environmental emissions. It is often detected in wastewater treatment plants (WWTPs) influents (up to the concentration of 130 μg L^{-1}), in fresh and sea waters (from few tens of ng L^{-1} up to few μg L^{-1}) or even tap water, suggesting that exist-

Please cite this article in press as: M. Markiewicz, et al., Primary degradation of antidiabetic drugs, J. Hazard. Mater. (2016), http://dx.doi.org/10.1016/j.jhazmat.2016.11.008