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TRACE UPLC-MS/MS ANALYSIS OF NEUROACTIVE DRUGS IN ENVIRONMENTAL WATERS: MOLECULARLY IMPRINTED SOLID-PHASE EXTRACTION (MISPE) TO IMPROVE SELECTIVITY AND DETECTION LIMITS

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Neuroactive drugs like antidepressants and benzodiazepines belong to the most widely prescribed pharmaceuticals. Apart from their therapeutic effects, they enter the environment through various pathways (e.g. via sewage treatment plant (STP) effluent or by land application of biosolids) and may affect the metabolics of aquatic and/or terrestrial organisms. Toxicological studies recently indicated that at ambient concentrations antidepressants induce biological effects in fish, mollusks and aquatic invertebrates.

We present the development, optimization, and validation of an innovative analytical method to quantify trace concentrations of a set of seven selected neuroactive pharmaceuticals in environmental waters. Hereby, the solid-phase extraction (SPE) potential of MIPs in terms of extraction recovery, breakthrough, precision, and selectivity is studied for the first time. Instrumental analysis by UPLC coupled to triple quadrupole MS allowed a rapid (run time = 7.5 min) and sensitive (instrumental detection limit $\leq$7 pg injected) quantification of the seven target analytes. A systematic optimization study revealed that mainly the selective serotonin reuptake inhibitors paroxetine, fluoxetine, and citalopram are selectively retained on the MIPs. Experiments performed in spiked river water, STP effluent and influent showed for these compounds breakthrough volumes up to 200 mL and extraction recoveries higher than 70%. Significantly lower MISPE recoveries are obtained for venlafaxine (up to a factor of 7), trazodone (up to a factor of 5), and diazepam (up to a factor of 20) illustrating the selective character of the MIP sorbent, even within one subgroup of pharmaceuticals.

With the novel MISPE-UPLC-MS/MS method, good precision (relative standard deviations better than 15%) and method detection limits (MDL) as low as 0.5 ng/L were obtained for the three most selectively retained compounds. Compared to a recently reported HLB-SPE based method (HLB = hydrophilic-lipophilic balanced polymers) developed for multi-residue pharmaceutical analysis, these MDL are up to a factor of 7 lower. The higher selectivity of the new MIP protocol resulting into cleaner extracts and hereby minimizing matrix effects induced ion suppression and baseline noise indicated to be the most probably explanation. The effect of selectivity is confirmed by considering MDL obtained with a second HLB method specifically optimized towards antidepressant extraction. Even in relative dirty samples like STP influent, this HLB-2 method including a rather strong washing step approximates the MISPE method in terms of sensitivity, exemplified by MDL not more than a factor of 2 lower with the latter method.

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