Towards Single System for Total Water Analysis. Screening of 325 PPCP in Tap and Surface Water.

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1. Overview

Single system LC-MS/MS multi-method approach for the development of an easy access automated exhaustive water analysis tool.

2. Introduction

There is growing concern over the exposure of humans to their chemical waste, flushed down everyday in the conventional wastewater network: pesticides, household chemicals, pharmaceuticals and personal care products (PPCP). In Europe, for example, two main texts are driving regulations: the *Drinking Water Directive* and the *Water Framework Directive*. In Japan, as another example, the regulation is established by the *Water Supply Act*, the *Water Pollution Prevention Act*, and *Act on Control of Household Products Containing Harmful Substances*.

The objective of this development is to set up a LC-MS/MS system, automatically switching between several methods, for total water analysis in routine. Firstly, this was applied to pesticides and PPCP. This poster focuses on the PPCP analysis. Many countries worldwide are regularly monitoring and assessing over a hundred PPCP from wastewater. Specific and highly sensitive detection is required. LC-MS/MS is the gold standard; however, it can hardly be exhaustive due to the variability of targets chemical properties. **Here we propose to develop a single automated system, switching between methods, for total water analysis.**

3. Methods

A Nexera X2 UHPLC was coupled to LCMS-8060 high-sensitivity triple quadrupole (Shimadzu Corporation). Analytical system is shown in *Figure 1*. Four different analytical conditions were performed, using acidic or basic mobile phases gradients, with either direct injection (150 uL injection, 22 min run time) or online SPE (1500 uL, 28 min). Acidic mobile phases were water and methanol, with acetic acid and ammonium fluoride. Columns were Shim-pack Velox Biphenyl 2.7µm, 100mm (Shimadzu Corporation). Basic mobile phases were water and acetonitrile, with ammonium hydroxide. Columns were Shim-pack Scepter HD-C18-80 3µm, 100mm. Columns i.d. were 2.1 mm for direct injections and 3 mm for online SPE. SPE cartridge was Evolute Express ABN 20µm 30 x 2.1mm (Biotage), with water and methanol for loading. The system was set up to switch automatically between mobile phases (LPGE), between columns (switching valve) and between direct injection and SPE (switching valve). Fluidic lines diagram is shown in *Figure 2*.

Figure 1. LC-MS/MS analytical system.

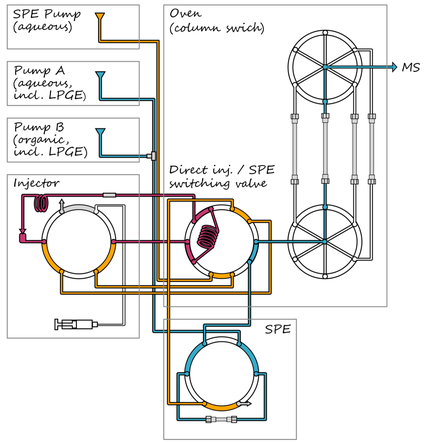

Figure 2. HPLC fluidic lines diagram.

4. Results

Regressions were performed using 10 calibration points (in 5 replicates), in the range 0.1-100ppt, both in Tap Water and Surface Water. All compounds were analyzed by each of the four previously described methods. A limited number of internal standards was used (9) to reduce the cost of the analysis. RSD values were below 20% at all levels for all compounds. Accuracy was in the range 80-120% for all replicates. These results show the methods robustness and accuracy.

Low limits of quantification (LLOQ) were evaluated and selected from the best analytical condition. In Tap Water: 6% of the compounds present a LLOQ within 50-100ppt (ng/L), 18% within 3-30ppt and 71% below or equal to 1ppt, showing the high sensitivity of the methods. From all compounds, 95% can be analyzed by at least one of the 4 methods (*Figure 3a*). In Surface Water (*Table 1*): 6% of the compounds present a LLOQ within 50-100ppt, 24% within 3-30ppt and 61% below 1ppt. From all compounds, 91% can be analyzed by at least one method, showing the wide coverage of this technique, even in a complex matrix (*Figure 3b*).

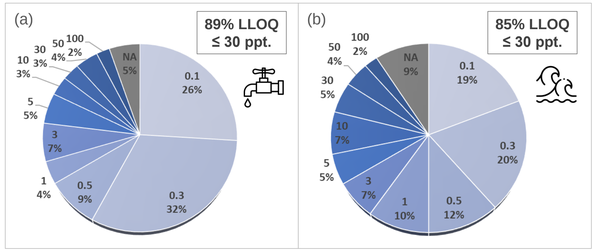

Figure 3. Best LLOQ (ppt) in (a) Tap Water and (b) Surface Water.

Table 1. Studied PPCP compounds, sorted by LLOQ in Surface Water.

PPCP compounds of Surface Water best LOQ in [50-100] ppt.			
10,11-Dihydrocarbamazepine	Ceftriaxone	Etoposide	Oxolinic acid
4-Hydroxy Diclofenac	Chlorhexidine	Fosamprenavir	Oxytetracycline
Allopurinol	Cytarabine	Maduramicin	Prednisolone
Azelnipidine	Esmolol	Methylparaben	Rifampicine
Doxycycline	Ethylparaben	Norfloxacine	Triclosan
PPCP compounds of Surface Water best LOQ in [3-30] ppt.			
17a-Estradiol	Chlorpromazine	Josamycin	Pravastatine
17a-Ethinylestradiol	Ciprofloxacine	Ketoprofen	Pristinamycin IIA
Acetaminophen	Clarithromycin	Marbofloxacine	Propylparaben
Acetazolamide	Clorsulon	Medroxyprogesterone	Ribavirin
Acetylsulfamethoxazole	Closantel	Mestranol	Rociletinib
Afatinib	Crizotinib	Metaflumizone	Ronidazole
Alimemazine	Dacomitinib	Metformin	Sertraline
Aminopyrine	Danofloxacin	Methotrexate	Spiramycin
Amiodarone	Diosmetin	Methylphenidate	Sulfamethoxazole
Amprolium	Doxepin	Miconazole	Tamoxifen
Androstenedione	Gemfibrozil	Naftidrofuryl	Tenofovir
Azithromycin	Drospirenone	Nicotine	Teriflunomide
Benzylpenicillin	Enrofloxacine	Nitrendipine	Tetracaine
Bithionol	Estrone	O-desmethylnaproxene	Salicylic acid
Caffeine	Furosemide	Ofloxacine	Tolfenamic acid
Cefotaxime	Genistein	Oxyclozanide	Trimetazidine
Cerdulatinib	Imatinib	Paraxanthine	Vortioxetine
Ceritinib	Iopamidol	Perindoprilat	
Chloramphenicol	Isoquinoline	Phenazine	
PPCP compounds of Surface Water best LOQ in [0.1-1] ppt.			
Abacavir	Desmethyldiazepam	Lopinavir	Ramipril
Acebutolol	Desvenlafaxine	Loratadine	Ranitidine
Albendazole	Diazepam	Lorazepam	Ritonavir
Altrenogest	Diazinon	Losartan	Roxythromycine
Amitriptyline	Diazoxide	Loxapine	Rufinamide
Amlodipine	Dibucain	Loxoprofen	Salbutamol
Amoxapine	Diclofenac	Mefenamic acid	Ceftiofur
Amprenavir	Dicyclanil	Meloxicam	Saquinavir
Antipyrine	Dihydroergotamine	Mepivacaine	Sildenafil
Atazanavir	Diltiazem	Metoclopramide	Sorafenib
Atenolol	Diphenhydramine	Metoprolol	Sotalol
Atenolol acid	Domperidone	Metronidazole	Sotrastaurin
Atorvastatin	Enzacamene	Midazolam	Sulfachloropyridazine
Baclofen	Erlotinib	Midodrine	Sulfadiazine
Bezafibrate	Erythromycin	Mirtazapine	Sulfadimethoxine
Bisoprolol	Fenbendazole	Molindone	Sulfamerazine
Buflomedil	Fenofibrate	Monensin A	Sulfamethazine
Bupropion	Fenofibric acid	Nadolol	Sulfamethizole
Butylparaben	Flumequine	Narasin	Sulfapyridine
Cabozantinib	Fluoxetine	Nelfinavir	Sulfaquinoxaline
Candesartan	Fluphenazine	Nevirapine	Sulfasalazine
Capmatinib	Gabapentine	Nicardipine	Sulfathiazole
Carazolol	Gefitinib	Nifedipine	Sulfisoxazole
Carbadox	Gestodene	Niflumic acid	Sumatriptan
Carbamazepine	Glibenclamide	Nilotinib	Sunitinib
Carbamazepine epoxide	Haloperidol	Nintedanib	Tadalafil
Carvedilol	Heptaminol	Norethisterone	Terbutaline
Cetirizine	Hydrochlorothiazide	Norgestimate	Thiabendazole
Chlormadinone	Hydroxymetronidazole	Norgestrel	Ticlopidine
Citalopram	Hydroxyprogesterone caproate	Norquetiapine	Timolol
Clemastine	Ibrutinib	Omeprazole	Tofacitinib
Clenbuterol	Ifosfamide	Oxazepam	Tramadol
Clindamycin	Imidapril	Pentoxifylline	Triclabendazole
Clomipramine	Imipramine	Perindopril	Triclocarban
Clonazepam	Indomethacin	Phenacetin	Trimethoprim
Clonidine	Iobitridol	Phenytoin	Trimipramine
Clopidogrel	Iohexol	Lamotrigine	Tylosin
Clotrimazole	Tipranavir	Pindolol	Vardenafil
Clozapine	Ipratropium	Piribedil	Venlafaxine
Cotinine	Irbesartan	Piroxicam	Verapamil
Cyamemazine	Ketorolac	Prazepam	Virginiamycin B
Cyclophosphamide	Lamivudine	Prilocaine	Warfarin
Darunavir	Iopromide	Primidone	Zolpidem
Dasatinib	Lenvatinib	Propranolol	Zonisamide
Desipramine	Levamisole	Propyphenazone	
Desloratadine	Lincomycin	Pyrimethamine	

The most exhaustive method alone is direct injection (DI) in acidic conditions. Its performances are very good. In Tap Water, we observe 92% total coverage, with 86% of the compounds presenting a LLOQ below 30 ppt (*Figure 4a*). In Surface Water, there is 86% total coverage, with 80% of the compounds presenting a LLOQ below 30 ppt (*Figure 4b*).

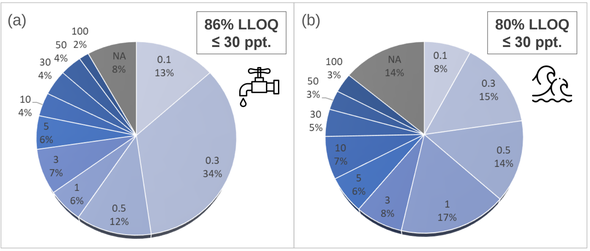

Figure 4. Acidic DI LLOQ (ppt) in (a) Tap Water and (b) Surface Water.

Looking to each method contribution, a large majority of compounds reach their best LLOQ when analyzed by direct injection (DI) in acidic conditions. This is widely true for Tap Water analysis, with 68% of the compounds (*Figure 5a*). However, the added value of the 4 methods platform gets more visible as the matrix gets more complex. In Surface Water (*Figure 5b*), 45% of the compounds reach a lower LLOQ by being analyzed by a different method than the acidic direct injection. The best LLOQ is obtained by SPE in acidic conditions for 16% of the compounds, by direct injection in basic condition for 16%, and by SPE in basic conditions for 13%. These results are showing the importance of the contribution of these additional methods.

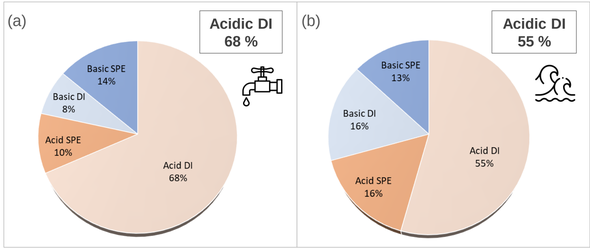

Figure 5. Best Method for Best LLOQ (% of compounds) for analysis in (a) Tap Water and (b) Surface Water.

5. Conclusion

This analytical setup has great capability and can automatically switch from method to method. Depending on local regulations, each or all methods can be considered by one as relevant. The given flexibility is maximal to find the best ratio between efficiency and exhaustivity. This LC/MS/MS single system and multi-method approach is a good tool for total water analysis, in particular, as shown here, to measure a large quantity of PPCP at low concentration in tap and surface water.