ThP082

Towards Single System for Total Water Analysis. LC-MS/MS screening of 325 PPCP Contaminants 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). 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 widely used, however it can hardly be exhaustive due to the wide variability of target chemical properties. Each method is developed as a compromise for a restricted list of compounds only. **Here we propose to develop a single automated system, switching between several methods, for total water analysis.**

3. Methods

A Nexera X2 UHPLC (Shimadzu Corporation) was coupled to LCMS-8060 high-sensitivity triple quadrupole (Shimadzu Corporation). Four different analytical conditions were performed, using acidic or basic mobile phases gradients, with either direct injection (150uL injection, 22min run time) or online SPE (1500uL, 28min). 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 2.1mm for direct injections and 3mm for online SPE methods. SPE cartridge was Evolute Express ABN 20µm 30 x 2.1mm (Biotage), with water and methanol for loading, and acetonitrile, methanol and isopropanol for rinsing.

4. Results

From the initial list of 325 compounds, 304 standards were available and confirmed by FIA. This study focuses on these 304 compounds. The system is set up so that it can switch automatically from one method to another. 304 target compounds were evaluated (Table 2.), in real sample conditions: tap water and surface water. Regressions were performed using 10 calibration points (in 5 replicates), in the range 0.1-100ppt. All compounds were analyzed by each of the four previously described methods. Multiplex analysis were performed. About 100 compounds were analyzed simultaneously. In other words, analyzed compounds were divided in groups of about 100 compounds injected separately. A limited number of internal standards was used (9) to reduce the cost of the analysis. Particular attention was paid so that their retention times were spread along the chromatogram both in negative and positive ionization modes. Data processing was performed using LabSolutions Insight software (Shimadzu Corporation), with no manual correction. RSD values for area and calculated concentration were below 20% at all levels for all compounds. Accuracy was comprised in the range 80-120% for all individual replicates. These results confirm the robustness and accuracy of the methods.

4.1. Best Low Limits of Quantification (LLOQ).

Low limits of quantification (LLOQ) were evaluated and selected from the best analytical condition for each compound. In Tap Water: 6% of the compounds presented a LLOQ within 50-100ppt (ng/L), 18% within 3-30ppt and 71% had a LLOQ of below or equal to 1ppt, showing the high sensitivity of the methods. From the 304 compounds, 95% could be analyzed by at least one of the four methods, demonstrating the wide coverage of this technique (Figure 1.). In Surface Water: 6% of the compounds presented a LLOQ within 50-100ppt (ng/L), 24% within 3-30ppt and 61% below or equal to 1ppt. From the 304 compounds, 91% could be analyzed by at least one of the four methods, showing again the wide coverage of this technique, even in a complex matrix (Figure 2.).

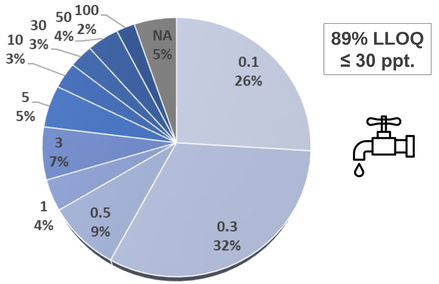

Figure 1. Tap Water Best LLOQ (ppt).

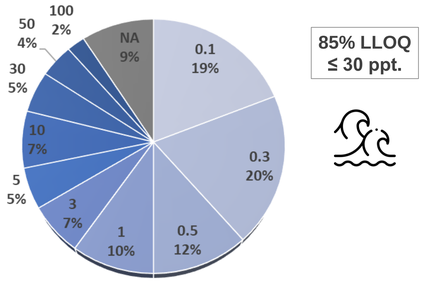

Figure 2. Surface Water Best LLOQ (ppt).

4.2. Contributions of individual Methods.

Here, we wanted to analyze the individual contribution of each method focusing on surface water data, more complex matrix. The most exhaustive method alone is direct injection (DI) in acidic conditions. Its performances are very good: 86% total coverage, with 80% of the compounds presenting a LLOQ below 30 ppt. So is there an added value of preforming any additional injection? Why to perform 4 analysis? The following chart (Figure 3.) shows figures to help one finds his own answers.

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	

Table 2. Studied PPCP compounds, sorted by LLOQ in Surface Water.

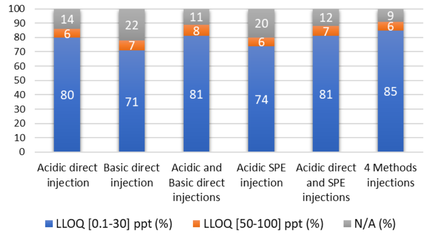

Figure 3. Surface water LLOQ depending on analytical conditions.

Basic conditions. Compared to acidic method used alone, injecting both in acidic and basic conditions (DI) has a low positive impact: 1% gain in the number of LLOQ below 30ppt and 3% gain in total coverage. Indeed, if some basic compounds show better retention and better signal to noise (S/N) in basic conditions, some others probably have their pKa getting closer to the mobile phase pH leading to poor peak shapes and higher LLOQs. Still, by this approach some specific compounds can be newly included in the [0.1-30] ppt LLOQ list: Mestranol, Norgestrel, Phenazine, Chlorpromazine and Tamoxifen.

Online SPE. Similarly, compared to DI alone, using both DI and SPE (acidic) shows a low positive gain: 1% in LLOQ below 30ppt and 2% in total coverage. Indeed, if some compounds are very well retained on the SPE and present a big increase in S/N, some others are negatively impacted, presenting low retention and degraded performances. Still, this approach gives additional LLOQ below 30 ppt: Aminopyrine, Androstenedione, Chlorpromazine, Ciprofloxacine, Clorsulon, Danofloxacin and Norgestrel.

Any combination is possible. Coupling acidic DI and basic SPE (not shown) would enable 7 more compounds to have a LLOQ below 30ppt: Estrone, 17a-Estradiol, 17a-Ethinylestradiol, Androstenedione, Norgestrel, Phenazine and Spiramycin.

Using 4 methods. Using all methods has a not negligible impact: 5% gain in LLOQ below 30ppt and 5% gain in total coverage. This is 14 compounds that couldn't be quantified by using only acidic DI: Estrone, Etoposide, Mestranol, Phenazine, 10,11-Dihydrocarbamazepine, 17a-Ethinylestradiol, Androstenedione, Azelnipidine, Danofloxacin, Fosamprenavir, Norfloxacine, Prednisolone and Tamoxifen.

This analytical setup has great capability and can automatically switch from method to method. Depending on local regulations, additional compounds reached by each method can be considered by one as relevant. The given flexibility is maximal and enable to individually decide the ratio between efficiency and exhaustivity.

5. Conclusion

This LC/MS/MS single automated system and multi-method approach appeared to be a good tool to measure a large quantity of PPCP with a wide variety of chemical properties at low concentration in tap and surface water, with the required method performances. It is a very promising start for a total water analysis LC-MS/MS system.