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ORIGINAL PAPER

Multiresidue methods for the analysis of pharmaceuticals, personal care products and illicit drugs in surface water and wastewater by solid-phase extraction and ultra performance liquid chromatography–electrospray tandem mass spectrometry

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Abstract The main aim of the presented research is to introduce a new technique, ultra performance liquid chromatography–positive/negative electrospray tandem mass spectrometry (UPLC–ESI/MS/MS), for the development of new simultaneous multiresidue methods (over 50 compounds). These methods were used for the determination of multiple classes of pharmaceuticals (acidic, basic and neutral compounds: analgesic/anti-inflammatory drugs, antibiotics, antiepileptics, beta-adrenoceptor blocking drugs, lipid regulating agents, etc.), personal care products (sunscreen agents, preservatives, disinfectant/antiseptics) and illicit drugs (amphetamine, cocaine and benzoylecgonine) in surface water and wastewater. The usage of the novel UPLC system with a 1.7 μm particle-packed column allowed for good resolution of analytes with the utilisation of low mobile phase flow rates (0.05–0.07 mL min^{-1}) and short retention times (method times of up to 25 min), delivering a fast and cost-effective method. SPE with the usage of Oasis MCX strong cation-exchange mixed-mode polymeric sorbent was chosen for sample clean-up and concentration. The influence of mobile phase composition, matrix-assisted ion suppression in ESI–MS and SPE recovery on the sensitivity of the method was extensively studied. The method limits of quantification were at low nanogram per litre levels and ranged from tenths of ng L^{-1} to tens of ng L^{-1} in surface water and from single ng L^{-1} to a few hundreds of ng L^{-1} in the case of wastewater. The instrumental and method intraday and interday repeatabilities were on average less than 5%. The method was successfully applied for the determination of pharmaceuticals in the River Taff (South Wales) and a wastewater treatment plant (WWTP Cilfynydd). Several pharmaceuticals and personal care products were determined in river water at levels ranging from single ng L^{-1} to single μg L^{-1}.

Keywords Pharmaceuticals · Personal care products · Illicit drugs · Ultra performance liquid chromatography–tandem mass spectrometry · Solid-phase extraction · Multiresidue method · Ion suppression

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Introduction

Pharmaceuticals and personal care products (PPCPs) constitute a group of emerging contaminants which have received considerable attention in recent years. PPCPs are regarded as being potentially hazardous compounds as many of them are ubiquitous, persistent and biologically active compounds with recognised endocrine-disruption functions. Additionally, due to their continuous introduction into the environment and synergic effects through combined parallel action, even compounds of a low persistence might cause unwanted effects in the environment [1, 2].

PPCPs are present in the aqueous environment at low ng per litre levels [1–31], which presents a significant analytical challenge. Techniques that meet the challenge are mainly chromatographic techniques coupled with mass spectrometry. Many papers tackling the problem of the analysis of PPCPs in the aqueous environment have been published over the last decade [5–31]. Due to both the concern and resulting growing interest regarding the presence and fate of many PPCPs in the environment as well as the high cost and duration of analysis, there is a need to introduce fast and sensitive multiresidue methods that are capable of the analysis of multiple classes of drugs within one analytical procedure. Because PPCPs, especially pharmaceuticals and their metabolites, are polar, gas chromatography is of limited value as it requires time-consuming derivatisation procedures. Therefore, liquid chromatography–mass spectrometry (LC/MS) using mainly ESI (electrospray ionisation) is the method of choice for the analysis of these polar compounds in complex matrices. Only recently, a few papers presenting multiresidue methods utilising solid-phase extraction and liquid chromatography coupled with electrospray ionisation mass spectrometry or tandem mass spectrometry for the analysis of up to 30 PPCPs within one analytical procedure were published [32–37]. However, almost all of these methods faced the problem of long retention times of analytes of up to 50 minutes of elution gradient time and an average mobile phase flow rate of 0.2 mL min^{-1}.

Several groups of pharmaceuticals, personal care products and illicit drugs (54 compounds) were the subject of the presented research (Table 1). The choice of pharmaceuticals was mainly based on prescription data in Wales and England [38, 39] and the metabolism routes of pharmaceuticals, mainly excretion as parent compounds and active main metabolites. The choice of personal care products (PCPs) was based on their high annual usage in a wide range of household products and concern over their possible effects on human and aquatic organisms [40]. Among the pharmaceuticals studied are: antibacterial drugs, anti-inflammatory/analgesics, antiepileptic, beta-blockers, lipid-regulating agents, H2-receptor antagonists and a few others. Among PCPs there were: sunscreen agents, preservatives, disinfectants/antiseptics and others. Detailed information on the presence, fate and effects of PPCPs on human and the environment can be found elsewhere [1–31]. Drugs of abuse were also studied as the verification of their presence in raw sewage will enable more precise estimation of their usage [1, 41]. This paper presents a comprehensive, fast and sensitive analytical procedure for 54 PPCPs utilising solid-phase extraction for sample preparation and ultra performance liquid chromatography coupled with tandem mass spectrometry (UPLC–MS/MS) for analyte identification and quantification.

Experimental

Chemicals and materials

All reference standards were of >95% purity and were purchased from Sigma-Aldrich (Gillingham, UK) and Sequoia Products Research Limited (Pangbourne, UK). All solvents used and mobile phase additives were of LC/MS quality. The following surrogate/internal standards (SS/IS) were used: phenacetin-ethoxy-1-^{13}C (98.52 atom%^{13}C; CAS No. 72156-72-0), caffeine-d9 (1,3,7-trimethyl-d9; CAS No. 72238-85-8), clofibric-d4 acid (4-chlorophenyl-d4; CAS No. 882-09-7), 3,4-dichlorobenzoic-d3 acid (2,5,6-d3; CAS No. 350818-53-0), bisphenol A-d16 (CAS No. 96210-87-6) and 4-chlorophenol-d4 (2,3,5,6-d4; CAS No. 344298-84-6). All surrogate/internal standards were purchased from Sigma-Aldrich and QMX Laboratories Limited (Essex, UK).

Different water and wastewater samples were used for method development and validation. These were:

- HQ water: ultrapure water (Neptune Purite, MJ Patterson Scientific Ltd, Luton, UK),
- BB water: surface water, collected from the source of the River Taff in Brecon Beacons National Park (Wales, UK), not affected by anthropogenic contaminants such as PPCPs; average dissolved organic carbon, 4.5 mg DOC L^{-1},
- WWTP wastewater: wastewater collected from Cilfynydd Wastewater Treatment Plant (Wales, UK).

Stock solutions of PPCPs (0.5–1 g L^{-1}) were prepared in methanol and stored in the dark at 4 °C. Working solutions were prepared fresh daily by diluting the stock solution with methanol and were stored at 4 °C. All glassware was deactivated with dimethylchlorosilane (5% DMDCS in toluene, Sigma-Aldrich) [44].

Sample collection and preparation

2.5-L silanized amber bottles with teflon-faced phenolic caps (Wheaton, Millville, NJ, USA) were used for sample collection. Immediately after collection, samples were acidified with 31% HCl to pH 2.0 and stored at 4 °C. River water samples were vacuum-filtered through a 0.7-μm glass fibre filter GF/F (Whatman, Maidstone, UK). Wastewater samples were primarily filtered through GF/D 2.7 μm glass fibre filter (Whatman) and subsequently through 0.7 μm glass fibre filter GF/F (Whatman). Two replicate grab samples were collected each time at each sampling point.

Ultra performance liquid chromatography–tandem mass spectrometry

Waters ACQUITY UPLC™ system (Waters, Manchester, UK) consisting of an ACQUITY UPLC™ binary solvent

Table 1 Chosen PPCPs and their properties [42, 43]

Group	Properties					
	Compound	CAS No	Molecular formula	MW	pK_a	log K_{ow}
Pharmaceuticals						
Antibacterial drugs	Trimethoprim	738-70-5	$C_{14}H_{18}N_4O_3$	290.32	7.1	0.8–1.4
	Sulfamethoxazole	723-46-6	$C_{10}H_{11}N_3O_3S$	253.28	5.8	0.9–2.5
	Amoxicillin	26787-78-0	$C_{16}H_{19}N_3O_5S$	365.40	2.8, 7.2	(−)0.6–0.9
	Chloramphenicol	56-75-7	$C_{11}H_{12}Cl_2N_2O_5$	323.13	11.0	(−)0.2–1.5
	Erythromycin	114-07-8	$C_{37}H_{67}NO_{13}$	733.93	8.9	3.1
	Metronidazole	443-48-1	$C_6H_9N_3O_3$	171.15	2.4	(−)0.3–0.02
Anti-inflammatory/analgesics	Paracetamol	103-90-2	$C_8H_9NO_2$	151.16	9.4	0.5–0.9
	Ibuprofen	15687-27-1	$C_{13}H_{18}O_2$	206.28	4.9	3.5–4.0
	Diclofenac	15307-86-5	$C_{14}H_{11}Cl_2NO_2$	296.15	4.2	4.2–4.5
	Ketoprofen	22071-15-4	$C_{16}H_{14}O_3$	254.28	4.5	3.6–3.1
	Naproxen	22204-53-1	$C_{14}H_{14}O_3$	230.26	4.2	3.2–3.3
	Aspirin	50-78-2	$C_9H_8O_4$	180.16	3.5	1.2–1.4
	Salicylic acid (aspirin metabolite)	69-72-7	$C_7H_6O_3$	138.12	3.0	2.3–2.4
	Mefenamic acid	61-68-7	$C_{15}H_{15}NO_2$	241.29	4.2	4.0–5.1
	Codeine	76-57-3	$C_{18}H_{21}NO_3$	299.36	8.2	1.2–2.0
	Tramadol	27203-92-5	$C_{16}H_{25}NO_2$	263.04	9.4	3.0
Antiepileptic drugs	Carbamazepine	298-46-4	$C_{15}H_{12}N_2O$	236.27	13.9	2.4–2.9
	Gabapentin	60142-96-3	$C_9H_{17}NO_2$	171.24	3.7, 10.7	(−)1.1–0.8
Beta-adrenoceptor-blocking drugs	Propranolol	525-66-6	$C_{16}H_{21}NO_2$	259.35	9.4	2.7–3.6
	Metoprolol	37350-58-6	$C_{15}H_{25}NO_3$	267.36	9.7	1.9–2.5
	Atenolol	29122-68-7	$C_{14}H_{22}N_2O_3$	266.34	9.2	0.2–0.5
Lipid-regulating agents	Clofibric acid	882-09-7	$C_{10}H_{11}ClO_3$	214.65	-	2.6
	Bezafibrate	41859-67-0	$C_{19}H_{20}ClNO_4$	361.82	-	4.3
	Simvastatin	79902-63-9	$C_{25}H_{38}O_5$	418.57	13.5	4.4–4.9
H2-receptor antagonists	Ranitidine	66357-35-5	$C_{13}H_{22}N_4O_3S$	314.41	8.2, 2.7	(−)1.1–1.9
	Cimetidine	51481-61-9	$C_{10}H_{16}N_6S$	252.34	6.8	0.4–0.9
	Sulfasalazine	599-79-1	$C_{18}H_{14}N_4O_5S$	398.39	-	3.7–4.8
	Sulfapyridine (sulfasalazine metabolite)	144-83-2	$C_{11}H_{11}N_3O_2S$	249.29	8.4	0.03–0.4
	5-Aminosalicylic acid (sulfasalazine metabolite)	89-57-6	$C_7H_7NO_3$	153.14	1.9	0.4–1.0
Diuretics	Furosemide	54-31-9	$C_{12}H_{11}ClN_2O_5S$	330.75	3.9	1.5–2.0
Triazides	Bendroflumethiazide	73-48-3	$C_{15}H_{14}F_3N_3O_4S_2$	421.42	8.5	1.9–2.1
Cardiac glicozides	Digoxigenin (metabolite of digoxin)	1672-46-4	$C_{23}H_{34}O_5$	390.51	-	1.1
Angiotensin II antagonists	Valsartan	137862-53-4	$C_{24}H_{29}N_5O_3$	435.52	3.7	5.2
Calcium channel blockers	Diltiazem	42399-41-7	$C_{22}H_{26}N_2O_4S$	414.52	7.7	2.7–3.1
Bronchodilators	Salbutamol	18559-94-9	$C_{13}H_{21}NO_3$	239.31	-	1.0
Antidepressants	Amitriptyline	50-48-6	$C_{20}H_{23}N$	277.41	9.4	4.4–4.9
Drugs of abuse, dopamine uptake inhibitors						
Amphetamine		300-62-9	$C_9H_{13}N$	135.21	10.1	1.8
Cocaine		50-36-2	$C_{17}H_{21}NO_4$	303.36	8.6	2.3
Benzoylecgonine (cocaine metabolite)		519-09-5	$C_{16}H_{19}NO_4$	289.32	-	(−)1.3
Personal care products						
Sunscreen agents	Benzophenone-1	131-56-6	$C_{13}H_{10}O_3$	214.22	-	3.0
	Benzophenone-2	131-55-5	$C_{13}H_{10}O_5$	246.22	-	-
	Benzophenone-3	131-57-7	$C_{14}H_{12}O_3$	228.24	-	3.8
	Benzophenone-4	4065-45-6	$C_{14}H_{12}O_6S$	308.31	-	0.4
Preservatives	Methylparaben	99-76-3	$C_8H_8O_3$	152.15	-	2.0
	Ethylparaben	120-47-8	$C_9H_{10}O_3$	166.17	8.3	2.5

Table 1 (continued)

Group	Properties					
	Compound	CAS No	Molecular formula	MW	pK_a	log K_{ow}
	Propylparaben	94-13-3	$C_{10}H_{12}O_3$	180.20	-	3.0
	Butylparaben	94-26-8	$C_{11}H_{14}O_3$	194.23	8.5	3.6
Disinfectants/antiseptics	Triclosan	3380-34-5	$C_{12}H_7Cl_3O_2$	289.54		4.8
	4-Chloroxylenol	88-04-0	C_8H_9ClO	156.61	9.7	3.3
	Chlorophene	120-32-1	$C_{13}H_{11}ClO$	218.68	-	4.2
	3,4,5,6-Tetrabromo-*o*-cresol	576-55-6	$C_7H_4Br_4O$	423.72	-	5.6
	p-Benzylphenol	101-53-1	$C_{13}H_{12}O$	184.23	-	3.4
Other	Bisphenol A	80-05-7	$C_{15}H_{16}O_2$	228.29	-	3.3
	4-*tert*-Octylphenol	140-66-9	$C_{14}H_{22}O$	206.32	-	5.3

manager, an ACQUITY UPLC™ sample manager, a UV detector (ACQUITY UPLC™ UV detector) and an ACQUITY UPLC BEH C18 column (1.7 μm; 1 mm× 100 mm) was used for the separation of analytes.

Initial studies involved an investigation into the choice of mobile phase and its additives, aiming at the highest improvement in compound separation during LC and ESI performance in both positive and negative ionisation modes. Studied solvents used as mobile phases were: H_2O, MeOH and acetonitrile. Among the mobile phase additives studied were basic additives (concentration used: 1–50 mM)—ammonia, ammonium formate and actetate, primary amines (methyl-, ethyl- and butylamine), secondary amines (dimethyl-, diethyl- dibutylamine), tertiary amines (trimethyl-, triethyl-, tributylamine)—and acidic compounds (concentration used: 0.05–0.5%): formic and acetic acid.

Two parallel LC methods were chosen for two groups of compounds showing the maximum sensitivity in positive or negative ionisation mode in the ESI source (Table 2). After initial investigations, water and methanol were chosen as mobile phases for both methods. Acetic acid (0.5%) was applied as a mobile phase additive in Method 1. 0.5% acetic acid and 5 mM NH_4OH were used as mobile phase additives in Method 2. The compositions of mobile phases, the gradient programs and the flow rates used in Methods 1 and 2 are presented in Fig. 1.

A Quatro Micro triple-quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ionisation (ESI) source was used for PPCP identification and quantification. The MS parameters for the method are gathered in Fig. 1. The analyses were performed in both positive (Method 1) and negative (Method 2) modes. Nitrogen, used as a nebulising and desolvation gas, was provided by a high-purity nitrogen generator (NM 30LA 230VOC, Peak Scientific Instruments Ltd., Renfrew, UK). Argon (99.999%) was used as a collision gas. MassLynx 4.1 (Waters) software was used to collect and analyse the obtained data.

The mobile phase was introduced into the ion source from LC without splitting. Mass spectrometric analyses were carried out in the multiple reaction monitoring (MRM) mode, measuring the fragmentation of the protonated (Method 1) or deprotonated (Method 2) pseudo-molecular ions of each analyte. A dwell time of 200 ms per ion pair was used. Chosen fragmentation products for each analyte were those with the most intense signals. The optimisation of MS parameters such as cone voltages, energy collisions and other instrumental parameters was done individually for each compound in a continuous-flow mode through the direct infusion of standard solutions at concentrations of 1 mg L^{-1} into the stream of the mobile phase. For confirmation purposes, the optimisation of precursor ion/product ion transitions was also undertaken with QuanOptimise software (Waters).

Solid-phase extraction

Sample preparation was undertaken with solid-phase extraction using the Gilson (Middleton, WI, USA) Aspec XL4. Evaporation of SPE extracts was carried out with TurboVap LV concentration workstation (Caliper, Runcorn, UK). The optimisation of the SPE method involved the type of adsorbent, pH value of the sample, elution conditions and eluting agents. The cartridges used were Oasis HLB, MCX, MAX, WCX and WAX (60 mg, Waters), Chromabond C18ec (200 mg, Anachem, Luton, UK) and Isolute ENV+ and HCX (100 and 200 mg respectively, Kinesis, St. Neots, UK).

Oasis MCX was found to be the most effective adsorbent for the two groups of PPCPs studied. The whole SPE extraction procedure is presented in Fig. 1.

SPE recovery and signal suppression

Absolute SPE recoveries for analysed PPCPs in HQ, BB water and wastewater (influent and effluent) were calculated as the ratio of the PPCP peak area in the sample (HQ,

Table 2 Optimised MRM conditions for the analysis of the chosen PPCPs by UPLC/MS/MS (CV: cone voltage in V; CE: collision energy in eV)

Compound	ESI	CV/CE	MRM1 (quantification)	CV/CE	MRM2 (confirmation)
Trimethoprim	+	42/22	290.9>230.0	42/22	290.9>123.0
Sulfamethoxazole	+	26/16	253.9>156.0	26/21	253.9>107.9
	-	30/17	251.9>156.0	30/25	251.9>91.9
Amoxicillin	+	26/28	365.9>113.9	26/15	365.9>159.9
Chloramphenicol	+	20/10	323.0>274.8	20/10	323.0>304.8
	-	27/15	320.8>151.8	27/15	320.8>256.0
Erythromycin-H_2O	+	26/15	716.4>558.2	26/34	716.4>158.1
Metronidazole	+	26/15	171.9>127.9	26/23	171.9>81.9
Paracetamol	+	26/16	151.9>110.0	26/24	151.9>92.9
Ibuprofen	-	20/8	205.0>161.1	-	-
Diclofenac	-	22/13	293.8>249.9	-	-
Ketoprofen	-	20/8	252.9>209.1	-	-
Naproxen	-	15/8	228.9>185.1	15/15	228.9>170.1
Aspirin	-	12/20	178.9>92.8	12/6	178.9>136.9
Salicylic acid	-	30/15	136.8>92.9	30/30	136.8>64.9
Mefenamic acid	-	30/15	240.0>196.1	-	-
Codeine	+	45/25	299.9>214.9	45/4	299.9>224.9
Tramadol	+	15/15	264.1>246.0	15/15	264.1>57.8
Carbamazepine	+	26/19	236.9>194.1	26/19	236.9>192.1
Gabapentin	+	26/10	172.2>154.1	26/10	172.2>137.0
Propranolol	+	34/18	259.9>183.1	34/16	259.9>116.0
Metoprolol	+	35/17	268.1>115.9	35/20	268.1>97.9
Atenolol	+	34/19	266.9>190.1	34/25	266.9>145.0
Clofibric acid	-	20/15	212.9>126.9	20/10	212.9>84.9
Bezafibrate	-	30/19	359.8>153.9	30/30	359.8>273.9
Simvastatin	+	25/10	419.0>284.9	25/10	419.0>199.0
Ranitidine	+	26/17	315.9>176.0	26/24	315.9>123.9
Cimetidine	+	26/15	252.9>159.0	26/15	252.9>117.0
Sulfasalazine	-	35/25	396.8>197.1	35/25	396.8>240.0
Sulfapyridine	+	26/16	249.9>156.0	26/16	249.9>184.0
5-Aminosalicylic acid	+	26/15	153.9>136.0	26/20	153.9>108.0
Furosemide	-	30/20	328.8>205.0	30/15	328.8>284.9
Bendroflumethiazide	-	45/25	419.8>289.0	45/25	419.8>327.8
Digoxigenin	-	34/30	389.3>327.2	38/30	389.3>134.9
Valsartan	+	20/15	436.6>234.9	20/15	436.6>290.9
	-	35/25	434.0>179.1	35/20	434.0>350.1
Diltiazem	+	35/20	415.0>178.0	35/20	415.0>310.0
Salbutamol	+	26/20	240.0>148.0	26/10	240.0>222.1
Amitriptyline	+	30/20	278.0>233.0	30/20	278.0>191.0
Amphetamine	+	18/10	135.9>119.0	18/16	135.9>90.9
Cocaine	+	34/22	303.9>182.1	34/22	303.9>81.9
Benzoylecgonine	+	30/25	289.9>168.1	30/18	289.9>104.9
Benzophenone-1	-	36/20	213.0>134.8	34/25	213.0>90.8
Benzophenone-2	-	26/20	245.0>108.7	26/15	245.0>135.1
Benzophenone-3	-	30/20	227.1>211.0	34/24	227.1>183.9
Benzophenone-4	-	44/24	307.0>227.1	42/35	307.0>211.1
Methylparaben	-	34/20	150.8>91.8	20/14	150.8>135.8
Ethylparaben	-	20/14	164.9>136.6	26/20	164.9>91.9
Propylparaben	-	34/25	179.0>91.8	20/16	179.0>136.0
Butylparaben	-	34/25	193.1>91.8	40/16	193.1>136.0
Triclosan	-	18/10	288.8>34.8	18/10	288.8>36.8
4-Chloroxylenol	-	34/15	156.0>34.8	34/15	156.0>120.1
Chlorophene	-	42/25	218.0>154.0	42/25	218.00>34.8
3,4,5,6-Tetrabromo-*o*-cresol	-	38/26	422.7>80.7	42/25	422.7>78.7
p-Benzylphenol	-	34/25	183.1>76.9	34/20	183.1>104.9
Bisphenol A	-	34/20	227.0>212.1	34/30	227.0>133.0

Table 2 (continued)

Compound	ESI	CV/CE	MRM1 (quantification)	CV/CE	MRM2 (confirmation)
4-*tert*-Octylphenol	-	34/20	205.1>134.0	34/25	205.1>133.0
IS/SS					
Phenacetin-ethoxy-1-^{13}C	+	34/15	180.9>139.0	-	-
Caffeine-d9	+	34/16	204.0>144.0	-	-
Clofibric-d4 acid	-	18/15	217.9>132.0	-	-
3,4-Dichlorobenzoic-d3 acid	-	25/15	194.0>149.9	-	-
Bisphenol A-d16	-	40/18	241.3>223.1	-	-
4-Chlorophenol-d4	-	32/16	130.8>34.4	-	-

BB water and wastewater) extract spiked before extraction with PPCPs (the peak area of PPCP in the unspiked sample extract was subtracted) to the PPCP peak area in the unextracted standard solution.

Signal suppression was evaluated for each PPCP as a percentage decrease in signal intensity in the sample matrix versus in deionised water. The following equation was used for the signal suppression calculation:

$$\text{Signal suppression}[\%] = \left(1 - \frac{I_S - I_0}{I_{HQ}}\right) \times 100 \quad (1)$$

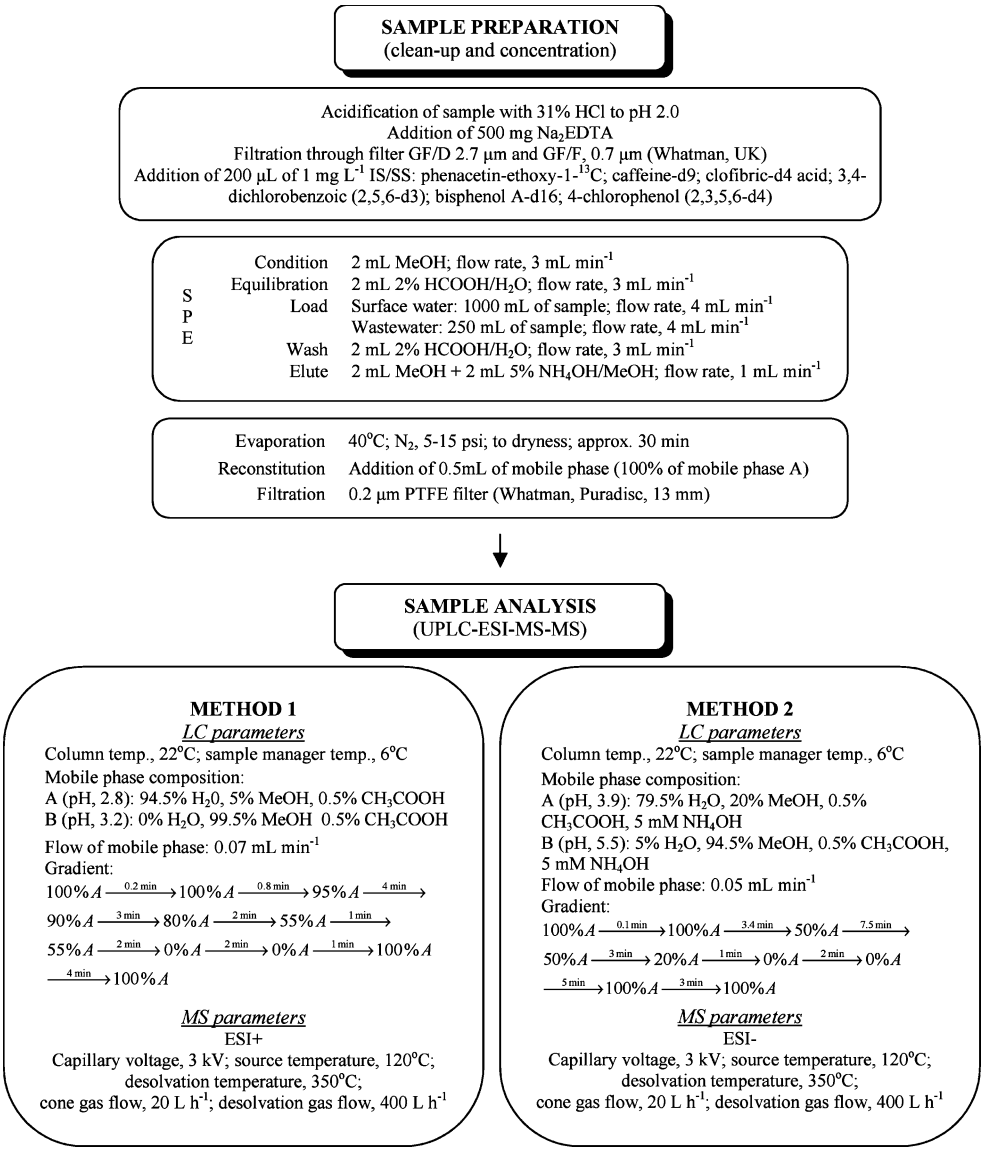

Fig. 1 Sample preparation and analysis—the procedure

where: I_S was the PPCP peak area in BB water and wastewater extract spiked after extraction with 200–500 μg $L^{-1}$of each PPCP, I_0 was the PPCP peak area in unspiked BB water and wastewater extract, and I_{HQ} was the PPCP peak area in HQ water extract spiked after extraction with 200–500 μg $L^{-1}$of each PPCP.

Quantification and method validation parameters

Compounds were quantified by MRM, using the highest characteristic precursor ion/product ion transitions and recording 1–2 transitions simultaneously using QuanLynx software (Waters). Twelve-point multicomponent internal standard calibration curves for the HQ water and BB water extract spiked with PPCPs before extraction (0–12,000 ng L^{-1}) were used for quantification of PPCPs.

All instrumental and method validation parameters such as linearity and range, accuracy, precision, detection and quantification limits and calibration curve were determined for HQ water spiked with known concentrations of PPCPs and BB water spiked with known concentrations of PPCPs before extraction. Detailed discussion concerning validation of the methods is presented elsewhere [44]. The linearity and range of the analytical procedure were checked by serial dilution of a stock solution of PPCPs (10 mg L^{-1}). Several concentration levels (that are typically measured in surface and wastewater) were used: 0–12,000 ng L^{-1} of each PPCP. Accuracy of the method was evaluated as the percentage of deviation from the known added amount of analyte in the sample.

Precision was evaluated as the relative standard deviation (RSD) of replicate measurements. Instrumental intraday precision and intraday precision of the analytical method were verified under the same operating conditions over a short interval of time. Nine determinations covered respectively three concentrations (10–1,000 μg L^{-1}) of acidified HQ standards or BB water extract spiked with PPCPs before extraction. Instrumental interday precision and interday precision of the analytical method were verified by determinations that covered three concentrations (10–1,000 μg L^{-1}) of HQ standards solutions or BB water extract spiked with PPCPs before extraction, with three replicates each undertaken on three different days.

Quantitation and detection limits were determined using a signal-to-noise approach. HQ water standard solutions were used for instrumental detection and instrumental quantification limit determinations ($IDL_{S/N}$ and $IQL_{S/N}$ respectively). BB water extracts spiked with PPCPs before extraction were used for method detection and method quantification limit determination ($MDL_{S/N}$ and $MQL_{S/N}$ respectively). The quantitation limit ($QL_{S/N}$) was estimated for the concentration of compound that gave a signal-to-noise ratio of 10:1. The detection limit ($DL_{S/N}$) corresponded to the concentration that gave a signal-to-noise ratio of 3:1. Method quantification limits (MQL_{calc}) for BB water and WWTP wastewater were also calculated using the following equation [31]:

$$MQL_{calc} = \frac{IQL_{S/N} \times 100}{Rec \times CF} \quad (2)$$

where: $IQL_{S/N}$ is the instrumental quantification limit [ng L^{-1}], Rec is the absolute recovery of the analyte [%], and CF is the concentration factor, which in this method denotes 2000 for BB water, 500 for wastewater.

Results and discussion

Liquid chromatography and mass spectrometry

Ultra performance liquid chromatography was used for the separation of analytes. This new technology offers significant advances in resolution, speed and sensitivity due to the utilisation of columns packed with sub-2 μm particles and high operating pressures of up to 15000 psi.

The two UPLC–MS/MS methods (Methods 1 and 2) were established to simultaneously analyse 54 PPCPs. Methanol and water were chosen as mobile phases for PPCP separation in both Methods 1 and 2. Acidic additive (0.5% acetic acid) was chosen as an additive in Method 1, as it is known to promote the protonation of basic molecules and, as a result, an increase in signal in the ESI+ interface. Basic additive ammonia was, on the other hand, added at the concentration of 5 mM to the mobile phases in Method 2 in order to increase retardation of acidic compounds, resulting in better separation of analytes. Acetic acid at a concentration of 0.5% was also added to mobile phases containing ammonia to lower the pH of the mobile phase from above 10 to below 5.

Good separation of almost all analytes was obtained due to the utilisation of a novel 1 mm internal diameter ACQUITY UPLC BEH C18 column with 1.7 μm bridged ethylsiloxane/silica hybrid (BEH) particles. As a result a fast, sensitive and cost-effective method using much lower mobile phase flow rates (0.05–0.07 mL min^{-1}), much shorter retention times of analytes (from 4.8 min to 18.6 min) and very short column equilibration times (3–4 min) when compared to methods established with the usage of conventional HPLC [32, 35] was developed.

The mass spectrometry parameters are presented in Table 2. The protonated (Method 1, ESI+) or deprotonated (Method 2, ESI-) pseudo-molecular ion of the molecule was chosen as a precursor ion. In the case of erythromycin only, the protonated ion of erythromycin-H_2O was analysed [44]. The most intensive product ion from each precursor ion was selected for quantification (MRM1). Retention time was the other primary criterion for compound identification.

Table 3 Performance data for PPCPs (instrumental/method limits of detection and quantification; absolute SPE recoveries)

PPCPs	Method	HQ water[a]			Surface water and wastewater[b]									
					BB water						WWTP effluent		WWTP influent	
		$IDL_{S/N}$ [μg L^{-1}]	$QL_{S/N}$ [μg L^{-1}]	SPE [%][d]	$R^{2,g}$	RSD[f] [%]	$MDL_{S/N}$ [ng L^{-1}]	$MQL_{S/N}$ [ng L^{-1}]	MQL_{calc} [ng L^{-1}]	SPE [%][d]	MQL_{calc}[c] [ng L^{-1}]	SPE [%][e]	MQL_{calc}[c] [ng L^{-1}]	SPE [%][e]
Pharmaceuticals: antibacterial drugs														
Trimethoprim	1	0.2	0.7	81	0.999	6	0.5	1.5	0.4	84	2	64–76	3	53–69
Sulfamethoxazole	1	0.1	0.4	67	0.998	6	0.1	0.5	0.3	60	3	30–50	3	32–39
Amoxicillin	1	2.5	10	53	0.998	11	2.5	10	12	41	31	16–31	87	23–35
Chloramphenicol	2	0.3	0.8	104	0.999	7	0.5	2	1.5	27	6	25–53	4	43–58
Erythromycin-H_2O	1	0.1	0.3	62	0.998	12	0.1	0.5	0.2	74	9	7–13	15	4–5
Metronidazole	1	0.2	1	35	0.999	9	0.5	1.5	1.5	34	8	26–30	16	13–21
Pharmaceuticals: anti-inflammatory/analgesics														
Paracetamol	1	0.5	2	9	0.998	7	0.5	11.5	11.5	9	80	5–20	267	3–15
Ibuprofen	2	0.1	0.5	66	0.999	5	0.1	0.3	0.3	86	2	43–67	4	26–61
Diclofenac	2	0.15	0.5	91	1.000	3	0.05	0.5	0.3	94	5	30–41	17	14–26
Ketoprofen	2	0.3	1.0	105	0.999	2	0.1	0.5	0.5	105	3	66–73	4	52–68
Naproxen	2	0.1	0.5	100	1.000	3	0.1	0.3	0.2	99	2	52–67	3	38–48
Aspirin	2	0.3	1.0	98	1.000	3	0.2	0.5	0.5	103	3	66–75	4	52–78
Salicylic acid	2	0.1	0.2	75	1.000	3	0.1	0.3	0.1	77	1	55–73	1	43–56
Mefenamic acid	2	0.15	0.5	81	0.997	5	0.1	0.3	0.3	83	5	20–35	17	6–31
Codeine	1	0.15	0.5	88	0.998	7	0.5	1.5	0.3	75	2	64–86	2	51–51
Tramadol	1	2	5	109	0.999	17	10	30	3	76	10	98–144	10	101–145
Pharmaceuticals: antiepileptic drugs														
Carbamazepine	1	0.05	0.2	107	0.999	13	0.1	0.5	0.2	68	1	55–64	1	35–76
Gabapentin	1	0.3	1	62	0.998	5	0.2	0.6	0.6	86	2	108	2	94–106
Pharmaceuticals: beta-adrenoceptor blocking drugs														
Propranolol	1	0.05	0.2	69	0.997	7	0.1	0.5	0.2	40	2	17–25	3	14–23
Metoprolol	1	0.07	0.2	85	0.995	4	0.1	0.5	0.2	55	1	41–55	1	28–70
Atenolol	1	0.15	0.5	75	0.999	6	0.2	1	0.3	90	1	78–84	2	51–76
Pharmaceuticals: lipid-regulating drugs														
Clofibric acid	2	0.05	0.5	84	1.000	2	0.1	0.3	0.3	96	1	73–92	1	72–79
Bezafibrate	2	10	30	104	0.997	2	4	10	13	115	85	71–135	94	64–101
Simvastatin	1	0.2	0.5	104	0.996	18	20	50	0.6	40	3	33–49	7	15
Pharmaceuticals: H2-receptor antagonists														
Ranitidine	1	0.25	1	63	0.998	10	1	3	1	44	9	23–36	12	16–24
Cimetidine	1	0.15	0.5	54	1.000	7	0.1	0.5	0.4	65	1	74–81	1.5	68–71
Sulfasalazine	2	0.3	2	66	0.998	3	0.5	1.5	1	72	23	18–75	85	5–16
Sulfapyridine	1	0.5	2	78	0.999	8	0.5	2	2	69	8	50–69	10	42–54
5-Aminosalicylic acid	1	2	5	23	0.998	10	5	15	48	5	172	6–8	159	6–13

Other pharmaceuticals														
Furosemide	2	2	6	76	1.000	11	2	6	3.8	79	43	28–41	117	10–23
Bendroflumethiazide	2	0.2	1.0	83	1.000	4	0.1	0.5	0.8	65	8	26–44	8	25–54
Digoxigenin	2	10	25	135	0.999	9	10	30	17	75	268	19–35	538	9–41
Valsartan	2	0.5	2.5	103	0.996	6	0.1	0.5	1	111	5	105–169	5	102–104
Diltiazem	1	0.1	0.5	72	0.998	6	0.5	1	3	9	8	12–13	20	5–24
Salbutamol	1	0.1	0.5	72	0.997	7	0.1	0.5	0.3	88	1.5	65–79	2	59–81
Amitriptyline	1	0.1	0.3	83	0.995	9	0.1	0.5	0.3	37	2	1–2	32	2–4
Drugs of abuse														
Amphetamine	1	0.3	1	107	0.999	4	0.2	1	1	91	3	72–109	3	73–105
Cocaine	1	0.05	0.2	90	0.998	6	0.1	0.3	0.2	70	1	49–50	1	43–47
Benzoylecgonine	1	0.05	0.2	96	0.996	10	0.2	1	0.1	131	1	70–98	1	61–69
Personal care products: sunscreen agents														
Benzophenone-1	2	0.15	0.5	105	0.999	3	0.1	0.3	0.2	99	2	48–54	3	31–43
Benzophenone-2	2	0.5	1.5	112	0.999	4	0.1	0.5	0.6	117	13	24–37	18	17–20
Benzophenone-3	2	7	20	57	0.998	6	5	15	10	97	80	50–81	104	39–49
Benzophenone-4	2	1.0	3	57	0.995	8	1	3	2	67	10	59–118	35	17–50
Personal care products: preservatives														
Methylparaben	2	0.1	0.3	75	0.999	5	0.1	0.3	0.2	60	3	18–34	4	14–30
Ethylparaben	2	0.1	0.3	83	1.000	4	0.1	0.5	0.2	75	0.6	29–63	3	21–72
Propylparaben	2	0.1	0.3	98	1.000	4	0.05	0.15	0.1	105	1	59–63	2	39–66
Butylparaben	2	0.2	0.5	101	0.998	4	0.1	0.3	0.2	126	1	72–85	2	47–69
Personal care products: disinfectants/antiseptics														
Triclosan	2	1	3	43	0.997	4	2	5	4	40	72	8–19	97	6–13
4-Chloroxylenol	2	10	30	36	0.999	5	10	30	17	144	84	119–186	102	98–139
Chlorophene	2	1	3	87	0.997	3	1	3	2	99	26	23–31	64	9–22
3,4,5,6-Tetrabromo-*o*-cresol	2	0.1	0.5	31	0.997	3	0.2	1	0.7	35	8	12–18	12	8–21
p-Benzylphenol	2	10	30	95	0.999	1	5	15	11	140	86	70–121	94	64–71
Other														
Bisphenol A	2	2.5	10	104	0.999	3	2	6	5	109	46	43–59	63	32–41
4-*tert*-Octylphenol	2	5	15	26	0.997	4	5	15	12	63	105	29–51	152	20–40

[a] HQ water spiked with pharmaceuticals
[b] BB water and wastewater spiked with pharmaceuticals before extraction
[c] MQL_{calc} calculated for the lowest recorded SPE recovery
[d] Absolute SPE recovery, STD <10%; 200–500 ng of PPCPs sorbed; SPE concentration factor 2000×
[e] Maximum and minimum absolute SPE recoveries calculated for WWTP samples over the period of two months; 200–500 ng of PPCPs sorbed; SPE concentration factor 500×
[f] Interday precision, RSD% (n=9)
[g] R^2 (linearity) calculated for BB water spiked with PPCPs before extraction

A less sensitive secondary transition (MRM2) was used as the second criterion for confirmation purposes. In the cases of ketoprofen, diclofenac, ibuprofen and mefenamic acid no secondary transition was observed.

Solid-phase extraction and matrix-assisted signal suppression

After the initial experiments, only one MCX Oasis adsorbent was chosen for sample clean-up and concentration using only one SPE procedure for all 54 compounds. Oasis MCX is a strong cation-exchange mixed-mode polymeric sorbent, which is capable of both ion-exchange and reversed-phase interactions. MCX sorbent is built upon the HLB copolymer. The additional presence of sulfonic groups allows for cation-exchange interactions. Therefore, MCX adsorbent is designed for the extraction of basic and neutral compounds. This capacity was utilised in the discussed method. Basic compounds were retained on the cartridge due to cation-exchange interactions. Acidic compounds were retained on the cartridge by means of reversed-phase interactions. Acidic pH of the solution (pH, 2) was maintained with HCl in order to ionise basic compounds and neutralise acidic compounds.

Absolute SPE recoveries obtained for the studied PPCPs in HQ, surface and wastewater are presented in Table 3. The results clearly indicate a significant reduction in absolute SPE recoveries of PPCPs occurring mainly in wastewater. It was observed that this decrease in the absolute SPE recovery of analyte is strongly related to the effect of the signal suppression of analytes in the ESI interface (Table 4). There are a few factors that are regarded as being responsible for signal suppression in the ESI interface. Matrix interferences are considered to contribute to the highest extent to signal suppression. However, mobile phase composition and ESI mode also significantly influence the ionisation of molecule in the ESI interface. The performances of sulfamethoxazole, chloramphenicol and valsartan under different conditions (matrix components, mobile phase composition and ESI mode) are good examples (Table 4). These three pharmaceuticals were found to form both protonated or deprotonated pseudo-molecular ions and therefore they could be analysed by means of both Method 1 (ESI+) and Method 2 (ESI−). Although very good sensitivities of both methods were observed in the case of analyses in HQ water, their performances were significantly affected in the presence of matrix components in wastewater. Furthermore, the extent of signal suppression and resulting absolute SPE recoveries varied for the two analytical methods studied using different mobile phase additives and ESI modes. Up to 86% signal suppression (Table 4), resulting in low SPE recovery (<11%) and high MQL (3000 ng L^{-1}), was

Table 4 Absolute SPE recovery and signal suppression for sulfamethoxazole, chloramphenicol and valsartan analysed with Methods 1 and 2

PPCPs/Method		HQ water[a]			Surface water and wastewater[b]									
					BB water				WWTP effluent			WWTP influent		
		$IDL_{S/N}$ [µg L^{-1}]	$IQL_{S/N}$ [µg L^{-1}]	SPE [%][d]	$MDL_{S/N}$ [ng L^{-1}]	$MQL_{S/N}$ [ng L^{-1}]	SPE [%][d]	SS [%][f]	MQL_{calc}[c] [ng L^{-1}]	SPE [%][e]	SS [%][g]	MQL_{calc}[c] [ng L^{-1}]	SPE [%][e]	SS [%][g]
Sulfamethoxazole	1	0.1	0.4	67	0.1	0.5	60	6	3	30–50	38–39	3	32–39	32–57
	2	0.5	1.5	48	1	3	21	29	3000	0.1–1	74–83	3000	0.1–11	80–86
Chloramphenicol	1	0.5	1.5	57	2.5	10	9	86	60	5–9	94–95	75	4–6	94–95
	2	0.3	0.8	104	0.5	2	27	73	6	25–53	50–76	4	43–58	59–77
Valsartan	1	0.5	1.5	146	0.2	1	48	60	1	232–241	(−)140–(−)160	2	184–187	(−)40
	2	0.5	2.5	103	0.1	0.5	111	(−)24	5	105–169	(−)10–(−)65	5	104–102	0

[a] HQ water spiked with pharmaceuticals
[b] BB water and wastewater spiked with pharmaceuticals before extraction
[c] MQL_{calc} calculated for the lowest recorded absolute SPE recovery
[d] Absolute SPE recovery, STD <10%; 200–500 ng of PPCPs sorbed; SPE concentration factor 2000×
[e] Maximum and minimum absolute SPE recoveries calculated for WWTP samples over the period of two months; 200–500 ng of PPCPs sorbed; SPE concentration factor 500×
[f] Signal suppression, STD <10%; SPE concentration factor 2000×
[g] Maximum and minimum signal suppression calculated for WWTP samples over the period of two months; SPE concentration factor 500×

observed in the case of sulfamethoxazole in wastewater influent analysed with Method 2 as opposed to Method 1, where only maximum 57% signal suppression, much higher absolute SPE recoveries (>39%) and low MQL (3 ng L^{-1}) were observed. Therefore, for this compound ESI+ and only CH_3COOH as a mobile phase additive are recommended to achieve a good sensitivity of the method. In the case of chloramphenicol, Method 2 was found to be less affected by matrix interferences, and therefore this method was used for the analysis of chloramphenicol in environmental samples (Table 4). The sensitivity of the method in the case of valsartan on the other hand was influenced by another phenomenon: signal enhancement, resulting in very high SPE recoveries. To reduce this effect, Method 2 was applied to the analysis of valsartan. In summary, not only matrix interferences but also mobile phase compositon and ionisation mode at the ESI interface jointly influence the sensitivity of the method and have to be carefully considered when establishing analytical procedures for the analysis of environmental samples.

To compensate for signal suppression of analytes in the ESI source and low SPE recoveries, six internal/surrogate standards were used. These were:

- Phenacetin-ethoxy-1-^{13}C (98.52 atom %^{13}C): trimethoprim, sulfamethoxazole, amoxicillin, erythromycin-H_2O, metronidazole, paracetamol, codeine, tramadol, carbamazepine, gabapentin, propranolol, metoprolol, atenolol, simvastatin, ranitidine, cimetidine, sulfapyridine, 5-aminosalicylic acid, salbutamol, amitryptyline, amphetamine, cocaine and benzoylecgonine
- Caffeine-d9 (1,3,7-trimethyl-d9): diltiazem
- Clofibric-d4 acid (4-chlorophenyl-d4): ibuprofen, diclofenac, ketoprofen, naproxen, aspirin, salicylic acid, mefenamic acid and clofibric acid
- 3,4-Dichlorobenzoic acid (2,5,6-d3): bezafibrate, furosemide
- Bisphenol A-d16: bendroflumethiazide, sulfasalazine, benzophenones, parabens, triclosan, chlorophene, 3,4,5,6-tetrabromo-*o*-cresol, *p*-benzylphenol, bisphenol A and 4-*tert*-octylphenol
- Chlorophenol (2,3,5,6-d4): digoxigenin, valsartan and 4-chloroxylenol.

The choice of standards was based on similarities in structure with PPCPs and similar performance in SPE–ESI–MS/MS. In the cases of compounds for which IS/SS did not compensate for ion suppression, dilution of samples was undertaken; these were 5-aminosalicylic acid, diltiazem, simvastatin, sulfamethoxazole, methylparaben, digoxigenin, mefenamic acid, triclosan and chlorophene. It was observed that up to eightfold dilution is necessary to avoid matrix-assisted signal suppression in 250-mL WWTP influent samples.

Quantification and method validation parameters

The mean correlation coefficients (R^2) of the calibration curves, which were on average higher than 0.997 for all studied analytes, show good linearity of the method in the studied range of 0–12000 ng L^{-1}. The accuracy was within −30–20%. Both instrumental and method intra- and inter-day repeatabilities, as indicated by the standard deviations calculated from the analysis of three replicates, were on average less than 5%.

The instrumental and method limits of detection and quantification were on average very low, showing the high sensitivities of the methods (Table 3). In surface water, method quantification limits determined using both the signal-to-noise approach and calculated using Eq. 2 varied from 0.1 ng^{-1} L to 48 ng L^{-1}. MQLs in wastewater were found to be much higher due to both lower extraction factors (2000 times in BB water and 500 times in wastewater) and matrix-assisted low SPE recoveries, which were directly linked to signal suppression in the ESI source. MQLs in wastewater varied from 1 ng L^{-1} to 538 ng L^{-1}. In general, the highest sensitivity was observed for antiepileptic drugs, beta-adrenoceptor blocking drugs, drugs of abuse and preservatives. Substituted phenols belonging to the group of disinfectants and antiseptics were found to have on average the highest MQLs, of up to 152 ng L^{-1}.

Environmental application

The newly established methods were applied to verify the presence of over 50 PPCPs in the Welsh environment. Several sampling points along the River Taff (South Wales) were chosen and the influence of wastewater effluent discharged to the river from WWTP Cilfynydd (Wales) on the quality of the river water was studied. Mass chromatograms obtained for a WWTP influent sample, which was extracted and analysed with Methods 1 and 2, are presented in Figs. 2 and 3. The River Taff was chosen for the research as it has its source in the Brecon Beacons National Park and is therefore not polluted with PPCPs. The river flows through several towns and receives treated communal wastewater from WWTP Cilfynydd. Several sampling points were chosen along the River Taff:

1. Brecon Beacons National Park: the source of the River Taff
2. Merthyr Tydfil: 23.5 km downstream, just after Merthyr Tydfil (population 55,000)
3. Abercynon: 12 km downstream of Merthyr Tydfil, just after Abercynon, 1 km upstream of WWTP
4. WWTP Cilfynydd (mainly communal wastewater, biological treatment: trickling filter beds, population

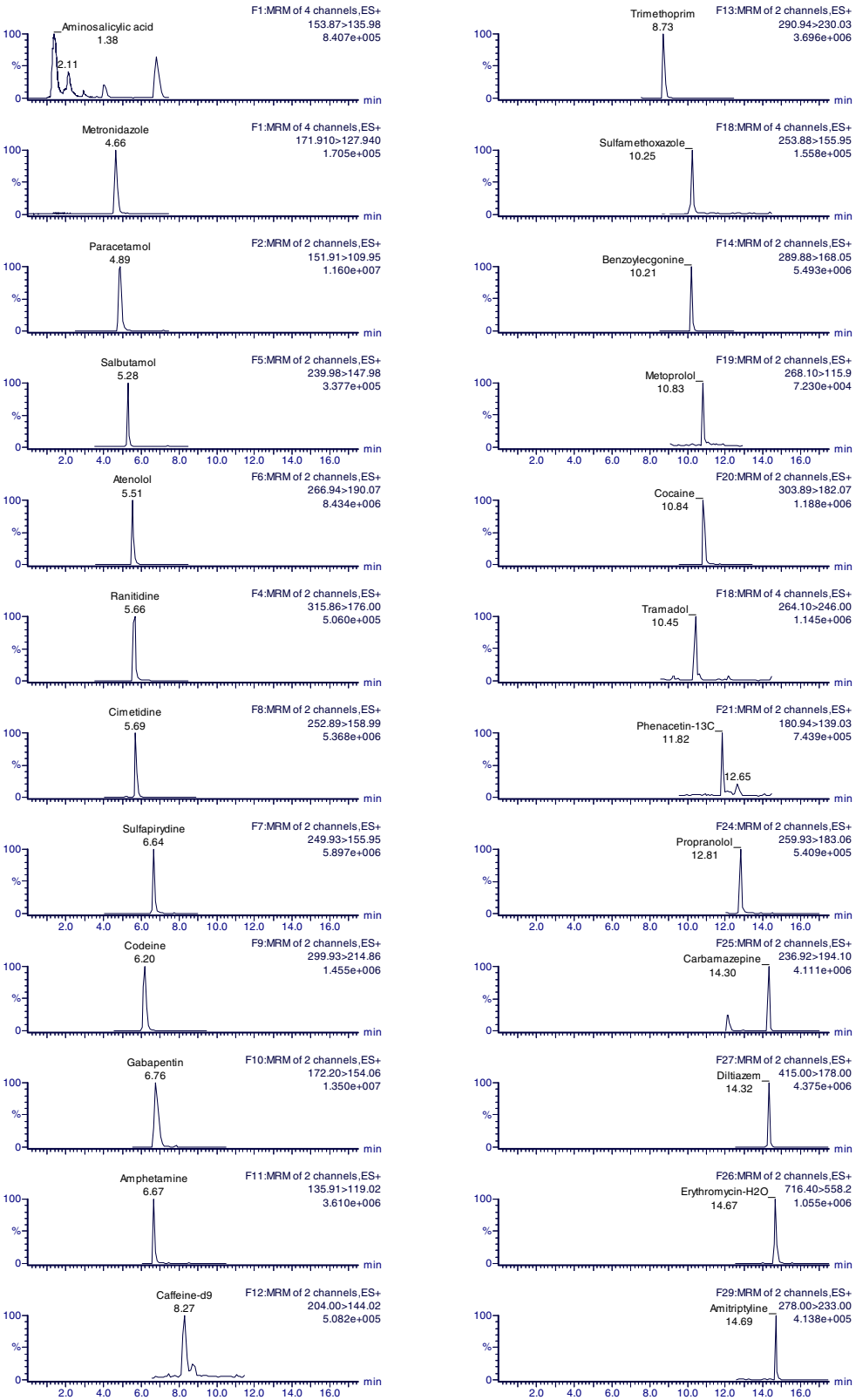

Fig. 2 UPLC/MS/MS separations for PPCPs detected in WWTP influent extracted by SPE and analysed with Method 1 (undetected PPCPs: amoxicillin, t=5.01 min and simvastatin, t=16.34)

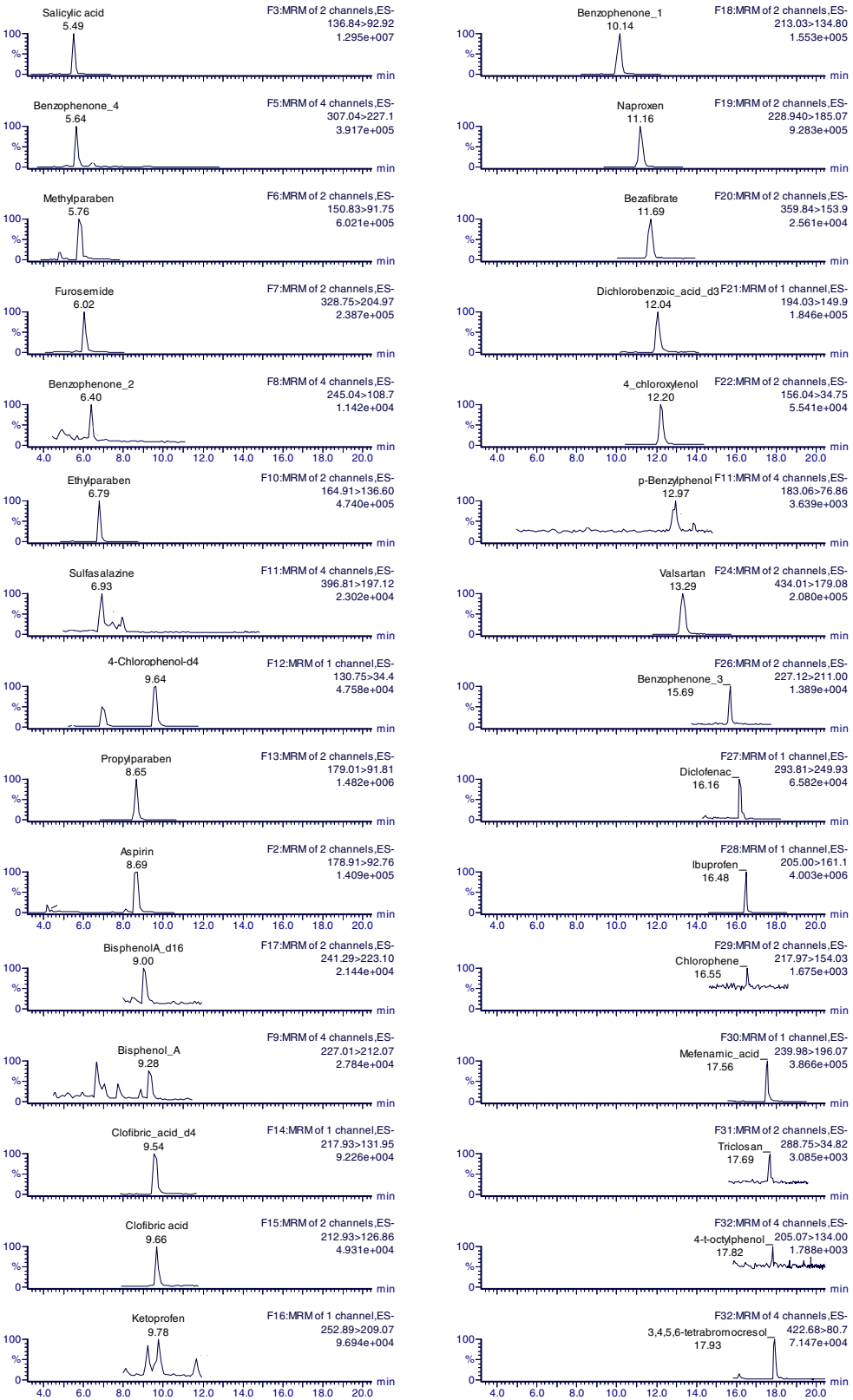

Fig. 3 UPLC/MS/MS separations for PPCPs detected in WWTP influent extracted by SPE and analysed with Method 2 (undetected PPCPs: digoxigenien, t=5.48 min; chloramphenicol, t=5.62; bendroflumethiazide, = 6.41; butylparaben, t=12.43)

Table 5 Concentration of PPCPs in the River Taff (two replicate samples)

Compound		Concentration [ng L^{-1}]				
		River Taff			WWTP Cilfynydd	
		Abcercynon	Pontypridd	Trefforest Estate	WWTP influent	WWTP effluent
Antibacterial drugs	Trimethoprim	<LOQ	108	57	1879	1004
	Sulfamethoxazole	<LOQ	1	<LOQ	<LOQ	12
	Amoxicillin	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Chloramphenicol	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Erythromycin-H_2O	<LOQ	40	26	404	830
	Metronidazole	<LOQ	4	5	2608	373
Anti-inflammatory/Analgesics	Paracetamol	62	185	388	492340	1826
	Ibuprofen	13	19	29	3742	227
	Diclofenac	9	28	22	70	123
	Ketoprofen	2	2	3	102	23
	Naproxen	12	41	50	1082	400
	Aspirin	<LOQ	<LOQ	<LOQ	966	<LOQ
	Salicylic acid	25	34	62	17461	209
	Mefenamic acid	2	10	3	444	115
	Codeine	27	230	224	9766	3948
	Tramadol	435	5970	3480	44700	59046
Antiepileptic drugs	Carbamazepine	7	251	137	2593	3117
	Gabapentin	210	1879	1231	18474	21417
Beta-blockers	Propranolol	7	31	22	542	388
	Metoprolol	7	10	9	110	68
	Atenolol	17	487	273	13874	2702
Lipid-regulating agents	Clofibric acid	<LOQ	3	101	52	17
	Bezafibrate	41	58	60	971	418
	Simvastatin	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
H2-receptor antagonists	Ranitidine	<LOQ	32	12	<LOQ	<LOQ
	Cimetidine	2	105	87	2494	2387
	Sulfasalazine	15	75	76	65	266
	Sulfapyridine	<LOQ	34	10	115	329
	5-Aminosalicylic acid	<LOQ	83	88	4789	3072
Other pharmaceuticals	Furosemide	<LOQ	61	117	2197	1144
	Bendroflumethiazide	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Digoxigenin	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Valsartan	13	28	33	676	344
	Diltiazem	<LOQ	5	6	920	95
	Salbutamol	<LOQ	1	<LOQ	130	66
	Amitriptyline	<LOQ	3	<LOQ	849	207
Drugs of abuse	Amphetamine	1	5	6	5236	127
	Cocaine	<LOQ	2	2	526	149
	Benzoylecgonine	<LOQ	92	78	1229	1597
Sunscreen agents	1-Benzophenone	6	7	9	306	32
	2-Benzophenone	<LOQ	<LOQ	4	25	1
	3-Benzophenone	28	37	36	971	143
	4-Benzophenone	10	227	214	5790	4309
Preservatives	Methylparaben	6	10	<LOQ	2642	0
	Ethylparaben	6	11	13	1036	50
	Propylparaben	7	6	6	1393	63
	Butylparaben	<LOQ	<LOQ	<LOQ	52	<LOQ
Disinfectants/ Antiseptics	Triclosan	10	15	10	70	33
	4-Chloroxylenol	<LOQ	<LOQ	124	21935	975
	Chlorophene	<LOQ	5	6	114	29
	3,4,5,6-Tetrabromo-*o*-cresol	21	147	170	844	1261
	p-Benzylphenol	<LOQ	58	47	3578	90
Other	Bisphenol A	<LOQ	25	18	540	35
	4-*tert*-Octylphenol	<LOQ	<LOQ	305	465	1459

serviced: ~110,000) discharging on-the-site-treated wastewater into the River Taff
5. Pontypridd: 2 km downstream of WWTP, just before Pontypridd (population 33,000)
6. Trefforest Estate: 7 km downstream of Pontypridd
7. Cardiff: 18 km downstream of Trefforest Estate, the bay area of Cardiff (population 320,000), where the river enters the Severn Estuary and the Bristol Channel.

The results are presented in Table 5. No or very low contamination of river water with PPCPs was observed for the first two sampling points, Brecon Beacons and Merthyr Tydfil, and therefore these results are not included in the table. A large increase in PPCP concentration was determined in Pontypridd, the fourth sampling point, which was located 2 km downstream of WWTP Cilfynydd. At two further sampling points (only the Trefforest Estate sampling point is included in Table 5) the concentrations of PPCPs decreased slightly but still remained high, which indicates that there is a significant influence of the treated wastewater discharge on the quality of water in the River Taff. The results presented in Table 5 clearly indicate that the wastewater plant does not efficiently remove all of the PPCPs that are present in the raw communal wastewater, resulting in the discharge of several PPCPs into river water.

Conclusions

This manuscript presents a novel analytical methodology using ultra performance liquid chromatography–positive/negative electrospray tandem mass spectrometry (UPLC–ESI/MS/MS) for the sensitive, fast and cost-effective analysis of 54 pharmaceuticals and personal care products in surface water and wastewater. The PPCPs analysed include multiple classes of pharmaceuticals (acidic, basic and neutral compounds: analgesic/anti-inflammatory drugs, antibiotics, antiepileptics, beta-adrenoceptor blocking drugs, lipid regulating agents, etc.) and personal care products (sunscreen agents, preservatives, disinfectant/antiseptics). SPE using only one type of sorbent, the Oasis MCX strong cation-exchange mixed-mode polymeric sorbent, was chosen for sample clean-up and concentration of all studied PPCPs, based on only one SPE procedure.

The main advantages of the method include its high sensitivity, with MQLs for PPCPs in surface water as low as 0.1 ng L^{-1}. Good separation of analytes in less than 20 min method time, very low column equilibration times (<4 min) and very low mobile phase flow rates (0.05–0.07 mL min^{-1}) were all achieved when a novel ACQUITY UPLC BEH C18 column packed with sub-2 μm particles was used. Additionally, a significant reduction in the usage of the mobile phase was achieved, which further allowed the cost of analysis to be reduced.

This manuscript also tackles problems associated with signal suppression in the ESI interface, which mainly results from the presence of matrix interferences and the mobile phase composition.

The method was successfully applied for the determination of pharmaceuticals in the River Taff (South Wales) and Cilfynydd Wastewater Treatment Plant. Several pharmaceuticals and personal care products were determined in river water at levels ranging from single ng L^{-1} to single μg L^{-1}. PPCPs were found in wastewater at concentrations of up to 500 μg L^{-1}.

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