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Determination of iodinated X-ray contrast media in sewage by solid-phase extraction and liquid chromatography tandem mass spectrometry

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ABSTRACT

A method for the quantitative determination of five iodinated X-ray contrast media (ICMs) in sewage was developed by solid-phase extraction and high-performance liquid chromatography–tandem mass spectrometry. A fused-core analytical column was successfully applied for the first time for the separation of ICMs. Oasis HLB was selected from the sorbents tested because of its higher recoveries. The optimized method allowed the determination of the ICMs at low ng/L levels in both influent and effluent sewage, with detection limits of 40 ng/L and 10 ng/L for most compounds in influent and effluent sewage, respectively.

The five ICMs studied were determined in all samples analysed, with iopromide being the analyte found at the highest concentration (8.9 μg/L), while iopamidol was the analyte found at lowest concentration (1.3 μg/L) in influent sewage. Effluent sewage did not show a significant decrease in ICM concentrations.

1. Introduction

Nowadays, one area on which research interests have focused is the presence of pharmaceutical and personal care products (PPCPs) in the environment due to their widespread use and incomplete removal during sewage treatment. Moreover, the presence of pharmaceuticals in the environment is a matter of concern because little is known about the toxicity derived from constant exposure to them, even at concentrations far below medical doses [1]. The pharmaceutical compounds most often found in the aquatic environment at relatively high concentrations (i.e. μg/L levels) include iodinated X-ray contrast media (ICMs) [2]. ICMs are the most widely-used pharmaceutical compounds for intravascular administration in radiographic procedures, as they create a distinction between the organ to be diagnosed and the surrounding tissue [3]. They are administrated in high doses up to 200 g/patient, with the total amount used worldwide estimated to be 3500 t/year [2]. After application, ICMs are eliminated within 24 h via urine and/or faeces in their unmetabolized form. Thus, they enter domestic sewage and are transported to sewage treatment plants (STPs). It is well-documented that conventional treatments in STPs do not efficiently remove ICMs [4], resulting in their presence at μg/L levels in effluent water from STP, surface water and groundwater [5–9].

Recently, efforts have been made to study the efficiency of different advanced tertiary treatments, such as membrane bioreactors [4], bioelectrochemical systems [10], UV radiation [11] and advanced oxidation/reduction processes [12], among others. Valuable information has been provided by these studies in relation to the occurrence of ICMs and their transformation products compared with the data obtained from conventional treatments [13]. Although most of these treatments improve the elimination of ICMs, none of them enable a quantitative removal.

Different analytical methods have been developed to determine ICMs from environmental samples [6,8,13–15]. With respect to aqueous matrices, the analytical method usually includes solid-phase extraction (SPE), in order to enrich the analytes and clean them up from the matrix sample, followed by liquid chromatography (LC) with mass spectrometry in tandem (MS/MS) using electrospray ionization (ESI) as the detection technique (LC–(ESI)–MS/MS), in order to quantify the analytes at low levels. Although all these methods achieve the determination of ICMs at ng/L levels, the polarity of these compounds make them difficult to extract using SPE. For instance, when the polymeric Isolute ENV+ was used as the SPE sorbent, the recoveries were between 35% and 95% [15,16]. To overcome this, Putschew et al. [14,17] used two cartridges in series (Isolute ENV+ and Envi-Carb) in order to extract ICMs from environmental samples with acceptable recoveries. However, the SPE step can be optimized further. Moreover, the analytical methods already developed are still scarce and some of them focus on a wider group of micropollutants that includes certain ICMs. Thus, new analytical methods are needed in order to increase knowledge regarding the presence of ICMs in the water environment.

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The aim of this study is to develop a simple and sensitive method based on SPE/LC–(ESI)MS/MS for the determination of ICMs at ng/L levels in sewage. Various recently commercially available SPE sorbents will be tested in order to select the most appropriate for this family of compounds.

2. Experimental section

2.1. Materials and reagents

The iodinated X-ray contrast media iopromide, iomeprol, iopamidol, iohexol and diatrizoic acid were purchased from Dr. Ehrenstorfer (Augsburg, Germany) with a purity level between 92.4% and 99.0%. Stock individual solutions were prepared by dissolving each compound in methanol to a concentration of 1000 mg/L and then stored at 4 °C in the refrigerator. A mixture of all compounds in water: methanol (1:1) at a concentration of 100 mg/L was prepared weekly. Working solutions were prepared daily.

Methanol and acetonitrile, both HPLC grade, were purchased from SDS (Peypin, France). Formic acid (98%) was purchased from Sigma-Aldrich (Steinheim, Germany). Hydrochloric acid (HCl), sulphuric acid (H_2SO_4) and nitric acid (HNO_3) were supplied by Prolabo (Foutenay-sous-Bois, France). Ultrapure water was produced by a water purification system from Veolia Waters (Barcelona, Spain). Nitrogen gas (N_2-99.995% quality) was supplied by Carburos Metálicos (Tarragona, Spain).

2.2. Sampling

The sewage samples were collected from the influent and effluent of two urban sewage treatment plants (STPs) located in the area of Tarragona (STP1 and STP2). These STPs mostly receive urban wastewaters and some industrial discharges. They are connected to similar population equivalents (around 140,000 inhabitants) with biological oxygen demand (BOD_5) for influent water of 400 mg/L. The average flow-rate is 30,000 m^3/day for STP1 and 16,000 m^3/day for STP2.

Twenty four-hours composite samples were collected by using pre-cleaned amber glass bottles, acidified to pH 3 (HCl) and stored at 4 °C until analysis.

2.3. Sample extraction

The water samples were filtered using 0.45 μm followed by 0.22 μm nylon filters (Whatman, Maidstone, UK) prior to the extraction step. 200 mg Isolute ENV+ (International sorbent technology, Mid Glamorgan, UK), 150 mg Oasis MCX (Waters, Milford, MA, USA), 150 mg Oasis MAX (Waters) and 500 mg Oasis HLB (Waters) cartridges were tested for the solid-phase extraction. They were connected to a manifold (Teknokroma, Barcelona, Spain) and a pump as a vacuum source.

Oasis HLB cartridges were selected and they were conditioned with 5 mL of methanol followed by 5 mL of ultrapure water. Samples of 100 mL (influent) and 250 mL (effluent) acidified with HCl to pH 2.6 were percolated through the cartridge at between 10 mL/min and 15 mL/min. The retained analytes were eluted with 5 mL methanol. The extract was then evaporated to dryness under a gentle flow of N_2 gas and redissolved with 1 mL of ultrapure water.

2.4. LC–(ESI)MS/MS

The chromatographic system was an Agilent 1200 liquid chromatograph coupled to a triple quadrupole mass spectrometer from Agilent Technologies (Waldbronn, Germany) with an ESI interface, an automatic injector, a degasser, a quaternary pump and a column oven. The chromatographic column was an Ascentis Express C_{18} Fused Core (50 × 4.6 mm, 2.7 μm particle size) from Supelco (Bellefonte, PA, USA) and the volume injected was 50 μL. The mobile phase flow-rate was 0.2 mL/min and the column temperature was kept at 25 °C.

A binary mobile phase with a gradient elution was used. Solvent A was ultrapure water with formic acid (pH 2.6) and solvent B was acetonitrile. The gradient was performed as follows: 5% B constant to 4 min, then %B linearly increased up to 25% at 6 min and kept constant until 13 min. Finally, it decreased to 5% in 3 min. All of the compounds were eluted within 13 min.

In order to achieve sensitive and selective detection of analytes, the (ESI)MS/MS parameters were optimized by the injection of each compound. Analyses were performed in the multiple reaction monitoring (MRM) mode under positive ionization. Optimized MS/MS parameters were as follows: a N_2 flow-rate of 12 L/min, a capillary voltage of 4000 V, a nebulizer pressure of 45 psi (N_2) and a source temperature of 350 °C. The cone voltage and collision energies were optimized for each compound. The cone voltage was between 120 V and 150 V and collision energies between 15 V and 60 V for all compounds. The retention time and two MRM transitions were compared to confirm the presence of the analytes. The most abundant MRM transition was used to quantify. These data, together with structure of the compounds, are collected in Table 1. Two time windows were used in order to improve the sensitivity: 0–9 min (iopamidol, diatrizoic acid, iohexol and iomeprol) and 9–16 min (iopromide).

3. Results and discussion

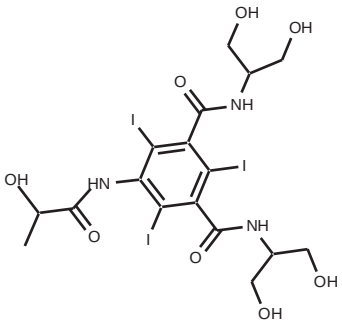
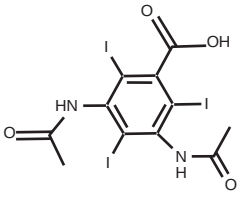
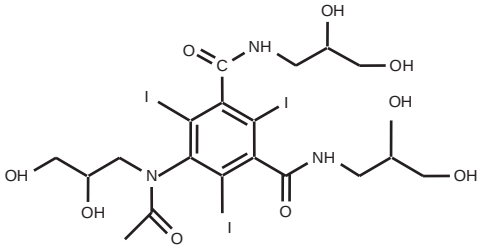
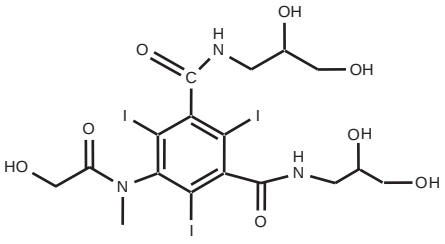
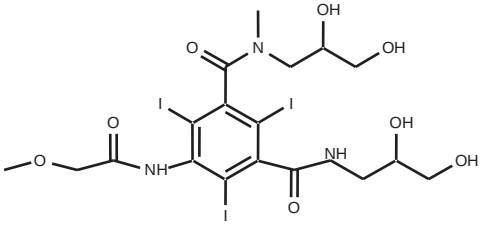
3.1. LC–(ESI)MS/MS

A chromatographic column with Fused-Core™ particle technology was used for the first time for the fast separation of five iodinated X-ray contrast media while maintaining lower backpressures and consequently, obtaining a method applicable to any LC. The separation took less than 13 min, which is equivalent to a reduction by half of the time needed with a conventional porous particle column [18]. It should be pointed out that, due to the polarity of these compounds, a small quantity of organic solvent was necessary in order to prevent co-elution. Moreover, the flow-rate was 0.2 mL/min, which means lower consumption of organic solvent.

Iopamidol, iomeprol, iohexol and iopromide gave two peaks caused by stereoisomerism [19], while both peaks only had a similar area in the case of iopromide. The smallest peak of iopamidol co-eluted with the largest peak for iomeprol and vice versa and they had identical transitions, as shown in Table 1. However, the contribution of the smallest peaks was less than 5% and, consequently, it was considered negligible.

All of the compounds were ionized under positive mode and, due to the amide groups present in their structures, they all yielded the corresponding protonated ($[M+H]^+$) parent ion as the most abundant. Thus, it was selected as precursor ion. Iopamidol and iomeprol have identical molecular weight and similar chemical structure which displayed an identical precursor ion and most abundant transitions. However, the abundance relation of both transitions was inverted. Both showed ions 687 and 559, probably due to the loss of $C_3H_9NO_2$, which corresponds to the cleavage of the amide bond, and $C_3H_9NO_2$ followed by the neutral loss of HI, respectively. This is in line with the fragmentation for iomeprol proposed by Zwiener et al. [20]. In the case of diatrizoic acid, both of the selected transitions have already been reported in the literature [2], with ions 361 and 233 being identified as the losses of 2I and 2I followed by HI, respectively. However, only one of the two transitions selected for

Table 1
Chemical structures and MRM conditions for LC–MS/MS determination of iodinated X-ray contrast media.

Compound	Structure	Precursor ion	Transition	Cone voltage (V)	Collision energy (V)
Iopamidol	 MW= 777	[M+H]$^+$	**778 > 559**	150	20
			778 > 687	150	20
Diatrizoic acid	 MW= 614	[M+H]$^+$	**615 > 361**	120	15
			615 > 233	120	30
Iohexol	 MW = 821	[M+H]$^+$	**822 > 804**	150	20
			822 > 529	150	45
Iomeprol	 MW= 777	[M+H]$^+$	**778 > 687**	150	20
			778 > 559	150	20
Iopromide	 MW=791	[M+H]$^+$	**792 > 300**	150	60
			792 > 559	150	35

In bold the MRM transition used for quantification.
MW: molecular weight.

iohexol and iopromide has been reported previously [2]. Ion 804, observed in the case of iohexol, has been assigned to the loss of a water molecule [18], while ion 559, observed in the case of iopromide, has been assigned to the consecutive loss of $C_4H_{11}NO_2$ followed by HI [2]. Ion 529, corresponding to iohexol, could be assigned to the cleavage of the amide bond (loss of $C_3H_9NO_2$) followed by the consecutive loss of HI, H_2O and C_3H_4O. Meanwhile, ion 300, corresponding to iopromide, could be assigned to the cleavage of the amide group followed by the loss of two HI, I and a water molecule.

The LC–MS/MS chromatographic procedure provided an excellent linear range ($R^2 > 0.999$) of 5–500 μg/L for all the compounds, except for iopamidol, that had a linear range of 0.5–500 μg/L, and diatrizoic acid, that had a linear range of 25–500 μg/L, after the injection of standards in ultrapure water.

3.2. SPE

Various sorbents (Isolute ENV+, Oasis HLB, Oasis MCX and Oasis MAX) were tested in order to evaluate their performance for SPE. Of these, Isolute ENV+ was selected because it has been widely used to extract ICMs from water samples. The polymeric sorbent Oasis HLB was selected because its structure contains polar *N*-pyrrolidone moieties, which can interact with the polar groups of ICMs. Although the strong ion-exchangers (Oasis MCX and Oasis MAX) have been never applied for the extraction of ICMs, preliminary analyses show that they could not retain most of our analytes. Both sorbents were tested by applying the supplier's protocol and about 62% to 78% and 62% to 80% of the analytes were not retained in Oasis MCX and Oasis MAX, respectively. Thus, these sorbents were excluded from the present study.

The efficiency of Isolute ENV+ and Oasis HLB was tested after the optimization of some parameters, using the following protocol initially: sorbents were conditioned by passing 5 mL of organic solvent (methanol or acetonitrile depending on the elution solvent tested) plus 5 mL of purified water, then 10 mL of a standard solution spiked to 100 μg/L at pH 2.6 (HCl) was loaded and the analytes were eluted with 5 mL of organic solvent (methanol or acetonitrile). This solvent was evaporated to dryness with nitrogen gas and the extract was redissolved with 5 mL of purified water.

The first parameter studied was the elution solvent (methanol or acetonitrile). Methanol gave the highest recoveries with both sorbents, mainly for the first compounds to be eluted. On average, recoveries with 10 mL methanol increased by about 14% to 46% with respect to those obtained with the same volume of acetonitrile. Consequently, methanol was selected as the elution solvent and it was also used to condition the sorbents.

The volume of solvent used for elution was then optimized by testing up to 3 aliquots of 5 mL each of methanol. No peaks were observed for the second and third elution when Oasis HLB was used and recoveries of only 3% to 9% were obtained in the second elution for Isolute ENV+. Thus, 5 mL of methanol was selected as the sufficient volume for quantitatively desorbing the analytes from both sorbents.

The sample volume was also tested between 10 mL and 500 mL and the results are shown in Table 2. Oasis HLB displayed higher retention of the analytes than Isolute ENV+ that could be caused not only by the different functional groups but also by the larger amount of sorbent. Even at 10 mL, recoveries were around 100% for all of the analytes when using Oasis HLB, while the other sorbent provided recoveries of between 63% and 84%. Good recoveries for all the analytes were obtained with Oasis HLB up to a volume of 100 mL and up to 250 mL for all the analytes except iopamidol and diatrizoic acid, which are the most polar analytes. At 500 mL, only iopromide, the last to be eluted, was quantitatively retained. However, Isolute ENV+ at 50 mL gave recoveries of about 52% to 58% for the first three compounds to be eluted and only the last two compounds to be eluted could be recovered quantitatively. In light of the results, Oasis HLB was selected for further experiments.

Table 2
Recoveries obtained by varying the sample volume of a standard solution.

Compound	Sample volume							
	10 mL		100 mL		250 mL		500 mL	
	A	B	A	B	A	B	A	B
Iopamidol	82	110	44	69	32	34	20	18
Diatrizoic acid	63	99	47	73	40	55	35	36
Iohexol	81	112	60	90	40	69	32	43
Iomeprol	82	111	73	88	51	80	44	56
Iopromide	84	101	85	82	72	85	65	83

A: Isolut ENV+.
B: Oasis HLB.
RSD ($n=3$) < 8%.

The last parameter optimized was the sample pH, by also testing the type of acid. About 100 mL of sample volume was used for these experiments. Although recoveries did not vary significantly when pH was modified to 2.6, 2.8, 3.5 and 4.5 with sulphuric acid or acetic acid depending on the pH, slightly higher recoveries were obtained at 2.6. Subsequently, the influence of the acid used (HCl, H_2SO_4, HNO_3) to control the pH was studied. Again, no significant differences on recoveries were observed but HCl was selected because it gave slightly higher recoveries.

In addition, the reduction of the water volume used to redissolve the final extract was also evaluated in order to achieve a higher preconcentration factor. This volume could be reduced down to 1 mL with no significant analyte losses.

Once the SPE procedure had been optimized, complex samples such as influent and effluent sewage were analysed in order to select the best sample volume to be preconcentrated, as well as for checking for possible matrix effects. In light of the results, sample volumes of 100 mL for influent sewage and 250 mL for effluent sewage were chosen, which is in line with our previous studies focusing on PPCPs [21]. Recoveries, calculated by comparing the signal from blank samples spiked before and after the SPE step, did not quantitatively differ from those obtained with standard solutions.

The matrix effect was evaluated in the two matrices and was calculated by comparing the chromatographic response obtained when spiking a sample blank after the SPE extraction with the chromatographic signal obtained from a standard solution at the same concentration. From the results, it could be observed that both matrices caused ion suppression for the two first eluted analytes (iopamidol and diatrizoic acid), while this effect was not significant in the case of the other analytes. As expected, due to the complexity of the matrix, ion suppression was higher in the influent samples (29% to 34%) than in the effluent samples (16% to 21%). Table 3 shows the final recoveries, calculated by analysing both matrices with the whole method.

A deuterated surrogate would have been used to minimize the error caused by ion suppression but this option was rejected due to its low commercial availability. Various deuterated compounds available in our laboratory were also tested but, due to their different structural and chemical properties, they were refused. Therefore, a matrix-matched calibration curve was used to correct the ion suppression.

3.3. Method validation

The method was validated with both influent and effluent sewage by evaluating linear range, limits of detection (LODs), limits of quantification (LOQs) and intra-day and inter-day repeatabilities.

Previous analyses of 100 mL influent and 250 mL effluent sewage showed no peaks at the same retention time of our analytes.

The linear range was obtained by analysing both matrices spiked to concentrations between 40 ng/L and 10,000 ng/L and the results are shown in Table 3. The compounds showed a good linear range ($R^2 > 0.997$) between 100 ng/L and 10,000 ng/L (except diatrizoic acid which had a linear range of 250–25,000 ng/L) and between 40 ng/L and 8000 ng/L (except diatrizoic acid which had a linear range of 100–10,000 ng/L) for influent and effluent sewage, respectively.

The LODs were calculated as the concentration that gave a signal-to-noise ratio (S/N) of approximately 3, whereas the LOQs were set at the lowest point in the linear range. As can be seen in Table 3, LODs ranged from 40 ng/L to 100 ng/L and from 10 ng/L to 40 ng/L for influent and effluent sewage, respectively.

The intra-day and inter-day repeatabilities were determined by spiking three replicates of influent sewage at 500 ng/L and effluent sewage at 200 ng/L. The results, expressed as %RSD, were lower than 9% for intra-day repeatability and lower than 12% for inter-day repeatability in both matrices (see Table 3).

These validation parameters are comparable to those already published by using SPE, mainly packed with Isolute ENV+ sorbent, and LC tandem MS [13,15,16]. However, a lower sample volume was used in comparison to certain published methods. For example, Hirsch et al. [15] obtained LOQs of 50 ng/L for a group of ICMs for effluent sewage by preconcentrating 1 L in an Isolute ENV+ cartridge, whereas, in our case, only 250 mL of the sample was used and similar LOQs were achieved.

3.4. Method application

The SPE/LC–MS/MS method developed was applied to determine the five ICMs in both influent and effluent sewage from two urban STPs.

Table 3
Validation data for influent and effluent sewage.

Compound	%R		Linear range (ng/L)		LODs (ng/L)		%RSDs[a]		%RSDs[b]	
	Influent	Effluent	Influent	Effluent	Influent	Effluent	Influent	Effluent	Influent	Effluent
Iopamidol	35	55	100–10,000	40–8000	40	10	8	6	10	8
Diatrizoic acid	44	71	250–25,000	100–10000	100	40	9	9	12	11
Iohexol	91	71	100–10,000	40–8000	40	10	7	6	10	9
Iomeprol	80	83	100–10,000	40–8000	40	10	6	7	9	8
Iopromide	83	82	100–10,000	40–8000	40	10	8	8	11	10

LOQs set at the lowest point into the linear range.

[a] Intra-day repeatabilities ($n=3$, 500 ng/L for influent and 200 ng/L for effluent).

[b] Inter-day repeatabilities ($n=3$, 500 ng/L for influent and 200 ng/L for effluent).

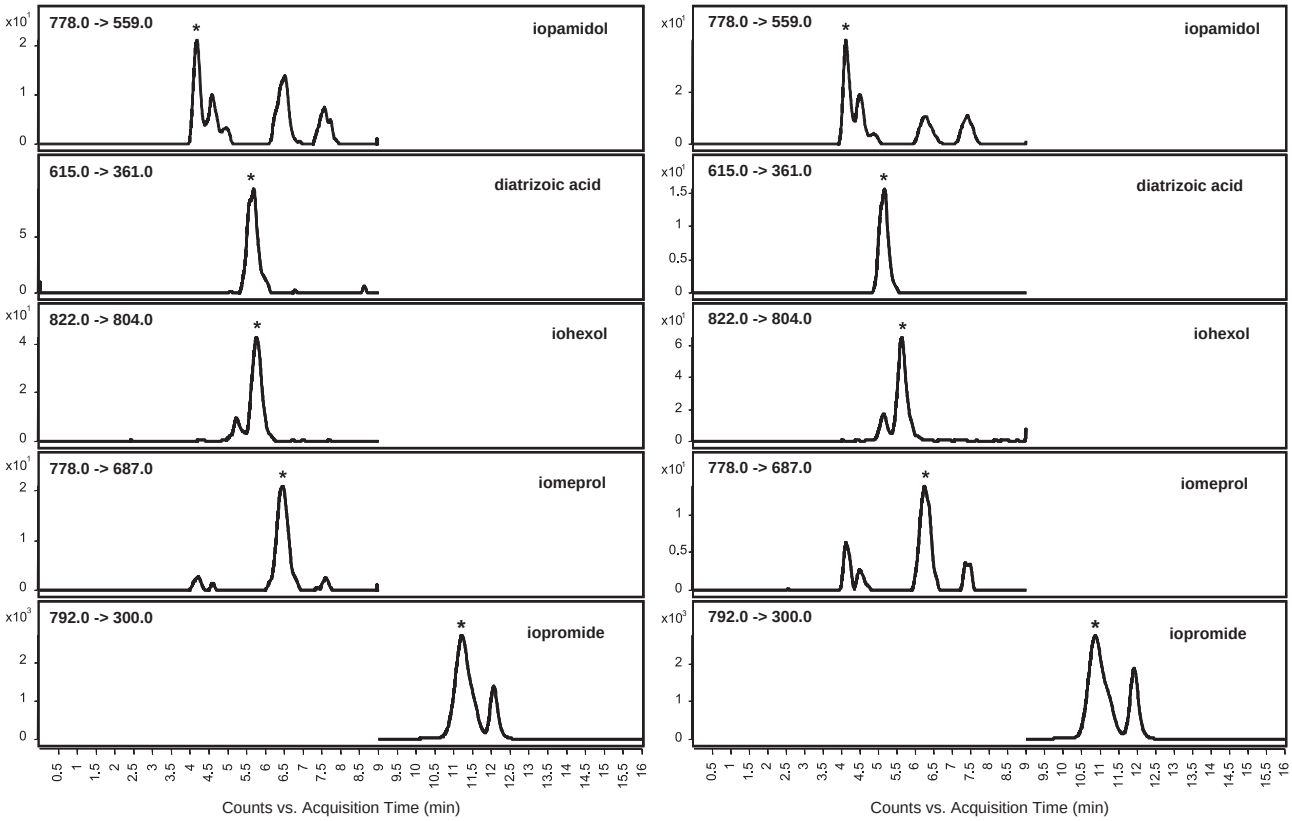


Fig. 1. MRM chromatograms corresponding to influent (left) and effluent (right) sewage samples collected at STP2. Concentrations correspond to I1 and E1 according to Table 4.

Table 4
Concentrations (ng/L) and ion rations of ICMs in samples analyzed from STP2.

	Iopamidol		Diatrizoic acid		Iohexol		Iomeprol		Iopromide	
Influent		**(14.8)**		**(5.3)**		**(13.2)**		**(60.2)**		**(50.1)**
I1	1627	(14.7)	4672	(5.5)	5420	(14.8)	4566	(55.9)	8885	(51.0)
I2	1480	(14.0)	3819	(5.6)	4965	(13.7)	4562	(61.1)	8621	(50.2)
I3	1347	(13.8)	3863	(5.7)	4523	(14.4)	4633	(59.0)	6767	(50.6)
Effluent		**(14.9)**		**(5.1)**		**(13.5)**		**(61.0)**		**(50.3)**
E1	861	(14.8)	2741	(5.3)	3461	(14.6)	3188	(66.9)	6665	(50.2)
E2	787	(14.8)	2820	(5.1)	3359	(13.3)	3521	(56.0)	6925	(50.2)
E3	763	(15.9)	2807	(5.2)	3357	(14.7)	3040	(64.0)	7082	(50.4)

Ion ratios (%) in spiked samples are in bold.
Ion ratios (%) in samples are in brackets.

Results showed that no significant differences were observed between the two STPs. All five ICMs were determined in all of the samples analysed and, in line with the literature [2,9,22], no significant elimination by conventional treatment was observed. Moreover, no significant differences were obtained between samples. For example, Table 4 shows results for STP2. In all cases, the presence of these compounds was confirmed by the ion ratio between quantification and confirmation transitions and their retention time, as can be seen in Table 4. Influent sewage showed concentrations ranging from 1.3 μg/L for iopamidol to 8.9 μg/L for iopromide whereas effluent sewage concentrations range from 0.8 μg/L for iopamidol and 7.1 μg/L for iopromide. Iopromide and iopamidol were the ICMs that were present in all samples at the highest and the lowest concentrations, respectively. MRM chromatograms for an influent and effluent sample from STP2 are shown in Fig. 1. Although the concentration levels found are in line with some publications also related to the presence of ICMs in sewage [8,14,18], higher concentrations have been reported by some authors [2].

4. Conclusions

A fused core particle analytical column has successfully been applied for the first time for separating a mixture of five ICMs, which leads to a significant saving in terms chromatographic time and, consequently, in solvents used for separation. Moreover, Oasis HLB sorbent displayed better performance than the widely-used Isolute ENV+ sorbent for the SPE extraction of the ICMs. Thus, the developed method based on SPE with Oasis HLB and LC–MS/MS allowed the determination of all of the ICMs at ng/L levels.

The method was applied to the analysis of sewage samples. All of the ICMs were determined at samples analysed at levels between 1.3 μg/L and 8.9 μg/L and between 0.8 μg/L and 6.7 μg/L for influent and effluent sewage, respectively. Iopamidol was the ICM present at the lowest concentration and iopromide at the highest. In line with current literature, the results showed no significant decrease after conventional sewage treatment.

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