Talanta 110 (2013) 196–201

Contents lists available at SciVerse ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

A rapid determination of acidic pharmaceuticals in environmental waters by molecularly imprinted solid-phase extraction coupled to tandem mass spectrometry without chromatography

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ARTICLE INFO

Article history:
Received 17 December 2012
Received in revised form
7 February 2013
Accepted 15 February 2013
Available online 13 March 2013

Keywords:
Pharmaceuticals
Direct coupling
Molecularly imprinted solid-phase extraction
Tandem mass spectrometry
Wastewaters

ABSTRACT

This study presents a rapid analytical method that involves an off-line molecularly imprinted solid-phase extraction (MISPE) specific for non-steroidal anti-inflammatory drugs (NSAIDs) as a selective sample pretreatment coupled directly to tandem mass spectrometry (MS/MS). The developed methodology provided sensitive and selective detection and quantification of six acidic pharmaceuticals in wastewaters without the chromatographic separation.

The optimised MISPE procedure enabled to extract effectively the studied analytes from effluent and influent wastewaters with satisfactory recovery values (from 62% to 103%).

The analytical method developed was validated using 50 mL of effluent wastewaters, obtaining limits of detection (LODs) lower than 0.1 $\mu g\ L^{-1}$ for all the compounds studied. The method was successfully applied for the determination of these acidic pharmaceuticals in effluent and influent wastewaters. The analytes and their concentration are in line with other studies in which these analytes are determined by SPE–LC–MS/MS in similar samples.

1. Introduction

Nowadays, rapid analytical methods are required in order to analyse the maximum number of samples in the minimum time period. Up to now, many analytical methods have been developed to determine acidic pharmaceuticals, such as non-steroidal anti-inflammatory drugs (NSAIDs), among others, in complex matrices, mainly using solid-phase extraction (SPE) followed by liquid chromatography (LC) coupled to mass spectrometry (MS) or tandem mass spectrometry (MS/MS) [1–4]. However, these methodologies usually involve time-consuming procedures from the sample collection right through to their quantification. In order to reduce analysis time, it should be worthy to improve on sample pretreatments and couple them directly to a specific and sensitive detection system, without chromatographic analysis.

MS or tandem MS is currently the most commonly used detection technique for the identification and quantification of pharmaceuticals in complex matrices due to its high sensitivity, selectivity and speed [5]. Despite its numerous advantages, this technique using an electrospray ionisation (ESI) source may suffer from ion suppression/enhancement caused by interferences present in complex matrices [6]. For this reason, removing as much as possible interfering matrix compounds in order to minimise these matrix effects is a challenge.

In recent years, few studies have reported the direct coupling of an extraction technique to a detection technique. For instance, the on-line SPE–MS system has been applied for the determination of clenbuterol in urine [7,8] and prednisolone in serum [9], while the coupling between SPE and MS/MS enabled to determine antihypertensive drugs in human plasma and urine [10]. These studies have been developed using non-selective SPE sorbents, whose protocols did not include an effective clean-up step, and many matrix compounds were still present in the SPE eluate, obtaining higher limits of detection (LODs) than expected.

To tackle this problem, it is necessary to purify the samples as much as possible in order to eliminate interferences. Molecularly imprinted solid-phase extraction (MISPE) has been defined as a selective extraction technique because of its molecular-recognition technology, which allows specific binding between the target molecule or template and the polymer structure [11,12]. Currently, new approaches are being developed in this field which apply these selective molecularly imprinted polymers (MIPs) coupled directly to detection techniques in order to eliminate as many of the interferences as possible without the losses of target analytes.

On this point, a few studies have been reported using MISPE–MS, such as for the determination of fluoroquinolones in urine [13], benzodiazepines in human plasma [14] and phenothiazines in urine [15], as well as another that used a MISPE-fluorescence detector (FD) to determine ochratoxin A in wheat samples [16]. These studies

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http://dx.doi.org/10.1016/j.talanta.2013.02.039

emphasised the selectivity and simplicity of the methodology in comparison with the classical methods which included SPE followed by LC prior to MS/MS for the determination of different drugs in environmental and biological matrices [17–23]. However, to the best of our knowledge, MISPE has never been coupled directly to MS/MS, which might significantly improve the sensitivity and selectivity of the methodology.

In view of this, the aim of the present work is to develop a rapid and selective analytical method for the determination of six acidic pharmaceuticals in wastewaters by MISPE–MS/MS.

2. Materials and methods

2.1. Materials

Clofibric acid, naproxen, ibuprofen, fenoprofen, diclofenac and gemfibrozil were purchased from Sigma-Aldrich (Steinheim, Germany). All pharmaceutical standards used were of high purity grade (>97%). As internal standard (IS), gemfibrozil-d_6 (98%) (100 mg L^{-1} in dioxane) from Cambridge Isotope Laboratories (Andover, USA) was used.

Stock solutions of individual standards were prepared by dissolving each compound in methanol (MeOH) at a concentration of 1000 mg L^{-1}. A mixture of all compounds in MeOH at a concentration of 50 mg L^{-1} was prepared weekly. Working solutions were prepared daily from these stock solutions diluted in MeOH/H_2O at pH 7 (60:40, v/v). These solutions were stored at 4 °C. The structures and pK_a values of these substances are presented in Table 1.

HPLC grade MeOH and acetonitrile (ACN) were purchased from SDS (Peypin, France). Ultrapure water was obtained from a water purification system (Veolia, Sant Cugat del Vallès, Spain) and nitrogen (N_2) (99%) was supplied by Carburos Metálicos (Tarragona, Spain). Acetic acid (CH_3COOH) (≥99.8%) from SDS (Peypin, France), hydrochloric acid (HCl) (37%) from Prolabo (Bois, France) and ammonium hydroxide (NH_4OH) (25%) from Panreac (Barcelona, Spain) were used to adjust the pH of the carrier liquid and the samples.

2.2. Sample collection

The wastewater samples were collected from the influent and effluent of two domestic sewage treatment plants (STPs), which are located in two cities with populations of around 120,000 habitants each, by using pre-cleaned amber glass bottles. All the samples were filtered using a 0.45 μm nylon membrane (Supelco, Bellefonte, PA, USA), acidified to pH 3 (HCl) and stored at 4 °C until analysis.

2.3. Molecularly imprinted solid-phase extraction

150 mg of a commercially available MIP, namely Affinilute MIP-NSAIDs (Biotage, Barcelona, Spain), were packed manually and placed into 6 mL polyethylene cartridge with 2 polypropylene frits (~10 μm) (Symta, Madrid, Spain). The cartridges were placed in an SPE manifold (Teknokroma, Barcelona, Spain) and connected to a vacuum pump. They were conditioned with 5 mL of ACN, 5 mL of MeOH and 5 mL of H_2O adjusted to pH 3. The samples adjusted to pH 3 were loaded through the MIP. A clean-up step was then performed with 5 mL of ACN:H_2O (40:60, v/v). In order to elute the retained analytes, 10 mL of MeOH:acetone (80:20, v/v) with 1% CH_3COOH was passed through the cartridge. Elution extracts were evaporated to dryness under a gentle flow of N_2. Before MS/MS injection, the elution fractions were reconstituted to a final volume of 1 mL of MeOH/H_2O at pH 7 (60:40, v/v), to which gemfibrozil-d_6 (IS) was added at 50 μg L^{-1}, in order to correct LC injection and ionisation variability.

2.4. Instrumentation

All extracts were injected by flow injection analysis (FIA) using an Agilent quaternary pump 1200 series and an automatic injector (the volume injected was 50 μL) connected to a 6410 series triple quadrupole mass spectrometer using ESI from Agilent Technologies (Waldbronn, Germany).

The optimised carrier liquid, used to push the extracts from the injector to MS/MS, was composed of MeOH/H_2O at pH 7 (60:40, v/v). The flow rate was set at 0.8 mL min^{-1}.

With respect to MS/MS detection, N_2 was used as the collision gas and its flow rate was set at 12 L min^{-1}. A source temperature of 300 °C, a nebuliser pressure of 40 psi (N_2) and a capillary potential of 4000 V were applied. Multiple reaction monitoring (MRM) in negative ionisation mode was used to determine all analytes. Table 1 details MRM transitions, cone voltage and collision energy for each compound.

3. Results and discussion

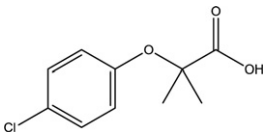
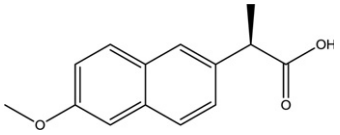
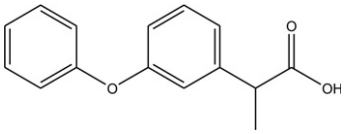
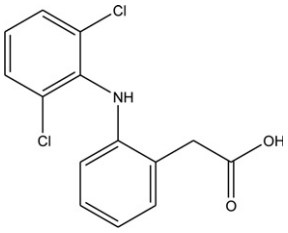
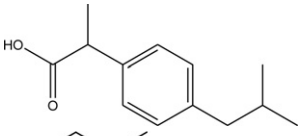
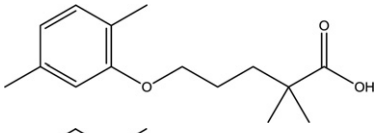
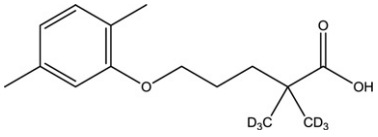
3.1. MS/MS conditions

The different MS/MS parameters were adjusted, injecting each compound at 250 μg L^{-1} individually by FIA. Table 1 shows the optimum MS/MS conditions for each analyte in negative ESI. It was possible to obtain two different MRM transitions (selected as quantifier and qualifier) for all target analytes, except for ibuprofen, the MS/MS spectrum of which only contained one diagnostic ion and, hence, only one MRM transition was achieved for this compound. However, this compound was not initially excluded from the study due to its high prevalence in environmental water samples at high concentration levels [23]. Moreover, we injected a mixture of all the analytes and we checked that the same response was obtained for each analyte, rather than injecting them individually by FIA mode. Thus, it means that the signal of each analyte did not interfere with the signal of the rest of analytes. Therefore, MS/MS can be considered selective for the studied compounds under these conditions.

Next, the composition of the carrier liquid was optimised in order to enhance the analyte response. In case that the analytes were first separated using LC and then detected by MS/MS, the mobile phase had to be selected to obtain both a successful separation and proper ionisation of the compounds. However, when working with the direct coupling MISPE–MS/MS, the only requirement of the carrier liquid composition is to achieve the best solvent for ionisation in ESI interface. With this in mind, different solutions of MeOH or ACN (as organic solvent) combined with acidic or basic water were tested as the carrier liquid. To be specific, the carrier liquid compositions were: MeOH/H_2O at pH 3 (80:20, v/v), ACN/H_2O at pH 3 (80:20, v/v), MeOH/H_2O at pH 7 (80:20, v/v), ACN/H_2O at pH 7 (80:20, v/v), MeOH/H_2O at pH 7 (60:40, v/v) and ACN/H_2O at pH 7 (60:40, v/v). It should be mentioned that, in all instances, the injected solution containing the analytes and IS were prepared in the same composition as the carrier liquid. Fig. 1 shows the response achieved for all the analytes studied with the different carrier liquids tested.

First of all, MeOH/H_2O at pH 3 (80:20, v/v) and ACN/H_2O at pH 3 (80:20, v/v) were tested. These are typical mobile phases applied in LC since at pH 3 these analytes are in the neutral form, which would be appropriate for separation along the LC column. Nevertheless, solutions at pH 3 are not the most suitable for promoting the ionisation in the negative ESI interface, as shown in Fig. 1, in which the lowest areas were obtained. When the aqueous phase was adjusted to pH 7, maintaining the composition of the carrier liquid (80:20, v/v) and in both MeOH and ACN, the response increased for all target analytes. This fact could be explained because, under these

Table 1
Structures, pK_a and experimental parameters employed for the MRM acquisition for all the studied analytes.

Analyte	Structure	pK_a[a]	MRM Transition	Cone voltage (V)	Collision energy (V)
Clofibric acid		3.2	**213>127** 213>85	75	10 5
Naproxen		4.8	**229>170** 229>185	50	10 5
Fenoprofen		4.2	**241>197** 241>93	75	5 45
Diclofenac		4.2	**294>250** 294>214	75	10 20
Ibuprofen		4.4	205>161	75	5
Gemfibrozil		4.8	**249>121** 249>127	75	10 10
Gemfibrozil-d_6		4.8	**255>121** 255>133	50	10 5

[a] pK_a values calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 for Solaris (© 1994–2011 ACD/Labs).

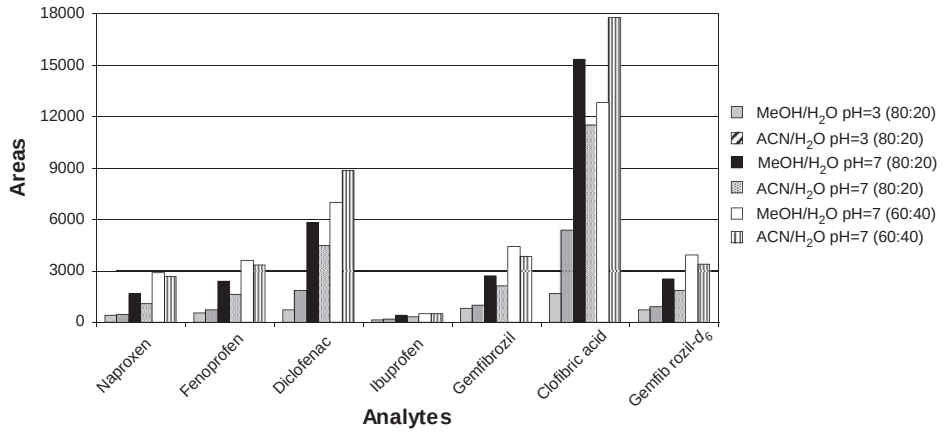


Fig. 1. Optimisation of carrier liquid used in MS/MS.

conditions, acidic pharmaceuticals were mostly deprotonated and arrived at the ESI interface as negatively charged ions. Moreover, slightly better results were achieved using MeOH instead of ACN, since the protic nature of the former provided a strong solvation of negative ions [24]. In addition, in order to obtain the highest possible sensitivity, a different composition of carrier liquid (60:40, v/v) was evaluated, using both MeOH and ACN with H_2O adjusted to pH 7. Again, the areas obtained in MeOH/H_2O at pH 7 (60:40, v/v) were slightly higher than those in ACN/H_2O at pH 7 (60:40, v/v), except in the case of diclofenac and clofibric acid.

Finally, MeOH/H_2O at pH 7 (60:40, v/v) was selected as a carrier liquid because this composition provided the best overall results.

The (ESI)–MS/MS procedure in MRM was validated for simultaneous determination of all the compounds. The instrumental method presented a good linear range ($n=6$) of 0.15–200 μg L^{-1} for all target analytes, except for ibuprofen (2–200 μg L^{-1}) by direct injection. LODs, calculated as the concentration which give a response corresponding a signal-to-noise ratio (S/N) of 3, ranged between 0.015 and 0.050 μg L^{-1} for all compounds, with the exception of ibuprofen (0.500 μg L^{-1}).

3.2. MISPE optimisation

MISPE performance was developed using a commercially available MIP, which was selective for NSAIDs and enabled the effective extraction of these compounds from complex matrices. This commercial MIP was used in a previous study in our research group [18] and its MISPE protocol was adapted to this work.

First, to promote the interactions between the analytes and the sorbents during the loading step, the sample pH was adjusted at 3, as we reported previously [18]. Once the analytes were retained onto the sorbent, the elution step was crucial to remove the analytes from the cartridge and the eluate extract also had to be a suitable solvent for the MS/MS system. As mentioned before, MeOH/H_2O at pH 7 (60:40, v/v) enabled a proper ionisation of all the analytes obtaining their highest response. However, this solvent was not able to release the interactions established between the sorbent and the analytes and an acidic elution solvent, different from the optimum carrier liquid, was necessary. For this reason, the evaporation step was included. Therefore, the same elution solvent used in the previous study, MeOH:acetone (80:20, v/v) with 1% CH_3COOH, was applied with an elution volume of 10 mL, and then, the evaporation procedure resulted in a 25-fold concentration as well as a solvent switch. When 25 mL of ultrapure water at pH 3 spiked at 2 μg L^{-1} was percolated through the cartridge using the above protocol, recovery values nearly of 100% for all target analytes were obtained.

Finally, a clean-up step is essential when analysing real samples using a MIP. Particularly, for this MIP, its high specificity towards the NSAIDs allows the removal of interferences present in the sample. As we detailed in our previous study [18], 5 mL of ACN/H_2O (40:60, v/v) was selected as the clean-up solvent and also applied in the present work. After loading 25 mL of ultrapure water at pH 3 spiked at 2 μg L^{-1}, we checked that the clean-up solution enabled to keep retained the studied analytes without losses, obtaining recovery values over 84%.

After the MISPE optimisation, the breakthrough volume percolated through the MIP was evaluated. Good recovery values were achieved with volumes up to 1000 mL of ultrapure water loaded (over 70%, except for diclofenac (56%)).

3.3. Application to real samples

Once the MISPE–MS/MS method was successfully applied in ultrapure water, the same protocol was applied to the analysis of environmental waters. In complex matrices such as wastewaters, ion suppression/enhancement is a common effect when ESI is used as MS interface because the analytes' response may vary depending on the matrix interferences [6]. Including the LC in the analytical methodology usually enables to separate the analytes from the matrix interferences during the chromatographic separation preventing their entrance into the ionisation interface at the same time. Therefore, if LC is not included, an effective sample pretreatment is needed to minimise this effect.

The ion suppression/enhancement effect was calculated as the percentage decrease in the signal obtained by the target analytes and IS spiked at 100 μg L^{-1} after a real sample extraction versus the intensity of the same amount of analytes in ultrapure water [18,25]. This effect was evaluated for effluent and influent wastewaters. When effluent and influent wastewaters were analysed, all the compounds showed high signal suppression with values up to 70%, except for clofibric acid and fenoprofen which presented the highest ion suppression (84%). This high effect could be explained due to the absence of the chromatographic separation in this method and, above all, the high content of organic matter present in these real samples. However, it should be pointed out that without the clean-up step almost all compounds were completely suppressed (nearly 100%). Thus, the clean-up step was necessary to remove as many interferences as possible.

Moreover, the applicability of the method was assessed in terms of extraction recoveries for target analytes in effluent and influent wastewaters, using 50 mL and 10 mL, respectively. The volume of the real samples was reduced as the complexity of the matrices increased in order to obtain similar recoveries as for ultrapure water. Table 2 shows the recovery values of the analytes in ultrapure water, effluent and influent wastewaters. These recovery values in environmental waters were evaluated by comparing them with a blank sample spiked before and after the MISPE procedure at the same final concentration. The recovery values ($n=3$) of the target analytes in effluent wastewaters ranged from 62% to 102% (Table 2). When influent wastewaters were passed through the MIP cartridge, the recoveries were between 83% and 103%, except for clofibric acid (69%). It should be mentioned that the recovery values for ibuprofen cannot be taken as definitive because one MRM transition was found for its quantification. So, the present method can only be considered semi-quantitative for ibuprofen. These recovery values are higher than those presented in previous methods [19,20] where similar group of analytes from the same type of samples were determined using procedures that involve off-line SPE/LC–MS/MS.

Bearing in mind the results from the ion suppression/enhancement study, the next step was to validate the MISPE–MS/MS method using a matrix-matched calibration in order to perform an accurate quantification of real samples due to this effect. Therefore, the method validation was developed using 50 mL of effluent wastewaters. It should be mentioned that gemfibrozil was found in real samples and its signal was subtracted from the spiked samples. The linear ranges were between 0.50 and 50 μg L^{-1} for all compounds, except for fenoprofen (0.15–50 μg L^{-1}) (r^2>0.993 and for ibuprofen (r^2>0.987)). For the target analytes without blank signals, LODs were determined as the concentrations corresponding to S/N of 3. However, for gemfibrozil that was present in the blank, the LOD was tentatively calculated as three times the standard deviation of the analyte signal in the blank ($n=3$). LODs were 0.10 μg L^{-1} for all pharmaceuticals, except for fenoprofen, which had a LOD of 0.05 μg L^{-1}. The repeatability and reproducibility between days of

Table 2
Recovery values (%) obtained when the acidic pharmaceuticals from different water samples were determined by MISPE–MS/MS.

Analyte	% Recovery value		
	Ultrapure-water[a]	Effluent wastewater[b]	Influent wastewater[c]
Clofibric acid	70	73	69
Naproxen	94	102	83
Fenoprofen	106	88	87
Diclofenac	56	62	88
Ibuprofen	130	94	84
Gemfibrozil	105	100	103

%RSD<19% ($n=3$).

[a] 100 mL spiked at 0.5 μg L^{-1}.
[b] 50 mL spiked at 1 μg L^{-1}.
[c] 10 mL spiked at 3 μg L^{-1}.

Table 3
Concentrations found for the acidic pharmaceuticals in effluent and influent wastewaters analysed from two STPs.

Analyte	Concentrations found ($\mu g\ L^{-1}$)	
	Effluent wastewaters	Influent wastewaters
Clofibric acid	<0.10–0.82	<0.10
Naproxen	<0.50–1.55	0.68–6.40
Fenoprofen	<0.05	<0.05
Diclofenac	<0.50–0.81	<0.50
Ibuprofen	2.64–5.46[a]	0.54–20.17[a]
Gemfibrozil	0.78–4.06	<0.50–2.39

[a] Tentatively quantified since the method is semi-quantitative for ibuprofen.

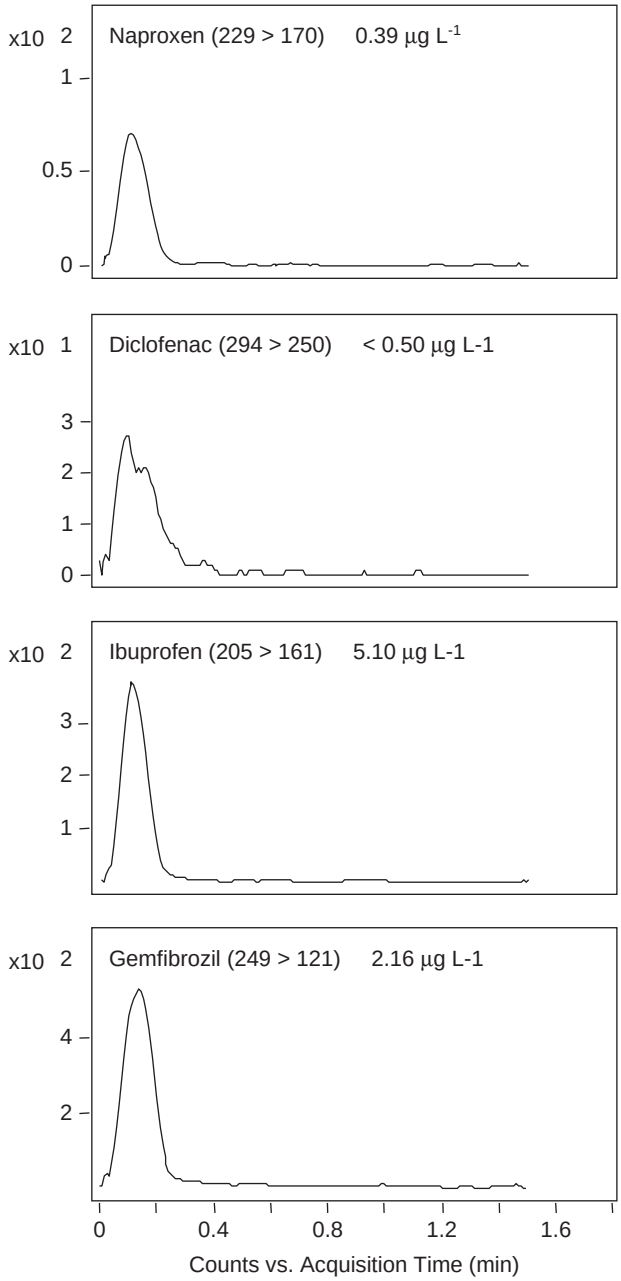


Fig. 2. MRM transitions of an effluent wastewater sample.

three samples spiked at 3 $\mu g\ L^{-1}$, expressed as % relative standard deviation (%RSD), were lower than 9% and 14%, respectively.

3.3.1. *Analysis of real samples*

To demonstrate the applicability of the MISPE–MS/MS, effluent and influent wastewaters from two STPs on different dates were analysed in triplicate. All the acidic pharmaceuticals were detected in both effluent and influent wastewaters, except fenoprofen (Table 3). For instance, Fig. 2 shows MRM chromatograms of an effluent wastewater sample. As expected, the most frequently detected compounds in wastewaters at high concentrations levels were gemfibrozil (<0.50–4.06 $\mu g\ L^{-1}$), naproxen (<0.50–6.40 $\mu g\ L^{-1}$) and ibuprofen, the concentration of the latter was tentatively quantified in the present method, as explained in Section 3.1. Moreover, higher concentrations of gemfibrozil were found in effluent than influent wastewaters. A possible explanation could be that the sampling of the influent and effluent wastewaters was not performed in the same time period as well as for a possible conversion of its conjugated metabolite to the original substance after the treatment processes [21,24]. These concentrations were similar to those obtained in other studies [19,21,23] performed in similar urban STPs, where the highest concentrations were also attributed to ibuprofen and naproxen. These levels showed the presence of these pharmaceuticals in environmental wastewaters.

4. Conclusion

A rapid analytical method consisting of off-line MISPE coupled directly to MS/MS (omitting the chromatographic separation) is able to determine six acidic pharmaceuticals in effluent and influent wastewaters with good recoveries (62–103%). Although considerable signal suppression/enhancement was obtained, using a matrix-matched calibration curve helped to balance this effect and obtain a reliable quantification of environmental water samples.

This coupling enabled to develop an analytical method which gave LODs at low levels of µg/L (0.05–0.10 $\mu g\ L^{-1}$) for effluent wastewater, despite of the absence of chromatographic separation. The promising results achieved with MISPE–MS/MS allowed the quantification of acidic pharmaceuticals in wastewaters from two different STPs.

Acknowledgements

The authors thank the Ministry of Science and Innovation (CTQ2011-24179) and the Department of Innovation, Universities and Enterprises (Project 2009 SGR 223) for financial support. N. Gilart would also like to thank the Department of Innovation, Universities and Enterprises and the European Social Fund for a predoctoral grant (FI-DGR 2011).

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