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Quantification of cytostatic platinum compounds in wastewater by inductively coupled plasma mass spectrometry after ion exchange extraction

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ABSTRACT

Cytostatic platinum compounds (CPCs) are pharmaceutical compounds widely used in chemotherapy. However, these compounds have important side effects and can be toxic to the biota once they are excreted by patients and reach the aquatic medium, even at low concentrations.Most of the works have focused on the determination of CPCs in hospital wastewaters using inductively coupled plasma mass spectrometry (ICP–MS). However, the determination of CPCs in samples from wastewater treatment plants (WWTPs) is very limited, probably due to the difficulty of extracting such hydrophilic compounds from these complex aqueous matrices.This paper presents a new optimised and developed method for the extraction and preconcentration of CPCs in wastewater samples based on ion exchange solid phase extraction and their determination by ICP–MS.Under the optimal conditions, the procedure has good reproducibility and repeatability (with deviations lower than 15%), with a relative recovery between 47 and 90% and a low matrix effect (lower than 24%). We have obtained the lowest limit of quantification achieved up until now (0.74 ng L^{-1}), thus allowing the determination of CPCs in new matrices. The described method was used for the determination of CPCs in wastewater from a WWTP and hospital wastewater of Gran Canaria Island (Spain). We have detected concentrations between 81.94 and 13,913 ng L^{-1} in hospital effluents and between 3.97 and 75.79 ng L^{-1} in wastewater treatment plants.

1. Introduction

Cytostatic platinum compounds (CPCs) are widely used anticancer drugs. More than 50% of cancer patients are treated with them or a mixture of them with other medications [1]. The oldest of them is cisplatin (Cis-Pt), a cytostatic compound widely used in the treatment of different types of cancer, such as testicular, ovarian and lung cancer [2]. Attempting to mitigate its side effects, other platinum-based compounds have been developed, including oxaliplatin (Oxa-Pt) and carboplatin (Car-Pt), which are also widely used against different types of cancer [3,4]. The problem with cytostatic compounds is that they can be carcinogenic, teratogenic and/or mutagenic, because they are not selective against the growth of cancer cells and rather act on all cells [5], and thus, the evaluation of their presence in the aquatic environment is necessary. ry.

High percentages of these compounds or their active metabolites are excreted through the urine [6]. Vyas et al. [7] suggests that the greatest proportion (around 75%) of platinum excreted by patients takes place outside the hospital, and they even foresee concentrations of 0.1 ng L^{-1} in environmental waters due to the effluents from the wastewater treatment plants (WWTPs). Predicted environmental concentrations of Johnson et al. [8] indicate the possible presence of Oxa-Pt in the range of ng•L^{-1} in sewage, although the limits of detection (LODs) reached for actual methods do not achieve these levels, and thus, it has not been possible to corroborate their hypothesis. For this reason, it is necessary to develop a method in order to achieve lower LODs than those obtained to date in order to quantify and monitor CPCs at low concentrations predicted in samples, such as WWTP effluents or river water.

Given that Cis-Pt is a compound widely used in anticancer therapies and that it has important adverse effects, different papers have studied its effects on the environment. *Zebrafish* liver cells were exposed to four cytostatic compounds including Cis-Pt, with an increase in DNA strand breakage formation found at low concentrations, concluding that side effects in aquatic organisms may be considered [9]. *Mytilus galloprovincialis* mussels were exposed to 0.1 μg L^{-1} Cis-Pt, which resulted in changes in the antioxidant capacity, causing oxidative stress in the digestive gland and the gills as well as neurotoxicity and DNA damage [10].

ICP-MS technique represent today a reference analytical methods for the analysis of metals in different type of samples, and numerous analytical procedures have been developed provides a highly sensitive and specificity [11–13]. The determination of CPCs have been carried out mainly by inductively coupled plasma mass spectrometry (ICP-MS) in samples from effluents from hospitals [6,14–17]. Measured concentrations of up to 762 μg L^{-1} platinum were obtained [17–21]. In all of these works, no procedures have been developed for the extraction and preconcentration of platinum compounds before their analysis, which have been carried out for the study of other cytostatic compounds. For that, it is necessary to optimise a preconcentration procedure, mostly using solid phase extraction (SPE) [5], to reach the limits of detection and quantification in which cytostatic compounds are usually present in the in-

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fluents and/or effluents of the WWTPs. To our knowledge, only Ghafuri. et al. [22] have tried to apply ENV+ SPE cartridges for the preconcentration of CPCs to determine these compounds in WWTPs, groundwater and drinking water using an non-specified EPA method. They achieved recoveries of between 0.70 and 0.78%. They were able to measured concentrations of CPCs in the ranges of 0.27–0.94 μg L^{-1} and 0.11–0.28 μg L^{-1} in influents and effluents of WWTPs, respectively, confirming the prediction of Johnson et al. [8]. However, CPC concentrations in groundwater and drinking water were lower than their limit of quantification, which ranged from 0.009 to 0.017 μg L^{-1}. If the hypothesis of Vyas et al. [7] is correct, lower LODs are necessary for the evaluation of CPCs in environmental waters.

CPCs are highly polar compounds, which are difficult to extract using conventional SPE cartridges, and probably, for this reason, there are not developed extraction methods for them. Ion exchange sorbents could be a very useful alternative to solve the retention problem that very polar compounds present with the most typically used reversed phase cartridges [23]. The main disadvantage in the use of ion exchange sorbents for the extraction of CPCs is the variable range of recoveries: between 64 and 124% for river water; 52–115% for wastewater [24] and 31–105% for Milli-Q water [25]. However, ion exchange sorbents have been successfully used before in the extraction of different pharmaceuticals from wastewater samples, achieving better limits of detection by reducing the matrix effect [26–30].

The aim of this work is to optimise an extraction and preconcentration procedure for CPCs based on ion exchange sorbents prior to their determination by ICP–MS to reach the best sensitivity and to be able to perform their monitoring in WWTPs and hospital effluents. For that, different ion exchange cartridges were tested and optimised through an experimental design for choosing the one with the best results and finding the optimal extraction conditions. Then, the optimised method was applied to determine these compounds in various environmental wastewater samples, and in this way, it is intended to alleviate the lack of knowledge about the presence of CPCs at low concentrations in this kind of matrix.

2. Experimental

2.1. Materials And reagents

Ultrapure water used was provided by a Milli-Q system (Milli-pore, Bedford, MA, USA). Methanol of HPLC grade was purchased from VWR (France). HCl and NaOH were used to modify the pH. The ionic strength was modified by the addition of NaCl (%, w/v). Carboplatin (Car-Pt) was purchased from Cymit-Química (Barcelona, Spain), and cisplatin (Cis-Pt) and oxaliplatin (Oxa-Pt) were purchased from Sigma-Aldrich (Madrid, Spain). Stock solutions were prepared by dissolving every compound in Milli-Q water at a concentration of 240 mg L^{-1}. A working solution was prepared daily. The structures and properties of the compounds are shown in Table 1.

The SPE cartridges Oasis MCX (strong cation exchange), Oasis WCX (weak cation exchange), Oasis MAX (strong anion exchange) and Oasis WAX (weak anion exchange) were kindly provided by Waters (Barcelona, Spain). After extraction, the determination was carried out with an ICP–MS instrument (iCAP RQICP-MS) from Thermo Fisher. The optimisation of the ICP–MS conditions were performed by the injection of a standard solution with the aim of obtaining the highest signal. The conditions of determination are summarised in Table S1.

2.2. Sample collection

Wastewater samples were sampled from the influent and effluent of a WWTP and from the effluent one of the most important hospitals of Gran Canaria Island (Spain). The samples were collected from a WWTP located in the city of Las Palmas de Gran Canaria (Gran Canaria Island, Spain), which has a population of almost 400,000 inhabitants. Influent WWTP samples were taken in the homogenization tank before starting the treatment and effluent WWTP samples were taken after secondary treatment of activated sludge.

The wastewater samples from the hospital were taken at two different ments, amongst others. In both cases the samples were taken every three months from October 2018 to July 2019. All samples were taken in 2.5 L amber bottles and acidified at a pH in the range of 2.5–3.5 in less than 1 h after intake. Subsequently, the samples were stored refrigerated at −4 °C until analysis. Before extraction, samples were filtered up to a size of 0.65 μm.

3. Results and discussion

3.1. Optimisation Of the ion exchange solid phase extraction

For this work, we carried out a systematic optimisation through an experimental design. In all cases, we used four exchange cartridges: strong cation exchange cartridges (Oasis MCX), weak cation exchange cartridges (Oasis WCX), strong anion exchange cartridges (Oasis MAX) and weak anion exchange cartridges (Oasis WAX)

To choose the most suitable conditions for the extraction of the compounds being studied, a 2^3 (three variables at two levels) experimental design was used using Minitab® 17.1.0. In order to study the significance of each variable and the correlation/interaction between them, the pH (3–9), sample volume (100–250 mL) and ionic strength (0–10% w/v of NaCl) were tested for all of the selected SPE cartridges ($n = 3$). Milli-Q water was spiked with a mixture of the three CPCs (Cis-Pt, Car-Pt and Oxa-Pt) at a concentration of 2.5 μg L^{-1} for all them. After extraction, all samples were dried under nitrogen and reconstituted in 5 mL of Milli-Q water + 2% HNO_3 before being injected into the ICP-MS. Results of the adsorption efficiency of every cartridge, measured as the relationship between the concentration of CPCs in Milli-Q water after extraction and a standard of the same concentration in Milli-Q water (2% HNO_3), are shown in Table S2.

The results show that the adsorption efficiencies for the MAX and WAX cartridges are very low in all conditions. The WCX cartridge obtains poor adsorption efficiencies (less than 30%) that are affected negatively by the presence of salt. For the MCX cartridges, it was found that the addition of NaCl to increase the ionic strength impairs the retention of analytes on the sorbent. In addition, it seems that the pH and volume variation does not affect the retention since in all of them, the extraction efficiency is approximately 45%. Although MCX cartridges at a pH = 3 seem to obtain the best adsorption, the results obtained at a pH = 9 were slightly lower. Therefore, to confirm that a pH = 3 is the best option, different pHs were tested with 0% ionic strength and a sample volume of 250 mL. Fig. 1 shows that the best adsorption rates were achieved with a pH = 3. Therefore, Oasis MCX cartridges at a pH = 3, 0% ionic strength and a sample volume of 250 mL were selected for subsequent studies. A larger sample volume could clog the cartridges when working with wastewater samples and a pH lower than 3 could destroy the cartridge.

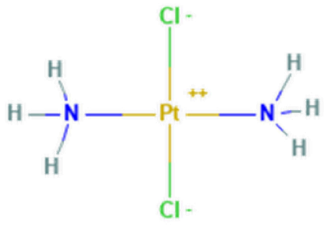
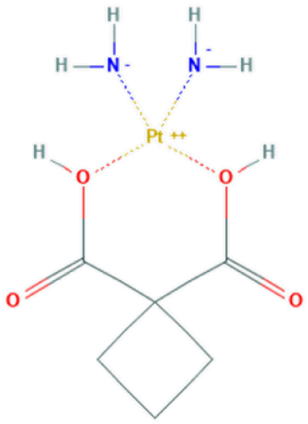
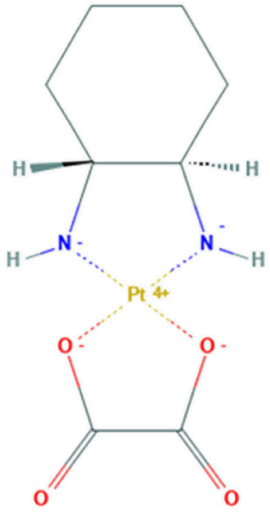
Under the optimal conditions, an adsorption efficiency of 45% of the CPCs onto the Oasis MCX cartridges was obtained. Relative recoveries were calculated taking into account the adsorption achieved.

Next, different elution solvents (MeOH, ACN and water) and mixtures of them were tried to extract the CPCs retained on the cartridge. None of them were able to extract the retained compounds. It could happen that the compounds were permanently retained on the cartridges, which is one of the main disadvantages of using strong ionic exchange sorbents, and thus, solvents with different additives were tested. Then, different percentages of ammonia (0%, 5%, 10%, 15%, 20% and 25%) (v/v) in methanol were tested for the elution of the retained compounds. Fig. 2 shows the results.

Best elution efficiencies were obtained with a percentage of 10% (v/v) ammonia, obtaining a relative extraction efficiency of 71%. Different volumes of elution (between 5 and 12.5 mL) were also tested, and it was observed that the recovery decreased slightly when the elution solvent volume was higher. Thus, 5 mL was fixed as the best elution volume, which also reduces the evaporation time and the use of a large volume of organic solvents. In these conditions, the theoretical preconcentration factor achieved by this new approach was 22.5 times, taking into account the retention in the cartridge.

3.2. Analytical parameters

Table 1
Properties and structures of the CPCs studied [27–29].

Name	Properties		Structure
Cisplatin	Molar mass:	300.05 g·mol^{-1}	
	Log $K_{O/W}$:	-8.24	
Carboplatin	Molar mass:	371.256 g·mol^{-1}	
	Log $K_{O/W}$:	-8.47	
Oxaliplatin	Molar mass:	395.278 g·mol^{-1}	
	Log $K_{O/W}$:	-2.81	
	Acid pK_a:	-11.72	
	Basic pK_a:	6.53	

pared in the CPC concentration range of 12.5 ng L^{-1}–10,000 ng L^{-1}. The linearity was calculated with excellent correlation coefficients (r^2) higher than 0.999.

The relative recoveries were studied using four different concentrations of CPCs in Milli-Q water corresponding to the different concentration levels at which CPCs are expected to be found in WWTPs: 100 ng L^{-1}, 500 ng L^{-1} and 1000 ng L^{-1}. The relative recoveries were calculated by comparing the signal of the extract of a spiked sample and the extract of a blank sample spiked after extraction. All experiments were performed in triplicate (n = 3). As can be seen in Table S3, the recoveries ranged between 64 and 75% in Milli-Q water.

To evaluate the precision of the method, the intra-day (n = 6) and inter-day (n = 3) relative standard deviations (RSD) were determined. The results are shown in Table S3. The results were satisfactory, obtaining intraday RSD in the range of 3–14% and interday RSD in the range of 10–15%.

The instrument limit of quantification (ILOQ) was established as the lowest point in the calibration curve, which is 0.74 ng L^{-1}, taking into account the preconcentration factor achieved. This value is suitable, taking into account the expected concentrations in wastewater. Moreover, the level of quantification achieved in this work is lower than those obtained in previous papers (10 ng L^{-1} [20], 90–150 ng L^{-1} [19] or 1000 ng L^{-1} [21]), in which an extraction procedure is not applied.

After testing the analytical parameters in Milli-Q water, we determined the analytical parameters in wastewater from the influent and effluent of a WWTP. The matrix effect was studied by comparing the signal of a standard in Milli-

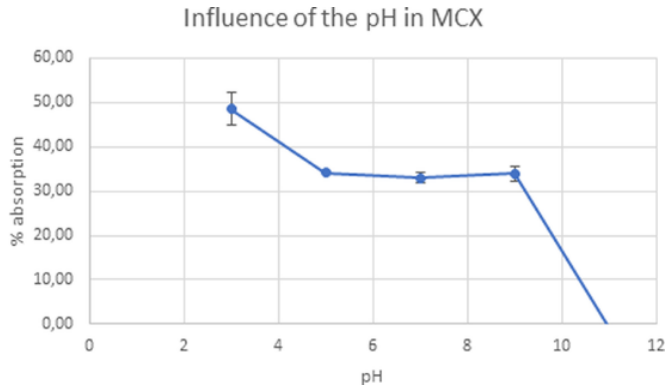


Fig. 1. xx

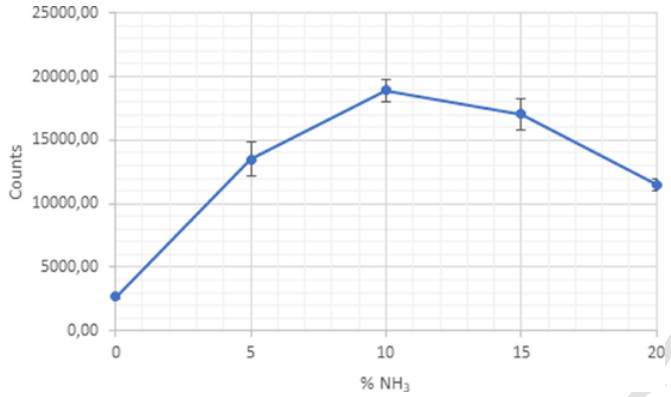


Fig. 2. xx

Q water with the extract of wastewater spiked after SPE. The formula to calculate the matrix effect was described by F. Gosetti et al. [31], in which 0% means no matrix effect, a positive value means loss of the signal, and a negative value means signal enhancement.

$$ME = 100 - \left(\frac{Wastewater\ spiked\ after\ SPE}{Standard\ in\ Milli - Q\ water} * 100 \right)$$

We found a very low matrix effect (Table S4). Recoveries were slightly lower (between 27 and 45%), and this can be explained by the presence of matrix interferences in the wastewater, which could reduce the effectiveness of the adsorption of the target compounds or because CPCs can remain adsorbed on the organic matter when the extract is dried.

To improve the extraction efficiency in wastewater, an elution in two steps was optimised. In these assays, all samples were spiked to a final concentration of CPCs of 1000 ng L^{-1}. The results are shown in Table 2.

Taking into account these results, we decided to perform the elution in the following two steps: a first elution with 5 mL of MeOH (5% HCOOH) + 5 mL Milli-Q water (5% NH_3) and a second elution with 5 mL of MeOH (10% NH_3). The results of the recoveries in the wastewater influent and effluent are shown in Table 3.

The procedure shows very good limits of detection, which are lower than those obtained to date, as well as good reproducibility and repetitiveness, almost without the presence of a matrix effect. Sometimes, it is preferable to work with a lower recovery if it means less interference to achieve a lower detection limit for the method [23]. Relative recoveries of CPCs between 47 and 90% were obtained for the influents and effluents of wastewater. In this way, we were able to study CPCs from hospital wastewater but also from influents and effluents of WWTPs.

Table 2
Relative recoveries of CPCs after two steps extraction.

Elution 1	Relative recovery (%)	Elution 2	Relative recovery (%)	TOTAL
5 mL MeOH	10	5 mL MeOH (10% NH_3)	38	48
10 mL MeOH	12	5 mL MeOH (10% NH_3)	40	52
5 mL MeOH (5% HCOOH)	9	5 mL MeOH (10% NH_3)	48	57
10 mL MeOH (5% HCOOH)	13	5 mL MeOH (10% NH_3)	42	55
5 mL Milli-Q water + 5 mL MeOH (5% HCOOH)	13	5 mL MeOH (10% NH_3)	36	49
5 mL MeOH (5% HCOOH) + 5 mL Milli-Q water	14	5 mL MeOH (10% NH_3)	31	45
5 mL Milli-Q water (5% HCOOH) + 5 mL MeOH (5% HCOOH)	10	5 mL MeOH (10% NH_3)	34	44
5 mL MeOH (5% HCOOH) + 5 mL Milli-Q water (5% HCOOH)	11	5 mL MeOH (10% NH_3)	46	57
5 mL MeOH (5% HCOOH) + 5 mL Milli-Q water (5% NH_3)	50	5 mL MeOH (10% NH_3)	10	60
5 mL Milli-Q water (5% NH_3) + 5 mL MeOH (5% HCOOH)	40	5 mL MeOH (10% NH_3)	28	68

Table 3
Relative recovery (%) of CPCs in influent and effluent water from WWTP.

Concentration (ng L^{-1})	Influent	Effluent
100	82	90
500	47	56
1000	82	66

3.3. Analysis of wastewater samples

Samples of wastewater were taken during one year from October 2018 to July 2019 every three months in a wastewater effluent from a hospital of the island and in a WWTP (influent and effluent). The hospital wastewaters were analysed directly by ICP-MS without preconcentration. Samples of the WWTP were preconcentrated by SPE before their determination by ICP–MS. Each extraction was performed triplicate ($n = 3$). The results are shown in Table 4.

As has been proven before, it is possible to analyse the CPC concentrations in the wastewater effluent from a hospital without the use of a preconcentration step since the concentrations from the hospital are large enough. We have analysed two different points of the hospital, and we have detected a higher concentration of CPCs in the part from the oncology and pharmacy units than in the part from the palliative unit. On the other hand, due to the low concentration of CPCs in the WWTP, it makes it necessary the use of a step of the extraction and preconcentration of the contaminants. With the procedure developed here, we have been able to study the presence of CPCs in the influent and effluent of a WWTP. We have found slightly higher concentrations in the effluent than in the influent. This may be due to

Table 4
Concentrations of CPCs obtained in the analysis of samples from the WWTP and hospital samples.

Sample	Date	Point	Concentrations (ng L^{-1})
Hospital effluent	OCT'18	Point 1	2282 ± 6,85
		Point 2	13,913 ± 28
	JAN'19	Point 1	86,59 ± 0,87
		Point 2	92,40 ± 1,02
	APR'19	Point 1	Not taken
		Point 2	81,94 ± 0,90
	JUL'19	Point 1	104,1 ± 0,41
		Point 2	448,8 ± 3,14
WWTP	OCT'18	Influent	27,01 ± 3,22
		Effluent	75,79 ± 5,61
	JAN'19	Influent	22,49 ± 3,69
		Effluent	74,02 ± 4,17
	APR'19	Influent	3,97 ± 0,25
		Effluent	56,08 ± 2,10
	JUL'19	Influent	38,68 ± 5,68
		Effluent	71,01 ± 4,55

ples. However, the concentrations are similar, and more studies should be carried out to confirm these results.

4. Conclusions

Cytostatic platinum compounds are compounds that have been shown to be cytotoxic and genotoxic; however, their concentrations in wastewater are not well documented, especially not as well as for cyclophosphamide, etoposide or tamoxifen, for example. This is probably because the methodologies optimised to date do not reach an adequate detection limit.

In order to analyse CPCs in wastewater samples from a WWTP, we have optimised and developed a new approach of extraction and preconcentration of very polar compounds using ion exchange sorbents, a strong cation exchange cartridge, prior to their determination by ICP-MS. We have optimised all of the variables that affect the process, and with this procedure we have managed to extract and preconcentrate CPCs, obtaining a method limit of quantification of 0.74 ng L^{-1}, with a low matrix effect and low intraday and interday deviations. This procedure allows us to measure and monitor concentrations of CPCs in samples from WWTPs as well as in samples from hospital effluents.

The method has been satisfactorily applied to real samples, and CPCs were detected in the range of 81.94–13,913ng L^{-1} in effluent samples from a hospital and between 3.97 ng $L^{-1}$and 75.79 ng L^{-1} in wastewater treatment plant samples.

CRediT authorship contribution statement

Sergio Santana-Viera: Investigation, Writing - original draft, Writing - review & editing. **María Esther Torres Padrón:** Writing - review & editing. **Zoraida Sosa-Ferrera:** Supervision, Writing - review & editing. **José Juan Santana-Rodríguez:** Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.microc.2020.104862.

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