



Determination of platinum traces contamination by graphite furnace atomic absorption spectrometry after preconcentration by cloud point extraction

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ABSTRACT

A simple and sensitive method is described for the determination of platinum surface contamination originating from cisplatin, carboplatin and oxaliplatin. Following extraction from swabs and preconcentration with the cloud point extraction (CPE) method, detection was by graphite furnace atomic absorption spectrometry (GFAAS). After desorption of platinum compounds from the swab, CPE involved on preconcentration of platinum in aqueous solution with diethyldithiocarbamate (DDTC) as chelating agent and Triton® X-114 as extraction medium. DDTC is not only a chelating agent, but may also be a good candidate for the inactivation of platinum compounds. DDTC is recommended by the World Health Organization (WHO) for the destruction of platinum-based anticancer drugs. The main factors affecting CPE efficiency, pH of the sample solution, concentrations of DDTC and Triton® X-114, equilibration temperature and incubation time, were evaluated in order to enhance sensitivity of the method. The desorption of platinum compounds from the swab was investigated in parallel. Since platinum is bound to DDTC, it must exchange with copper in order to enhance platinum atomizing by GFAAS. A preconcentration factor of 29 was obtained for 10 mL of a platinum solution at 10 µg mL⁻¹. In optimal conditions, the limit of detection was 0.2 ng mL⁻¹, corresponding to 2.0 ng of platinum metal on the swab. Absorbance was linear between 0.7 and 15 ng mL⁻¹. The proposed method was applied for the determination of surface contamination by platinum compounds with correct results.

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1. Introduction

Cytotoxic drugs are widely used to treat cancer. Occupational exposure to these drugs has been recognized as a potential health hazard. Platinum compounds constitute a class of DNA-damaging anticancer agents [1] and are widely used in cancer therapy. Cisplatin, oxaliplatin and carboplatin are good tracers because these three molecules account for more than 11.7% of all chemotherapy agent vials used in Paris hospitals (Paris Public Hospital Authority in-house report: Cytostatic drugs consumption in 2007).

In addition, platinum levels in the environmental are very low, resulting only from catalytic converters in automobiles [2] and so the metal can be used as tracer of contamination of the workplace or packaging materials (vials and handling chemotherapeutic agents). Contact of chemotherapeutic agents with skin of the hospital staff is carcinogenic, mutagenic and/or teratogenic [3–6]. As a result

of the permeability of gloves to cytotoxic agents, staff must follow safety rules such as double gloving (nitrile gloves then natural latex gloves) that are changed every 30 min during drug reconstitution [7]. In order to reduce risks, contamination must be monitored and preparation procedures changed if necessary. Contamination was detected inside the isolator used to prepare chemotherapeutic agents. It was detected on the surface of the infusion bag containing the chemotherapeutic agents and on gloves in contact with infusion bags filled with them [8].

This study was conducted to develop a simple and sensitive analytical technique for the evaluation of surface contamination by platinum compounds, the cytotoxic drug tracer. After sampling with a swab and desorption of platinum compounds in aqueous solution, graphite furnace atomic absorption spectrometry (GFAAS) is a suitable technique to determine platinum concentrations. GFAAS is known to be a sensitive, specific, precise technique, easily used in routine. Sample preconcentration is still required to retain sensitivity, however, since GFAAS analysis of platinum contamination involves trace quantities. The CPE method using Triton® X-114 is used to preconcentrate metal cations such as chromium, aluminum, copper, nickel or cobalt prior to atomic absorption spectrophotometry, flow injection analysis or high-performance liquid

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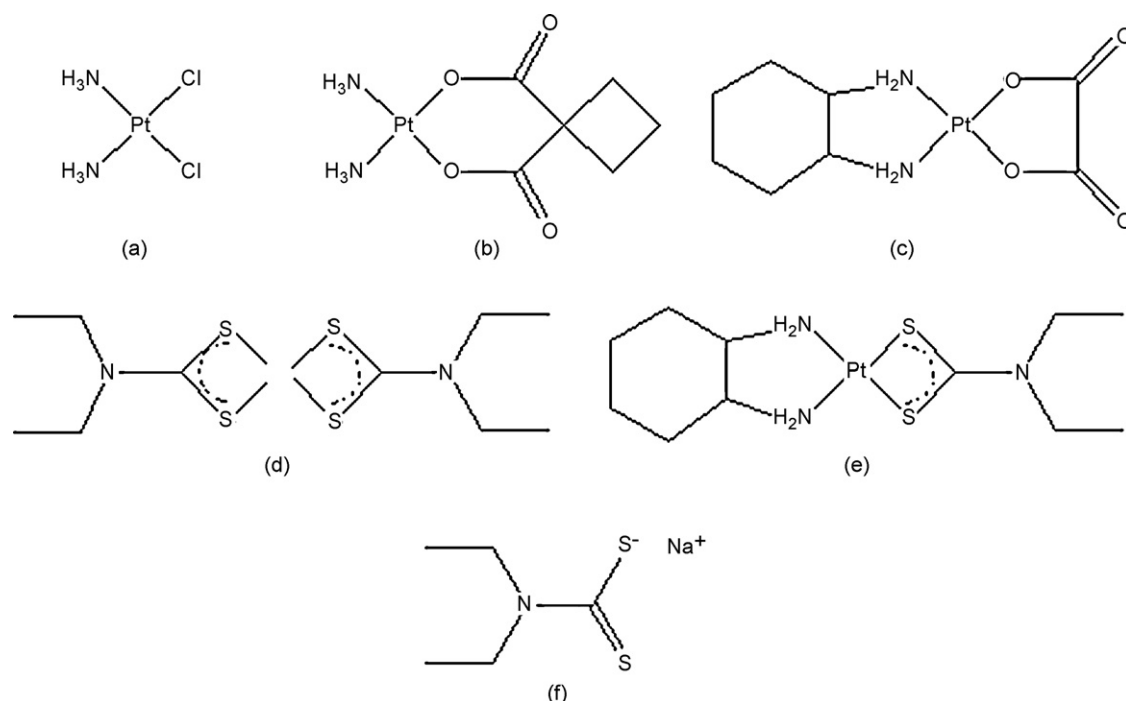


Fig. 1. Formulas of platinum salts: cisplatin (a), carboplatin (b) and oxaliplatin (c), DDTC (f) and complexes obtained in the presence of cisplatin and carboplatin (d) or of oxaliplatin (e).

chromatography [9–13]. The small volume of surfactant-rich phase obtained with this methodology enables extraction methods to be designed that are simple, inexpensive, efficient, rapid, easy to use and that do not require organic solvents for a green chemistry. This technique is based on the property of most non-ionic surfactants in aqueous solutions to form micelles following increase of cloud point temperature [14,15]. During their formation, micelles entrap hydrophobic substances, isolating them from the rest of the aqueous solution.

In this work, we first studied the optimal desorption of platinum compounds from swabs. Preconcentration of platinum compounds with a CPE method based on complexing platinum compounds with DDTC [16] (Fig. 1) and using Triton® X-114 as non-ionic surfactant, was then investigated. The main factors affecting CPE efficiency were studied. The remaining micellar phase was then diluted in acid hydro-alcoholic solution containing copper as chemical matrix modifier and was found to be optimal for the analyses of this work. The proposed method was applied to determining environmental contamination by platinum compounds (cisplatin, oxaliplatin, carboplatin).

2. Experimental

2.1. Instrumentation

The instrument used for atomic absorption measurements was a Varian® SpectrAA GFAAS (Australia) graphic furnace AA spectrophotometer (model 220Z) with Zeeman background correction and equipped with an adapted autosampler, an ultraAA® platinum lamp and a pyrolytically coated graphite tube (Varian® partition tubes (coated)-GTA, Part No. 63-100012-00). A platinum hollow-cathode lamp was used as radiation source at 265.9 nm with a slit width of 0.5 nm. Lamp current was set at 10.0 mA. The volume of automatic sample injection was 20 µL; the internal Argon 5.6 (Messer®) flow rate was 3 L min⁻¹ and was stopped during atomizing. Details of the GFAAS heating program are listed in Table 1.

A Metrohm® 713 pH meter model (Metrohm, France) with a combined electrode was used for pH measurements.

A thermostatted water bath (Polystat 33®, Bioblock Scientific France) maintained at the desired temperature (45 ± 1 °C) was used for the cloud point experiments. A Jouan BR4i centrifuge (Thermo

Table 1
GFAAS heating program.

Step	Furnace temperature (°C)	Ramp time (s)	Hold time (s)	Internal gas flow (L min ⁻¹)	
1	40	0.0	0.1	3	Drying
2	120	55.0	0.0	3	
3	600	10.0	5.0	3	
4	1300	5.0	5.0	3	Ashing
5	1300	0.0	0.5	0.0	
6	2700	0.9	2.0	0.0	Atomizing
7	2850	1.0	0.0	3	
8	40	22.0	0.0	3	Cleaning

Electron Corporation, USA) was used to accelerate phase separation during cloud point extraction. A Branson S210 ultrasonic bath (USA) and a Top-Mix vortex mixer (Bioblock Scientific, France) were used for swab desorption. Dilutions were prepared using a Gilson 402 dilutor dispenser (Gilson, USA). Fifteen millilitres of (17 mm × 120 mm) conical polystyrene Falcon tubes (Becton Dickinson, USA) were used for samples and were preferred over polypropylene tubes because of lower platinum adsorption. Autoclavable clean tip swabs with notched handle (TX715[®] Large Alpha[®] Sampling Swab) were obtained from ITW Texwipe (USA).

2.2. Reagents and solutions

All reagents used were of analytical reagent grade or higher. The ultrapure water used for all preparations was obtained from Milli Qplus 185 with Qpack[®]2 (Millipore, USA). The non-ionic surfactant Triton[®] X-114 and sodium diethyldithiocarbamate trihydrate (DDTC) were obtained from Sigma–Aldrich (USA) and used without further purification. Methanol GR for analysis was purchased from Merck (Germany) and 65% ISO nitric acid for analysis was obtained from Antibioticos s.p.a., a division of Carlo Erba[®] Reagenti (Italy). Working standard solutions were obtained by suitably diluting standard solutions. These standard solutions of platinum, copper, mercury, iron, chromium, zinc, cobalt, lead, cadmium and silver were CertiPUR[®] standard solutions (Merck, Germany). The platinum compounds used in this work had an international marketing authorization and were obtained from Merck (Germany) for cisplatin, Faulding (Australia) for carboplatin and Sanofi-Aventis (France) for oxaliplatin.

2.3. Procedures

2.3.1. Sample collection

The head paddle of the swab was moistened on one side with 200 μL of water. In general, sampling was performed by wiping a defined surface area of 10 cm × 10 cm. Surfaces for which it was not possible to take a 10 cm × 10 cm sample, however, the entire surface of the object was sampled (individual drug vial, gloves). All swab samples were collected with a uniform sampling procedure by wiping in two different directions (horizontal and vertical). Swabs were turned to wipe the surface with the same procedure. After breaking the handle, the head paddle was placed in the conical tube and 10 mL of pure water were added to the sample as desorption solvent. The tube was mixed on a vortex mixer for 30 s and the swab was removed.

2.3.2. Platinum preconcentration by CPE

For CPE preconcentration, the entire aqueous solution (10 mL) containing the analytes, 1% (w/v) DDTC and 0.21% (w/v) Triton[®] X-114 were heated in a thermostatted water bath at 60 °C for 45 min. Phase separation could be accelerated by centrifugation at 2205 g for 10 min at 25 ± 1 °C and the mixture was then chilled in an ice-bath for 15 min to increase viscosity of the surfactant-rich phase. The supernatant was removed by simply inverting the tube for 3 min and the surfactant-rich phase was about 50 μL .

2.3.3. Platinum analysis by GFAAS

300 μL water–methanol (80/20, v/v) containing 0.1 M HNO₃ and 10 mg L⁻¹ of copper (II) were added to the surfactant-rich phase to reduce its viscosity just before GFAAS. Twenty of the 350 μL of the diluted surfactant-rich phase were introduced by an automatic sampler for GFAAS. Calibration was against platinum standards subjected to the same CPE procedure and a blank undergoing the same procedure was assayed in parallel to samples and calibration solutions.

3. Results and discussion

3.1. Factors affecting sample collection

3.1.1. Surface sampling

According to the literature [17,18], a broad range solvent wiped has been used to sample platinum compounds in the workplace. In this work, three solvents were evaluated as wiping solutions for stainless steel surfaces: purified water, 1% aqueous HNO₃ and 10⁻⁴ M aqueous HCl. Surfaces of 100 cm² were spiked with cisplatin, carboplatin and oxaliplatin and recoveries of the order of 60% were acceptable for the solvents. The acid solutions (HCl and HNO₃) were corrosive towards stainless steel and were not sterile for use inside of the isolator; water was selected as the wipe. Two hundred microlitres of water were added to one side of the head paddle to clean the surface and the other side was used to dry it. This technique leads to about 60% recovery for the three platinum compounds. The advantage of this wipe solvent is that sterile water is not corrosive and can be used for aseptic surface sampling in isolators.

3.1.2. Desorption

An ultrasound bath is the usual method for desorption of platinum compounds from the swab or wipes [18,19]. Sonication time was initially optimized for carboplatin contamination. Swabs were first sonicated for 15 min; providing recoveries of about 75%, but longer sonication times surprisingly reduced apparent desorption. A double desorption (5 mL, two times 15 min) was tested but did not significantly increase desorption results. One possible explanation for this is adsorption of platinum compounds on the swab or the conical tube. Adsorption was then determined in polypropylene, polystyrene or glass tubes in the bath for 60 min; there was practically no adsorption with glass (97% recovery) or polystyrene tubes (96.3% recovery). Adsorption by swabs was then tested using a carboplatin solution: recovery decreased (<70%) when the tubes (glass or polystyrene) contained a swab. Thus, platinum compounds adsorb to the swab during sonication, possibly on the polyester head of the swab but more probably on the polypropylene handle. Since ultrasonic desorption of swabs was insufficient, simple vortex mixing was investigated. It was found that 30 s were required for virtually total desorption of all of platinum compounds tested. Desorption was >90% and platinum losses at this step are explained primarily by the loss of aqueous solution on the swab head.

3.1.3. Sample storage before CPE

Three conditions of sample storage after surface sampling were tested for cisplatin, carboplatin and oxaliplatin: (i) swabs were kept in dry tubes, (ii) swabs were kept in water to recover substances wiped. In both cases, swabs were vortexed 30 s just before CPE. Finally swabs were kept in water, vortexed for 30 s, removed immediately and the solutions were stored without the swab for 14 days at room temperature (21 ± 1 °C). It was not possible to store samples with swab because desorption was unacceptable after 1 day (recoveries <90%) and decreased rapidly with time. The most effective storage of platinum compounds (recoveries >90%) was obtained when the swab was removed rapidly (<6 h) and extracted by CPE in less than 6 days; after 6 days, recoveries decreased.

3.2. Factors affecting CPE preconcentration

The technique is based on the property of most non-ionic surfactants in aqueous solutions to form micelles. When the solutions are then heated to a temperature known as the cloud point temperature, they separate into a small volume of surfactant-rich phase and a dilute aqueous phase. CPE can be used for the preconcentration of metal ions after the formation of sparingly water soluble com-

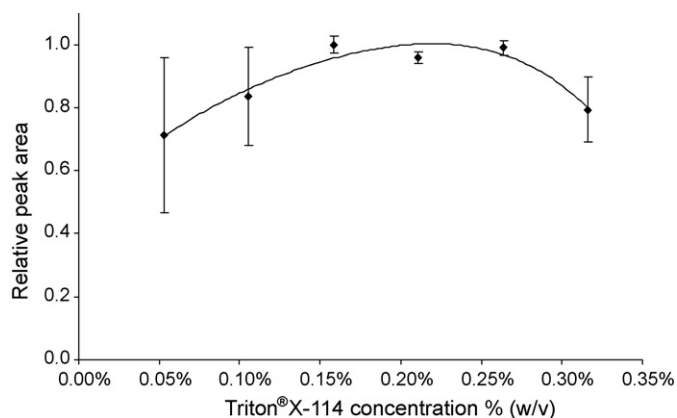


Fig. 2. Effect of the Triton® X-114 concentration (% w/v) on the cloud point extraction of $10 \mu\text{g L}^{-1}$ Pt (II) ($n=3$). Other conditions: 1% (w/v) DDTC, dilution of the surfactant-rich phase by 300 μL water/methanol (80/20, v/v) containing 0.1 M HNO_3 and 10mg L^{-1} copper (II), GFAAS conditions as in Table 1.

plexes. The efficiency of CPE depends on the hydrophobicity of the ligand and the complex formed, apparent equilibrium constants in the micellar medium, kinetics of complex formation and transfer between the two phases.

3.2.1. Effect of Triton® X-114 concentration

Triton® X-114 was chosen to form of the surfactant-rich phase due to its extraction efficiency and enrichment factor [1,3]. In addition, Triton® X-114 is inexpensive, non-toxic and has a low cloud point temperature (22°C). Triton® X-114 was preferred over Triton® X-100 because the latter has a high cloud point temperature (65°C) and the surfactant-rich phase was more difficult to isolate because viscosity is lower than that of Triton® X-114. The Triton® X-114 concentration could maximize extraction efficiency by minimizing the phase volume ratio thus maximizing its enrichment factor. The effect of Triton® X-114 concentration was investigated between 0.053 and 0.32% (w/v). Fig. 2 shows quantitative extraction when the Triton® X-114 concentration was around 0.20% (w/v). The concentration of 0.21% (w/v) was thus chosen as the optimum surfactant concentration for obtaining the highest extraction efficiency.

3.2.2. Effect of DDTC concentration

In this work, DDTC was used as chelating agent to detoxify platinum-based compounds because of the highly hydrophobic nature of its metal complexes. The effect of DDTC concentration was tested between 0.005 and 2% (w/v) (Fig. 3). CPE efficiency for

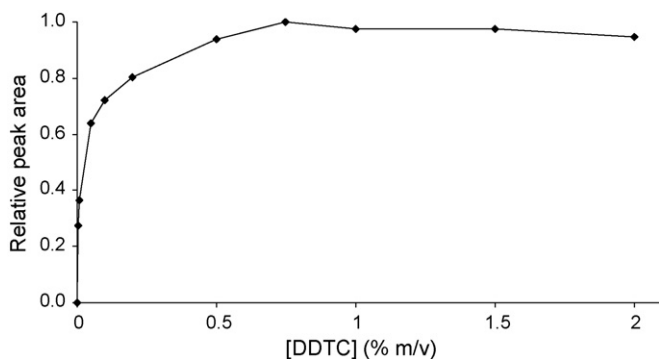


Fig. 3. Effect of DDTC concentration (% w/v) on the cloud point extraction of $10 \mu\text{g L}^{-1}$ Pt (II) ($n=1$). Other conditions: 0.21% (w/v) Triton® X-114, dilution of the surfactant-rich phase with 300 μL water/methanol (80/20, v/v) containing 0.1 M HNO_3 and 10mg L^{-1} copper (II), GFAAS conditions as in Table 1.

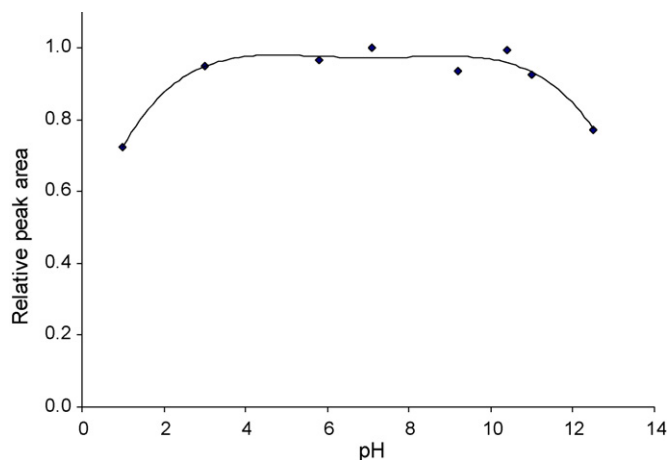


Fig. 4. Effect of pH on the cloud point extraction of $10 \mu\text{g L}^{-1}$ Pt (II) ($n=1$). Other conditions: 1% (w/v) DDTC, 0.21% (w/v) Triton® X-114, dilution of the surfactant-rich phase with 300 μL water/methanol (80/20, v/v) containing 0.1 M HNO_3 and 10mg L^{-1} copper (II), GFAAS conditions as in Table 1.

Pt(II) increased rapidly as concentration increased to 0.2% (w/v) and then remained constant as the DDTC concentration was increased up to 0.75% (w/v). The DDTC concentration subsequently used was 1% (w/v).

3.2.3. Effect of pH on CPE

Since pH plays a unique role in metal chelate formation and subsequent extraction [14], the pH of the sample solution was the next critical factor examined for its effect on CPE preconcentration. The pH range examined was 1–13. Maximal absorbance was obtained in the pH range of 3.0–10.5 (Fig. 4). CPE extraction of metal ions involves the prior formation of a complex with a sufficient quantity of hydrophobic chelating agent to be extracted in the small volume of surfactant-rich phase, thereby furnishing desired preconcentration. The pH of the solution was thus about 7.0, using ultrapure water for all work.

3.2.4. Effects of equilibration temperature and incubation time

Platinum compounds must be heated for derivatizing DDTC to detoxify them. Formation of the $[\text{Pt-DDTC}_2]$ complex minimizes the toxicity of cisplatin, oxaliplatin and carboplatin. The temperature and duration of micelle-mediated extraction play two roles: (i) derivatizing platinum compounds by DDTC and (ii) quantitative extraction of $[\text{Pt-DDTC}_2]$ complexes by the micelle. It is therefore essential to maintain the reaction time above a minimum threshold for quantitative extraction. Optimal equilibration temperature and incubation time are necessary to complete reactions, to obtain phase separation easily and preconcentration as efficiently as possible. The effects of incubation times from 30 to 120 min and of equilibration temperatures from 45 to 90°C were investigated in order to optimize extraction. It was found that CPE efficiency increased when equilibration temperature increased from 45 to 60°C , and reached a maximum between 60 and 90°C for cisplatin and carboplatin. At temperatures higher than 60°C , CPE efficiency decreased for oxaliplatin, probably due to the instability of the specific complex formed with this drug and so the equilibration temperature used was 60°C . Studies of the effect of incubation time showed that maximum extraction efficiency occurred after 45 min for the three compounds and then remained practically constant as incubation time increased further. An equilibration temperature of 60°C and a time of 45 min were adequate for quantitative extraction and were used in subsequent experiments.

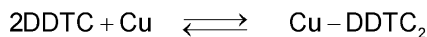
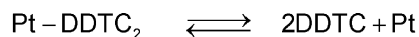
3.3. Factors influencing GFAAS analysis

3.3.1. Dissolution of the surfactant-rich phase

In order to decrease the viscosity of the extract so it could be pipetted, the surfactant-rich phase was diluted with 200–300 μL of 0.1 M HNO_3 in methanol [10–13,20]. The viscosity of Triton[®] X-114 decreases in methanolic acid solutions, but evaporation of these solutions was about 50% after 90 min at room temperature (21 ± 1 °C). Other solvents were used to reduce viscosity and facilitate sample handling such as dimethylformamide [21], despite its toxicity [22] and volatility. Triton[®] X-114 is soluble in aqueous mineral acids, which is why an aqueous solution of 0.1 M HNO_3 was studied for dissolving the extract. Evaporation was no longer a problem but the RSD values were high (>10%) over time that can be explained by the diphasic separation of the sample. We thus used water/methanol (80/20, v/v) acidified with 0.1 M HNO_3 to limit evaporation (<5% after 150 min) and phase separation.

3.3.2. Metal–dithiocarbamate complex exchange

When the surfactant-rich phase was diluted with an acidified aqueous or methanolic solution to determine the platinum concentration by GFAAS, platinum absorption was low compared to platinum in aqueous solution. This is probably due to the high stability of the [platinum–DDTC₂] complex and the composition of the matrix (DDTC, Triton[®] X-114). It was believed that the [platinum–DDTC₂] complex masked absorption because of the high affinity of platinum for DDTC and thus interfered with the atomizing of platinum. Metal ions can be used to displace the [platinum–DDTC₂] complex by exchange between the complex and metal species.



Published data on the extraction constants of metal diethyldithiocarbamates [23] and the use of freshly precipitated metal diethyldithiocarbamates [24] as reagents for the selective extraction of different ions were useful for evaluating higher conditional stability constant. Extraction constants of metals with diethyldithiocarbamate have been reported [24] and $\log K_{\text{ex}}$ values are in the following order: Hg (44.4), Cu (26.1), Ni (24.0), Pb (20.2), Cd (17.8), Co (14.7), Zn (15.4), Fe (13.4) and Mn (8.0). K_{ex} values include the stability constant of metal dithiocarbamates and partition coefficients [23].

Metal ions, Cr, Fe, Zn, Co, Pb, Cd, Ag, Hg and Cu, were added to the surfactant-rich phase containing the [platinum–DDTC₂] complex by diluting with 300 μL of a methanolic solution containing 0.1 M HNO_3 and 10 mg L^{-1} of metal ions. In all cases, platinum absorption increased and was highest with copper ($\text{Cu} > \text{Ag} > \text{Cd} > \text{Pb} > \text{Co} > \text{Zn} > \text{Fe} > \text{Cr} > \text{Hg}$). This is practically the same order as that published by Cesur [24] except for Hg. Copper was thus used in subsequent work. The effect of the copper (Cu^{2+}) concentration in the dissolution solution was then investigated in the range of 0–100 mg L^{-1} (Fig. 5). Recovery increased from 0.1 to 7.5 mg L^{-1} and then remained constant. A copper concentration of 10 mg L^{-1} in the dissolution solution was chosen and platinum absorption increased 4.7-fold in the presence of copper compared to its absence.

3.4. Analytical figures of merit

Calibration graphs were obtained by preconcentrating 10 mL of a sample containing known quantities of platinum, cisplatin, car-

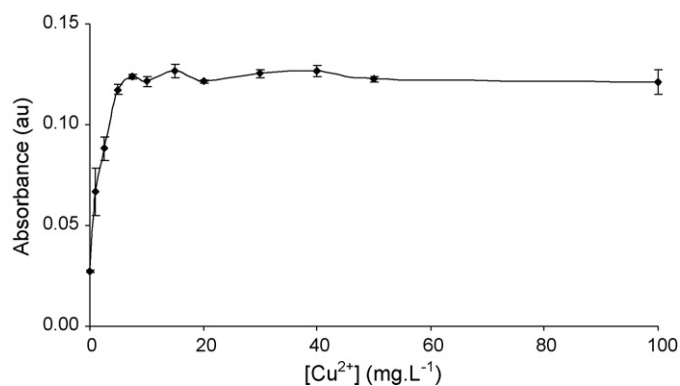


Fig. 5. Effect of copper (II) concentration in the dissolution solvent on the absorption of 10 $\mu\text{g L}^{-1}$ Pt (II) ($n=3$). Other conditions: 1% (w/v) DDTC, 0.21% (w/v) Triton[®] X-114, dilution of the surfactant-rich phase with 300 μL water/methanol (80/20, v/v) containing 0.1 M HNO_3 , GFAAS conditions as in Table 1.

boplatin and oxaliplatin. In the experimental conditions used, there was no difference in the slopes obtained with the three platinum compounds and platinum. Known quantities of platinum were thus used to determine the characteristics of the method. In optimal experimental conditions, the calibration curve for platinum is linear from 0.7 to 15 ng mL^{-1} (slope = 0.0111 ± 0.0001 ; Y intercept $(2.6 \pm 71.2) \times 10^{-5}$). The correlation coefficient (r) was higher than 0.9986 with a mean of 0.9991. The precision for six replicates of 2 ng mL^{-1} of platinum solutions were analyzed in three analytical runs. Within-run and between-run precisions were evaluated using the relative standard deviation (RSD) and did not exceed 3.1%. The limit of detection (LOD) of this method, calculated as 3 times the standard deviation of the blank signal, was 0.2 ng mL^{-1} , corresponding to 2.0 ng of platinum on the swab. Statistical processing of the raw data demonstrated the accuracy of the method. The main recovery was 99.3% with a 95% confidence interval between 95.8 and 103.1%. The limit of quantification (LOQ) of this method, however, calculated as ten times the standard deviation of the blank signal, as 0.6 ng mL^{-1} . The enrichment factor, calculated as the ratio of absorption of preconcentration sample over that obtained without preconcentration was 29.

3.5. Analysis of samples

The analysis technique described enables about 50 samples to be processed daily, compatible with the complete mapping of an installation for the reconstitution of chemotherapy agents. The method was applied to the determination of platinum contamination on different surfaces: stainless steel surfaces inside isolators, floors, drug vials, drug storage boxes, transport boxes, gloves (nitrile, vinyl, latex and neoprene) and infusion bags. Platinum contamination was found in 63% of the swab samples ($n=120$). Substantial levels of contamination were found inside the isolators and on the outside of drug vials delivered to hospital pharmacies, as previously reported [17,25].

3.6. Comparison of analysis techniques for the environmental surveillance of hospital staff exposed to platinum salts

This comparison shows that inductively coupled plasma-mass spectrometry (ICP-MS) is the technique of choice for the detection of traces as a result of its sensitivity. In addition, no sample pretreatment is necessary aside from desorption from compresses. On the other hand, the technique required specific costly equipment (Table 2), explaining why alternative analysis techniques are proposed in the literature. Stripping voltammetry is a widely used method for the analysis of traces because it concentrates the ana-

Table 2
Comparison of analysis techniques or the environment surveillance of hospital staff exposed to platinum salts.

Instrumentation	Sample preparation	Limit of detection	Matrices (sampling)	Ref.
ICP-MS	Direct nebulization	1 ng per vial (0.05 $\mu\text{g L}^{-1}$)	Drug vials (wipes)	[17]
ICP-MS	Direct nebulization	0.2 ng m^{-2} 0.1 ng per glove	Surfaces (wipes)	[26]
ICP-MS	Direct nebulization	0.05 ng per sample (0.5 ng L^{-1})	Surfaces (wipe)	[18]
Stripping voltammetry	Ashing in a muffle furnace + derivatization by hydrazine and formaldehyde	0.1 ng per sample	Drug vials (wipe pads)	[25]
GF-AAS	Derivatization by DDTC + LL extraction	0.5 $\mu\text{g L}^{-1}$	Rinse water	[27]
GF-AAS	Evaporation (50 mL)	5 ng per sample	Surfaces (wipe)	[19]
GF-AAS	Derivatization by DDTC + cloud point extraction	2 ng per sample	Surfaces (swab)	In this work

lyte at the electrode. Stripping voltammetry nevertheless provides access to free ions in solution or to ions bound to labile complexes. It is thus necessary to digest samples of platinum derivatives (muffle furnace), making the technique unsuitable for large series. The limits of detection of GFAAS make it a technique more interesting than flame atomic absorption spectrometry (FAAS) or inductively coupled plasma-atomic emission spectrometry (ICP-AES), but its performance falls short of ICP-MS. The sample must thus be concentrated before placing it in the furnace, also because a small sample volume (<100 μL) is required by the method. Two preconcentration techniques have been published: the first involves derivatizing platinum salts before liquid-liquid extraction [27] and the second is double evaporation of a large volume of aqueous solution in an evaporator flask [19]. Both techniques are time-consuming and in no case can be used for large series of analyses. The technique we are proposing is an alternative to ICP-MS. Its advantage is a lower limit of detection than other GFAAS techniques, with a more rapid and easier to use preconcentration step. DDTC derivation and preconcentration with the cloud point technique are conducted simultaneously when heating at 60 °C, since the surfactant-rich phase is easily recovered after centrifugation.

4. Conclusion

We have developed and validated a sensitive and reliable GFAAS method for the determination of platinum in samples of surfaces. This method was applied to the evaluation of platinum contamination in the preparation units of hospital pharmacies. In this work, the use of a micelle system for preconcentration offers several advantages including ease of use, rapidity, low cost, safety and a good preconcentration factor (about 29 after dissolution of the surfactant-rich phase) with high recoveries and good extraction efficiency. The surfactant-rich phase can easily be introduced in the GFAAS graphite furnace after dilution, with limited evaporation and release of platinum by DDTC decomplexing using copper as matrix modifier.

References

- [1] V. Brabec, J. Kasparkova, Modifications of DNA by platinum complexes. Relation to resistance of tumors of platinum antitumor drugs, *Drug Resist. Updates* 8 (2005) 131–146.
- [2] R. Schierl, G. Fruhmman, Airborne platinum concentrations in Munich city buses, *Sci. Total Environ.* 182 (1996) 21–23.
- [3] P.J.M. Sessink, M.C.A. Van de Kerkhof, R.B.M. Anzion, J. Noordhoek, R.P. Bos, Environmental contamination and assessment of exposure to antineoplastic agents by determination of cyclophosphamide in urine of exposed pharmacy technicians: is skin absorption an important exposure route? *Arch. Environ. Health* 49 (1994) 165–169.
- [4] A.S. Ensslin, R. Huber, A. Pethran, H. Römmelt, R. Schierl, U. Kulka, G. Fruhmman, Biological monitoring of hospital pharmacy personnel occupationally exposed to cytostatic drugs: urinary excretion and cytogenetics studies, *Int. Arch. Occup. Environ. Health* 70 (1997) 205–208.
- [5] A.S. Ensslin, Y. Stoll, A. Pethran, A. Pfaller, H. Römmelt, G. Fruhmman, Biological monitoring of cyclophosphamide and ifosfamide in urine of hospital personnel occupationally exposed to cytostatic drugs, *Occup. Environ. Med.* 51 (1994) 229–233.
- [6] T.H. Connor, R.W. Anderson, P.J.M. Sessink, L. Broadfield, L.A. Power, Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United-States, *Am. J. Health-Syst. Pharm.* 56 (1999) 1427–1432.
- [7] P.E. Wallemacq, A. Capron, R. Vanbinst, E. Boeckmans, J. Gillard, B. Favier, Permeability of 13 different gloves to 13 cytotoxic agents under controlled dynamic conditions, *Am. J. Health-Syst. Pharm.* 63 (2006) 547–556.
- [8] S. Crauste-Manciet, P.J.M. Sessink, S. Ferrari, J.Y. Jomier, D. Brossard, Environmental contamination with cytotoxic drugs in healthcare using positive air pressure isolator, *Ann. Occup. Hyg.* 49 (2005) 619–628.
- [9] A.N. Tang, D.Q. Jiang, Y. Jiang, S.W. Wang, X.P. Yan, Cloud point extraction for high-performance liquid chromatographic speciation of Cr(III) and Cr(IV) in aqueous solutions, *J. Chromatogr. A* 1036 (2004) 183–188.
- [10] H. Sang, P. Liang, D. Du, Determination of trace aluminum in biological and water samples by cloud point extraction preconcentration and graphite furnace atomic absorption spectroscopy detection, *J. Hazard. Mater.* 154 (2008) 1127–1132.
- [11] M. Ghaedi, A. Shokrollahi, F. Ahmadi, H.R. Rajabi, M. Soylak, Cloud point extraction for the determination of copper, nickel and cobalt ions in environmental samples by flame atomic absorption spectrometry, *J. Hazard. Mater.* 150 (2008) 533–540.
- [12] J.L. Manzoori, G. Karim-Nezhad, Sensitive and simple cloud point preconcentration atomic absorption spectrometry: application to the determination of cobalt in urine sample, *Anal. Sci.* 19 (2003) 579–583.
- [13] C.D. Stalikas, Micelle-mediated extraction as a tool for separation and preconcentration in metal analysis, *Trends Anal. Chem.* 21 (2002) 343–355.
- [14] E.K. Paleologos, D.L. Giokas, M.I. Karayannis, Micelle-mediated separation and cloud-point extraction, *Trends Anal. Chem.* 24 (2005) 426–436.
- [15] S. Rubio, D. Pérez-Bendito, Supramolecular assemblies for extracting organic compounds, *Trends Anal. Chem.* 22 (2003) 470–485.
- [16] D. Bouvet, A. Michalowicz, S. Crauste-Manciet, D. Brossard, K. Provost, EXAFS and IR structural study of platinum-based anticancer drugs degradation by diethyl dithiocarbamate, *Inorg. Chem.* 45 (2006) 3393–3398.
- [17] H.J. Mason, J. Morton, S.J. Garfitt, S. Iqbal, K. Jones, Cytotoxic drug contamination on the outside of vials delivered to a hospital pharmacy, *Ann. Occup. Hyg.* 47 (2003) 681–685.
- [18] E.E.M. Brouwers, A.D.R. Huitema, E.N. Bakker, J.W. Douma, K.J.M. Schimmel, G. van Weringh, P.J. de Wolf, J.H.M. Schellens, J.H. Beijnen, Monitoring of platinum surface contamination in seven Dutch hospital pharmacies using inductively coupled plasma mass spectrometry, *Int. Arch. Occup. Environ. Health* 80 (2007) 689–699.
- [19] G. Leboucher, F. Serratrice, V. Bertholle, L. Thore, M. Bost, Evaluation of platinum contamination of a hazardous drug preparation area in a hospital pharmacy, *Bull. Cancer* 89 (2002) 949–955.
- [20] J. Chen, K.C. Teo, Determination of cadmium, copper, lead and zinc in water samples by flame atomic absorption spectrometry after cloud point extraction, *Anal. Chim. Acta* 450 (2001) 215–222.
- [21] M.B. Gholivand, A. Babakhanian, E. Rafiee, Determination of Sn(II) and Sn(IV) after mixed micelle-mediated cloud point extraction using alpha-polyoxometalate as a complexing agent by flame atomic absorption spectrometry, *Talanta* 76 (2008) 503–508.
- [22] J.H. Sohn, M.J. Han, M.Y. Lee, S.K. Kang, J.S. Yang, Simultaneous determination of N-hydroxymethyl-N-methylformamide, N-methylformamide and N-acetyl-S-(N-methylcarbonyl)cystein in urine samples from workers exposed to N,N-dimethylformamide by liquid chromatography-tandem mass spectrometry, *J. Pharm. Biomed. Anal.* 37 (2005) 165–170.
- [23] J. Stary, K. Kratzer, Determination of extraction constants of metal diethyldithiocarbamates, *Anal. Chim. Acta* 40 (1968) 93–100.
- [24] H. Cesur, Solid-phase extractions with freshly precipitated metal-diethyldithiocarbamates and atomic absorption spectrophotometric determination of copper, *J. Trace Microprobe Techn.* 21 (2003) 627–636.
- [25] O. Nygren, B. Gustavsson, L. Ström, A. Friberg, Cisplatin contamination observed on the outside of drugs vials, *Ann. Occup. Hyg.* 46 (2002) 555–557.
- [26] H.J. Mason, S. Blair, C. Sams, K. Jones, S.J. Garfitt, M.J. Cuschieri, P.J. Baxter, Exposure to antineoplastic drugs in two UK hospital pharmacy units, *Ann. Occup. Hyg.* 49 (2005) 603–610.
- [27] R. Raghavan, J.A. Mulligan, Low level (PPB) determination of cisplatin in cleaning validation (rinse water) samples. I. An atomic absorption spectrometric method, *Drug Dev. Ind. Pharm.* 26 (2000) 423–428.