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VALIDATION OF A METHOD TO QUANTIFY PLATINUM IN CISPLATIN BY INDUCTIVELY-COUPLED PLASMA

Maykel Gonzalez Torres[1], Carolina Munoz Torres[2], Ataulfo Martinez Torres[3], Susana Vargas Munoz[4], Rogelio Rodriguez Talavera[4], Alvaro de Jesus Ruiz - Baltazar[4], Witold Brostow[5, *]

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Abstract. *Cis*-diaminedichloroplatinum(II), also known as cisplatin, has been quantified by use of inductively-coupled plasma. We measured cisplatin indirectly by determining the platinum concentration in the samples. We focus on the determination of Pt from cisplatin in water. We demonstrate that the total concentration of the drug can be quantified through the content of platinum with acceptable linearity, precision, repeatability, accuracy, limit of detection and limit of quantification. Our method is applicable among others for monitoring quality of control samples for cisplatin regulatory submissions and for determination of the cisplatin release profiles in biomarker implants *in vitro*.

Keywords: cisplatin, inductively-coupled plasma, cancer drug.

1. Introduction

Cisplatin has been used since 1969 as a chemotherapeutic drug for the treatment of cancer [1]. It is known as the first member of a group of platinum-containing complexes that are responsible for triggering apoptosis [2]. However, some side-effects such as asototoxicity, nausea, neuropathy and nephrotoxicity have prompted researchers to propose analytical methods to determine the cisplatin concentration and hence to control the dosages that are administered in chemotherapy [3].

This control allows unpreventable severe side effects to be reduced [4]. Nowadays, the mechanism of the toxicity of cisplatin is not completely identified, which has propelled scientists to perform the cisplatin determination in biological fluids using different techniques [5].

Selective methods such as high-performance liquid chromatography (HPLC) have been applied for the determination method of cisplatin in biological systems [6], while inductively-coupled plasma can also be used for this end [7]. The use of different methods is justified by the nature of this drug, because it can be hydrolyzed to give diverse hydroxo-bridged complexes [8]. It is thought that the hydrated cisplatin species such as monoaqua- and diaqua cisplatin are responsible for the drug's biological effects [9].

As cisplatin is administered to the human body as a buffered aqueous injection solution, the accurate determination of its species and platinum is of concern. On the other hand, the characterizations of products and processes are important for pharmaceutical companies to certify the equipment-cleaning validation studies [10].

In addition, some active pharmaceutical ingredients (APIs) such as cisplatin are organic, but they are often monitored by the determination of an inorganic compound, in this case platinum, to verify the use of appropriate concentrations for therapy and optimize therapeutic regimes by evaluating the drugs prior to the dosage [11].Until now, several techniques have been performed for the quantification and validation of platinum [12] such as atomic absorption spectrometric method (AAS) [13], and high-performance liquid chromatography (HPLC) [14]. However, these methods have shortcomings with regards the detection limits, interferences, and complex manipulation of the samples before use. Moreover, inductively-coupled plasma (ICP) has been shown to be a more suitable technique which has been used coupled with a mass spectrometer or HPLC for

[1] Centro de Ciencias de la Complejidad, Universidad Nacional Autónoma de México,
Circuito Exterior, Circuito Mario de la Cueva 20, Insurgentes Cuicuilco, Ciudad de México 04510, Mexico
[2] Centro de Geociencias, Universidad Nacional Autónoma de México, Campus Juriquilla. Boulevard Juriquilla 3001, Santiago de Querétaro, Querétaro C.P 76230, Mexico
[3] Laboratorio de Neurobiologia Molecular y Celular,
Instituto de Neurobiología (INB), Universidad Nacional Autónoma de México, Querétaro 76230, Mexico
[4] Centro de Física Aplicada y Tecnología Avanzada,
Universidad Nacional Autónoma de México. Campus Juriquilla.
Boulevard Juriquilla 3001, Santiago de Querétaro, Querétaro C.P 76230, Mexico
[5] Department of Materials Science and Engineering, University of North Texas, 3940 North Elm Street, Denton, TX 76207, USA
[*] *wkbrostow@gmail.com*

the quantification of separated cisplatin species [15]. The water-soluble species of cisplatin has also been successfully determined by the inductively-coupled plasma–atomic emission spectroscopy (ICP-AES) [7, 16]. In general, ICP is one of the most important techniques contributing to the protection of human health because of its versatility [17]. It has increased researchers' interest in the field of biomedical monitoring activities [18].

Although platinum concentration in cisplatin can be accurately quantified with high precision using ICP-AES in the aqueous media, to the best of our knowledge, a validation of its determination has not yet been reported. In the past, a spectrophotometric method was validated for the determination of cisplatin hydrochloride in the dissolution. Nonetheless, there is still little information regarding the determination of cisplatin in the aqueous media because most of the research has been focused upon the determination in biological fluids [19]. Cisplatin (total concentration of all species) can be estimated from the determination of Pt in the aqueous cisplatin samples.

The aim of this work is the development and validation of a sensitive inductively coupled plasma method for the determination platinum in cisplatin in the aqueous media for the first time. This new proposed method gives us the capability to deal with a suitable alternative for cisplatin determination studies, because it can not only be successfully applied to clinical studies that support the cisplatin regulatory submissions, but it can also be used to determine the cisplatin release profiles in biomarkers that are synthesized to be introduced in the human body for therapeutic purposes, as demonstrated in our earlier study [20].

2. Experimental

2.1. Reagents and Materials

cis-Diammineplatinum(II) dichloride (cisplatin) was purchased from Sigma(Lot # MKBT4784V, St Louis, MO, USA). A certified Pt standard solution at a concentration of 10 μg/ml was provided by Centro de Geociencias (CGeo) laboratories and used as an external standard (EE). A diluted buffer solution of *cis*-DDP prepared with 1 mg/ml cisplatin, 1 mg/ml mannitol BP, and 9 mg/ml sodium chloride BP in water for injection British Pharmacopeia (BP) (Blastolem RU ®) was used as the control sample (MC). Double-distilled water was used to prepare the calibration curve of fifteen different cisplatin concentrations (Sigma) within the range from 3 ppb to 500 ppm (0, 0.0034, 0.0268, 0.3738, 0.4132, 0.9447, 2.0418, 3.9197, 7.8927, 15.6252, 31.3873, 62.4906, 125.1123, 249.8462, and 500.2299). Nalgene high-density polyethylene (HDPE) bottles were used to guarantee the accuracy of the calibration curve. The samples were directly injected into the ICP-AES without previous digestion.

2.2. Instrumentation

The cisplatin samples were made using an iCAP 6500 Duo (ICP-AES) [21-24] which employs a charged injection device detector, allowing the measurement of a broad range of metal concentrations. Table 1 shows the main instrumental characteristics used in this study [25].

Table 1

Instrument parameters (ICP-AES)

Parameter	Setting
Nebulizer	Glass concentric
Spray Chamber	Glass cyclonic
Center tube	2 mm
Pump tubing	Sample orange-white Drain white-white
Nebulizer Gas Flow	0.7 l/min
Plasma Gas Flow	12 l/min
Auxiliary Gas Flow	0.5 l/min
RF Power	1150 W
Sample Flush Time	45 s
Pump Speed	45 rpm
Plasma view	axial
Sample flow rate	1 ml/min
Resolution	Normal
Replicates	3
Peak algorithm	Peak area
Pt wavelength	214.42 nm
Calibration Eq.	Linear through zero
Point per peak	3
Integration Time	Low (166–230 nm); 15s High (230–847 nm); 5s

2.3. Experimental Procedure

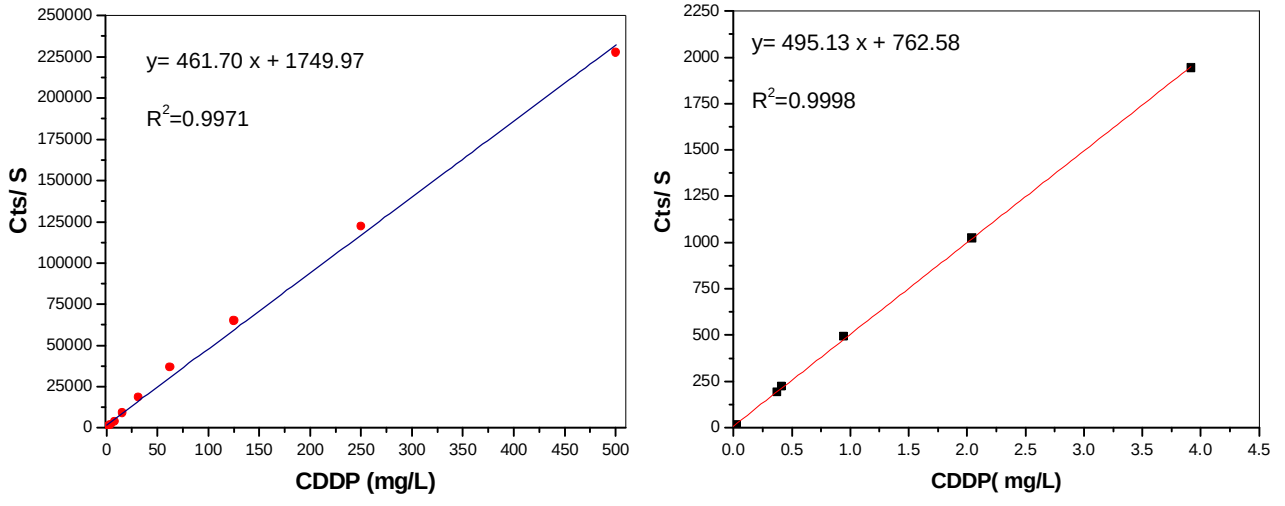
The samples of the cisplatin calibration curve were recorded without clogging the nebulizer using the iCAP 6500 Duo detector coupled to a computer. The blank (double-distilled water) did not show the detection of Pt. The prepared samples were introduced directly without previous digestion or pretreatment. The signals were stable for all working wavelengths (203.6, 214.42, 217.4, 224.5 and 265.9 nm). However, we have selected the analyte line Pt(II) at 214.42 nm to streamline processing procedures, because it has shown greater sensitivity than the rest of the lines. The EE samples were prepared from a certified Pt standard solution at a concentration of 10 µg/ml (30.79 ml) diluted in 61.62 ml of doubly-distiller water, and the MC samples were obtained by dissolving 1000 ppm (13.91 ml) of buffer solution of *cis*-DDP in 100 ml of distilled water.

3. Results and Discussion

The ICP-AES-iCAP 6500 Duo detector measures Pt independently if Pt or cisplatin solution is used. However, the detector signal is different for each sample because of the energy implied in the process, in this case, to break up the cisplatin molecules into their respective atoms and the subsequent detection of the metal (matrix effect) [26]. In addition, the intensity of the Pt emission is a direct indicator of its concentration. Nonetheless, there is also a correlation of the cisplatin and Pt concentration, given by their weight mass. The division of the Pt standard atomic weight (195.084 g/mol) and the cisplatin molecular mass (300.05 g/mol) is 0.6501 and represents the percentage of Pt in the cisplatin samples. For instance, a 1000 ppm cisplatin (control sample) contains approximately 650 ppm of Pt. In this sense, the validation is carried out knowing that some results refer to cisplatin concentrations while others (like the external standard) are attributed to the Pt concentration itself. This is because the signal of the equipment is dependent on the nature and the metal concentration of the sample [27-29].

3.1. Linearity and Range

The linearity of the methods was surveyed by analyzing the cisplatin working standard solution in the concentration range mentioned hereafter (0–500 ppm). The results of the linearity are summarized in Table 2. It is of note that the method displays an acceptable linearity for the studied range, with a correlation coefficient ranging from 0.9971 to 0.9998 (see Fig. 1a). The correlation moved closer to 0.9998 in the 0–4 ppm range (see Fig. 1b). We highlight this last range because the application of this method in the cisplatin release profiles of scaffolds *in vitro*, involves the determination of low levels of platinum, in the range of 0–10 ppm [20]. The recovery of CDDP was calculated as the percentage of the MC or EE measured concentration divided to the corresponding nominal concentration. Average recovery values ≥99.48 ± 0.6 % were obtained using the analyte line Pt(II) at 214.42 nm. The measurements were assessed on cisplatin standard samples prepared on seven consecutive days. The mean concentration and ICP-AES signal values are reported in Table 2 and calibration curves (Fig. 1) [30].



a) b)

Fig. 1. Calibration plots for Pt (214.42 nm) determination in CDDP standards: 0–500 mg/ml (a) and 0–4 mg/ml (b)

Table 2

Linearity of cisplatin standards

CDDP[a], μg/ml	CDDP[b], μg/ml	Pt[b], μg/ml
0.0000	0.0000	0.0000
0.0033	0.0034	0.0022
0.0267	0.0268	0.0174
0.3718	0.3738	0.2429
0.4110	0.4132	0.2685
0.9398	0.9447	0.6140
2.0300	2.0418	1.3271
3.9000	3.9197	2.5478
7.8500	7.8927	5.1302
15.560	15.62	10.156
31.230	31.3873	20.402
62.170	62.491	40.619
124.47	125.11	81.330
248.57	249.84	162.40
497.67	500.23	325.15
Slope	495.13	762.58
intercept	8.10	8.11
R^2	0.9998	0.9998
R	0.9999	0.9999
SD	0.0062	0.0062

Notes: [a] prepared concentration, [b] measured concentration; CDDP – cisplatin; SD – standard deviation; R – correlation coefficient; R^2 – determination coefficient (R and R^2 were determined in the 0–4 ppm range)

Table 3

Method accuracy results for CDDP aqueous solutions

CDDP[a], μg/ml	EE[b], μg/ml	TC[c], μg/ml	CF[d], μg/ml	R, %	R.S.D[e], %	MR[f], %
	0.2482	0.4911	0.4853	98.81	0.21	
0.2429	0.4956	0.7385	0.7290	98.71	0.82	99.52
	0.9605	1.2034	1.216	101.04	0.94	

Notes: [a] cisplatin; [b] external standard; [c] total concentration (CDDP+EE); [d] Pt concentration found; [e] relative standard deviation (n = 3) and [f] mean recovery

3.2. Accuracy

Accuracy of the method was evaluated by performing the addition of the standard and determining the recoveries of platinum from the combined samples. The analysis was performed in samples of known compositions. The total concentration sample obtained by a combination of the calibration curve working standard (0.2429 μg/ml) and different concentration of the EE (see Table 3) was measured in triplicate (0.4911, 0.7385 and 1.2034 μg/ml, respectively). As can be seen, the mean percentage of the recovery and the relative standard deviation indicated that the method is suitable for the determination of Pt in cisplatin aqueous samples. However, it is important to state that in the case of buffer injectable cisplatin solutions, the dilutions of small aliquots (*i.e.* 1 ml in 99 ml of double-distilled water) are recommended. Low concentration of cisplatin for injection (Blastolem RU®) is suggested to avoid errors due to the matrix effect. This effect in the detector signal is more probable when the concentration of cisplatin (buffer) is approximately over 100 ppm.

3.3. Specificity and Sensitivity

This study is specific for the determination of Pt in cisplatin samples in water. It was evaluated by the analysis of the ICP-AES signal of distilled water as placebo, the CDDP standard solutions (calibration curve), cisplatin control samples (90.45 μg(Pt)/ml of the injection ampoule) and the external standards (0.9605; 0.4956 and 0.2482 μg(Pt)/ml). The method was specific for 203.6, 214.42, 217.4, 224.5 and 265.9 nm wavelengths that are the corresponding to Pt. However, it is reported herein

214.42 nm specifically. It is of note that even the double-distilled water produces a signal; hence, we strongly suggest withdrawing at most, 10 ml of the injection ampoule, and dissolving it in 90 ml of water, in order to minimize the effect of the buffer in the ICP detector (matrix effect). The results of the recoveries (over 99 %) indicated that there was no interference in the samples.

The calibration plots for Pt determination in CDDP standards at different working wavelengths (203.6; 214.42; 217.4; 224.5 and 265.9 nm) are shown in Fig. 2. The analytical sensitivity was assessed by determining the concentration (µg(Pt)/ml) at which the mean response of the ICP-AES is statistically beyond the double-distilled water signal. This response corresponded to the minimum detectable concentration of Pt in the cisplatin samples. The line slopes confirmed that the wavelength at 214.42 nm is the plot that brings a greater instrument signal related to the minimal noticeable concentration.

The variables σ and S are the standard deviation of response and the slope of calibration curve, respectively. The average σ value obtained from the wavelength at 214.42 nm, and measured during seven consecutive days and by analyzing the CDDP samples by three analysts, was found to be 0.0162 ± 0.008 µg(Pt)/ml. As can be seen the analyte can be detected at very low concentration by using this method.

The result is in agreement with previous investigation using ICP-MS for the determination of platinum in biological fluids, the atomic absorption spectrometric (AAS) method for the determination of Pt in human plasma and the determination of cisplatin by several methods [31-33].

The estimation of the limit of detection (LD) (Table 4) was calculated by the equation:

$$LD = \frac{3.3s}{S} \quad (1)$$

3.4. Sample and Standard Stability

We have examined the stability of the CDDP working standard solution and the control samples. The results indicated that both samples are stable for at least seven days. Room temperature was used in the ICP-AES detection, but the samples were stored at 277 K after the measurements in order to avoid important changes in the concentration. It is of note that although control samples were also stable, the stability is not of concern because injectable ampoules are sealed, and cisplatin is prepared with a buffer solution.

3.5. Precision (Robustness)

The precision of the presented method was studied as the repeatability by determining the ICP-AES concentration values of the determination of the CDDP samples prepared in the same experimental conditions on the same working day and their determination during seven consecutive days with the use of three different analysts (see Tables 4 and 5, Fig. 3).The mean % relative standard deviation (R.S.D, %), also known as a coefficient of variation (CV), was 0.38 %. On the other hand, the CV values determined in the intermediate precision analysis was evaluated by three different analysts during seven days and showed values of 0.6 % in the average. The CV values were minor than 2 % in all cases. This is in agreement with a precise and reliable method [10, 34].

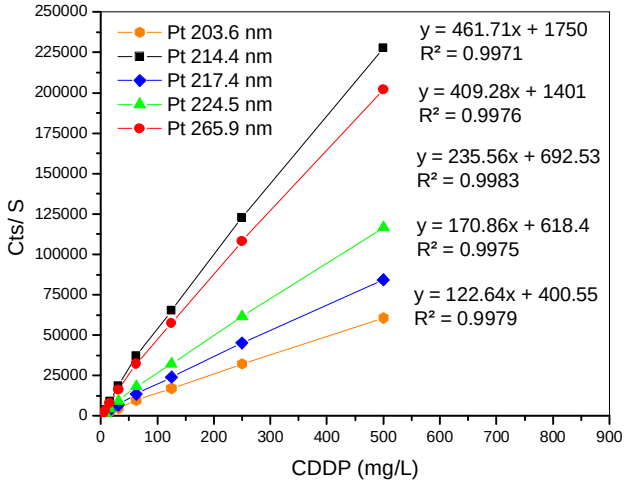


Fig. 2. Calibration plots for Pt determination in CDDP standards at different working wavelengths

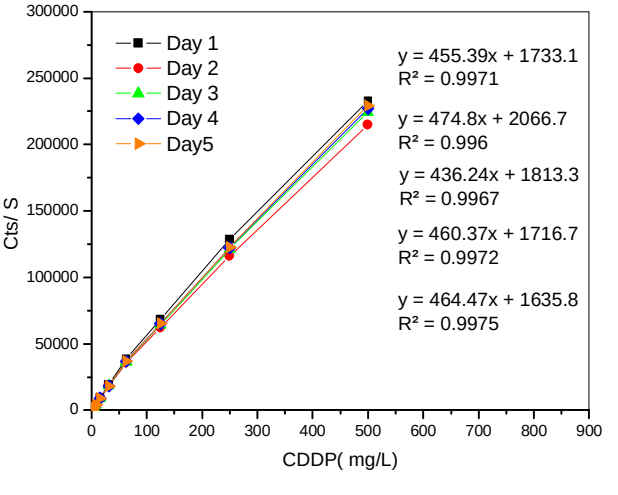


Fig. 3. Calibration plots for Pt determination in CDDP working standards during five days

Table 4

Robustness results for CDDP aqueous solutions (repeatability)

	Pt (214.4 nm)						
	Cts/S						
Rep. 1	0.0133	0.0674	0.0331	0.0134	0.0167	0.0228	0.0121
Rep. 2	0.0164	0.0735	0.0287	0.0056	0.0152	0.0179	0.0062
Rep.3	0.0175	0.0675	0.0268	0.0047	0.0214	0.0223	0.0138
Rep. 4	0.0111	0.0534	0.0269	0.0049	0.0241	0.0272	0.0063
Rep. 5	0.0111	0.051	0.0254	0.0088	0.0071	0.0144	0.0121
Rep. 6	0.0133	0.054	0.0259	0.0077	0.0068	0.0151	0.0083
Rep. 7	0.0136	0.0545	0.0271	0.0015	0.0163	0.0205	0.0093
$\overline{X}$	0.0137	0.0602	0.0277	0.0049	0.0154	0.02	0.0097
σ	0.0024	0.009	0.0026	0.0062	0.0065	0.0046	0.003
$\%\sigma$	0.1781	0.149	0.094	1.266	0.4257	0.2274	0.306
LD	0.0080	0.0296	0.0086	0.0204	0.0216	0.0151	0.0099
LQ	0.0243	0.0898	0.0260	0.0618	0.0655	0.0456	0.0301

Notes: $\overline{X}$ – arithmetic mean; σ(R.S.D) – standard deviation; Rep. – replication; $\%\sigma$ ((R.S.D %) – % relative standard deviation

Table 5

Method precision results for CDDP aqueous solutions

Standard, mg/l	Day 1[a]	Day 2[b]	Day 3[c]	Day 4[a]	Day 5[b]	Day 6[c]	Day 7[a]
	Pt214.4						
	Cts/S						
0	2.83	2.107	2.313	2.217	1.552	2.651	0.2427
0.00335	3.241	2.174	2.201	2.572	2.484	2.84	2.83
0.02678	15.74	13.27	14.18	13.83	13.8	14.44	13.81
0.3738	202.4	185.3	192.2	192.5	189.6	185.6	196.1
0.4132	233.7	216	221.5	222.2	221.7	218.8	226.8
0.9447	515	472.5	485	484.7	528.1	469.5	493.4
2.0418	1085	1003	1020	1023	997.4	1015	1063
3.9197	2067	1885	1928	1946	1919	1922	2014
7.8927	4196	3798	3913	3920	3866	3880	4044
15.625	9626	8863	9025	9052	8959	8959	9378
31.387	19440	18000	18380	18280	18290	18260	19090
62.491	38660	35820	36410	36820	36890	36610	38100
125.11	68300	62110	64330	65100	65370	64620	66870
249.85	128700	116300	121200	122300	122700	122200	125800
500.23	232900	214900	224400	226900	229200	228300	236300

Notes: [a] Analyst 1; [b] Analyst 2; [c] Analyst 3

3.7. Limit of Detection (LQ)

The estimation of the limit of detection (LQ) (Table 4) was calculated by the equation:

$$LQ = \frac{10s}{S} \quad (2)$$

The mean LQ obtained was 0.0490 ± 0.025 µg(Pt)/ml. This obtained value is consistent with the LD and revealed that the results of CDDP working standards are carried out over the quantification limit value. It is worth mentioning that the outcome obtained through this method meets the requirements for the determination of platinum from cisplatin in the aqueous media[35].

3.8. Survey of Results and Discussion

The proposed method is suitable for the quantification of Pt in cisplatin aqueous samples, but it does not differentiate between different species of cisplatin. This disadvantage can be overcome by coupling ICP with mass spectrometry or HPLC, but this is not the aim of this study. Then again, the matrix effects of the samples produced by mannitol BP and sodium chloride in the buffer samples is important for concentrations over 50 ppm; therefore, we suggest using the concentrations recommended here.

According to the results obtained in this study, two main regions can be distinguished in the validation of the determination of platinum in aqueous cisplatin by the ICP-AES technique. On the one hand, there is a narrow region ranging from 0–4 ppm (mg/L), while, on the other hand, there is a wider region of 0–500 ppm. The validation performed during research indicates that low CDDP concentrations were the most adequate to measure the chemotherapy drugs. In our earlier work, we demonstrated that the levels of released cisplatin in biomarkers are found to be lower than four ppm in all cases [20]. Moreover, the validation results were compared with other validation methods [36, 37]. Conclusively, the limit of detection obtained in this work suggests that this method can be applied for concentrations over 0.02 μg(Pt)/ml which support the application proposal.

It is known that the optimal effects of CDDP therapy can be obtained by exposing the target to high concentrations for sufficient time to eliminate tumor cells [38]. However, the human pharmacokinetic studies revealed that from 25 to 45 % of intravenously injected cisplatin is excreted in the urine, while the rest is distributed throughout the body [39, 40]. Hence, small quantities, in the order of ppb (μg/l) or possibly ppt (0.001 ng/l) are able to reach tumoral cells [41-43]. In this sense, the selective and local administration of cisplatin through biomaterial implants appears to be a more suitable and promising way to improve cancer treatment [44-47]. This work makes an effort to report an easy, sensitive, and reliable method to test *in vitro* anticancer cisplatin delivery systems.

4. Conclusions

A new method was proposed for the determination of platinum in aqueous cisplatin. The drug was injected directly into an ICP-AES detector. This approach was applied for the determination of platinum in CDDP injection samples and standards that were prepared in double-distilled water. The method was validated and the results indicated that the validation assay was successfully implemented. It allowed quantifying the concentration of Pt over a wide range, with acceptable linearity, sensibility, exactitude, precision, and specificity. We concluded that this technique was suitable and reliable for the quantification of platinum in cisplatin regulatory submissions and to determine the cisplatin release profiles in biomarkers before they are infused into cancer patients.

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ОЦІНКА МЕТОДУ КВАНТИФІКАЦІЇ ПЛАТИНИ У ЦИСПЛАТИНІ ІНДУЦІЙНО-ЗВ'ЯЗАНОЮ ПЛАЗМОЮ

Анотація. *Розглянуто можливість кількісного визначення цис-діаміндихлороплатини(II), відомої як цисплатин, безпосереднім застосуванням індуктивно зв'язаної плазми, зокрема визначенням концентрації платини з цисплатину у воді. Доведено, що загальна концентрація препарату може бути кількісно визначена через вміст платини з прийнятною лінійністю, чіткістю, повторюваністю, точністю, межею виявлення та межею кількісного визначення. Показана можливість застосування методу для моніторингу якості контрольних зразків для нормативного подання цисплатину та для визначення профілів вивільнення цисплатину в біомаркерних імплантатах* in vitro.

Ключові слова: *цисплатин, індуційно-зв'язана плазма, препарат від раку.*