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SPECTROPHOTOMETRY DETERMINATION OF PLATINUM(II) FROM PLATINUM BASED CISPLATIN AND CARBOPLATIN ANTICANCER INJECTIONS

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Spectrophotometric method has been developed for the determination of platinum(II) after derivatization with bis(2-hydroxynaphtaldehyde) ethylendiimine (H_2HN_2en). The complex was extracted in chloroform at pH 8. The absorbance was measured at 355 nm.The linear calibration curve was obtained with 1-5µg/ml platinum. The platinum was determined from cisplatin and carboplatin injections with relative standard deviation (RSD) of 0.7 to 2.2%.

Copper(II), nickel(II) and palladium(II) also reacted with H_2HN_2en, and absorbed at 390 nm , 328 nm and 330 nm respectively. The copper, nickel, cobalt and iron when added at the concentration similar to platinum did not affect the determination of platinum with relative error within 5%.

Keywords : Cis-platin, Carbo-platin, Determination, Spectrophotometry.

1. Introduction

Cis-platin [cis-dichlorodiamino-platinum(II)] and Carboplatin[cis-diammine (1,1-cyclobutane dicarb oxylato)platinum(II)] are platinum containing drugs used for chemotherapy of cancer patients. These cytotoxic drugs are inserted into the body and work at destroying cancer cells, much quicker than normal healthy cells. Cis-platin is used commonly for testes, ovaries, lungs, head, neck, breast, stomach and lymphoma cancers [1].

A number of analytical and pharmacokinetic studies of cis-platin in biological fluids have been made [2,3]. The analytical methods reported for the determination of platinum from biological samples include atomic absorption (flame and nonflammable) [3-5], inductively coupled plasma atomic emission (ICP-AE) [6], electro analytical techniques [7-8], neutron activation analysis [9], gas [10] and liquid chromatography [10-14].

The spectrophotometric methods are interesting because they involve less expensive equipment and required sensitivity is achieved by using suitable complexing reagents. Marczenko has reviewed spectrophotometric determination of platinum [15] and indicated that various reagents have been used for the determination of platinum, but high selectivity reagents have rarely been reported. Bis (salicylaldehyde)ethylenediimine is reported as a complexing reagent for metal ions [16-18]. The change of phenyl with naphthyl group could enhance the spectrophotometric sensitivity of complexing reagent, because of better delocalization of the charge. The reagent bis(2-hydroxynaphthaldehyde)ethylenediimine (H_2 H N_2en) was considered and H_2HN_2en has been reported as a complexing reagent for copper(II) and nickel (II) and their structures has been determined [19-25]. The present work examines the potentials of the reagent H_2HN_2en for the spectrophotometric determination of platinum(II) from pharmaceutical preparations.

2. Experimental

The reagent bis(2-hydroxynaphthaldehyde) ethylenediimine (H_2HN_2en) was prepared by condensation of 2-hydroxynaphthaldehyde with ethylenediamine in 2:1 molar ratio in ethanol as reported **[10]**. The reagent was recrystallized from methanol and melting point was noted 312 ^oC.

2.1 Solvent extraction

To an aliquot of solution (1-5ml) containing 0-50 µg of platinum(II) reagent solution (H_2HN_2en) 4 ml (0.02%w/v in methanol) was added. This solution

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was added to 1ml buffer solution of pH 8 and mixture was heated on water bath for 15 minutes at (70–75 °C). The contents were allowed to cool and were transferred to separating funnel. Chloroform (5ml) was added and the contents were well mixed .The organic layer was separated and extract was transferred to 10ml flask. The extraction was repeated with 3 ml chloroform .The volume was adjusted upto 10 ml with chloroform, adding 1 ml absolute ethanol. The absorption spectra of metal chelates against reagent blank were recorded on Hitachi 220 spectrophotometer at 355 nm.

2.2 Analysis of platinum from cisplatin and carboplatin injections

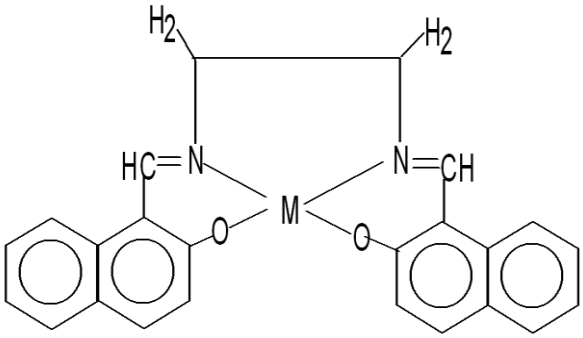
Solution (4ml) from cisplatin injection (Platosin, PCH pharma Cheme Karachi) containing 0.5mg/ml cisplatin and carboplatin (1ml) David Bull Laboratories (DBL), Australia containing 10mg/ml carboplatin were added to hydrochloric acid (37%) (5ml) and was heated to near dryness. The residues was dissolved in hydrochloric acid (37%) (3ml) and again heated to near dryness. The residue was dissolved in water and volume was adjusted to 25 ml with water .The solution (2-3) ml was taken and solvent extraction procedure was followed as in 2.1. The absorbance was measured at 355 nm against reagent blank and the amount of platinum from cisplatin and carboplatin injections were estimated from calibration curve.

2.3. Reagents

GR grade chemicals: sodium acetate, acetic acid, boric acid, borax, ammonium chloride, ammonia, chloroform, acetonitrile, hydrochloric acid (37%) (E. Merck), palladium(II) chloride, platinum(II) chloride, nickel(II) chloride, copper(II) chloride, 2-hydroxy-1-naphthaldehyde and ethylenediamine (Fluka) were used. Freshly prepared doubly distilled water was used through out the work. The buffer solutions in the pH range of 1-10 at unit interval were prepared from the following: potassium chloride (1M)—hydrochloric acid(0.1M), pH 1-2, sodium acetate (1M)-acetic acid (1M) pH 3-6, ammonium acetate(1M)- acetic acid (1M) pH 7, boric acid (1M)- borax (1M) pH 8-9 and ammonium chloride (1M)-ammonia pH 10.

4. Results and Discussion

The reagent was prepared with 80% theoretical yield and its I.R spectrum indicated peaks as could be expected from its structure (Fig. 1). The reactions of reagent towards copper (II), nickel (II),



M= Cu(II) , Ni(II), Pd(II) and Pt(II)

Figure 1. Structural diagram of the reagent (H_2HN_2en).

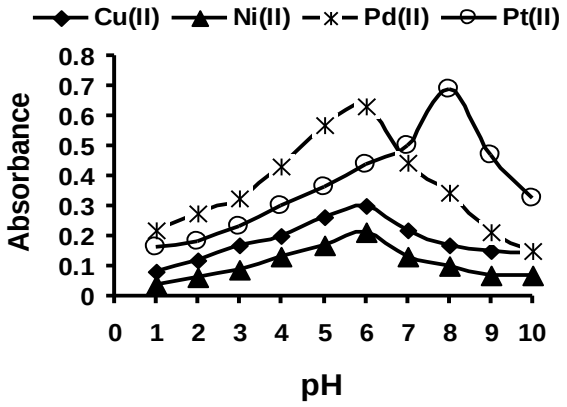


Figure 2. Effect of pH on copper(II), nickel(II), palladium(II) and platinum(II) as H_2HN_2en chelates.

palladium(II) and platinum(II) were examined by spectrophotometry. The effect of the pH on the formation of the complexes within pH 1-10 was investigated. Maximum color development for copper(II), nickel(II) and palladium(II) were observed at pH 6, but platinum(II) indicated color at pH 8 (Fig. 2). Effect of heating time and amount of reagent solution added on derivatizing was measured for heating time (3 to 20 min) at 75 °C and addition of 1 to 5 ml of 0.02% w/v reagent solution in methanol. The optimal results were obtained with 5 to 15 min heating time and 15 min was selected for further experiments. The addition of 4 ml of 0.02% reagent solution was considered as optimum. The complexes formed were highly stable and did not show any change in the absorbance upto 24 hrs. The complexes indicated a reasonable sensitivity for platinum(II) (Table 1) and the reagent was examined for the determination of platinum from pharmaceutical

Table-1. Quantitative Spectrophotometric data of metal chelates of reagent H_2HN_2en

Metal chelates	λ_{max} (nm)	ε(L.mole^{-1} cm^{-1})	Calibration range (μg ml^{-1})	r^2	Sandell's sensitivity (μg ml^{-1})
Cu (II)	390	1x10^2			
	310	1.5x10^3	50 -250	0.998	4.0
Ni (II)	328	5.5x10^2	4 - 32	0.997	1.0
Pd (II)	330	1.4x10^4	1 - 5	0.998	0.06
Pt(II)	355	1.4x10^4	1 - 5	0.999	0.07

Table 2 Spectrophotometric analysis of Pt(II) from pharmaceutical preparations.

Sample	Metal ion	Amount of metals reported	Amount found (RSD%)
Platosin (cisplatin)inj.	Pt(II)	1.27μg/ml	1.31 μg/ml (2.2)
Carboplatin inj.	Pt(II)	6.3 μg/ml	6.26 μg/ml (0.67)

preparations. The linear calibration curve for platinum (II) was obtained with 1-5 μg/ml with coefficient of determination (r^2) 0.999. The sandell's sensitivity for platinum(II) observed was 70ng/ml. Effect of copper(II), nickel (II), cobalt (II) and iron(II), manganese (II), chromium (III), calcium(II), magnesium (II), lead(II), cadmium (II) and mercury (II) on the determination of platinum(II) at the similar concentrations as platinum(II) (3μg/ml) was examined and did not interfere. The copper (II) and nickel (II) also react with the reagent to form coloured complexes, but the complexes indicate low sensitivity and did not affect the determination of platinum (II) with relative error within 5%. Palladium (II) introduced positive error, but palladium (II) is generally not present in the biological fluids or pharmaceutical preparations to affect the determination of platinum (II). The reagent H_2HN_2en indicates better spectrometric sensitivity for platinum (ii) than commonly known reagent dithiozone [26].

Cisplatin and carboplatin injections were analyzed for the contents of platinum and the results obtained (Table 2) are with relative deviation (RD) of 0.7–2.7% from reported value by manufacturer and relative standard deviation (RSD) of 0.7 – 2.2%.

5. Conclusion

Simple spectrophotometric method has been described for the analysis of platinum based anticancer drugs. The platinum(II) derivative formed with H_2HN_2en was highly stable with molar absorptivity 1.4 x10^4 L.mole^{-1} cm^{-1}. The analytical results correlated reasonably with expected values and indicated RSD of 0.7 to 2.2%.

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