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Notes

Stability of carboplatin in 5% glucose solution exposed to light

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Abstract

The degradation of carboplatin (3.2 mg ml^{-1} and 0.8 mg ml^{-1}) in 5% glucose infusion solution at different experimental conditions was studied. It was observed that the degradation rate of carboplatin under illumination increases notably with respect to the rate obtained in the dark. The time course of carboplatin in solution follows a first-order kinetics with rate constants that depend on the incident light intensity and little with temperature. The time in which 10% of carboplatin has been degraded (t_{90}) lies between 1 and 10 h depending on the experimental conditions. From the results obtained in the present work it is concluded that under clinical conditions, protection from light must be necessary.

Keywords: Kinetics; Stability; Carboplatin; Degradation; Photodegradation

Carboplatin [cis-diammine (1,1-cyclobutanedicarboxylat-platinum II)], an analogue of cis-diamminedichloro-platinum II (cisplatin) was synthesized to obtain a drug with antitumor properties similar to those of cisplatin, but without side effects such as renal toxicity, severe nausea, and vomiting. The antitumor activity of carboplatin in ovarian cancer (Van Echo et al., 1984) and small cell lung cancer (De Waal et al., 1990) has been demonstrated. The structures of carboplatin and cisplatin are shown in Fig. 1.

Carboplatin is used mainly in hospitals for administration by intravenous infusion (Cheung et al., 1987). It must be considered that carboplatin similar to these platinum complexes can be sensitive to light, promoting photodegradation (Pujol et al., 1991). In this paper the photodegradation of carboplatin in 5% glucose infusion solutions at different experimental conditions is studied. A high performance liquid chromatographic (HPLC) method is used for analytical measurements of the drug. Kinetics measurements are made under different illumination conditions at 25°C.

Carboplatin for injection (Paraplatin®) was obtained from Bristol-Myers Laboratoires (Barcelona, Spain) and was prepared in 5% glucose solution in glass bottles (Grifols Laboratoires, Barcelona, Spain). HPLC grade methanol was supplied by Tecknocroma (San Cugat del Vallés, Spain). Double distilled water was used after filtration through a Milli Q system (Mil-

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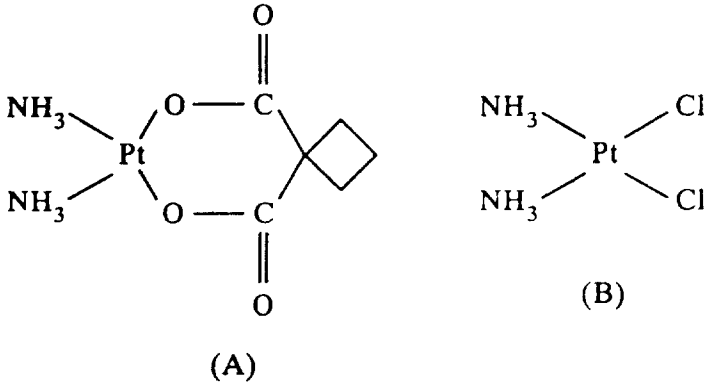

Fig. 1. Molecular structure of (A) carboplatin and (B) cisplatin.

lipore, Barcelona, Spain) and a second vacuum filtration in a helium atmosphere. All other chemicals were, at least, of reagent grade and used as received.

All experiments were carried at 25°C in a open thermostated 50 ml Pyrex cell. In the photochemical experiments a 250 W Xe lamp (Applied Photophisics, Barcelona, Spain) was used as light source. The intensity of incident light inside the cell was measured using an uranyl oxalate actinometer.

Carboplatin disappearance in solution was monitored by HPLC by comparing the peak area of the drug with standard aqueous solutions, using a liquid chromatograph with an isocratic pump and diode array. A UV-light detector (Hewlett Packard, HP-1090) coupled to an integrator (Hewlett Packard, HP-3396) was use for the HPLC assay. A Spherisorb-Ph column (25 cm × 4.6 mm i.d., 5 μm particle size) was used as the stationary phase. The mobile phase had a flow rate of 0.8 ml min^{-1} under isocratic conditions of water-methanol (98/2, v/v). The ultraviolet detector was set at 210 nm. Under these conditions, the retention time for carboplatin was 4.4 ± 5% min. The reproducibility and linearity of the method were studied, and the stability-indicating capability was demonstrated (Prat et al., 1994). Fig. 2 shows the chromatogram obtained of carboplatin, 3.2 mg ml^{-1} in 5% glucose solution under illumination conditions.

The ratio of peak area of the drug to the peak area of the reference standard solution was used for quantification. The initial concentration of carboplatin was designated as 100%; all subsequent concentrations were expressed as percentages of the initial concentration. The samples were exposed under different illumination conditions (2.05, 1.22, 0.82 and 0.33 Eins min^{-1}) for 8 h. Stability was defined as $<10\%$ loss of initial drug concentration.

Under illumination, the degradation of carboplatin (3.2 mg ml^{-1} and 0.8 mg ml^{-1}) in 5% glucose solution was found to observe pseudo-first-order kinetics. The observed rate constants (k_{obs}) for the overall degradation of carboplatin were calculated by linear regression from the slope of linear plots of the logarithm of residual carboplatin concentration against time. In Table 1, the rate parameters (rate constant and t_{90}) for carboplatin photodegradation at different experimental conditions are summarized. It must be pointed out that the rate constant increases with increasing light intensity.

The rate of carboplatin degradation can be expressed as made up of two contributions. $r = K_{th}c + K_{ph}c$ where K_{th} and K_{ph} are the thermal and photochemical rate constants of the process, respectively. However, it must be said that in the dark the aqueous solutions of carboplatin at 25°C are very stable (Prat et al., 1994). As a consequence, K_{th} can be neglected and: $r = K_{ph}c$.

The photochemical rate constant, K_{ph}, can be related to the light intensity absorbed per mole of carboplatin by means of the following expression (Pujol et al., 1993). $K_{ph} = (fI)/(c_i V)$ where f is the quantum yield of the carboplatin photodegrada-

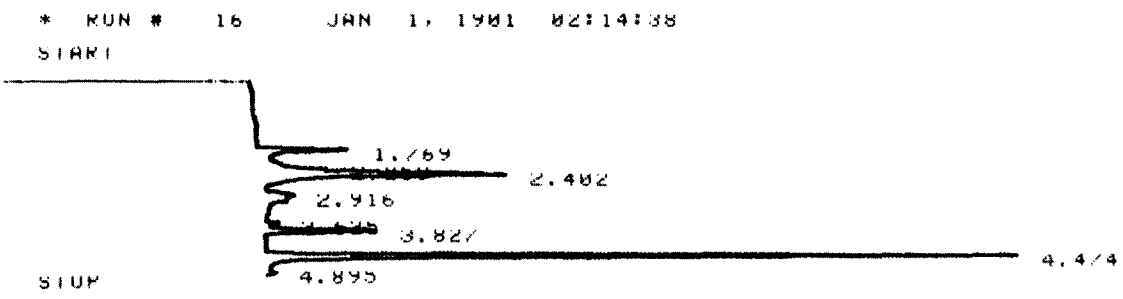

Fig. 2. Chromatogram of carboplatin (3.2 mg ml^{-1} in 5% glucose solution) exposed at laboratory conditions for 2 months.

Table 1
Rate-parameters and quantum yield (ϕ) of photodegradation at different initial concentration of carboplatin in 5% glucose solution, light intensitites [I] at 25°C of temperature

C (mg ml^{-1})	1×10^6 (Eins min^{-1})	$K_{ph} \times 10^4$ (min^{-1})	t_{90} (h)	ϕ (mol $Eins^{-1}$)
0.8	2.05	(9.30 ± 0.53)	(1.88 ± 0.06)	(4.85 ± 0.27) x 10^{-2}
0.8	1.22	(5.50 ± 0.14)	(3.18 ± 0.08)	(4.84 ± 0.13) x 10^{-2}
0.8	0.82	(3.22 ± 0.13)	(5.44 ± 0.22)	(4.22 ± 0.17) x 10^{-2}
0.8	0.33	(2.73 ± 0.17)	(6.40 ± 0.41)	(8.89 ± 0.57) x 10^{-2}
3.2	2.05	(6.42 ± 0.42)	(2.72 ± 0.18)	(1.35 ± 0.09) x 10^{-1}
3.2	1.22	(4.30 ± 0.20)	(4.07 ± 0.19)	(1.52 ± 0.07) x 10^{-1}
3.2	0.82	(2.08 ± 0.20)	(8.40 ± 0.81)	(1.09 ± 0.11) x 10^{-1}
3.2	0.33	(1.80 ± 0.13)	(9.72 ± 0.61)	(2.35 ± 0.17) x 10^{-1}

tion, I the intensity expressed as moles of incident photons per minute, c_i the initial concentration of carboplatin and V is the solution volume. In Table 1, the quantum yield of carboplatin photodegradation at different experimental conditions are summarized.

The quantum yield of carboplatin photodegradation increases with the concentration attaining a maximum value at lower intensity (0.33×10^6 Eins min^{-1}).

This study has shown that the degradation of carboplatin (3.2 mg ml^{-1} and 0.8 mg ml^{-1} in 5% glucose solution) is accelerated in the presence of light. At 25°C the t_{90} values for carboplatin (Table 1) suggest that under clinical conditions, protection from light must be necessary.

Acknowledgements

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