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Notes

Stability and compatibility study of carboplatin with three portable infusion pump reservoirs

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Summary

The stability of carboplatin in admixture stored in portable pump reservoirs was investigated. Admixtures containing 1 mg/ml carboplatin in 5% dextrose injection were placed in drug reservoirs of three different portable infusion pumps. Because of possible conversion of carboplatin to cisplatin, carboplatin and cisplatin concentrations were monitored simultaneously for 28 days using a simple high-performance liquid chromatographic procedure. No precipitation or change in color or pH was observed during the 28 day storage period. The percentage of the initial concentration remaining at 28 days at all storage temperature was up 97%. A 14% increase was observed in Infusor® stored at +35°C. Cisplatin formation was not detected in all reservoirs. Carboplatin was stable at all temperatures for 28 days when stored in the tested reservoirs.

Carboplatin, *cis*-diammine 1,1-cyclobutane dicarboxylate platinum(II), is a second generation platinum-containing antitumor agent analogue of cisplatin. Carboplatin has a broad spectrum of antitumor activity similar to that of cisplatin and is less nephrotoxic and emetogenic than cisplatin (Calvert et al., 1982).

A previous stability study (Cheung et al., 1987) in commonly used intravenous solutions has shown that carboplatin should not be diluted with solution containing chloride ions because of possible conversion to cisplatin. Recently, Allsopp et al. (1991) have observed that the time for 5% degradation of carboplatin in 0.9% sodium chloride was 29.2 h and have proposed a mechanism for the degradation of carboplatin. Other studies showed carboplatin was stable in pre-filled syringes used in an ambulatory continuous infusion regime (Northrott et al., 1991), or in Parker Micropump medication reservoirs for 14 days at +4 and +37°C (Jewell et al., 1991).

In this study, the stability of carboplatin was determined in three pump reservoirs under conditions of prolonged storage at 4, 22 and 35°C.

Cisplatin was purchased from Sigma (St Louis, MO, U.S.A.) and carboplatin was supplied by Bristol Laboratories (Paris la Défense, France). 1,1-Cyclobutane dicarboxylic acid was obtained

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from Merck (Darmstadt, Germany), and cyclobutane monocarboxylic acid, transplatin and hexadecyltrimethylammonium bromide from Sigma.

Solutions were assayed for cisplatin and carboplatin content using a high-performance liquid chromatography (Rochard et al., 1993).

The liquid chromatographic system consisted of an L6000 pump (Merck), a Wisp model 710B sample injector (Waters Associates Inc., St Quentin Yvelines, France), a Waters 990 UV-Visible photodiode array detector, an APC model IV NEC personal computer with Waters 990 software and plotter.

Isocratic reversed-phase chromatography was performed at ambient temperature with a Nucleosil C18 column (150 × 4.2 mm i.d., 5 mm particle size, Merck). The mobile phase consisted of 0.01 M phosphate buffer pH 7.0 containing hexadecyltrimethylammonium bromide ($5.5\ 10^{-4}$ M).

Three types of delivery systems were studied. The first was a 100 ml plasticized polyvinyl chloride container (lot B 11717) for the Pharmacia Deltec pump (Pharmacia Deltec Inc., St Paul, MN, U.S.A.), the second was an 80 ml ethylene vinyl acetate container (RES 80 A, lot 91H09) for the Celinject C01 portable infusion pump (Celsa Laboratories, Chasseneuil France), and the last was a 60 ml elastomeric balloon (lot L012534R) that acts as both the reservoir and driving force of a disposable drug pump Infusor® (Baxter Healthcare Corp., Deerfield, IL, U.S.A.).

All infusions were prepared under aseptic conditions. Vials containing carboplatin (150 mg in 15 ml water for injection lot 10129) were obtained from Bristol Laboratories (Paris la Défense, France). This solution was diluted with 5% glucose to give a concentration of 1 mg/ml.

Each drug reservoir was filled with the 1 mg/ml solution. All air was removed from the reservoirs. The filled drug reservoirs were stored in duplicate under dark conditions in a refrigerator (+4°C), at room temperature (+22 ± 1°C) and in an incubator (+35 ± 0.5°C).

To compare stability data to those observed with PVC and glass containers, infusion solutions of 1 mg/ml carboplatin were simultaneously prepared in 100 ml PVC infusion bags and 50 ml glass bottles containing 5% dextrose.

Samples were withdrawn at 0, 1 2, 3, 4, 7, 14, 21 and 28 days and observed visually for discoloration and precipitation. The pH values were checked by using a pH meter Schöt Gerate (model CG 820, Hofheim, Germany). Immediately after dilution in water for injection, samples were subjected to HPLC assay in duplicate.

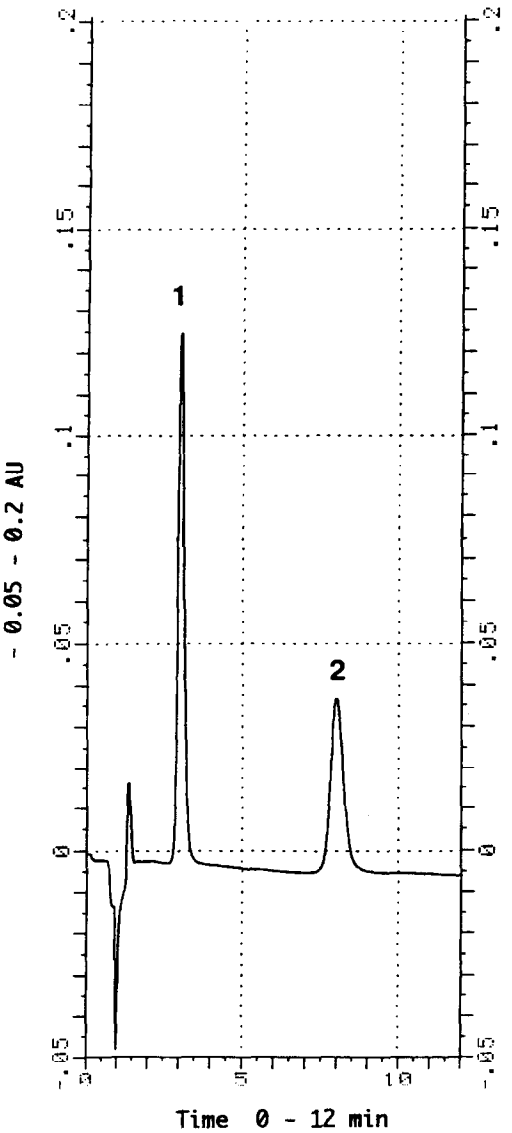

Fig. 1. HPLC chromatogram of carboplatin (1) (50 mg/ml) and cisplatin (2) (50 mg/ml) (Column: Nucléosil 5 μm, detector 216 nm).

The chromatogram of cisplatin and carboplatin is illustrated in Fig. 1. Drugs were simultaneously and rapidly well separated, identified and quantified. Cisplatin and carboplatin eluted at approx. 8 and 3 min, respectively.

Table 1 summarises the validation data of the assay procedure for each drug. We observed good linearity between peak area and concentration over the range 5–60 mg/l. The correlation coefficients were all at least 0.990.

Within-day accuracy and precision of the assay were determined by preparing and analysing 10 replicate samples of each concentration. Control samples of carboplatin (5, 20, 50 mg/l) and cisplatin (5, 20 mg/l) were assayed over a 1 month period to calculate between-day precision and accuracy.

The results demonstrate that this HPLC method had acceptable accuracy and precision.

The stability indicating ability of HPLC assay system was determined using degradation products and forced degraded samples. Cisplatin and carboplatin peaks were separated from degradation products of cisplatin. The retention times of transplatin and diaquodiammine platinum were 1.3 and 1.5 min, respectively. Cyclobutane mono- and dicarboxylic acids were not eluted with this mobile phase.

HPLC chromatograms of carboplatin control solution, and samples of the same solution subjected forcibly to degradation (1 N HCl, 1 N NaOH and 6 vols H_2O_2 solutions heated at +70°C for 2 h) are shown in Fig. 2.

Cisplatin is detectable only in acidic solution containing chloride ion. Other degradation products peaks appear on all HPLC chromatograms, but are eluted and detected without interference from paraplatin and cisplatin peaks.

No visible changes in color or precipitate were noted in any of the admixtures for 28 days. The pH of mixtures stored in pump reservoirs determined to be 4.47–4.85 did not change over the storage period at +4 and +22°C, being 4.39–4.90 on day 28. At +35°C a decrease in pH was observed in carboplatin solutions stored in Infusor® (4.47 on day 0 and 3.95 on day 28) and Celinject® (4.80 on day 0 and 4.17 on day 28).

The percentages of the initial carboplatin concentration remaining for each condition are presented in Table 2. The percentage of the initial concentration remaining at 28 days was in the range of 96.2–114.0% in portable pump reservoirs, 98.5–100.5% in PVC bags and 94–95% in glass bottles. An increase in the carboplatin concentration partially due to water permeation was noted in the reservoirs stored at +35°C (14% increase with Infusor® and 4% with Celinject®). With Pharmacia Deltec®, PVC bags and glass bottle no increase in the carboplatin concentration was observed. An increase in the carboplatin concentration may explain the observed pH variation.

TABLE 1

Validation data of the HPLC assay procedure of carboplatin and cisplatin

Drug	Within-day variability				Between-day variability			
	Conc. spiked (mg/l)	Conc. found (mg/l), mean (SD)	Accuracy (%)	Coefficient of variation (%)	Conc. spiked	Conc. found (mg/l), mean (SD)	Accuracy (%)	Coefficient of variation (%)
Carboplatin	5	4.94 (0.04)	98.8	0.84	40	40.34 (0.63)	100.8	1.55
	20	20.52 (0.18)	102.6	0.87	50	49.78 (1.02)	99.5	2.06
	50	50.86 (0.39)	101.7	0.77	60	60.07 (1.24)	98.8	2.06
Cisplatin	5	4.75 (0.24)	95.2	4.9	5	4.83 (0.41)	96.6	8.4
	20	20.02 (0.60)	100	3.0	20	19.67 (0.51)	98.4	2.6

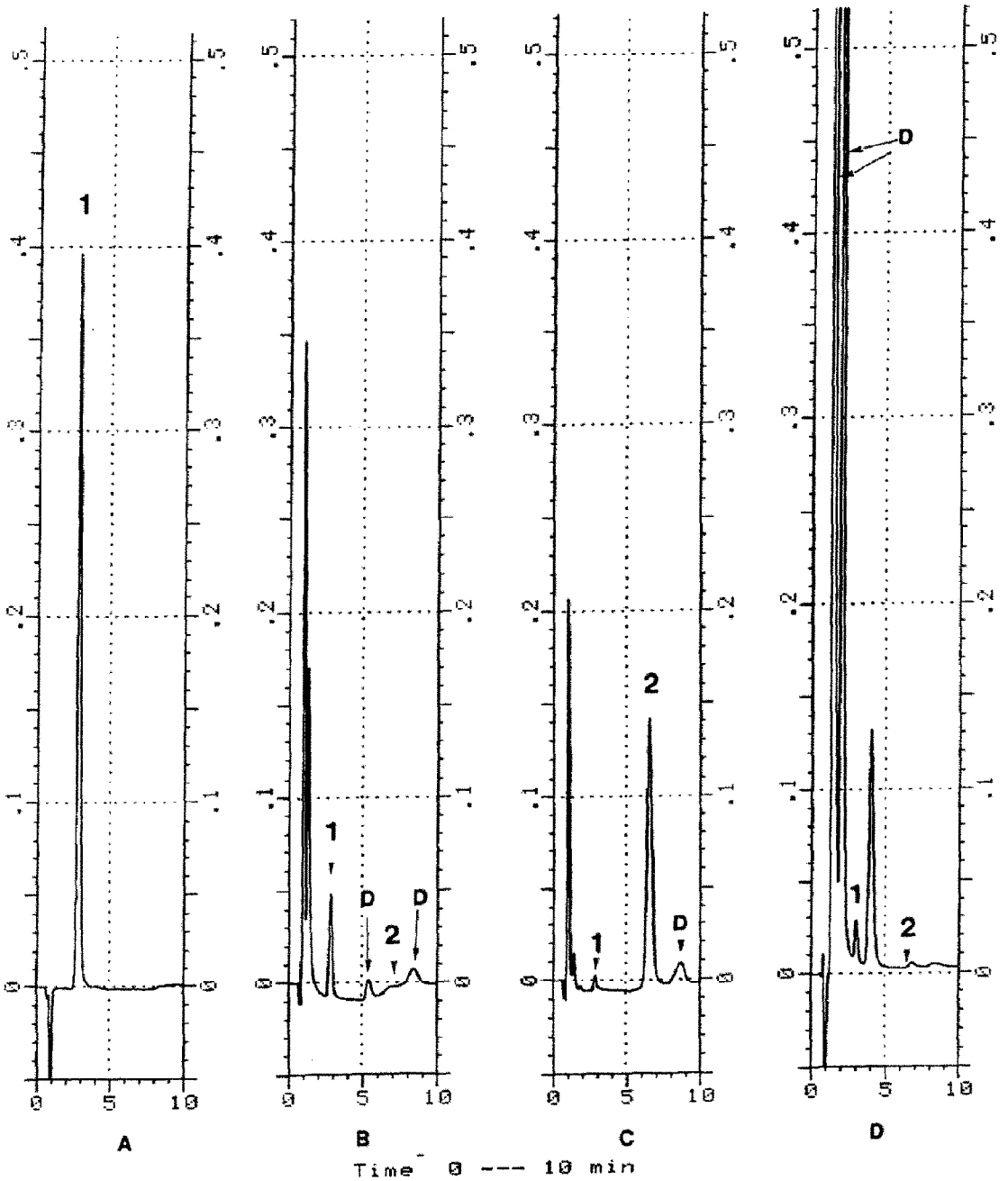

Fig. 2. HPLC chromatograms of control solution of carboplatin (A) and the same solution after 2 h at 70°C with 1 N NaOH (B), 1 N HCl (C), and 6 vols hydrogen peroxide (D). (1) Carboplatin, (2) cisplatin, (D) degradation products.

We have previously reported this phenomenon with Celinject® reservoirs with fluorouracil, doxorubicin and cytarabine (Rochard et al., 1992).

No degradation product peaks appeared in any chromatograms and the carboplatin spectrum in all runs was similar to the reference spectrum.

TABLE 2

Stability of carboplatin

Storage temperature (°C)	Time zero concentration (mg/l)	% initial concentration [a]							
		Day 1	Day 2	Day 3	Day 4	Day 7	Day 14	Day 21	Day 28
Glass bottle									
4	932	101.40 (0.08)	97.17 (0.11)	100.20 (0.14)	99.06 (1.15)	98.83 (0.83)	100.37 (0.05)	97.60 (0.07)	94.48 (1.52)
22	970	101.51 (0.18)	99.50 (0.17)	99.99 (0.04)	100.38 (0.31)	98.75 (0.04)	96.65 (0.90)	95.76 (2.05)	95.09 (0.61)
35	952	99.59 (0.25)	100.37 (1.59)	99.27 (1.57)	99.61 (0.55)	97.78 (0.24)	98.64 (3.88)	96.79 (0.13)	93.92 (0.60)
PVC bag									
4	981	101.07 (0.87)	101.44 (0.60)	104.44 (0.57)	102.05 (0.64)	102.50 (0.64)	102.22 (2.99)	97.35 (0.40)	100.0 (0.47)
22	970	100.63 (0.29)	100.92 (1.62)	103.97 (0.46)	101.56 (0.08)	102.50 (0.57)	100.71 (2.29)	98.11 (0.86)	100.43 (0.23)
35	984	100.46 (0.28)	104.10 (1.21)	103.43 (0.45)	102.01 (0.30)	103.29 (0.59)	100.71 (1.01)	99.63 (0.04)	98.64 (0.97)
Infusor®									
4	1024	96.58 (0.58)	97.52 (0.42)	97.43 (0.30)	100.18 (0.67)	97.47 (0.81)	95.52 (1.15)	95.88 (1.57)	96.91 (0.32)
22	1024	95.86 (0.08)	99.15 (0.84)	97.97 (0.42)	101.30 (0.50)	99.53 (0.90)	99.76 (1.18)	98.05 (1.15)	100.08 (0.39)
35	1024	96.05 (0.28)	101.08 (0.47)	100.96 (0.89)	101.75 (1.14)	101.91 (0.24)	107.96 (0.53)	110.87 (1.02)	114.36 (0.38)
Celinject®									
4	1003	100.19 (0.59)	97.88 (1.36)	98.74 (1.27)	100.35 (0.41)	101.28 (0.35)	100.02 (1.49)	101.31 (0.39)	101.81 (1.10)
22	1003	99.50 (0.33)	98.35 (0.25)	100.72 (0.31)	101.38 (1.03)	101.47 (1.18)	101.80 (0.32)	100.48 (1.13)	102.05 (0.27)
35	1003	99.22 (0.20)	98.58 (0.86)	99.30 (3.93)	103.23 (0.97)	103.03 (0.75)	103.00 (0.36)	99.30 (0.56)	104.29 (1.66)
Deltec®									
4	1051	100.61 (1.02)	99.35 (0.69)	99.19 (0.34)	100.29 (0.58)	101.07 (0.66)	95.94 (0.52)	97.17 (0.76)	96.19 (1.01)
22	1051	101.33 (0.71)	101.48 (1.02)	99.53 (0.77)	100.04 (0.57)	101.32 (0.73)	97.72 (0.26)	95.72 (0.31)	96.52 (1.18)
35	1051	101.89 (0.42)	103.00 (1.04)	100.64 (0.07)	100.39 (0.38)	102.44 (0.65)	97.92 (0.81)	99.42 (0.89)	98.34 (1.39)

[a] Values expressed as mean ± SD ($n = 4$).

In conclusion, carboplatin was stable in 5% glucose in the infusion pump reservoirs tested when stored at +4 and +22°C for 28 days. At +35°C water permeation was observed with ethylvinyl acetate and latex containers. This loss of water did not occur with PVC or glass. Carboplatin was stable at all temperature with polyvinyl chloride containers.

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