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Stability and compatibility study of a carboplatin solution in syringes for continuous ambulatory infusion

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Abstract

The aim of this study was to verify the physico-chemical stability and compatibility between a 10 mg/ml carboplatin parenteral solution and the portable pump Intellijject® when stored at 25°C over an 8-day period. During this study, the pH was determined and carboplatin degradation products were assayed by a validated HPLC method. The compatibility study consisted of the titration of reducing substances, TLC of extracted additives, assay of extracted ions by AAS, resistivity measure, dynamometric test and UV, visible and IR absorption spectrophotometry. Stability and compatibility studies showed that a 10 mg/ml carboplatin parenteral solution remained chemically stable in the Intellijject® pump over a period of 8 days under the tested conditions.

Keywords: Carboplatin; Stability; Plastic compatibility; Continuous infusion

1. Introduction

Portable programmable pumps are very useful for the administration of a certain number of antineoplasic drugs. They decrease undesirable effects, facilitate ambulatory administration and optimize the efficiency. Intellijject® is a portable i.v. infusion system that allows simultaneous administration of one to four drugs each via a 30 ml single-use syringe driven by a computer that sets administration parameters (speed, duration, number of syringes...).

Sewell et al. (1991) have shown that a 10 mg/ml solution of carboplatin was stable for 5 days to 4°C in pumps Models MS 36® (Grasby Medical, Ltd).

Solutions of 1 mg/ml prepared either with sterile water for injection or 5% glucose are stable for 14 days at 4 and 37°C (Northrott et al., 1991) and for 28 days at 4 and 22°C (Rochard et al., 1994) using different portable pumps. Poor stability was

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Table 1
Chromatographic conditions of carboplatin dosage (CBP) and its degradation products: cyclobutane acid 1,1 dicarboxylic (CBDCA) and cis diammine diaquoplatine (CDDPT)

	Column	Mobile phase	Detection UV (nm)	Duration of analysis (min)	Retention time (min)
CBP	Microbondapack® NH_2 (Waters, Paris, France) 300 × 3.9 mm	Acetonitrile/water, 87:13	230	8	6.6
CBDCA	Microbondapack® C18 (Waters, Paris, France) 300 × 3.9 mm	Pic A Low UV/water/acetonitrile, 2:88:10	220	5	2
CDDPT	Vydac® (Touzart et Matignon, Paris, France)	Ammonium hydrogenophosphate buffer[a]	200	7	6

[a]46 g ammonium hydrogen phosphate in 1 l purified water.

observed when 1 mg/ml carboplatin solutions were prepared in normal saline (24 h) (Cheung et al., 1987). This is the result of interactions between chloride ions, inducing cisplatin.

The aim of this work was to verify the stability and compatibility of a commercial solution of carboplatin (10 mg/ml) protected from the light at 25 ± 2°C using the Intelliject® system over an 8-day period.

2. Materials and methods

The 30-ml syringes for the Intelliject® pump (Aguettant, Lyon, France) are constituted of a body in polypropylene and a black piston in polypropylene supplied with a green silicone joint.

The injectable solution of 10 mg/ml carboplatin was from Paraplatine®, Bristol Myers Squibb, Paris, France.

Stability and compatibility studies were performed using three 30-ml syringes, each being filled with 15 ml of a 10 mg/ml solution of carboplatin over 8 days at 25 ± 2°C and protected from light.

For each test, three determinations were made for each syringe, and Student's test was used for statistical analysis.

A complete analysis of the carboplatin solution was carried out: dosage of carboplatin and its degradation products, organoleptic characteristics, i.e. color, limpidity, pH measurement, sliding power, UV-visible spectrum.

HPLC measurements of carboplatin (CBP) and of its two main degradation products, acid cyclobutane 1,1 dicarboxylic (CBDCA) and diammine diaquoplatine (CDDPT), were performed using a Beckman Gold System apparatus (Beckman, Gagny, France) equipped with a solvent delivery system (Beckman Module 126), an UV detector (Beckman Module 166) and interfaced with an auto sampler (Sedex 100, Sedere, Touzart et Matignon, Vitry/Seine, France) set with a 20 μl loop. The mobile phase was pumped in isocratic mode and flow rates were 2 ml/min for the CBP and the CBDCA and 1.4 ml/min for the CDDPT. Details of the other experimental conditions are given in Table 1.

A series of tests was made for each syringe: UV-visible absorption spectrophotometry, reducing substance, plasticizer agents and silicone oil according to the European Pharmacopoeia, sodium, calcium, zinc, chromium, vanadium measurement or identification, IR spectrum on the body and the piston of the syringes.

A test of aging accelerated on the filled syringe (50°C) and on elements of the syringe (body, piston, joint of piston) at 124°C/15 min was performed.

A dynamometric test allowed evaluation of possible modifications of the sliding power in syringes and possible physico-chemical modifications (state of surface, dimensional variations) were undertaken. Sliding power is the ratio between work (W) and length of displacement (L). The

Table 2
Carboplatin (mg/ml) stored in an Intellijject® syringe at 25°C for 8 days

		D0	D1	D2	D4	D8
Assay 1	Mean	10.11	10.06	10.07	9.97	9.86
	C.V. %	0.50	0.61	0.51	0.57	0.36
Assay 2	Mean	10.01	9.99	10.09	10.06	9.96
	C.V. %	0.69	0.27	1.03	0.25	0.63
Assay 3	Mean	9.97	10.23	10.08	10.11	9.93
	C.V. %	0.35	1.51	0.69	0.19	0.81
Mean	Mean	10.03	10.09	10.08	10.05	9.93
	C.V. %	0.78	1.37	0.68	0.77	0.77

Lhomargy apparatus (Lhomargy, DY20, Paris, France) is a 20 N captor and a syringe fixation system. The syringe plunger was pushed by the compression rod. The sliding force (F in Newton) was calculated by the ratio $F = W/L$. The work was measured by the area under the curve (AUC) of the plot. The length (L) of displacement was read on the 'X-axis' of the plot.

3. Results and discussion

The 10 mg/ml solution of carboplatin stored in the Intellijject® syringe is stable for 8 days at 25°C (Table 2) ($P < 0.001$). No degradation product (CBDCA, CDDPT) was identified over this period. No variation of organoleptic characters or pH (5.4 ± 0.1) was observed under the same experimental conditions. A commercial carboplatin solution is stable for 3 years at room temperature protected from the light in a glass bottle (Anonymous). The polypropylene is poorly permeable to water and the number of additives is generally very low (stearate calcium or zinc).

The results of UV, Visible and IR absorption, determination of the content in reducing substances (0.3 ml of $KMNO_4$), the plasticizer amount and silicone oil (0.05 mg/cm^2), ions (sodium < 0.4 ppm, calcium < 0.05 ppm, zinc < 0.9 ppm, chromium and vanadium < 0.01 ppm) outline the lack of interference between solution and syringe. The IR spectrum reveals the presence of silicone oil from the syringe but shows no evidence of interaction between carboplatin and plastic.

Accelerated aging tests shows no significant variation for all parameters studied. At 124°C/15 min sodium concentration was up to 2 ppm. This suggested a possible alteration of the surface of the plastic during the section into pieces of the different parts of the syringe to perform the test.

Dynamometric tests (Table 3) show that the work was more important in traction than in thrust. In normal functioning, syringes are used in thrust. There is no significant difference after 8 days of contact. A moderate increase of the work could be related to the occurrence of a slight modification of the silicone during storage.

4. Conclusion

An injectable solution of 10 mg/ml carboplatin (Paraplatine®, Bristol Myers Squibb, Paris, France) is stable for 8 days at room temperature (25°C) in 30-ml syringes for the Intellijject® pump (Aguettant, Lyon, France).

Table 3
Dynamometric test in Intellijject® syringe after 8 days of contact at 25°C with a 10 mg/ml carboplatin solution

Days	Strength		W (10^{-2} J)	L (10^{-2} m)	F (N)
D0	Push	Mean	19.0	5.4	3.5
		C.V. %	13	2	13
D0	Traction	Mean	30.3	5.6	5.4
		C.V. %	16	2	14
D8	Push	Mean	23.7	5.5	4.3
		C.V. %	16	9	9
D8	Traction	Mean	34.9	5.6	6.2
		C.V. %	8	2	8

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