Introduction
The potential use of platinum co-ordination complexes as antitumour agents has been reported in the literature [1]. It has been demonstrated that cisplatin [cis-diamminedichloroplatinum(II)] is active in a variety of solid tumours [2 3]. The drug is administered intravenously. The lyophilized dosage form is reconstituted and diluted with a variety of parenteral vehicles containing sodium chloride, mannitol, glucose and other substances.

The stability of cisplatin was studied in a large number of the parenteral solutions which might be employed [4 5] and the effects of some of the more common components of the commercial parenteral solutions was determined under various conditions to make it possible to predict the stability of the drug [6 7]. Cisplatin is known to be unstable in aqueous solutions. The primary mode of decomposition involves displacement of the chloride ligand and so increasing the chloride ion concentration improves the stability of the drug in aqueous solution [8-10].

Actually, the solution most employed as a parenteral vehicle for cisplatin administration was the sodium chloride 0.9% solution. In this vehicle, cisplatin shows a good stability [4 7], no more than 3% of the total drug concentration degraded over a 24-h time period.

The purpose of this report is to present work which studied the cisplatin stability in sodium chloride 0.9% contained in glass bottles, polyvinyl chloride bags (PVC), polyethylene (PE) and polypropylene (PP) containers. Experiments were carried out to delineate the stability of cisplatin in sodium chloride infusion solution related to the container material. Since drug infusion solutions are, in general, refrigerated prior to use to limit possible microbial growth, the possible precipitation of the drug at refrigeration temperature was also checked.

Methods
Materials
Cisplatin for injection (Placis®; Wassermann Laboratories, Barcelona, Spain; Lot D1) was prepared in sodium chloride 0.9% free of preservatives in glass bottles (Grifols Laboratories, Barcelona, Spain; Lot C-84), in polyvinyl chloride bags (Grifols Laboratories, Lot C-02) in polyethylene bags (Palex Laboratories, Barcelona, Spain; Lot C4 127 8A) and polypropylene bags (Ern Laboratories, Valencia, Spain; Lot B-40-3). The Placis® vial contains 1,000 mg of powder composed of 5% (wt/wt) cisplatin, 50% (wt/wt) mannitol and 45% (wt/wt) sodium chloride.

Chromatographic assay method
The decomposition of cisplatin at room temperature was followed by means of a high pressure liquid chromatographic (HPLC) system similar to that de-
Kinetics measurements
Fresh solutions of Placis® (1,000 µg·ml⁻¹) were prepared by adding distilled water to the formulated vial (sodium chloride in the formulated vial providing the necessary chloride ion concentration). The reconstituted solutions were further diluted with sodium chloride 0.9% for injection to final cisplatin concentration of 166.6 µg·ml⁻¹. Cisplatin solutions were prepared in triplicate in glass containers and also in plastic containers (PVC, PE and PP). These admixtures were stored at 30°C in the absence of light. Aliquots were taken at specific time intervals and the concentration of cisplatin was determined by HPLC assay as described above.

The solubility of cisplatin at refrigerator temperature (4°C) was investigated in clear glass containers. The solutions were observed at periodic intervals over two weeks for possible precipitation.

Results and discussion
When the loss of cisplatin at 30°C in sodium chloride 0.9% injection solution stored in the dark was monitored no decomposition was observed within the time period studied. The increase of the results found in the PVC container could be the result of the evaporation process usually observed in this type of containers as published before [12]. The system appeared to be at equilibrium. These results are in good agreement with those presented in the literature [4 6]. It is assumed that the major route of decomposition of cisplatin in an aqueous medium involves the replacement of one chloride ion. The loss of the second chloride ion may not contribute substantially to the overall decomposition rate. The reaction is reversible. When enough liberated chloride ions accumulate in the medium, the reaction reaches an equilibrium. The sodium chloride acts as a stabilizing agent.

Table 1 lists the percentage of intact drug remaining at equilibrium for all cases studied. Cisplatin appears to be stable for at least two weeks in a sodium chloride 0.9% solution and a concentration of 166.6 µg·ml⁻¹. Cisplatin stability was identical whether the admixtures were stored in plastic bags or in glass bottles. The type of container apparently had no effect on the stability of cisplatin.

Finally, no precipitation was observed when solutions of cisplatin at 166.6 µg·ml⁻¹ in sodium chloride 0.9% injection were stored and refrigerated at 4°C within the time period studied.

<table>
<thead>
<tr>
<th>Type of container</th>
<th>Percentage of initial concentration* at indicated time (days)</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Glass</td>
<td>100</td>
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<tr>
<td>PVC</td>
<td>100</td>
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<tr>
<td>PE</td>
<td>100</td>
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<tr>
<td>PP</td>
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*Mean ± standard deviation, n = 3.