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Oral Sustained-release Cisplatin Capsule

TAKESHI HOUJOU, KOUSUKE NAKANO, OSAMU IKE*, HIROMI WADA*, SIGEKI HITOMI*, YUUKO SHINMI, NORIYUKI DANNO, YUKAKO YOSHIKAWA AND KANJI TAKADA

*Department of Pharmaceutics and Pharmacokinetics, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607, Japan, and *Department of Thoracic Surgery, Chest Disease Research Institute, Kyoto University, Sakyou-ku, Kyoto 606, Japan*

Abstract

An oral sustained-release cisplatin preparation was prepared by combining microporous water-insoluble pharmaceutical polymer, ethylcellulose, a membrane and a gel-forming polymer, poly(acrylic) acid (Carbopol). As cisplatin is an extremely hydrophilic and small compound, it was difficult to control the release rate solely by the micropores on the ethylcellulose capsule.

To retain cisplatin within the capsule, gel-forming polymer was formulated inside the capsule. The release rate of cisplatin was dependent both on the number of micropores of the capsule and the formulated amount of Carbopol. The number of micropores ranged from 20 and 30 to 60, and the formulated amount of Carbopol varied from 15 to 100 mg. In-vitro release experiments suggested that the release rate decreased as the formulated amount of Carbopol increased when the pore number was 60 and 30. However, when pore number was decreased to 20, the effect of the amount of Carbopol was not clearly observed.

In the in-vivo study using rabbits, the sustained-release cisplatin capsule was evaluated in comparison with solution after oral administration of 20 mg drug. With the pore number of 60, C_{max} was $0{\cdot}46 \pm 0{\cdot}02$ $\mu g\ mL^{-1}$ at 4 h and thereafter serum concentrations declined rapidly. When the pore number was 30, serum cisplatin level–time profiles showed long-acting patterns and AUC was reversely correlated with the formulated amount of Carbopol. C_{max} and t_{max} were $0{\cdot}41 \pm 0{\cdot}02$ $\mu g\ mL^{-1}$ and $3{\cdot}33 \pm 0{\cdot}88$ h, respectively and $0{\cdot}23 \pm 0{\cdot}01$ $\mu g\ mL^{-1}$ was obtained at 24 h after oral administration of capsule having 30 pores and 15 mg of Carbopol.

We conclude that the possibility of developing an oral sustained-release cisplatin preparation is feasible.

Cisplatin or cis-diamminedichloroplatinum(II) has been used as a potent chemotherapeutic agent for various solid tumours (Loehrer 1984; Muggia 1991). In spite of its good antineoplastic activity against ovarian, lung, bladder, breast, head and neck, and testicular cancers (Gottlieb & Drewinko 1975; Jacobs 1980; Perry et al 1986), its clinical use is limited due to the unexpected severe toxicity such as renal failure (Pinzani 1994). Acute and cumulative renal toxicities associated with histological damage have been demonstrated in both animal and human studies (Offerman et al 1984; Daugaard et al 1986). Several theories concerning the pathophysiological mechanism behind this toxicity have been suggested (Los et al 1991). One of the probable principles is that the therapeutic efficacy of cisplatin seems to be proportional to the administered dose (-Egorin et al 1984; Marina et al 1993). Therefore, there has been a continuous search for biological and pharmacological strategies to protect the kidney from toxicity and thus permit the administration of high dose of cisplatin; these strategies include several methodologies, namely modification of administration modes, development of new formulations, and the use of chemoprotectors. Additionally, other platinum analogues with less nephrotoxicity have been discovered (Muggia 1989; Ruckdeschel 1994). However, these agents have reduced antitumour activity compared with cisplatin or have other in-herent toxicities restricting their use. Continuous intravenous infusion therapy with low dose of cisplatin has been attempted to overcome these clinical problems (Forastiere et al 1988). In addition, poly(ortho ester) matrics for controlled release of another clinically well-used anti-tumour agent, 5-fluorouracil, has been prepared and its anti-tumour activity was evaluated using a clinically relevant model in mice (Seymour et al 1994).

Recent advances in antiemetic agents and regimens have greatly reduced cisplatin's gastrointestinal side effects, but cumulative renal toxicity and ototoxicity remain a problem. Continuous cisplatin therapy with low dose is one of the approaches to overcome the clinical disadvantage of cisplatin. In the field of gastric cancer chemotherapy, the direct application of chemotherapy to the site of tumour progression or recurrence, i.e. the peritoneal cavity, has been tried (Sautner et al 1994). Intraperitoneal cisplatin application has yielded favourable results in patients with small-volume peritoneal diseases of ovarian cancer. In addition, side effects of intraperitoneal cisplatin were minor in comparison with other chemotherapeutic drugs. To accomplish such a therapy with oral medication, we have attempted to prepare an oral sustained-release cisplatin preparation and the efficiency has been evaluated both in-vitro and in-vivo.

Materials and Methods

Materials

Cisplatin was a gift from Nippon Kayaku Co. Ltd. (Tokyo, Japan). Sucrose, Tween 80 and Triton X-100 were obtained from Nacalai Tesque Co. Ltd. (Kyoto, Japan). Poly(acrylic) acid (Carbopol 934P NF) was obtained from Chugai Boyeki Co. Ltd. (Tokyo, Japan). Ethylcellulose (grade 100G) was a gift from Shin-etsu Chemical Industry (Tokyo, Japan). Size 0 hard gelatin capsule was obtained from Yoshida Shoten (Himeji,

Correspondence: K. Nakano, Department of Pharmaceutics and Pharmacokinetics, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607, Japan.

Japan). Male white albino rabbits were obtained from Nihon Nousan (Yokohama, Japan). All other materials were commercial products of reagent grade.

Cisplatin test solution for intravenous infusion and oral administration was prepared by dissolving cisplatin in saline at a concentration of 1·0 mg mL^{-1}.

Test capsules

Ethylcellulose capsules were prepared according to the method precisely described in our previous report (Niwa et al 1995; Takaya et al 1995). Briefly, 11·25% ethylcellulose solution in a mixture of methylene chloride and methanol (4:1) was filled into the number 0 capsule body and cap, respectively. By allowing solvent to evaporate in a refrigerator for 12 h, the inner surface of the gelatin capsule was coated with ethylcellulose, approximately 150 μm thick. After dissolving the gelatin in warm water at 37°C, ethylcellulose capsules were obtained. Micropores (800 μm) were mechanically opened to give pore numbers of 20, 30 and 60. Twenty milligrams of cisplatin, 450 mg sucrose, 200 mg Tween 80 and 15, 25, 50 or 100 mg Carbopol were mixed well. The resultant mixture was put into the ethylcellulose capsule body and the cap was attached to the body with concentrated ethylcellulose solution.

Dissolution test of the capsules

Dissolution testing of sustained-release cisplatin capsules was carried out on a reduced scale. Test capsule was put into a 20-mL vial in which 5 mL of JP 1st fluid (pH 1·2) was introduced. The paddle, 10 × 4 mm, was used with a rotation speed of 250 rev min^{-1}. The dissolution medium was degassed by sonication and maintained at 37°C throughout the test period. To simulate the transition from gastric to intestinal pH, samples of 1st fluid were replaced 1 h later with the JP 2nd fluid (pH 6·0). To determine the release of cisplatin from the test capsules, 0·5-mL samples of the dissolution medium were removed for analysis every hour and subsequently replaced with fresh dissolution medium. The platinum content of dissolution samples was determined by atomic absorption spectrophotometry using a Shimadzu AA-640-12 atomic absorption spectrometer (Shimadzu Co., Kyoto, Japan) with a GFA-2 graphite furnace atomizer (wavelength, 265·9 nm; spectral width, 3·8 nm; lamp current, 12 mA). The furnace temperature programme consisted of drying at 200°C for 45 s, ashing at 900°C for 30 s, and atomizing at 2600°C for 10 s. Platinum concentration was linearly related to absorbance in the range 0–50 μg mL^{-1}. Samples were quantified by comparison with authentic standards.

Bioavailability study using rabbits

Three adult male white albino rabbits weighing from 2·8 to 3·3 kg were fasted overnight for at least 12 h. At 30 min before drug administration, 0·5 mL blood was removed from the right ear vein. For the intravenous infusion of cisplatin solution, a disposable Vennula S-5 intravenous catheter was inserted into the left ear vein. The cisplatin solution (1·0 mg mL^{-1}) was infused for 2 h using a variable-speed infusion pump, SP220i syringe pump (World Precision Instruments Inc., FL) at an infusion rate of 5 mL h^{-1}, infusing a total dose of 10 mg cisplatin to each rabbit. Through a cannula into the right ear vein, blood samples (2·0 mL) were collected throughout the infusion period at 0, 60, 90 and 120 min, and up to 24 h post-infusion at 10, 20, 30 min, 1, 1·5, 2, 3, 4, 6, 8, 10, 12, and 24 h. The serum was obtained by centrifugation of blood for 10 min at 8000 *g* after standing at room temperature, 3°C) for 20 min, and was stored in a deep freezer at − 50°C until analysed.

Cisplatin solution and capsule were also orally administered to the rabbits, where the administered dose was 20 mg/rabbit. In the case of the administration of cisplatin solution, 20 mL cisplatin test solution was administered through vinyl tubing (6·0 mm i.d., 8·0 mm o.d., 50 cm length) which was introduced into the rabbit stomach. Thereafter, the tubing was rinsed twice with 5 mL warm water (37°C). For the administration of cisplatin capsule, test capsule was attached to the nozzle of the vinyl tubing used for the administration of cisplatin solution. After the tubing was introduced into the stomach of the rabbit, the tubing was flushed with 10 mL warm water. After drug administration, 2·0-mL blood samples were collected. The standard sampling schedule was 0·5, 1, 1·5, 2, 3, 5, 10, 12, and 24 h. A standard solid meal of commercial food was given 6 h after drug administration. No additional food was given during the study although free access to water was allowed. The serum was also obtained by centrifugation of blood at 8000 *g* for 20 min. These serum samples were immediately frozen in a deep freezer at − 50°C until analysed. Serum cisplatin concentration was measured by an atomic absorption spectrophotometry described above after the defrosted serum sample was diluted with double-distilled deionized water containing Triton X-100 (1·0%). Standard serum cisplatin samples were prepared by adding known amounts of cisplatin to the blank rabbit serum. The calibration was linear over 0–2·0 μg mL^{-1}.

Data analysis

A non-compartmental pharmacokinetic analysis was applied to the data. The terminal elimination rate constant, λ z, was determined by a linear regression of at least three data points from the terminal portion of the serum concentration–time plots using a non-compartmental pharmacokinetic analysis program, HARMONY (Yoshikawa et al 1995). The area under the serum concentration–time curve after administration, AUC, was calculated using the linear trapezoidal rule up to the last measured serum concentration. The area under the first moment curve after administration, AUMC, was also calculated using the linear trapezoidal rule up to the last measured serum concentration. The terminal elimination half-life, t½, was determined by dividing ln 2 by λ z. The mean residence time, MRT, was calculated as AUMC/AUC.

Statistics

All values are expressed as their means ± s.e. Statistical differences were assumed to be reproducible when $P < 0.05$ (two-tailed *t*-test).

Results

In-vitro dissolution

The dissolution characteristics of cisplatin from the microporous capsules are shown in Fig. 1. The dissolution rate of cisplatin from the test capsules increased on increasing the number of micropores from 20 to 30. However, there was no significant difference in the dissolution profiles between the capsules having micropore numbers of 30 and 60. Where the formulated amount of gel-forming polymer, Carbopol, was increased to

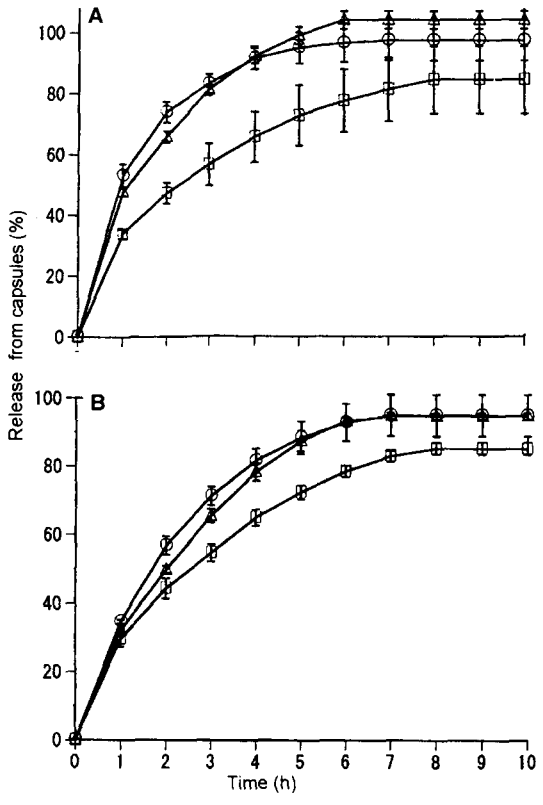

FIG. 1. Dissolution profiles of cisplatin from capsules having different micropore number (□ 20, ○ 30, △ 60) and different formulated amounts of Carbopol (A: 25; B: 50 mg). Each point represents the mean ± s.e. of three experiments.

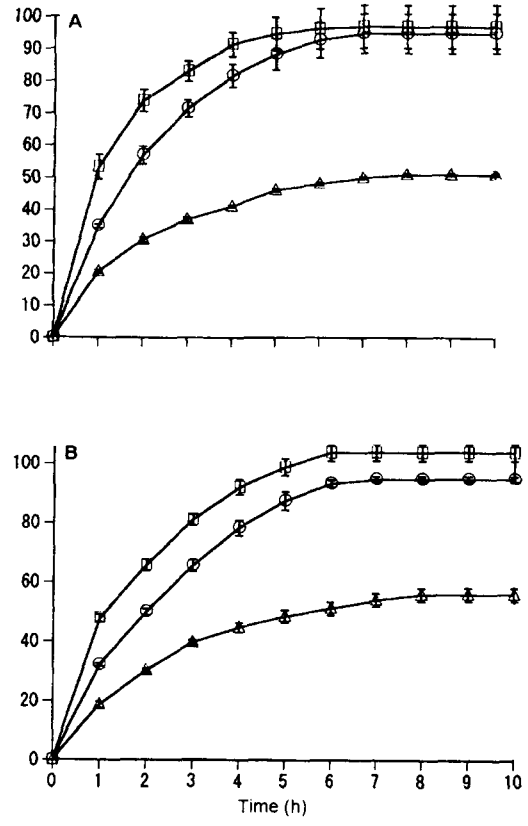

FIG. 2. Dissolution profiles of cisplatin from capsules containing different amounts of Carbopol (□, 25; ○, 50; △, 100 mg) with different micropore numbers (A: 30; B: 60). Each point represents the mean ± s.e. of three experiments.

100 mg, the effect of micropore number on the dissolution rate of cisplatin disappeared. The effects of amount of Carbopol on the dissolution profile of cisplatin are shown in Fig. 2. As the micropore number increases to 30 and 60, the effect of the amount of Carbopol on the dissolution rate of cisplatin appears clearly. However, when the micropore number is 20, there is not a significant difference in the dissolution profiles of cisplatin between the two groups of capsules containing 25 and 50 mg Carbopol.

In-vivo systemic availability

Based on the above in-vitro dissolution experiment, the effects of both the number of micropores on the water-insoluble capsule and the content of the gel-forming polymer, Carbopol, on the systemic availability of cisplatin were studied using rabbits. Cisplatin was administered to rabbits by an intravenous infusion, 10 mg, for 2 h and the serum concentration vs time curve is shown in Fig.3. The mean peak level, $2{\cdot}91 \pm 0{\cdot}45$ μg mL^{-1}, was obtained at the end of the infusion period, and thereafter serum cisplatin level declined rapidly with a terminal elimination half-life of $28{\cdot}5 \pm 3{\cdot}2$ h. To obtain the systemic availability of cisplatin, cisplatin solution was orally administered to the same rabbits, at a dose of 20 mg (Fig. 3). The peak level, $0{\cdot}72 \pm 0{\cdot}02$ μg mL^{-1}, appeared 0·5 h after oral administration and the value was about one-quarter that obtained in the intravenous infusion experiment, although the intravenous dose was half of the oral dose. As shown in Table 1, the AUC obtained after intravenous infusion was $23{\cdot}34 \pm 3{\cdot}25$ μg h mL^{-1}, and that obtained after oral administration of solution was $2{\cdot}86 \pm 0{\cdot}23$ μg h mL^{-1}. Therefore, the systemic availability of cisplatin solution was estimated to be 6·2%, when corrected for dose. These results suggest that the systemic availability of cisplatin is very low.

The systemic level of cisplatin after oral administration of sustained-release cisplatin capsule was investigated using the

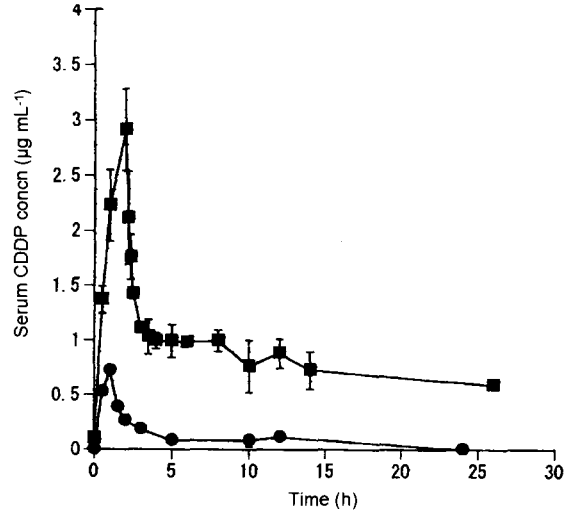

FIG. 3. Serum cisplatin concentration vs time curves (■) during and after intravenous infusion of cisplatin 10 mg per rabbit, and (●) after oral administration of cisplatin 20 mg per rabbit. Each point represents the mean ± s.e. of three experiments.

Table 1. Efect of Carbapol content and micropore number on the pharmacokinetic parameters of cisplatin after administration to rabbits.

Preparation	Carbopol (mg)	Pore number	t½ (h)	AUC (h μg mL^{-1})	Bioavailability (%)	MRT (h)
Intravenous solution			28·49 ± 3·22	23·34 ± 3·25		10·32 ± 0·46
Oral solution				2·86 ± 0·23	6·2	5·72 ± 0·20
Capsule	15	20	24·37 ± 5·78	3·78 ± 0·26	8·0	11·11 ± 0·51
		30	9.30 ± 0·65	5·52 ± 0·49	12·0	8·82 ± 0·27
		60	2·94 ± 0·06	2·94 ± 0·06	6·4	6·28 ± 0·12
	25	20	10·75 ± 1·13	4·12 ± 0·48	8·7	7·29 ± 4·17
		30	27·72 ± 10·28	7·22 ± 0·60	15·3	10·92 ± 0·34
		60	1·61 ± 0·01	3·42 ± 0·09	7·2	6·78 ± 0·09

Mean ± s.e. ($n = 3$).

same rabbits, where the administered dose was 20 mg. Fig. 4 shows the effect of the formulated amount of Carbopol on the serum cisplatin concentration vs time curves after oral administration to rabbits. After oral administration, serum cisplatin concentration gradually increases (after a lag time) and thereafter was maintained for over 10 h. These serum–time curves suggest the sustained-release fashion of cisplatin from the test capsules. To estimate the systemic availability of these capsules, the AUC values were calculated and are presented in Table 1. Comparison of the AUC values indicate that the formulated amount of Carbopol in the capsule does not affect the systemic availability of cisplatin under the conditions of micropore number of 20, 30 and 60.

From these data, the mean residence time (MRT) was calculated and the values are shown in Table 1. Compared with the MRT of oral cisplatin solution, MRT for the capsule was increased suggesting a sustained release of cisplatin from the capsule.

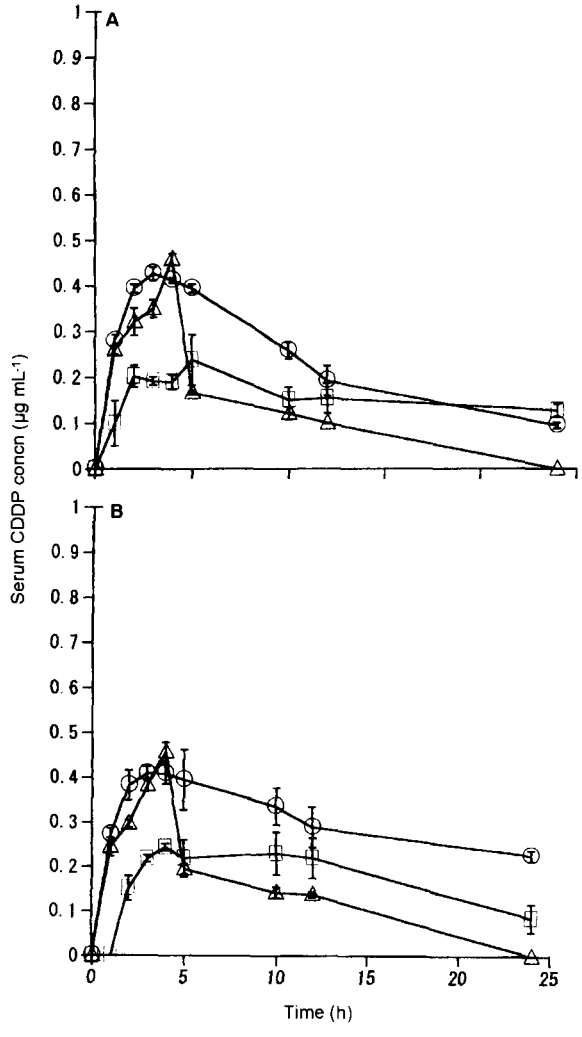

FIG. 4. Effect of micropore number (□ 20, ○ 30, △ 60) on serum cisplatin concentration vs time profiles after oral administration of 20 mg to rabbits where the formulated amount of Carbopol was 15 mg for Fig. 4A and 25 mg for Fig. 4B. Each point represents the mean ± s.e. of three experiments.

Discussion

Clinically, cisplatin is used as a single agent or in combination with other cytotoxic drugs, as an intravenous infusion. When cisplatin was administered to patients, a long half-life in the systemic circulation was reported to be 8·4–17·6 days (Fish et al 1994). As the serum cisplatin concentration decays tri-exponentially, this half-life corresponds to the terminal phase. However there are no reports on the systemic availability of cisplatin from the gastrointestinal tract. Our results concerning the systemic availability of cisplatin after oral administration in rabbits show that systemic availability of cisplatin from the gastrointestinal tract is very low, approximately 6·0 %. However, the systemic availability of cisplatin from the sustained-release capsule was higher, approximately 6·4–15·3%, than that of the oral solution. Therefore, it is suggested that the duration of the absorption phase is prolonged rather than that the absorption rate was increased.

As cisplatin is extremely hydrophilic and is a small molecule as compared with other drugs used in sustained-release preparations, such as theophylline, it is difficult to control the release rate by the conventional sustained-release methodologies (Hendeles et al 1984). The most widely used method for sustained-release preparations is by combining two portions, a fast-release fraction and a slow-release fraction, in a tablet or capsule. However, because of unwanted effects of cisplatin on the gastrointestinal tract, a preparation having slow and continuous releasing characteristics must be designed to avoid any large release of cisplatin into the gastrointestinal tract. A water-insoluble microporous capsule was prepared and its sustained-release characteristics were examined. However, cisplatin was almost entirely released from the capsule within 3 h, and to reduce the release rate, a gel-forming polymer, Carbopol 934, was added to the formulation. Carbopol 934 was selected, as it has the strongest gel-forming ability (Smart 1992;

Mortazavi & Smart 1994). If another polymer having less gel-forming ability was used, there is a possibility that the gel would be partly released from the capsule through the micropore and would attach to the surface of the gastrointestinal mucosa (Matharu & Sanghavi 1992), resulting in necrosis.

In this study, by formulating 25 mg of Carbopol into the formulation, a sustained-release was obtained in the in-vitro release experiment and serum cisplatin level was maintained for a long time, as judged by an increase in MRT (7–15 h). To obtain more prolonged release characteristics, the formation of a rigid gel-network would be required. For this purpose, the inclusion of hydrophobic entities or a change in the cross-linking agent are two possible methods in which prolonged sustained-release may be obtained. The gel-formation of Carbopol is dependent on the negative charge of its carboxy groups (Gu et al 1988). As the environmental pH decreases, for example at the acidic pH of the stomach, the carboxy groups tend to be un-ionized and Carbopol loses its gel characteristics (Duchene et al 1988). Taking these points into consideration, an in-vitro release experiment was performed at pH 1·0 (gastric pH). However, the burst phenomenon was not observed. Furthermore, in the in-vivo experiment using rabbits, there was an absorption lag-time for cisplatin after oral administration of the test capsules. If the burst phenomenon occurred just after the oral administration, serum cisplatin would increase immediately after the administration as in the case of solution. The present results exclude the possibility of a burst of cisplatin from the capsule in the stomach.

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