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Potentiation of anticancer effects of microencapsulated carboplatin by hydroxypropyl α-cyclodextrin

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Abstract

Cyclodextrins are cyclic oligosaccharides that can change physicochemical properties of drugs by forming inclusion complexes with them. These changes may enhance the therapeutic potential of drugs by diminishing their decomposition before they enter tissues and by altering how they enter tissue. Carboplatin is an anticancer drug that is active against brain tumors and has recently been tested as a potential agent for interstitial chemotherapy. To test whether complex formulation with cyclodextrins would improve interstitial treatment with carboplatin, we studied the efficacy of carboplatin–cyclodextrin complexes, free and encapsulated, in an experimental rat glioma model. Carboplatin hydroxypropyl α-cyclodextrin complexes were incorporated into ethylcellulose microcapsules at a 2.2% w/w loading. We found that carboplatin was released from these microcapsules in a sustained manner for at least 110 days in vitro, that the rate was faster than that of encapsulated carboplatin alone, and that hydroxypropyl α-cyclodextrin protected the carboplatin from degradation. Further, the complex was more effective than carboplatin alone when tested on monolayers of F98 glioma cells. For testing the efficacy of the carboplatin–hydroxypropyl cyclodextrin complex in the rat glioma model, 56 Fischer rats were injected in the left hemisphere with F98 glioma cells. Five days later the rats were randomly divided into seven groups. Median survival of the first control group receiving no treatment was 20 days. The second group receiving an intratumoral injection of carboplatin had a median survival of 1 day, indicating severe cytotoxicity. The third group receiving systemic carboplatin had a median survival of 34 days. Median survival of the fourth group which received empty microcapsules was 24 days. The fifth group, treated with microcapsules loaded with hydroxypropyl α-cyclodextrin alone, showed a median survival of 20 days. The sixth group, treated with microcapsules loaded with carboplatin alone, showed a median survival of 34 days. The seventh group, treated with microcapsules loaded with carboplatin–hydroxypropyl α-cyclodextrin complex, showed a median survival of 51 days. This experiment demonstrated that the microencapsulated carboplatin–hydroxypropyl α-cyclodextrin complex is more effective than the nonencapsulated carboplatin. This study also shows that interstitial delivery of carboplatin–hydroxypropyl cyclodextrin complexes from a microencapsulated formulation is effective against experimental brain tumors.

Keywords: Carboplatin; Hydroxypropyl cyclodextrins; Microcapsules; Sustained release; Interstitial chemotherapy; Cancer

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1. Introduction

The transfer of drugs from the bloodstream into the brain is limited by the blood–brain barrier; consequently it is often difficult to attain therapeutic drug concentrations within the brain. This is of particular importance in the treatment of brain tumors, which are both resistant to drug treatment and locally invasive. In order to obtain high concentrations of chemotherapeutic drugs in the brain, systemic administration requires such large amounts of the drug that toxic side effects are common. To avoid such problems, interstitial chemotherapy, whereby biocompatible polymers impregnated with antitumor agents are surgically implanted directly into the neoplastic lesions, offers the advantage of delivering a high concentration of drug directly to the tumor bed, and thus reducing systemic toxicity. Indeed, incorporation of carmustine (BCNU), which is lipid-soluble, into biocompatible polymers and their implantation into the tumor bed after resection has successfully prolonged survival in patients with malignant astrocytomas [1]. Similar treatment with water-soluble drugs, however, has proven more challenging.

The known effects of cyclodextrins in changing the properties of certain therapeutic drugs by reducing their decomposition before they enter tissues and by altering how they enter tissues [2–12] suggested to us the possibility of using cyclodextrins to change the properties of water-soluble drugs known to effective against a variety of brain tumors. Such drug–cyclodextrin complexes could be incorporated into specifically designed microcapsules [13–17] and then used for interstitial chemotherapy. For this purpose we chose to investigate whether the effects of carboplatin (*cis*-diamino (1,1-cyclobutanedicarboxylato) platinum), a second-generation platinum drug, would be enhanced by complex formation with cyclodextrins. We chose to study carboplatin for several reasons. The toxicity [18–21], antitumor activity, and pharmacokinetics have been studied in detail [22–24]; it is active against a variety of brain tumors, particularly in children; when delivered locally it is effective against experimental brain tumors; and it has been shown to form complexes with cyclodextrins [25,26], which have been used to control drug release from the matrix in certain formulations [27–30].

In the present study we incorporated carboplatin and carboplatin–hydroxypropyl α-cyclodextrin complex into ethylcellulose microcapsules and studied kinetics of the release of the carboplatin in vitro. We then examined the efficacy of the carboplatin–hydroxypropyl α-cyclodextrin complexes delivered locally to the brain an experimental glioma model in the rat.

2. Materials and methods

2.1. Materials

Carboplatin was purchased from Bristol–Myers Pharmaceutical Corporation (Syracuse, NY, USA). 2-Hydroxypropyl α-cyclodextrin was purchased from Pharmatec (Alachua, FL, USA), and 2-hydroxypropyl β- and 2-hydroxypropyl γ-cyclodextrin were purchased from Research Biochemicals (Natick, MA, USA); all had a degree of substitution of hydroxypropyl group between 5 and 7. Ethylcellulose (48% ethoxy content, viscosity of a 5% solution 100 cp) was purchased from Aldrich (Milwaukee, WI, USA) and sorbitan mono-oleate (Span 80) and other chemicals were purchased from Sigma (St. Louis, MO, USA).

2.2. Analytical determination

High-performance liquid chromatography (HPLC) was used to measure carboplatin concentrations. The HPLC system consisted of Milton Roy ConstaMetric 3000 solvent delivery unit, a Merck Hitachi AS4000A autosampler, a Beckman Ultrasphere ODS 5 μm (150 × 4.6 mm) column and a Spectra-Physics SP8450 UV–vis. detector, which was operated at 229 nm. The flow rate was 1.5 ml/min. The mobile phase consisted of water and aqueous stock solution of tetrabutylammonium phosphate (93:2) in which the retention time of carboplatin was 2 min. For the tetrabutylammonium phosphate stock solution, 13.5 g of tetrabutylammonium hydrogen sulfate were dissolved in 127 ml of water, 5.4 ml of phosphoric acid (85%) were added, and the pH was adjusted to 7.4 with a 5 M aqueous sodium hydroxide solution.

2.3. Preparation of the microcapsules

Microcapsules were prepared by the emulsion–solvent evaporation method [31]. In a typical experiment, the uncovered coating vessel (1000 ml capacity) was fitted with a glass stirrer (stirring rate 400 rpm). The dispersed phase in the emulsion was made by dissolving ethylcellulose (2 g) in 100 ml of ethanol, and adding 900 mg of hydroxypropyl α-cyclodextrin, followed by 100 mg of carboplatin. The continuous phase of the emulsion consisted of n-heptane (90 ml), paraffin preliquidium Ph. Eur. (180 ml), and sorbitan mono-oleate (2.7 ml). The two phases were mixed in the coating vessel and were stirred continuously under ambient conditions until all the ethanol had evaporated (about 19 h). The microcapsules that formed (diameter, 1400–1500 μm) were then filtered, washed with n-heptane, and dried overnight in a desiccator. The total drug content of the microcapsules was determined by dissolving 20 mg of the microcapsules in 25 ml of methanol, filtering through a 0.45 μm membrane filter, and after appropriate dilution with methanol, analysis by HPLC.

2.4. Scanning electron micrograph of the microcapsules

The microcapsules were mounted on aluminum stubs, sputter-coated (Eswards S150B sputter-coating apparatus) with a thin layer of Au/Pd and examined using a Cambridge Instruments Stereoscan 240 scanning electron microscope.

2.5. Kinetic studies of degradation of carboplatin in solution

The effects of hydroxypropyl cyclodextrins on the degradation of carboplatin were determined by adding a stock solution of carboplatin in methanol to the aqueous solutions and adjusting the pH to the stated value at the stated temperature. An aqueous sodium phosphate buffer (pH 7.4, $\mu = 0.2$) was used. In the experiment in which cell culture medium was used to study decomposition of carboplatin, minimal essential medium (Gibco-BRL, Grand Island, NY, USA) supplemented with 10% fetal bovine serum, and containing L-glutamine (292 μg/ml) and penicillin (80.5 μg/ml) was used. For studying the

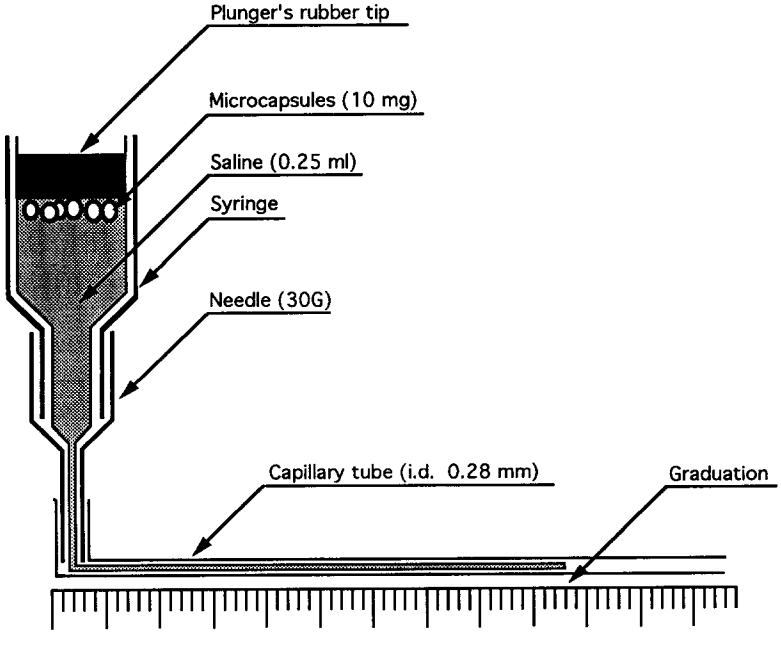

Fig. 1. Apparatus for measuring the uptake of water by microcapsules.

effect of the concentration of hydroxypropyl cyclodextrins on carboplatin decomposition, the initial concentration of carboplatin was 1 mM and the concentrations of hydroxypropyl cyclodextrins were 50, 20, 5 or 2 mM. At the stated intervals, aliquots of the reaction mixture (20 μl) were injected directly onto the HPLC column; the pseudo-first-order rate (k_{obs}) was determined by linear regression in which the natural logarithm of the peak height of the drug was plotted against time.

2.6. Release kinetics of carboplatin from microcapsules in vitro

Release of carboplatin conditions was assessed by using microcapsules containing 0.57% w/w carboplatin (and no hydroxypropyl α-cyclodextrin), or 2.2% w/w carboplatin and the stated concentration of hydroxypropyl α-cyclodextrin. The microcapsules (10 mg) were placed into glass scintillation vials (10 ml) containing 5 ml of 0.9% sodium chloride. The vials were then kept in an incubator at 37°C and the solution was removed for analysis of carboplatin content and replaced with fresh solvent at the stated times throughout the entire length of the study (110 days). The concentration of carboplatin was measured as described above.

2.7. Swelling of microcapsules in vitro

The uptake of water by the microcapsules was measured by means of the apparatus designed by Horiuchi et al. [30]. The microcapsules (10 mg; diameter 1400–1500 μm) loaded with carboplatin alone or carboplatin–hydroxypropyl α-cyclodextrin were placed into the syringe containing 0.25 ml of saline. The volume of water taken up was read from a calibrated capillary tube (id 0.28 mm) at 25°C (Fig. 1).

2.8. Studies on cells in vitro

The F98 glioma cell line was obtained from Goodman, Ohio State University, and grown at 37°C in minimal essential medium supplemented with 10% fetal bovine serum, L-glutamine (292 μg/ml), and penicillin (80.5 μg/ml) in a humidified atmosphere enriched with 5% CO_2. The cells were detached with 0.25% trypsin solution (in Hanks' balanced salt solution without calcium and magnesium) and counted with a Coulter particle counter. The cell monolayers were prepared by plating 10^4 cells in medium (1 ml) into 10 × 8 mm tissue culture dishes and incubating for 24 h. Medium was then replaced by either 1 ml of medium containing the stated concentrations of carboplatin or by 1 ml of medium containing the 2.0 mg of microcapsules loaded with or without 2.2% w/w of carboplatin. The cells were detached with 0.05% trypsin on day 5 or day 7, and counted.

2.9. In vivo efficacy studies

Fifty-six adult male Fischer rats weighing between 200–250 g were obtained from Harlan Sprague–Dawley (Indianapolis, IN, USA). The animals were anesthetized by intraperitoneal injection of 3–5 ml/kg of an isotonic aqueous saline containing ketamine hydrochloride 25 mg/ml, xylazine 2.5 mg/ml, and 14.25% ethanol. The head of the animal was then shaved and prepared with 70% ethanol and Prepodyne solution. The skull was exposed by midline scalp incision and a 3 mm burr hole on the left parietal bone was made, 2–3 mm from a midline and 5–6 mm behind the bregma. The animal was placed into a stereotactic head frame (Trent–Wells, South Gate, CA, USA) and a Hamilton microsyringe with a 26 gauge needle which was attached to the adjustable arm of the stereotactic frame was used to inject 10 μl of suspension containing 10^5 F98 glioma cells at a depth of 3.5 mm. After slow withdrawal of the needle the wound was washed with saline and the scalp was closed with staples. Five days later the rats underwent re-operation and were randomly divided into seven groups for experiments I and II; which encompassed groups 1–3 and 4–7, respectively. Group 1 received no treatment; group 2 received an intracerebral injection of carboplatin alone (0.2 mg in 10 μl); and group 3 received an intraperitoneal injection (30 mg/kg once a week for 3 weeks). The following groups received implantation of microcapsules; 1–2 mm under the surface of the brain through the same burr hole that was used to inject glioma cells. Group 4 received empty microcapsules; group 5 received microcapsules (10 mg) loaded with hydroxypropyl α-cyclodextrin alone; group 6 received microcapsules loaded with carboplatin alone

(2.2% w/w); and group 7 received microcapsules (10 mg) loaded with the complex of carboplatin and hydroxypropyl α-cyclodextrin (2.2% w/w). Any bleeding was allowed to subside spontaneously, and the wound was irrigated with 0.9% sodium chloride and closed with surgical staples. Survival was plotted on a Kaplan–Meier survival curve and statistical significance was determined by a nonparametric Kruskal–Wallis analysis of variance followed by a nonparametric studentized Newman–Keuls test for multiple comparisons.

3. Results and discussion

3.1. Kinetics of carboplatin release from microcapsules

Microcapsules containing a carboplatin–hydroxypropyl α-cyclodextrin complex were prepared as described by Huang and Ghebre-Sellassie [29] and consisted of a visually uniform population of regularly shaped solid spheres (Representative specimen, Fig. 2); the average loading of carboplatin was 2.2% w/w.

The release of carboplatin from these microcapsules into 0.9% sodium chloride is shown in Fig. 3. Within the first 10 days, 25% of the carboplatin was released. In the microcapsules loaded with carboplatin alone, drug was released after an initial burst,

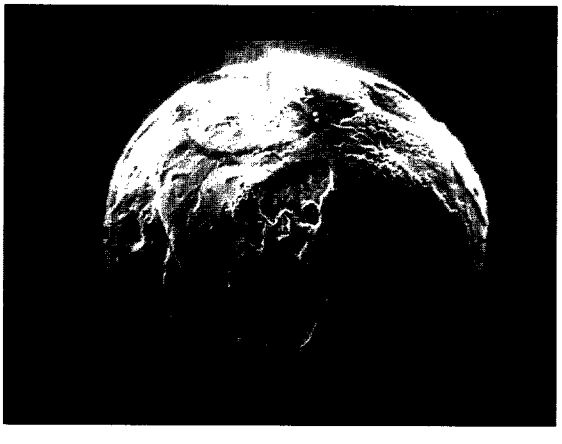

Fig. 2. Scanning electron micrograph of microcapsules containing complex of carboplatin and hydroxypropyl α-cyclodextrin at (47.3 ×).

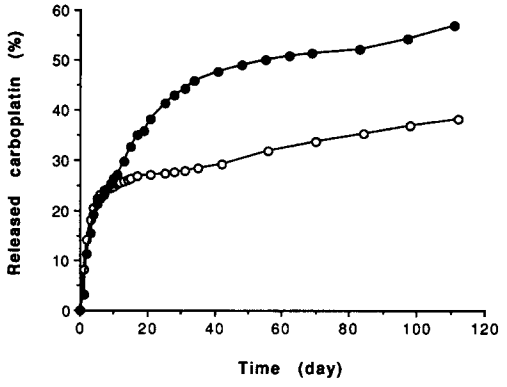

Fig. 3. Release profile of carboplatin from microcapsules containing carboplatin alone (○) and the complex of carboplatin and hydroxypropyl α-cyclodextrin (●) into unstirred 0.9% sodium chloride at 37°C.

with a steady rate for 110 days and total release of about 37%. In the microcapsules loaded with the carboplatin–hydroxypropyl α-cyclodextrin complex, 48% of the carboplatin was released within the first 40 days, after which release continued at a steady rate until 56% of carboplatin was released at 110 days.

The release of carboplatin from the microcapsules is expected to be strongly affected by swelling of these microcapsules. The enhanced release of carboplatin from microcapsules loaded with the carboplatin–hydroxypropyl α-cyclodextrin complex when compared with microcapsules loaded with carboplatin alone could be attributed to the difference in degree of hydration and subsequent swelling of these microcapsules. Therefore, the uptake of water by the microcapsules was measured. Water was taken up gradually, with saturation occurring at 48 h for the microcapsules loaded with carboplatin alone or carboplatin–hydroxypropyl α-cyclodextrin (Fig. 4). The uptake rate was significantly faster, however, when the microcapsules were loaded with the complex of carboplatin and hydroxypropyl α-cyclodextrin, compared with the rate in microcapsules loaded with the carboplatin alone ($p < 0.05$ at 18, 24 and 30 h). These results suggest that the incorporation of the complex into the ethylcellulose matrix may improve the hydration of these microcapsules.

The decomposition of carboplatin is another problem that may decrease its therapeutical effects. The

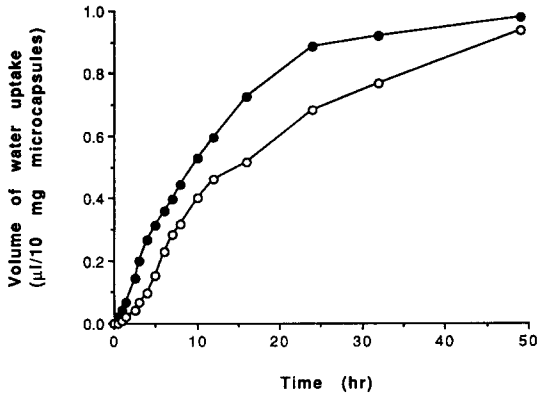

Fig. 4. Swelling of microcapsules containing carboplatin alone (○) and the complex of carboplatin and hydroxypropyl α-cyclodextrin (●) at 25°C.

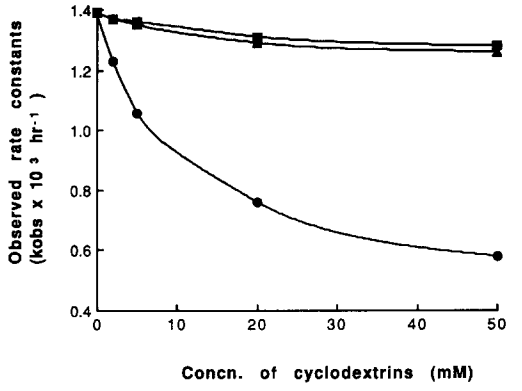

Fig. 5. The rate constants (h^{-1}) of the degradation of carboplatin in the presence of hydroxypropyl cyclodextrins in phosphate buffer (pH 7.4, $\mu = 0.2$) at 37°C. (●) with hydroxypropyl α-cyclodextrin, (▲) with hydroxypropyl β-cyclodextrin, (■) with hydroxypropyl γ-cyclodextrin.

implanted drug is exposed for month-long periods not only to the polymeric matrix, but also to tissue components that may diffuse into matrix. Carboplatin is known to be stable for at least 24 h in simple infusion fluid but is decomposed when exposed to substances contained in tissues [32]. The degradation of carboplatin in phosphate buffer followed pseudo-first-order kinetics and we found that the rate was decelerated by the addition of hydroxypropyl cyclodextrins. Fig. 5 shows the effects of the concentration of hydroxypropyl cyclodextrins on decomposition of carboplatin in sodium phosphate buffer (pH 7.4, $\mu = 0.2$) at 37°C. The degradation rate constants of carboplatin were decreased by hydroxypropyl cyclodextrins and the profiles were compatible with the formation of 1:1 carboplatin–hydroxypropyl cyclodextrin complexes [31,32]. The rate constants (k_c) and association constants (K_c) of the carboplatin–hydroxypropyl α-cyclodextrin complex were calculated and are presented in Table 1. The degradation of carboplatin is significantly suppressed by the formation of a complex with hydroxypropyl α-cyclodextrin ($k_c/k_0 = 0.30$). The association constant of this complex is larger than those of complexes formed with hydroxypropyl β-cyclodextrin and hydroxypropyl γ-cyclodextrin. These results suggest that the smaller hydroxypropyl α-cyclodextrin cavity is of optimal size for forming a complex and protecting carboplatin against degradation. Carboplatin incorporated into microcapsules was also stabilized by hydroxypropyl α-cyclodextrin. After incubation at 37°C for 170 h in phosphate buffer (pH 7.4, $\mu = 0.2$), microcapsules containing only carboplatin had 76% intact drug, while those containing carboplatin–hydroxypropyl α-cyclodextrin had 94% intact carboplatin.

Table 1
Rate constants [a] for carboplatin decomposition and the association constants of the corresponding complexes

Systems	k_0 ($\times 10^3$ h^{-1}) [b]	k_c ($\times 10^3$ h^{-1}) [c]	K_c (M^{-1}) [d]
Carboplatin alone	1.39 ± 0.03	–	–
Hydroxypropyl α-cyclodextrin complex	–	0.42 ± 0.02	98
Hydroxypropyl β-cyclodextrin complex	–	1.22 ± 0.05	63
Hydroxypropyl γ-cyclodextrin complex	–	1.25 ± 0.05	67

[a] Each value represents the mean ± S.E. of 3 experiments.
[b] k_0: Rate constant for decomposition of carboplatin in phosphate buffer (pH 7.4, $\mu = 0.2$) at 37°C.
[c] k_c: Rate constants of carboplatin in hydroxypropyl cyclodextrin complexes in phosphate buffer (pH 7.4, $\mu = 0.2$) at 37°C.
[d] K_c: Association constants of carboplatin–hydroxypropyl cyclodextrin complexes in phosphate buffer (pH 7.4, $\mu = 0.2$) at 37°C.

3.2. Effects of carboplatin, hydroxypropyl α-cyclodextrin, and their complex on glioma cells in vitro

We next examined the effects of carboplatin, hydroxypropyl α-cyclodextrin, and their complex on monolayers of F98 glioma cells at the 5th and 7th days after seeding on tissue culture plates (Fig. 6). The growth of F98 cells was significantly suppressed by carboplatin at 75 ng/ml. Hydroxypropyl α-cyclodextrin of concentrations of 65 and 25 mg/ml had significant cytotoxic effects ($p < 0.01$), but that of 5 mg/ml had no effect at all. Hydroxypropyl α-cyclodextrin at all concentrations tested enhanced the cytotoxic effects of carboplatin; the enhancement was significant ($p < 0.05$ for hydroxypropyl α-cyclodextrin of 5 mg/ml plus carboplatin versus carboplatin alone). The actual concentrations of free and complexed carboplatin at an equilibrium of 1:1 complexation can be calculated from the association constant of 98 M^{-1} given in Table 1; the carboplatin–hydroxypropyl α-cyclodextrin complex provided 82%, 66%, and 28% of the total carboplatin in the presence of 65, 25 and 5 mg/ml hydroxypropyl α-cyclodextrin, respectively. However, the media in which the cells are grown is supplemented with

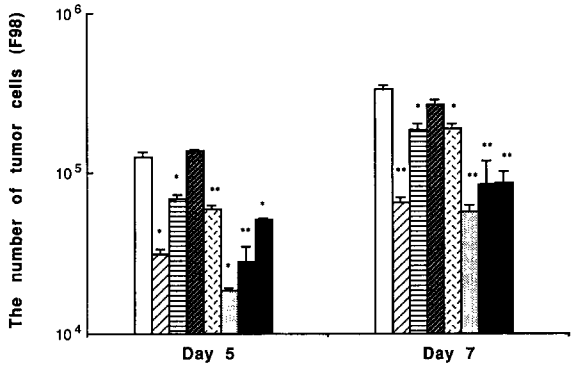

Fig. 6. Effects of carboplatin and hydroxypropyl α-cyclodextrin on glioma cells (F98) at days 5 and 7 after seeding. (Open bar) control, (shaded bar) 65 mg/ml hydroxypropyl α-cyclodextrin, (striped bar) 25 mg/ml hydroxypropyl α-cyclodextrin, (grilled bar) 5 mg/ml hydroxypropyl α-cyclodextrin, (fish-bone bar) 0.075 μg/ml carboplatin, (dotted bar) 0.075 μg/ml carboplatin and 65 mg/ml hydroxypropyl α-cyclodextrin, (shaded dot bar) 0.075 μg/ml carboplatin and 25 mg/ml hydroxypropyl α-cyclodextrin, (filled bar) 0.075 μg/ml carboplatin and 5 mg/ml hydroxypropyl α-cyclodextrin. Each value represents the mean ± S.E. of 4 experiments. * $p < 0.01$ versus control. ** $p < 0.001$ versus control.

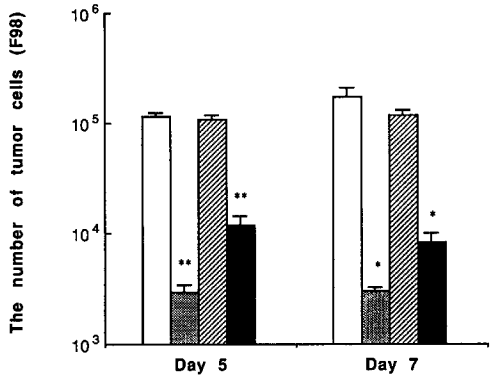

Fig. 7. Effects of carboplatin in solution, microcapsules containing the carboplatin–hydroxypropyl α-cyclodextrin complex, and microcapsules containing only hydroxypropyl α-cyclodextrin on monolayers of glioma cells at days 5 and 7 after seeding. (Open bar) control, (dotted bar) 40 μg/ml carboplatin solution, (shaded bar) microcapsules (2 mg) containing hydroxypropyl α-cyclodextrin without carboplatin, (filled bar) microcapsules (2 mg) containing carboplatin–hydroxypropyl α-cyclodextrin complex. Each value represents the mean ± S.E. of 4 experiments. * $p < 0.05$ versus control. ** $p < 0.01$ versus control.

many lipophilic compounds (amino acids, lipids and vitamins), and these compounds can form complexes with hydroxypropyl α-cyclodextrin and thus can compete with carboplatin [33,34].

The effects of carboplatin and its complex with hydroxypropyl α-cyclodextrin, in solution and after encapsulation, on monolayers of glioma cells (F98), are compared in Fig. 7. The microcapsules (2 mg) loaded with 2.2% w/w of carboplatin clearly suppressed the growth of the cells. As expected, the cytotoxic effects of encapsulated carboplatin on cells were smaller than, or at most equal to, those of the nonencapsulated drug. Nevertheless, although only 23% and 28% of the carboplatin contained in the microcapsules was released at day 5 and 7, respectively, in the medium supplemented with bovine serum, the amount of released carboplatin (about 10 and 13 μg/ml) was sufficient to exert significant cytotoxicity: cell growth at the dose of 1 μg/ml was suppressed by 90% at day 5.

3.3. Efficacy of microencapsulated carboplatin–hydroxypropyl α-cyclodextrin complex in vivo

The effects of various formulations of carboplatin on the brain glioma model in rats are compared in

Table 2. In experiment I, the rats in the control group (group 1) were dead within 3 weeks, with median survival of 20 days. Group 2, treated with an intratumoral injection of carboplatin, died earlier than the control group, presumably due to the high cytotoxicity of carboplatin; 75% were dead within 2 days. Group 3, treated with an intraperitoneal injection of carboplatin had a slightly improved median survival (34 days) and showed an increased lifespan (73.5%). However, the treatment of groups of intratumoral and intraperitoneal injections of carboplatin did not show a significant difference when compared to the control group in a Kaplan–Meier survival curve. In experiment II, groups 4 and 5, receiving either empty microcapsules or microcapsules loaded with hydroxypropyl α-cyclodextrin alone did not show a significant difference from that of the control group in experiment I; suggesting that results of both experiments can be directly compared. Group 6 that received microcapsules loaded with carboplatin alone had a slightly improved median survival (34 days). Group 7 treated with microcapsules loaded with the complex of carboplatin and hydroxypropyl α-cyclodextrin had the longest median survival (51 days). The Kaplan–Meier curves for the crucial four groups are shown in Fig. 8. The incorporation of the carboplatin–hydroxypropyl α-cyclodextrin complex into the microcapsules showed a significantly prolonged survival in the rat glioma model ($p < 0.025$ versus control group); based on a nonparametric Kruskal–Wallis analysis of variance followed by a nonparametric studentized Newman–Keuls test for multiple comparison.

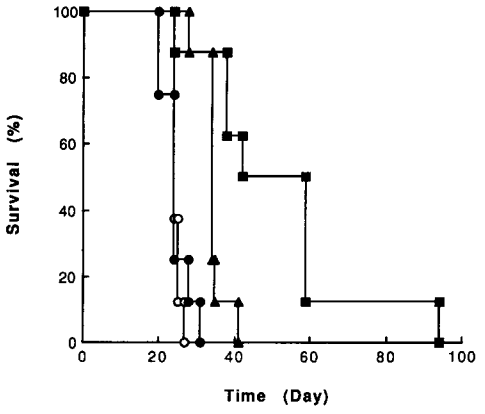

Fig. 8. Efficacy of carboplatin on glioma cells (F98) intracerebrally implanted into rats. (○) Control (microcapsules empty), (●) microcapsules containing only hydroxypropyl α-cyclodextrin, (▲) microcapsules containing only carboplatin (0.2 mg), (■) microcapsules containing a complex of carboplatin (0.2 mg) and hydroxypropyl α-cyclodextrin.

Table 2
Efficacy of carboplatin treatments against brain glioma (F98)

Experiment	Group and treatment	Median survival (days)	Increase life span [a,b] (%)
I	1. Control	20	–
	2. Intratumoral injection of carboplatin	1	−37.1 ± 39.9
	3. Systemic injection of carboplatin	34	73.5 ± 8.4
II	4. Control (Microcapsules empty)	24	–
	5. Implantation of microcapsules loaded with hydroxypropyl α-cyclodextrin alone (without carboplatin)	20	−1.0 ± 5.3
	6. Implantation of microcapsules loaded with carboplatin alone (without hydroxypropyl α-cyclodextrin)	34	39.1 ± 5.0 [c]
	7. Implantation of microcapsules loaded with carboplatin-hydroxypropyl α-cyclodextrin complex	51	109.6 ± 30.6 [d]

[a] Each value represents the mean ± S.E. of 8 rats in each group.
[b] Increase life span = (survival days in each group/survival days in control group × 100) − 100.
[c] $p < 0.001$ versus microcapsules without carboplatin.
[d] $p < 0.01$ versus microcapsules without carboplatin.

The present studies provide evidence that formation of complexes of carboplatin with cyclodextrins, by stabilizing the active drug against the decomposition and by affecting its release from implantation improves the survival of animals with experimental brain tumors treated by means of interstitial chemotherapy. The results may provide an additional refinement in the development of the best system for local delivery of bioactive anticancer agents in the treatment of brain tumors.

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