Timed-Release Depot for Anticancer Agents

SEYMOUR YOLLES *x, THOMAS D. LEAFE *, and FRANCIS J. MEYER ‡

Abstract □ The timed-release of anticancer agents from composites with poly(lactic acid) was studied in rats. In the case of cyclophosphamide–poly(lactic acid) composites, 67% of the administered dose was released within 34 days. With *cis*-dichlorodiammineplatinum (II), the amount of drug released was only 9.3% within the same period. This difference might be attributed to the different solubilities of these two drugs in the polymer. Electron spectroscopy chemical analysis, a new tool, was used to investigate the extent of diffusion of drugs in polymer films.

Keyphrases □ Cyclophosphamide—timed-release formulation with poly(lactic acid), release characteristics, electron spectra □ *cis*-Dichlorodiammineplatinum (II)—timed-release formulation with poly(lactic acid), release characteristics, electron spectra □ Anticancer agents—poly(lactic acid) timed-release formulations of cyclophosphamide and *cis*-dichlorodiammineplatinum (II) □ Timed-release formulations—cyclophosphamide and *cis*-dichlorodiammineplatinum (II) with poly(lactic acid)

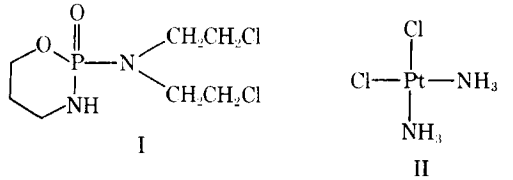
The controlled release of narcotic antagonists from composites with poly(lactic acid) in film and in particle form was reported previously (1, 2). No data have been found on the release of anticancer agents from polymeric matrixes. The present investigation was undertaken to determine in experiments *in vivo* the amounts of two potent anticancer agents, cyclophosphamide[1], 2-[bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorine 2-oxide (Compound I), and *cis*-dichlorodiammineplatinum[2] (II) (Compound II) (3–5), released from poly(lactic acid) composites.

EXPERIMENTAL

The electron spectra were recorded on an electron spectrometer for chemical analysis[3]. The scan rate was 0.05 ev/sec. The recorder used the following parameters: integral *X–Y*; *X* axis scale, 2 ev/cm; *Y* sensitivities compared on the same basis.

Preparation of Cyclophosphamide (I)–Poly(lactic acid) Composites—A mixture of 0.3680 g of I, 1.3996 g of poly(lactic acid) (1), and 0.0975 g of tributyl citrate was dissolved in 100 ml of methylene chloride. The solution was evaporated to dryness; the residue, wrapped in aluminum foil, was melt-pressed[4] at 170° under a total load of 3 metric tons for 30 sec (shims 0.91 mm thick were used) to produce translucent films of uniform thickness in which no imperfection due to air or gas was observed.

Preparation of *cis*-Dichlorodiammineplatinum (II)–Poly(lactic acid) Composites—Compound II (0.5078 g) was added to a solution of poly(lactic acid) (1) (1.8675 g) and tributyl citrate (0.1257 g) in methylene chloride. The fine suspension was evaporated to dryness, and the residue was pressed as in the preparation of I composites. The films obtained were opaque and of uniform thickness, in which no imperfection due to air or gas was observed.



I

II

[1] Cytoxan, Mead Johnson Laboratories, Evansville, Ind.

[2] Colonial Metal Inc., Elkton, Md.

[3] DuPont 650 electron spectrometer. The authors thank Mr. John Flynn of E. I. DuPont Co. for assistance with and use of the DuPont 650 electron spectrometer.

[4] Carver laboratory press model C.

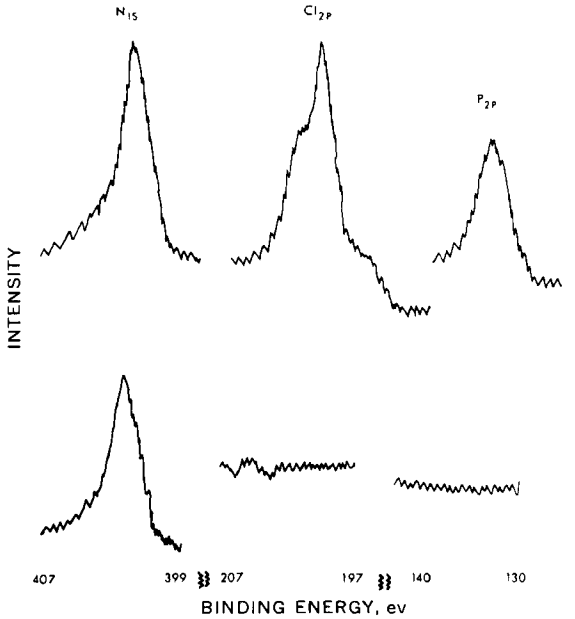


Figure 1—*Electron spectra of a I–poly(lactic acid) composite before implantation (top) and at the end of the experiment (bottom).*

Experiments *In Vivo* with I Composites—These experiments were performed on groups of three male Sprague–Dawley rats following the implantation method previously described (1), using films of 2-cm² size and 120-mg weight (average of three tests) and containing 20% of drug. The amount of I released during the test was determined from the percentages of nitrogen and phosphorous present in the film at the end of the test (N, 0.77%; P, 0.70%) compared with those present in the film before implantation (N, 2.14%; P, 2.37%).

Experiments *In Vivo* with II Composites—These experiments were performed on groups of three male Sprague–Dawley rats by the implantation method previously described (1), using films of 2 cm² and 360-mg weight (average of three experiments) and containing 20% of drug or 47 mg of platinum per rat. The release rate of drug as a function of time was determined by measuring periodically the amounts of platinum excreted in urine during the test. The total amount of drug released from the composite was determined from the percent of platinum found in the film at the end of the test (Pt, 11.8%) compared with that present in the film before implantation (Pt, 13.01%).

RESULTS AND DISCUSSION

As shown by the amounts of nitrogen and phosphorus present in the I–poly(lactic acid) composites before and after the *in vivo* test, an average of 67% of the administered dose is released over 34 days. This result demonstrates the feasibility of a sustained delivery of I from the poly(lactic acid) composite. This feasibility is further substantiated by the electron spectroscopy chemical analysis spectra of the composite recorded before implantation and at the end of the test (Fig. 1). The peaks of chlorine and phosphorus atoms show a considerable decrease in intensity at the end of the test.

Determination of the release rate of I by measuring the amounts

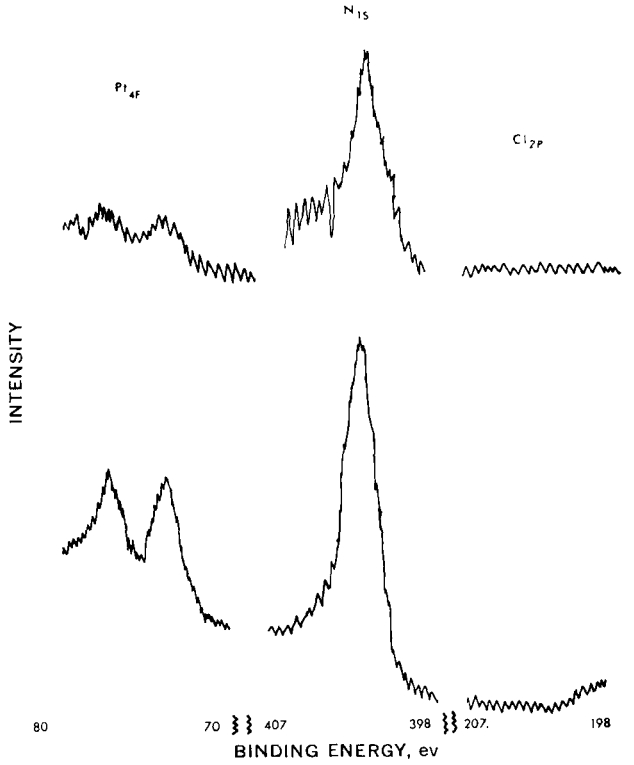


Figure 2—*Electron spectra of II–poly(lactic acid) composite before implantation (top) and at the end of the experiment (bottom).*

of nitrogen and phosphorus excreted in urine was not performed since nitrogen and phosphorus compounds are normally present in urine.

The release rate of II from poly(lactic acid) composites, determined from the amount of platinum in urine, is slow and decreases to a small amount after 18 days from implantation (Table I). The cumulative amount of drug in the urine, expressed as percent of the administered dose, is 3.85; the amount of drug released from the composite during the test, calculated from the amount of drug remaining in the film at the end of the test, is 9.3%. These results indicate that a significant amount of drug unaccounted for either remains sequestered within the animal or is eliminated through ways other than the urine. The presence of large amounts of drug left in the composite at the end of the experiment is also shown by the electron spectroscopy chemical analysis spectra (Fig. 2).

The relatively low amount of platinum compound in the surface

Table I—Amounts of Platinum and Cumulative Percent of Dose Excreted in Urine

Period, days	Milligrams of Platinum in 4 Days	Cumulative Milligrams of Platinum	Cumulative Percent of Dose
0–4	0.88	0.88	1.87
4–8	0.52	1.40	2.97
8–12	0.24	1.65	3.21
12–18	0.06	1.71	3.63
18–26	0.05	1.76	3.74
26–34	0.05	1.81	3.85

of the original film, as shown by the electron energy spectra, is attributed to its very low solubility in the polymer and its low rate of diffusion. But I, being more soluble in the polymer, appeared to a considerable extent in the surface of the original film. These solubility observations are further borne out by the physical appearance of the respective films, that of I being translucent and that of platinum compound being opaque. The electron spectroscopic technique is being studied further for measuring the diffusion rate of drugs in polymer films.

In addition, differences in the release of these two drugs can be attributed to differences in solubilities in water. The solubility of I in water is 40 g/liter (6) and that of II is 2.2 g/liter (7).

These results prove the feasibility of a timed-release system for delivering anticancer agents and suggest that this concept of timed release is of great potential for use in cancer therapy.

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[x] To whom inquiries should be directed.