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Coprecipitates of trifluoperazine embonate and polymers: duration of action by intramuscular route

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Nylon microcapsules of trifluoperazine embonate, prepared by the interfacial condensation of hexane diamine and sebacyl chloride, show activity over two or more weeks after injection intramuscularly as suspensions into beagles (Florence, Jenkins & Loveless, 1973). Provided that biologically acceptable encapsulating agents can be found the results with the microencapsulated drug suggest that such formulations would be an approach to the preparation of prolonged acting parenterals. Not all polymers can be formed by interfacial condensation procedures and thus cannot readily produce conventional microcapsules. In a programme of work aimed at producing injections with activity over several weeks we have prepared polymer-drug mixtures by a simple process of coprecipitation, and tested the resulting products in beagles. One of these preparations employing polymethylmethacrylate has shown duration of activity equivalent to that of the conventional nylon microcapsule formulation. Although polymethylmethacrylate is not a bio-degradable polymer, its physicochemical properties are well characterized. It is one of a series of polyacrylates being studied in our laboratories. Its use here is simply to demonstrate the prolongation of release possible with coprecipitation techniques. The combination may have a use in experimental animal studies.

Poly DL-aspartic acid was prepared from DL-aspartic acid by thermal polymerization at 160–180° following the method of Neri, Antoni & others (1973). The intrinsic viscosity of two samples in dimethylformamide (DMF) was 13–14 ml g^{-1}. While no molecular weights can be deduced from these data others have found molecular weights in the range 5000 to 15 000 after similar preparation techniques (Alexander & Lundgren, 1966). Polymethylmethacrylate (PMMA) was BDH material of 'high molecular weight'. Coprecipitates of trifluoperazine embonate and the two polymers were prepared by dissolving drug and polymer in DMF and adding the solution to a rapidly stirred volume of water. Both polymers and drug are insoluble in water. The drug-polyaspartic acid system was prepared by dissolving 0·4 g drug and 2 g polymer in 60 ml DMF. The solution was poured into 250 ml water and the resulting precipitate dried in an oven under vacuum at 30° ± 1° over P_2O_5. The dried product was ground and ball milled for 1 h. Microscopy showed that the number mean diameter was 2 μm (range 1–25 μm). Similar methods were employed for the polymethylmethacrylate product but in addition to the 5:1 polymer: drug ratio a preparation with a 10:1 polymer: drug ratio was obtained. Particle size distributions of the products were very similar. The formulations were tested in beagle dogs (10–17 kg) using the subcutaneous apomorphine challenge test. Doses of 5 mg kg^{-1} were administered by deep intramuscular injection into the thigh, in the form of suspensions of the coprecipitate particles in sesame oil.

Fig. 1 summarizes the results. Return of the measured response to 60% of the control value is a reasonable measure of duration. Examination of Fig. 1 shows that a solution of the drug in polyethylene glycol allows the response to return to 60% in 6 days; the polyaspartic acid preparation returns to 60% values at 11 days and is equivalent to the PMMA preparation in which the drug; polymer ratio is 1:10. When the drug comprises 16% of the formulation the PMMA preparation equalled the performance of the best nylon 6:10 preparations previously reported (Florence, Jenkins & Loveless 1976). This PMMA formulation is effective in producing 100% inhibition of the response to the apomorphine challenge at 3 days whereas the other preparations begin to show a decreased effectiveness at this time.

Dissolution rates of drug were measured by stirring the powdered material in buffer at pH 7·4; results in Fig. 2 are compared with dissolution from drug particles precipitated from DMF without polymer. These results suggest that reduction of dissolution below a certain value (which appears to be about 4×10^{-8}M min^{-1}) diminishes the biological effectiveness of the formulation. Obviously if release of drug is too slow effective concentrations of drug are not achieved because of the relatively rapid metabolism of the drug species. A satisfactory *in vitro* model would require simulation of removal of drug from the cir-

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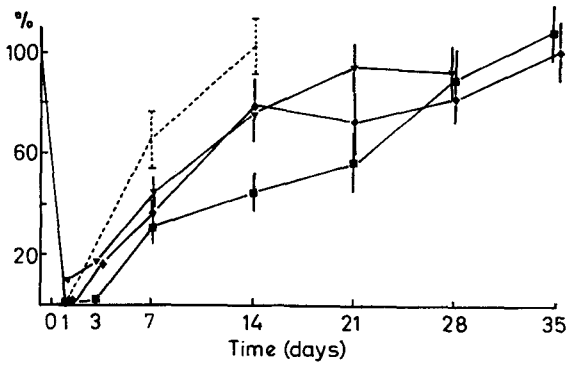

FIG. 1. Biological results from three formulations, plotted as a percentage of pre-drug response as a function of time. Broken line shows results from drug injected as a solution in polyoxyethylene glycol 400 at the same dose level. ▼-5 mg kg^{-1} trifluoperazine embonate as TFPE-DL-poly(aspartic)acid coprecipitate, ■-5 mg kg^{-1} TFPE as TFPE-PMMA (1:5) coprecipitate, ◆-5 mg kg^{-1} TFPE as TFPE-PMMA (1:10) coprecipitate. All administered in sesame oil.

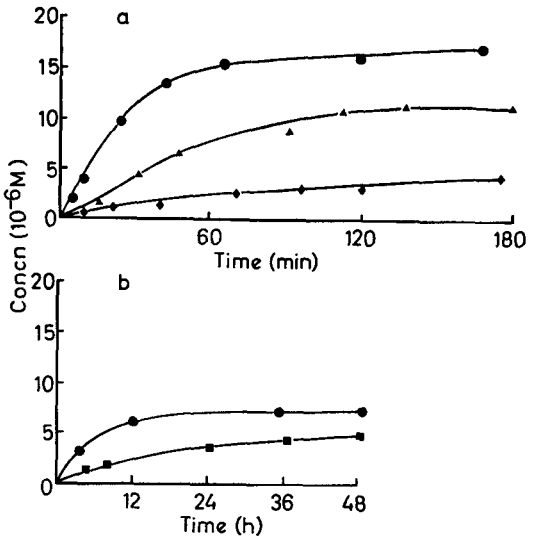

FIG. 2 (a). Dissolution results. Concentration of TFPE released into pH 7·4 buffer from coprecipitates ●-TFPE without polymer, ▲-TFPE-poly(aspartic) acid, ◆-TFPE-PMMA (1:5) coprecipitate. (b). Comparison of dissolution from the ●-1:5 and ■-1:10 TFPE-PMMA coprecipitates.

culation by metabolism, perhaps by use of a lipid phase. Thus the simple *in vitro* test we have employed will not be able to predict the biological effectiveness of the formulations.

Under the scanning electron microscope the polyaspartic acid-drug precipitates appear to be less porous than the polymethylmethacrylate-drug particles; after dissolution of the drug the latter have large depressions visible on their surfaces suggesting the removal not of individual microcrystals but of relatively large agglomerates of drug, about 0·5 μm diameter. Their appearance is not unlike that of the nylon capsules described by Jenkins & Florence (1973).

The readily prepared formulations described here show a prolongation of activity comparable with that obtained with nylon microcapsules in similar experiments. The polyaspartic acid preparation is less effective than one of the PMMA preparations, the relatively high solubility of the polyamino-acid in body fluids probably being a factor in the limited duration of activity in animals; *in vitro* dissolution experiments prove of limited use in ranking the effectiveness of these formulations as prolonged release agents.

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