PREDNISOLONE RELEASE FROM ALBUMIN MICROSPHERES: IN-VITRO AND IN-VIVO STUDIES BY INTRA-ARTICULAR INJECTION INTO RABBITS

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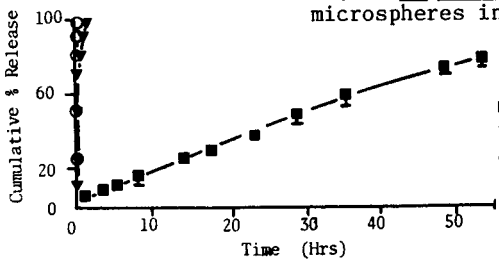
Albumin microspheres are investigated as a delivery system for prednisolone for the treatment of rheumatoid arthritis, by direct injection of the microspheres into the joints. Rabbit serum albumin (RSA) microspheres have been shown to be significantly more biocompatible when injected into rabbit knee joints, than other biodegradable polymers studied; polylactic acid, poly-butylcyanoacrylate and gelatin (Ratcliffe et al 1984).

RSA microspheres, 23 μm, were prepared by a w/o emulsion method (Tomlinson et al 1984) using fraction V RSA, highly refined olive oil and prednisolone or H prednisolone. Micronized drug particles were suspended in aqueous RSA solution (25 % w/w). 0.4 ml of this suspension was added to 125 ml of olive oil and emulsified. The microspheres were stabilised by either chemical crosslinking using glutaraldehyde (0 to 5% w/w in the microspheres) or by heat denaturation of the RSA (155 °C for 1 to 24 hrs.). In vitro drug release from the microspheres into isotonic phosphate buffer pH 7, at 37 °C was determined under sink conditions by U.V. analysis, correcting for RSA absorbance. In vivo drug release was evaluated by monitoring tritium blood levels in 24 adult male New Zealand White rabbits. The rabbits had received an intra-articular injection of either microspheres containing ^{3}H prednisolone (12 rabbits) or a ^{3}H drug suspension (12 rabbits).

In vitro studies showed that heat stabilisation was more effective at sustaining prednisolone release than chemical stabilisation. The greater the extent of heat stabilisation the slower the drug release rate. A half-life for drug release of 25 hrs could be achieved using microspheres stabilised for 24 hrs at 155 °C. Figure 1 compares the in vitro drug release profiles of prednisolone from the most sustained microsphere preparations prepared by the heat and chemical methods.

According to the in vitro data heat stabilised microspheres were expected to give sustained release of drug in vivo. This is confirmed by the in vivo studies. Significant levels of tritium were detected up to 6 to 8 days following injection for prednisolone microspheres with an in vitro half-life of drug release of 2 hrs. In vivo release rates were dependent on the extent of stabilisation although this effect was not as significant as with the in vitro data.

Fig 1. In vitro release of prednisolone from RSA microspheres into phosphate buffer, pH 7 at 37°C.



Ratcliffe, J.H. et al (1984) J. Pharm. Pharmacol. 36: 431-436.
Tomlinson, E. et al (1984) in Microspheres and Drug Therapy, ed. Davis, S.S. et al, Elsevier Sci. p. 75-89.