PREPARATION AND CHARACTERISATION OF ALBUMIN MICROSPHERES FOR INTRAARTERIAL TUMOUR TARGETTING OF CYTOTOXIC COMPOUNDS

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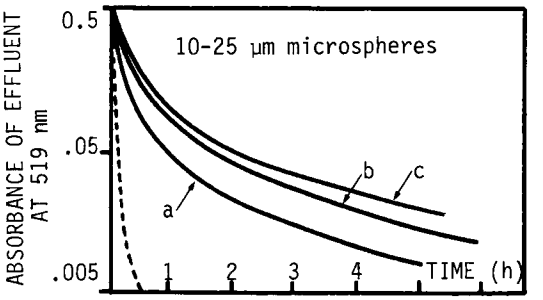
Although in vitro studies may show a compound to have antitumour activity, often its nonideal pharmaceutical and pharmacokinetic properties combine to reduce its clinical effectiveness. Attempts to use carriers for the vectoring of such agents to tumour areas have caused (inter alia) liposomes,nanoparticles and microspheres to be studied. Kanke et al (1980) have shown that organ distribution of nonbiodegradable microspheres (3-12μm) after IV injection is dependent upon their size. This communication reports our initial findings on the preparation,characterisation and release properties of human serum albumin microspheres that have been prepared for intraarterial delivery of cytotoxic agents following tumour capillary blockade.

Microspheres have been manufactured according to modifications of various methods (Widder et al,1979;Lee et al,1981) which involve emulsification of a drug/protein solution with in situ or post-manufacture stabilisation of microspheres with cross linkers (eg 0.1-25% glutaraldehyde). Drug incorporation is dependent upon the drug and protein concentrations,with upto 300μg per mg microsphere drug incorporation possible. Size and size distribution of the microspheres is dependent upon mix-cell design, stirring speed and protein concentration. The nature of the emulsion oil is also critical. The equation gives the relation between average size and stirring speed found for a 25% aqueous protein/olive oil system in the absence of cross-linker with a speed range of 400-1400rpm. (Sizing with a Coulter counter).

microsphere size (μm) = -38 log speed(rpm) + 127 n=6 ; r=0.996.

Additionally,5 μm size fractions can be taken using Veco microsieves. To examine for compound release microspheres have been incorporated into a stainless steel column packed with glass beads. Buffer (pH 7) or acidic or trypsin solutions have been pumped through this column and the release of compound followed spectrophotometrically. The figure gives typical results:



Release of alizarin red from microspheres prepared in the absence (a) and presence of 1% (b) and 5% (c) glutaraldehyde. Broken line indicates the fate of an alizarin red solution of similar concentration injected into a microsphere-free column.

Model compounds studied include organic dyes,iodinated benzenes,hydrophobic ions,as well as adriamycin,5-fluorouracil and bleomycin. Results show that drug carrying microspheres of high load capacity can be produced in 5μm fractions from 1 to 40μm, that compound release is dependent upon not only the character of the spheres but also on the nature of the compound studied and the release environment,(eg enzyme and acid effect much faster drug release).Depending upon these variables constant release between 1 and 150 hours can be achieved. Further studies are planned for the use of tomographic gamma scintigraphy to examine the in vivo disposition of both drug and carrier in normal and tumour model animals.

Widder,KJ et al. (1979) J.Pharm.Sci.,68: 79-82.
Kanke,M et al. (1980) J.Pharm.Sci.,69: 755-762.
Lee,TK et al, (1981) Science, 213: 233-235.

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