FACTORS AFFECTING HIGH SHEAR PREPARATION OF ALBUMIN MICROSPHERES

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Biodegradable microspheres have been extensively investigated as potential vehicles for targeted delivery within the body. The particle size of such vehicles has been shown to be a determining factor in their biological fate after intravenous or intraarterial administration. More recently the oral administration of microspheres in the 50 nm to 1 μm size range in rats has shown that such particles may be absorbed intact from the GIT (Jani et al 1989). Crosslinked albumin, manufactured into microspheres, has been employed as a suitable monolithic carrier material into which both hydrophobic and hydrophilic drugs have been incorporated (Tomlinson 1983). Previous methods of preparing such microspheres have the disadvantage of relatively lengthy preparative procedures and low percentage yield (Evans 1972, Yapel 1985). Although a faster, high yield method has been described (Townes et al 1989) it has not been optimised or the resultant microspheres fully characterised. It was the purpose of this study to determine the effects of shear rate, albumin concentration, cross-linker (glutaraldehyde) concentration and pH of albumin solution upon the particle size of albumin microspheres produced using the high shear technique. Bovine serum albumin solution (3 ml, 33.3% w/v; pH 5.4) was emulsified in 50 ml oleic acid, 7 ml butanol and 1 ml glutaraldehyde (16.6% w/v) using a Silverson homogeniser. Test batches of microspheres were also prepared as follows:

	Shear rate(s^{-1})	pH	Albumin Conc.(% w/v)	Glutaraldehyde Conc.(% w/v)
1.	6700-14000	5.4	33.3	16.7
2.	8800	3.0-10.0	33.3	16.7
3.	8800	5.4	33.3	10-25
4.	8800	5.4	16.7-33.7	16.7

Particle sizing was carried out by direct analysis of scanning electron micrographs. Number length mean diameters, as a function of pH and glutaraldehyde concentration are shown in Table 1.

Table 1. Mean particle diameter (μm) as a function of pH and glutaraldehyde concentration.

pH	3.0	4.0	4.9	5.4	6.0	7.0	8.0	9.0	10.0
mean	6.04	1.15	0.87	0.78	1.09	0.98	0.76	1.08	1.18
(SD)	1.06	0.34	0.51	0.21	0.27	0.31	0.26	0.21	0.32

Glut.Conc.(%w/v)	10	15	20	25
mean	0.76	0.89	0.90	1.05
(SD)	0.27	0.29	0.23	0.27

The resultant particles at pH 3 were relatively large and microspheres could not be formed at lower pH. This phenomenon was attributed to the increasing positive charge of albumin at pH values below the isoelectric point. Increasing the maximum shear rate in the system from 6700 s^{-1} to 8800 s^{-1} decreased mean particle size from 1.99 μm to 0.74 μm, whereas increasing the shear rate further up to 14000 s^{-1} increased mean particle size to 1.04 μm. Decreasing albumin concentration from 36.7% w/v to 16.7% w/v decreased mean particle size from 1.22 μm to 0.62 μm. These results show that the use of high shear rate conditions with appropriate control of other preparation variables has applicability in the ready production of sub-micron particles suitable for drug delivery via different routes.

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