HAEMOGLOBIN, TRANSFERRIN AND ALBUMIN/POLYASPARTIC ACID MICROSPHERES AS CARRIERS FOR THE ANTICANCER DRUG, ADRIAMYCIN

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The matrix of microspheres (MS) may play an important role in controlling drug delivery to target organs, drug release and subsequent uptake. Therefore, development of matrices for drug carriers appears a promising approach to alter MS characteristics and fate in the body. This research was undertaken to exploit firstly, proteins other than albumin (alb) and secondly, to explore complexation of drug with biopolymers, in the formation and resulting properties of Adriamycin (Adx)-loaded MS. Drug-loaded MS of haemoglobin (Hb), transferrin (Trf) and alb + polyaspartic acid (PAA) were prepared by stabilisation through cross-linking with glutaraldehyde of w/o emulsion droplets containing the protein and drug (Willmott et al., 1985). Drug incorporation, release rates and retention were compared to results obtained using alb alone (see Table).

In vitro drug release was examined using a continuous flow system in which MS immobilised on a glass wool column kept at 37°C were subjected to a constant flow of buffer and fractions collected at hourly intervals. We have shown (Willmott et al., 1985) that *in vivo* biodegradation of the matrix becomes significant about 24hrs after injection; therefore, *in vitro* release of Adx from intact MS was monitored up to 20hrs and the amount retained recorded. Total amounts of drug incorporated into MS following solubilisation of matrix in trypsin, and amount subsequently eluted *in vitro* were estimated both by fluorimetry (FL) and by a HPLC technique that separates native Adx from other fluorescent Adx-derived products (Cummings et al., 1984).

The table shows that the different materials employed influence MS characteristics. Compared to MS prepared from Alb, those prepared using Hb and Trf did not offer any advantage in terms of increasing drug incorporation or slowing release rate. However, the use of PAA increased Adx incorporation fourfold, and moreover reduced the rate of drug release. Trf MS released only 50% of incorporated drug within 20hrs and presumably had the highest proportion available for release via biodegradation *in vivo*. Particle size (50% weight average) did not affect release rate. Thus alb MS of 20-60μm had virtually superimposable drug release profiles, as did alb-PAA MS of 10-36μm.

Sample	Adx Incorpn (μg/mg)		Adx Retained (%)		Release Rate
	FL	HPLC	FL	HPLC	R_{50} (HR)
Adx in soln.	-	-	0	2	$2.3^{\pm}$ 0.1(6)
Albumin MS	$12.1^{\pm}1(9)$	$9.1^{\pm}1(9)$	$32.6^{\pm}6(3)$	$21^{\pm}3(3)$	$4^{\pm}0.2(3)$
ALB+PAA MS	32.4	36.9	15.4	22.2	6.4
TRF MS	12.3	8.9	49.7	NT	4
HB MS	15	8	41	30	2.6

Errors are Mean$^{\pm}$ ISE; ( ) - no. of observations; R_{50} - time taken to release 50% of total Adx released; Adx incorpn. - μg drug/mg MS; Adx retained - % of total incorporated remaining after 20 hr. MS prepared with 1% glutaraldehyde.

Willmott, N. et al (1985) Biopharm. and Drug Disposition. 6:91-104
Cummings, J. et al (1984) J.Chromatography. 311: 125-133