The organ uptake of intravenously administered colloidal particles can be altered using a non-ionic surfactant (Poloxamer 338)

L. Illum and S.S. Davis*

Royal Danish School of Pharmacy, 2 Universitetsparken, 2100 Copenhagen O, Denmark and **Department of Pharmacy, University of Nottingham, University Park, Nottingham NG7 2RD, England*

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Small polystyrene particles coated with a high M_r non-ionic surfactant (Poloxamer 338) are diverted from the reticuloendothelial system of the liver and spleen to other tissue sites. These results are discussed in terms of the adsorption of the Poloxamer to the particle surface and the implications for drug targeting.

Colloidal particle *Reticuloendothelial system* *Poloxamer* *Drug targeting* *Non-ionic surfactant* *Phagocytosis*

1. INTRODUCTION

Small colloidal particles such as liposomes, microspheres and nanoparticles have been suggested as possible carriers for the selective delivery of drugs to tissue sites in particular tumours [1–3]. However, the cells of the reticuloendothelial system in the liver and the spleen effectively remove the great majority of such particles [4,5]. As a consequence, attention is now being focussed on the use of colloidal particles for the passive delivery of drugs to the reticuloendothelial system itself, for example in the treatment of Leishmaniasis [6]. The uptake of particles by the reticuloendothelial system is normally very rapid but can be delayed, though not significantly altered, by surface coatings [7,8]. Particles can be diverted to other sites by blocking the reticuloendothelial system using excess of placebo colloid or by preinjection with, for example, dextran sulphate [9,10]. However, this approach would not be applicable in clinical practice. It is established that the physicochemical characteristics in particular size, surface charge and surface hydrophobicity of the particles are important determinants in phagocytic uptake [11,12]. Therefore we have investigated in detail the colloidal science aspects of surface coatings. We have predicted that the coating of a particle with a high M_r non-ionic polymeric material, that would give rise to a hydrophilic surface with a low surface charge and the opportunity for steric stabilisation [13,14], should give rise to a minimum uptake by the reticuloendothelial system, thereby allowing particles to reach other sites. The polyoxyethylene–polyoxypropylene series of non-ionic surfactants were selected for examination. These have the correct physicochemical characteristics [15] and some have already been employed in pharmaceutical formulations administered intravenously in man [16,17]. They have also been used clinically in extracorporeal circulation systems [18]. It would seem that they have good biocompatibility and low toxicity [19].

2. EXPERIMENTAL

Polystyrene microspheres in the size range 50–60 nm were obtained from Polyscience (Northampton) and surface labelled with ^{131}I as in [20]; 100–120 μCi labelled material (0.5 ml $\approx 2 \times 10^{13}$ nanoparticles) were administered to New Zealand

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White rabbits (2.5 kg) via the marginal ear vein. The particles were suspended either in saline or in water containing 1% of Poloxamer 338 or Poloxamer 188 (Ugine Kuhlmann, Bolton). The distribution of the particles in various body organs was followed using external scintigraphic imaging [20]. Dynamic and static images were recorded at suitable times during an 8-day period. Circulating activity in the blood was determined using a gamma probe technique [21]. After 8 days the animals were killed and the activity in various organs as well as the carcass was measured [20].

3. RESULTS

Scintigraphic evaluation of the distribution of particles shows that the organ distribution of the polystyrene particles could be altered using a surface coating of Poloxamer 338 but not with Poloxamer 188 (fig.1). Uncoated particles and those coated with Poloxamer 188 were taken out of the circulation rapidly and were deposited mainly in the liver and spleen. Approximately 90% of the particles were deposited in these organs and the half time for clearance was of the order of 50 s. The amounts deposited in the heart and lungs as

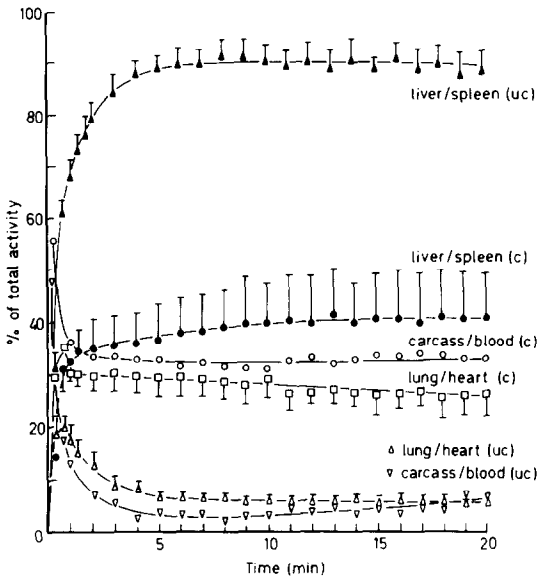

Fig.1. Effect of coating on the distribution of polystyrene latex. Activity-time profiles for different body regions after administration of uncoated and Poloxamer 338-coated polystyrene latex particles (50 nm) (n = 3, mean ± SE). Uncoated: liver/spleen (▲); lung/heart (△); carcass/blood (▽). Coated: liver/spleen (●); lung/heart (□); carcass/blood (○).

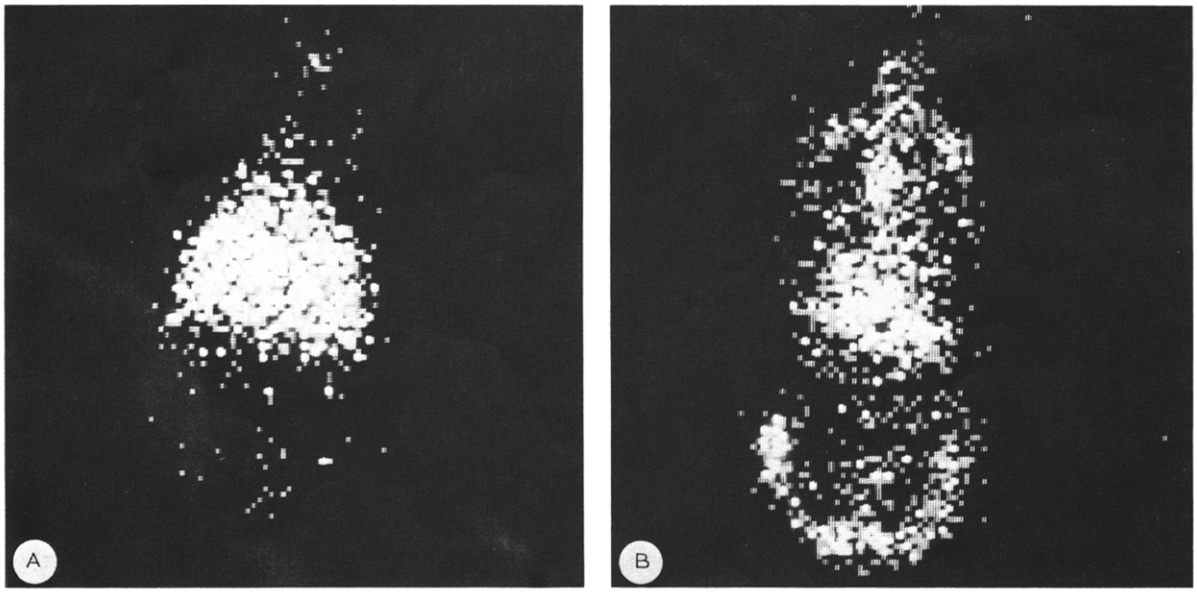

Fig.2. Scintiscans of rabbits 3 h after intravenous administration of uncoated and Poloxamer 338-coated polystyrene particles (50 nm). (A) Uncoated; (B) Poloxamer 338-coated.

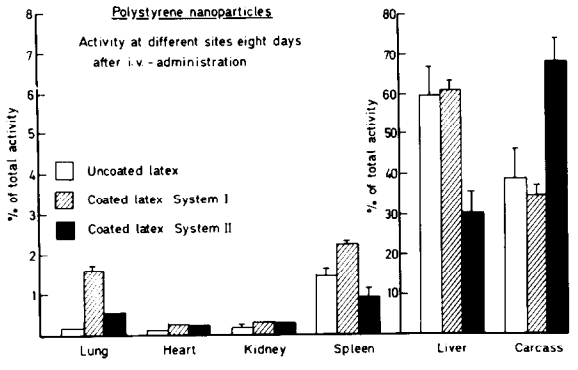

Fig.3. Distribution of uncoated and Poloxamer 188- and Poloxamer 338-coated polystyrene particles (50 nm) in various organs 8 days after intravenous administration (n = 3, mean ± SE).

well as the carcass and remaining in the blood, were negligible. In contrast, the particles coated with Poloxamer 338 showed a very different distribution pattern (fig.1). Although some particles were taken up rapidly by the liver and spleen the total quantity in these organs was greatly reduced. Higher activities were found in the lung and heart regions as well as in the carcass and blood. The measured profiles for blood clearance for the uncoated and the Poloxamer 188-coated systems were very different to that seen for the Poloxamer 338 system. For the last system sustained levels of activity were observed. These differences in distributions are clearly shown in the scintiphotos (fig.2a,b). The diversion of particles from the liver/spleen region to the bone marrow and soft tissue is apparent.

The data for organ deposition for the 3 systems are shown in the form of a histogram (fig.3). Coating the particles with Poloxamer 188 gives rise to a significant increase in the number of particles reaching the lung but does not reduce significantly the liver and spleen uptakes. The particles coated with Poloxamer 338 have higher levels in the lungs, spleen and carcass and a corresponding reduction in the quantity reaching the liver.

4. DISCUSSION

Non-ionic surface active agents of the Poloxamer type are adsorbed strongly to the surface of colloidal particles. The polyoxypropylene group of the Poloxamer polymer functions as the anchoring moiety. The polyoxyethylene groups remain free in the external aqueous environment and can give rise to colloidal stability by a repulsion effect through a steric enthalpic-entropic mechanism of stabilisation [13]. Poloxamer 188 has an average M_r of 8350 with an ethylene oxide building block of an average value (in mol) of 75, while Poloxamer 338 has an average M_r of 14000 and an ethylene oxide block of an average value (in mol) of 128. These differences in molecular characteristics can give rise to different adsorbed layer thicknesses of 14 nm and 26 nm for 188 and 338, respectively [15], as well as differences in surface charge in the absence and presence of serum [14,22]. Thus it is to be expected that a colloidal particle coated with Poloxamer 338 will present a hydrophilic surface of high M_r with a structure (loops and tails) that will give rise to good colloid stability and minimal adhesive properties [24]. The higher M_r Poloxamer (338) will be more effective in this respect than the low M_r Poloxamer (188).

Authors in [14] have shown that the uptake of emulsion droplets coated with Poloxamers by mouse peritoneal macrophages and a soil amoeba species was dependent on the nature of the Poloxamer; Poloxamer 188-coated particles being cleared more rapidly than those coated with Poloxamer 338. In [23] a similar effect was demonstrated when studying the blood-clearance of emulsion systems administered intravenously to mice.

We believe that the reduced uptake of the Poloxamer 338-coated particles in the liver and their diversion to other tissue sites is related directly to the physical properties of the adsorbed Poloxamer layer. It is known that the complement system is activated when it comes in contact with synthetic polymer surfaces and that certain complement components can be taken up rapidly [25]. Particles coated with complement will be cleared rapidly by the liver and spleen. The coating of the particles with Poloxamer 338 reduces or even eliminates the uptake of the opsonic material [12] and the subsequent phagocytic engulfment by the Kupffer cells is minimised [12]. Poloxamer 338 is much more effective in this respect, either because of its greater stabilising effect or its somewhat stronger binding to the surface of the particles. There is no evidence to suggest that Poloxamer can cause blockade of the reticuloendothelial system, indeed the quantity of Poloxamer administered (2 mg/kg) is but a

fraction of the quantity of other materials employed for this purpose (20 mg/kg) [10].

Our results suggest that the judicious use of non-ionic surfactants can be exploited to direct intravenously administered colloidal drug carrier particles away from the reticulo-endothelial system so they are able to reach other target sites (e.g., tumour tissue).

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