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Adsorption kinetics of plasma proteins on solid lipid nanoparticles for drug targeting

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Abstract

The interactions of intravenously injected carriers with plasma proteins are the determining factor for the in vivo fate of the particles. In this study the adsorption kinetics on solid lipid nanoparticles (SLN) were investigated and compared to the adsorption kinetics on previously analyzed polymeric model particles and O/W-emulsions. The adsorbed proteins were determined using two-dimensional polyacrylamide gel electrophoresis (2-DE). Employing diluted human plasma, a transient adsorption of fibrinogen was observed on the surface of SLN stabilized with the surfactant Tego Care 450, which in plasma of higher concentrations was displaced by apolipoproteins. This was in agreement with the "Vroman-effect" previously determined on solid surfaces. It says that in the early stages of adsorption, more plentiful proteins with low affinity are displaced by less plentiful with higher affinity to the surface. Over a period of time (0.5 min to 4 h) more interesting for the organ distribution of long circulating carriers, no relevant changes in the composition of the adsorption patterns of SLN, surface-modified with poloxamine 908 and poloxamer 407, respectively, were detected. This is in contrast to the chemically similar surface-modified polymeric particles but well in agreement with the surface-modified O/W-emulsions. As there is no competitive displacement of apolipoproteins on these modified SLN, the stable adsorption patterns may be better exploited for drug targeting than particles with an adsorption pattern being very dependent on contact time with plasma.
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Keywords: Plasma protein adsorption kinetics; Solid lipid nanoparticles; Two-dimensional polyacrylamide gel electrophoresis; Vroman-effect; Poloxamer 407; Poloxamine 908

1. Introduction

Plasma protein adsorption on particulate drug carriers for intravenous injection is generally regarded as the determining factor for the in vivo behavior of nanoparticles and microparticles (Juliano, 1988; Müller and Heinemann, 1989; Price et al., 2001; Thiele

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et al., 2003). For example, binding of opsonins (e.g. immunoglobulin G, complement factors, and fibrinogen) promotes phagocytosis and removal of the particles from the systemic circulation by cells of the mononuclear phagocytic system (MPS) (Leroux et al., 1995; Camner et al., 2002). In contrast, binding of dysopsonins (e.g. albumin) promotes prolonged circulation time in the blood (Moghimi et al., 1993; Ogawara et al., 2004). Moreover, surface-enriched proteins can mediate an uptake of the particles by specific target-cell populations (Kreuter et al., 2002; Müller and Schmidt, 2002). Therefore, the plasma protein adsorption patterns on different carrier systems were analyzed in vitro employing two-dimensional polyacrylamide gel electrophoresis (2-DE) (Blunk et al., 1993; Thode et al., 1997; Harnisch and Müller, 1998; Lück et al., 1998b; Gessner et al., 2001).

In these studies, the particles were incubated routinely for 5 min in citrated plasma and subsequently the adsorbed proteins were eluted from the surface and analyzed by 2-DE. An incubation time of 5 min was chosen because in general the first 5 min after i.v. injection are decisive for the fate of the particles. In case recognition by the MPS occurs, up to 90% of the injected dose are taken up by the liver macrophages (O'Mullane et al., 1987; Liliemark et al., 1995). In case particles "survive" these first 5 min, prolonged blood circulation was found (Illum et al., 1987; Cattel et al., 2003). Therefore, the protein adsorption pattern acquired in the first 5 min is the most important one, determining MPS recognition or MPS escape (at least for a certain time).

When using plasma, it is important to bear in mind that the addition of an anticoagulant such as sodium citrate – which chelates bivalent cations like calcium – leads to inactivation of the amplifying systems such as complement or coagulation (Babensee et al., 1998; Yamazaki et al., 1999). Nevertheless, in this study plasma is a more appropriate incubation medium for evaluating competitive adsorption in vitro than serum, because in many other studies the adsorption of typical plasma proteins, such as fibrinogen, onto different types of particles was demonstrated (Blunk et al., 1993; Lück et al., 1997; Jahangir et al., 2003; Archambault and Brash, 2004; Unsworth et al., 2005) and the adsorption of a single protein strongly depends on the composition of the mixture from which the adsorption appears (Price et al., 2001; Cornelius et al., 2002b). However, when a correlation between the in vivo behavior of particulate drug carriers and their protein adsorption detected in vitro is approached, it is important to consider the protein adsorption patterns obtained after incubation in both plasma and serum. In a strict sense, only investigations using blood can provide expressive answers with regard to adsorption of plasma proteins onto surfaces in vivo.

Protein adsorption onto solid surfaces has been reported to be time-dependent. In fact, the adsorption patterns have to be regarded as a product of a sequence of adsorption of more plentiful proteins with lower affinity and their displacement by less plentiful proteins with higher affinity to the investigated surface (Vroman et al., 1980; Vroman and Adams, 1986). This displacement often occurs within seconds or even within a fraction of a second and this early transient adsorption is called "Vroman-effect". Its extent depends on the surface onto which the proteins are adsorbed (Boisson-Vidal et al., 1991; Brash and Ten Hove, 1993). Blunk et al. (1996) demonstrated such a "Vroman-effect" with polymeric model particles employing different dilutions of plasma. The dilution produces a prolonged resistance time of the plentiful proteins on the surface as the concentration of the lower plenty proteins having a higher affinity to the surface decreases significantly (Vroman and Adams, 1986). However, Harnisch and Müller (2000) observed no competitive displacement of plasma proteins on emulsion droplets and concluded that the differences in the adsorption kinetics are due to the different chemical nature of the systems, the resulting different surface properties and consequently the different binding facilities of the proteins to the surface.

Another interesting carrier system for parenteral drug delivery, showing good tolerability in vivo (Weyhers et al., 1995; Olbrich et al., 2004), is the solid lipid nanoparticles (SLN) (Müller et al., 2000; Müller et al., 2002; Wissing et al., 2004). The 2-DE technique was previously modified and successfully transferred to SLN (Göppert and Müller, 2004). The goal of the first part of this study was to investigate if it also exists a "Vroman-effect" on SLN, as they have a solid matrix as the polystyrene model particles, or if the adsorption kinetics are similar to the emulsion systems as they also have a lipid matrix, i.e. are chemically very similar. Furthermore, the adsorption kinetics of plasma proteins on poloxamer 407-stabilized SLN (P407-SLN) and poloxamine 908-stabilized SLN (P908-SLN) over

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