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Biodistribution properties of nanoparticles based on mixtures of PLGA with PLGA–PEG diblock copolymers

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Abstract

The basic characteristics and the biodistribution properties of nanoparticles prepared from mixtures of poly(lactide-co-glycolide) (PLGA) with poly(lactide-co-glycolide)–poly(ethylene glycol) (PLGA–PEG) copolymers were investigated. A PLGA(45)–PEG(5) copolymer of relatively low PEG content and a PLGA(5)–PEG(5) copolymer of relatively high PEG content were included in the study. Increasing the PLGA–PEG content of the PLGA/PLGA–PEG mixture, or when PLGA(45)–PEG(5) was replaced by PLGA(5)–PEG(5), a decrease in the size of the nanoparticles and an increase in the rate of PEG loss from the nanoparticles were observed. The blood residence of the PLGA/PLGA(45)–PEG(5) nanoparticles increased as their PLGA–PEG content was increased, reaching maximum blood longevity at 100% PLGA(45)–PEG(5). On the contrary, the blood residence of PLGA/PLGA(5)–PEG(5) nanoparticles exhibited a plateau maximum in the range of 80–100% PLGA(5)–PEG(5). At PLGA–PEG proportions lower than 80%, the PLGA/PLGA(45)–PEG(5) nanoparticles exhibited lower blood residence than the PLGA/PLGA(5)–PEG(5) nanoparticles, whereas at PLGA–PEG proportions higher than 80%, the PLGA/PLGA(45)–PEG(5) nanoparticles exhibited higher blood residence than the PLGA/PLGA(5)–PEG(5) nanoparticles. These findings indicate that apart from the surface PEG content, the biodistribution properties of the PLGA/PLGA–PEG nanoparticles are also influenced by the size of the nanoparticles and the rate of PEG loss from the nanoparticles.

Keywords: Poly(lactide-co-glycolide)/poly(lactide-co-glycolide)–poly(ethylene glycol) nanoparticles; Biodistribution; Physicochemical characteristics

1. Introduction

Among the polymeric nanoparticles currently under investigation for controlled drug delivery and drug targeting applications, those receiving most attention are probably the nanoparticles based on the biocompatible and biodegradable poly(lactide)–poly (ethylene glycol) (PLA–PEG) and poly(lactide-co-glycolide)–poly(ethylene glycol) (PLGA–PEG) copolymers (Gref et al., 1995; Peracchia, 2003; Avgoustakis, 2004). Nanoparticulate drug carriers must show persistence in systemic circulation after intravenous (i.v.)

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administration in order to be useful for controlled drug delivery and/or targeting applications. The biodistribution properties of PLA–PEG or PLGA–PEG nanoparticles have been studied in experimental animals after labeling them with radioactive agents. Although the biodistribution data obtained may be influenced from the type of the label, which makes difficult a direct comparison of the data from different studies, the studies conducted have led to the establishment of certain facts for the biodistribution properties of the PLA–PEG and PLGA–PEG nanoparticles. First, the markedly increased blood circulation time and reduced liver uptake of the pegylated PLA or PLGA nanoparticles after i.v. administration to mice or rats compared to the non-pegylated nanoparticles has been demonstrated (Gref et al., 1994; Stolnik et al., 1994; Bazile et al., 1995). After intravenous administration, the PLA–PEG and PLGA–PEG nanoparticles remain in the systemic circulation for hours, whereas the PLA and PLGA nanoparticles are removed from blood within few minutes. It is generally accepted that the cells predominantly involved in the capture of nanoparticles administered intravenously are the macrophages of liver and spleen and circulating monocytes (MPS cells). Data reported by Zambaux et al. (2000) suggested, however, that the phagocytic circulating cells involved in the uptake of pegylated PLA nanoparticles were mainly neutrophilic granulocytes.

The composition of the pegylated nanoparticles affects the effectiveness of the PEG steric barrier and the size of the nanoparticles and, as a result, determines the biodistribution properties of the nanoparticles (Stolnik et al., 2001; Mosqueira et al., 2001; Avgoustakis et al., 2003). An increase in the PEG/PLA or PEG/PLGA ratio initially increased but later decreased blood circulation time of PLA–PEG or PLGA–PEG diblock nanoparticles prepared by the solvent displacement method (Stolnik et al., 2001; Avgoustakis et al., 2003). A possible explanation for these results may be that at relatively high PEG/PLA or PEG/PLGA ratios, although PEG still forms an effective steric barrier to opsonization on the surface of the nanoparticles, the size of the nanoparticles is sufficiently low to permit the nanoparticles to reach tissues that the bigger nanoparticles (those having relatively low PEG/PLA or PEG/PLGA ratios) cannot. In support to this explanation, recent observations indicated that very small particulates can pass through the sinusoidal fenestrations in the liver and gain access to the parenchymal cells of the liver (Stolnik et al., 2001).

PLGA–PEG nanoparticles were found to exhibit linear, dose-independent pharmacokinetics for a dose range of 150–1050 μg per mouse whereas the PLGA nanoparticles followed non-linear, dose-dependent pharmacokinetics in a similar doses range (Panagi et al., 2001). In addition to the prolonged blood residence (Avgoustakis et al., 2003), the dosage-independence of the pharmacokinetics of the PLGA–PEG nanoparticles would provide further advantages for their application in controlled drug delivery and targeting.

In order to increase drug entrapment efficiency, mixtures of PLA with PLA–PEG can be applied in the preparation of the nanoparticles instead of PLA–PEG alone (Quellec et al., 1998). The use of PLA (PLGA) with PLA–PEG (PLGA–PEG) mixtures allows for the easy adjustment of PEG content of the nanoparticles by simply mixing the appropriate amounts of PLA (PLGA) and PLA–PEG (PLGA–PEG). This provides an easy means to control the colloidal properties of the nanoparticles (Zambaux et al., 1999; Gref et al., 2000). In this work, we present data on the basic physicochemical and biodistribution properties of nanoparticles prepared from mixtures of PLGA with two different PLGA–PEG copolymers. The effect of mixture composition, i.e. type of PLGA–PEG copolymer and its weight fraction in the mixture, on nanoparticle biodistribution is reported.

2. Materials and methods

2.1. Materials

DL-Lactide (LE) and glycolide (GE) were purchased from Boehringer Ingelheim (Germany). They were recrystallized twice from ethyl acetate and dried under high vacuum at room temperature before use. Monomethoxypoly(ethyleneglycol) (mPEG, molecular weight 5000) was obtained from Sigma (St. Louis, MO) and dried under high vacuum at room temperature before use. Stannous octoate, sodium cholate and cholesterylaniline (5-cholesten-3β-[*N*-phenyl]amine, CA) were also obtained from Sigma. Sepharose CL-4B gel was purchased from Pharmacia (Sweden) and Biogel A15m from Bio-Rad. Tetrahydrofuran of HPLC grade and miscellaneous chemical reagents and solvents, all of analytical grade, were obtained from