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Reducing cytotoxicity while improving anti-cancer drug loading capacity of polypropylenimine dendrimers by surface acetylation

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ABSTRACT

Polypropylenimine (PPI) dendrimers have been widely used as effective delivery vehicles for drugs and nucleic acids during the past decade. However, biomedical applications of PPI dendrimers were limited because of their serious cytotoxicity and low drug loading capacity. In the present study, acetylated PPI dendrimers with different degrees of acetylation ranging from 14.2% to 94.3% were synthesized and used to encapsulate drugs, including methotrexate sodium, sodium deoxycholate and doxorubicin. Acetylated PPI dendrimers with a degree of acetylation >80% showed a significantly decreased cytotoxicity (>90% cell viability) on MCF-7 and A549 cells. The drug loading capacity of acetylated PPI dendrimers increased proportionally with the degree of acetylation on the dendrimer surface. In addition, 94.3% acetylated PPI dendrimers exhibited a pH-responsive release profile of anticancer drugs loaded within the nanoparticles. The cytotoxicities of methotrexate sodium and doxorubicin on MCF-7 and A549 cells were significantly reduced when they were complexed with acetylated PPI dendrimers with high degrees of acetylation (>80%), owing to sustained drug release from the dendrimers. The results suggest that surface acetylation can reduce the cytotoxicity and improve the anticancer drug loading capacity of cationic dendrimers, and that acetylated PPI dendrimers are promising vehicles for anticancer drugs in clinical trials.

1. Introduction

Polypropylenimine (PPI) dendrimers are the first commercially available dendrimers synthesized by a divergent strategy using diaminobutane as the central core and propylene imine as repeat units [1]. They are widely used as templates for the synthesis of dendrimer-encapsulated nanoparticles and as scaffolds for the construction of magnetic resonance imaging contrast agents, especially in drug and gene delivery [2–4]. PPI dendrimers have excellent aqueous solubility, and therefore a large number of hydrophobic cavities in their interior can effectively improve the solubility and stability of various hydrophobic drugs [5]. In addition, PPI dendrimers with a high density of active groups on their surface can be easily functionalized with therapeutic agents, targeting moieties, solubilizing ligands and imaging units for targeted cancer diagnosis and therapy [6]. However, PPI dendrimers, especially those with a cationic surface, are not ideal candidates for biomedical applications, owing to their serious toxicity [7–9]. For instance, G5 amine-terminated PPI dendrimer at a low concentration of 1 μg ml^{-1} caused 83.2% and 76.9% cell death on HepG2 and COS-7 cells, respectively [7]. Also, G5 cationic PPI dendrimer showed significant decreases in red blood cell count, hemoglobin content and mean corpuscular hemoglobin value, as well as a substantial increase in white blood cell count [7]. Exposing macrophages to G2 or G3 cationic PPI dendrimers caused dramatic changes in macrophage cell size and significant fluctuation in mitochondrial membrane potential [10]. Cationic PPI dendrimers showed rapid clearance from the blood circulation system after intravenous or intraperitoneal injection, leading to low bioavailability of the administered drugs [11]. Administration of G4 cationic PPI dendrimer caused obvious changes in the behavior of animals, such as decreased food and water consumption, and lower rate of gain in body weight [12].

Besides the non-negligible in vitro and in vivo toxicity, PPI dendrimers have extremely low drug loading capacity for a list of hydrophobic drugs [13]. PPI dendrimers have smaller molecular size and interior cavities compared with polyamidoamine (PAMAM) dendrimers [14]. Though PPI dendrimer with a more hydro-

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