Chapter 18
Multifunctional Dendrimers for Drug Nanocarriers

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ABSTRACT

Dendrimers are nanosized, monodisperse, highly branched polymers with well-defined topological structure which have attracted much attention for drug delivery recently. To further improve the performance of dendrimers in drug delivery, various functional dendrimers are developed by decorating the dendrimers with targeting agents, imaging agents, or stimuli-sensitive moieties. They show good biocompatibility, visibility, tumor targeting and stimuli-sensitive properties for drug or gene delivery. This chapter will focus on the design of multifunctional nanocarriers based on the dendrimers. Therefore, the chapter will provide the ideas for designing the dendrimers based nanocarriers for controllable drug delivery and let more people know the development of dendrimers for drug delivery in recent years.

INTRODUCTION

In the recent years, significant progress has been achieved in the field of nanotechnology, especially in drug delivery (Shi, Votruba, Farokhzad, & Langer, 2010; Elsabahy & Wooley, 2012; Markman, Rekechenetskiy, Holler, & Ljubimova, 2013). Some traditional drugs have to face the drawbacks, such as poor aqueous solubility, undesired side-effects and low bioavailability (Allen & Cullis, 2013; Patel, Zhou,

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Piepmeier, & Saltzman, 2012), which dramatically decrease their applications in clinic. With the quick development of nanotechnology, numerous nanocarriers have been employed to solve these problems, because of their outstanding performance with targeting, delayed release, high solubility and dispensability. Most widely used nanocarriers based on polymers such as nanoparticles, micelles and liposomes are efficient, while they are metastable *in vivo* for the self-assembled nanocarriers and it is difficult to precisely control the size, structure and the surface properties of the nanocarriers (Markman et al., 2013; Torchilin, 2014). Furthermore, conventional polymers are typically polydisperse in molecular weight, resulting in poorly controlled the physicochemical properties of nanocarriers, which inevitably cause serious issues in pharmacokinetic study in clinical trials.

Contrast to the conventional polymers, dendrimers are nanosized, monodisperse, highly branched polymers with well-defined topological structure which have attracted much attention for drug delivery applications (Astruc, Boisselier, & Ornelas, 2010; Mintzer & Grinstaff, 2011). Most of them can improve the aqueous solubility and bioavailability of drugs by physically encapsulating in the voids or covalently attaching to the surface groups (D'Emanuele & Attwood, 2005). Dendrimers also have other advantages in drug delivery, such as stable structure, passive tumor targeting by enhanced penetration and retention (EPR) effect, large number of peripheral functional groups, monodisperse size, reproducible synthesis and hydrophobic interiors for drug encapsulation (Cheng, Zhao, Li, & Xu, 2011; Lee, MacKay, Fréchet, & Szoka, 2005; Medina & El-Sayed, 2009). In addition, the dendrimers are feasible modified by functional groups such as active targeting moieties, drugs, imaging agents and stimuli-sensitive elements (Cheng et al., 2011; Singh, Gupta, Asthana, & Jain, 2008). More importantly, the use of dendrimers as drug carriers has reproducible pharmacokinetics which plays a vital role for the drug delivery system in clinical application (Cheng et al., 2011).

The original research of dendrimers started in 1978 by Vögtle and his coworkers, who synthesized the dendritic arms with a central core in a controllable way (Vögtle, Buhleier, &Wehner, 1978). In the early 1980, the dendrimers were boosted by Denkewalter, Tomalia (Tomalia et al., 1985), and Newkome (Newkome, Yao, Baker, & Gupta, 1985). Until now, various dendrimers have been developed, such as polyamidoamine (PAMAM), poly(propyleneimine) (PPI), peptide dendrimers and hybrid dendrimers. The idea of encapsulating guest molecules in dendritic hosts was first proposed by Maciejewski' in 1982. Since then, more and more researchers focused on the development of dendrimers as drug carriers. Jansen et al. (1995) demonstrated that the release of guest molecules entrapped in a "dendritic box" was related to the shapes of the guest molecules, the interior cavities and architecture of the dendrimers. One of the earliest examples that dendrimers served as antitumor drug carriers was achieved by conjugating cisplatin (20–25% by weight) onto the surface groups of a generation (G)-3.5 sodium carboxylate terminated PAMAM dendrimer (Malik, Evagorou, & Duncan, 1999). The solubility of cisplatin was enhanced tenfold and the tumor accumulation levels of platinum (from cisplatin) by EPR effect were fiftyfold greater for the dendrimer-cisplatin than free cisplatin at equivalent doses. In addition, the dendrimer-cisplatin showed better antitumor activity than free cisplatin *in vivo*. In another study, Ihre et al. (2002) reported another polyester dendritic system based on the monomer unit 2,2-bis(hydroxymethyl) propanoic acid for drug delivery. The antitumor drug doxorubicin (DOX) was conjugated on the surface of the dendrimer via a pH-sensitive linkage, demonstrating the feasibility of applying these polyester dendrimers in drug delivery.

While, the conventional dendrimers also face some barriers for more efficient drug delivery as carriers, such as unsatisfied tumor targeting capability, serious side-effects on normal organs, premature