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Linear–dendritic block copolymer for drug and gene delivery

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ABSTRACT

Dendrimers as a new class of polymeric materials have a highly ordered branched structure, exact molecular weight, multivalency and available internal cavities, which make them extensively used in biology and drug-delivery. Concurrent with the development of dendrimers, much more attention is drawn to a novel block copolymer which combines linear chains with dendritic macromolecules, the linear–dendritic block copolymer (LDBC). Because of the different solubility of the contrasting regions, the amphiphilic LDBCs could self-assemble to form aggregates with special core–shell structures which exhibit excellent properties different from traditional micelles, such as lower critical micelle concentration, prolonged circulation in the bloodstream, better biocompatibility, and lower toxicity. The present review briefly describes the type of LDBC, the self-assembly behavior in solution, and the application in delivery system including the application as drug carriers and gene vectors. The interactions between block copolymers and drugs are also summarized to better understand the release mechanism of drugs from the linear–dendritic block copolymers.

Contents

1. Introduction

Supermolecular self-assembly is an important tool for preparing functional material with structural and hierarchical order in the field of the biopolymer science [1]. One of the typical applications in the

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field of supermolecular self-assembly is polymeric micelles formed by amphiphilic block copolymers in an aqueous solution, in which hydrophobic and hydrophilic segments constitute the cores and outer shells of the micelles, respectively. The hydrophobic core can serve as a microenvironment for incorporating hydrophobic drugs such as anticancer drugs by hydrophobic interactions. The hydrophilic outer shell serves as a stabilizing interface between the hydrophobic drug and the external medium, which can avoid the micelles being quickly taken up by the reticuloendothelial system after intravenous (iv) administration [2]. In addition, the polymeric micelles formed by linear block or graft copolymers described in previous literatures [3–6] have unique structures and lower critical micelle concentrations (CMC) than those of conventional surfactants [7]. Although the amphiphilic macromolecules are of various advantages such as drug solubilization and prolonged stability in the blood circulation, the polymeric chain structure for the biomedical application is frequently limited to fabrication of biodegradable polymeric micelles by using the diblock and/or triblock linear copolymer.

Recently, a new family of micelles formed from highly branched dendritic polymers with amphiphilic characteristics has been reported. Dendrimer is a type of novel polymer, which has three-dimension, highly ordered branched structure and exact molecular weight [8,9]. In general, the structure of dendrimer contains inner central cores, repeated units named generation and high density of functional groups (–NH_2,–COOH, *etc.*) on the surface [10]. Dendrimers as the most attracting candidates have unique features. In contrast with the linear polymeric micelles, dendritic micelles are more stable to various environmental effects, such as dilution, shear force, and pH value due to structural advantages, and they do not exhibit initial burst release of guest molecules. However, they also have limitations such as poor solubility in aqueous solution, predicting unacceptable toxicity, which limits the clinical application of dendrimers [11,12].

Linear–dendritic macromolecules in which linear polymers are conjugated to dendritic macromolecules are a type of hybrid materials that have attracted increasing interest in recent years. Because of the conjugation of two different types of macromolecules, the linear and dendritic, hybrid materials combine advantageous properties of dendritic macromolecules and linear copolymers [13]. Different sizes and shapes of supramolecular assemblies can be prepared depending on the shapes and properties of the linear and dendritic parts. More importantly, due to the different solubility of the contrasting regions, hybrid macromolecules could self-assemble to form aggregates with special core–shell structures which possess some unique advantage such as biodegradability and biocompatibility [12].

This review sums up the current literature on the hybrid block copolymer consisting of linear chains attached to the dendrimers which can either be a perfect dendrimer or an imperfectly branched dendritic segment. The type and self-assembly behavior of linear–dendritic block copolymers as well as the potential applications in drug delivery system will be discussed. Emphasis will be placed on the application in delivery system including the applications as drug carriers and gene vectors.

2. The types of linear–dendritic block copolymer

As for the architecture, the linear–dendritic copolymer hybrids may be divided into six major groups (Fig 1): AB diblock linear–dendritic copolymers, ABA triblock linear–dendritic copolymers, side chain functional or dendronized linear–dendritic copolymers, linear–hyperbranched polymers, multi-arm star copolymers and linear–dendrimer-grafts polymers. Emphasis of this review will be placed on linear–dendritic diblock copolymers, linear–dendritic triblock copolymers, linear–hyperbranched polymers, and linear–dendrimer-grafts polymers. However, the dendronized linear–dendritic copolymers and multi-arm star copolymers will not be related here.

2.1. AB diblock and ABA triblock linear–dendritic copolymers

AB diblock linear–dendritic copolymers contain the linear A block and dendritic B block, while ABA triblock linear–dendritic copolymers use B as the linear block and A as the dendritic block. The common linear chains in linear–dendritic block copolymers reported in the literature include poly(ethylene oxide) (PEO), poly(ethylene glycol) (PEG), poly(methylmethacrylate) (PMMA), poly(styrene) (PS), poly(N-isopropylacrylamide) (PNIPAM) or Poly(2-isopropyl-2-oxazoline) (PiPrOx) [14]. PEO or PEG is mostly used because of its low cytotoxicity, low hemolyticity, and non-immunogenicity [15]. PMMA or PS usually can be used in photoresponsive polymers as the non-absorbing material to reduce the otherwise large optical absorption of azopolymers, while PNIPAM or PiPrOx has been found to develop stimuli-sensitive polymers due to the change of its propensity response to external temperature. As for the dendritic block, in addition to biodegradable organic dendrimers such as polyether dendrimers, polyester dendritic system, citric acid dendrimers, peptide dendrimers, and triazine dendrimers, carbosiloxane dendrimers, one of the silicon-based dendrimers, have come into scientists' eyes as potential nano-sized drug delivery vehicles due to the presence of both organic moiety and inorganic framework. Namazi and coworkers designed novel amphiphilic

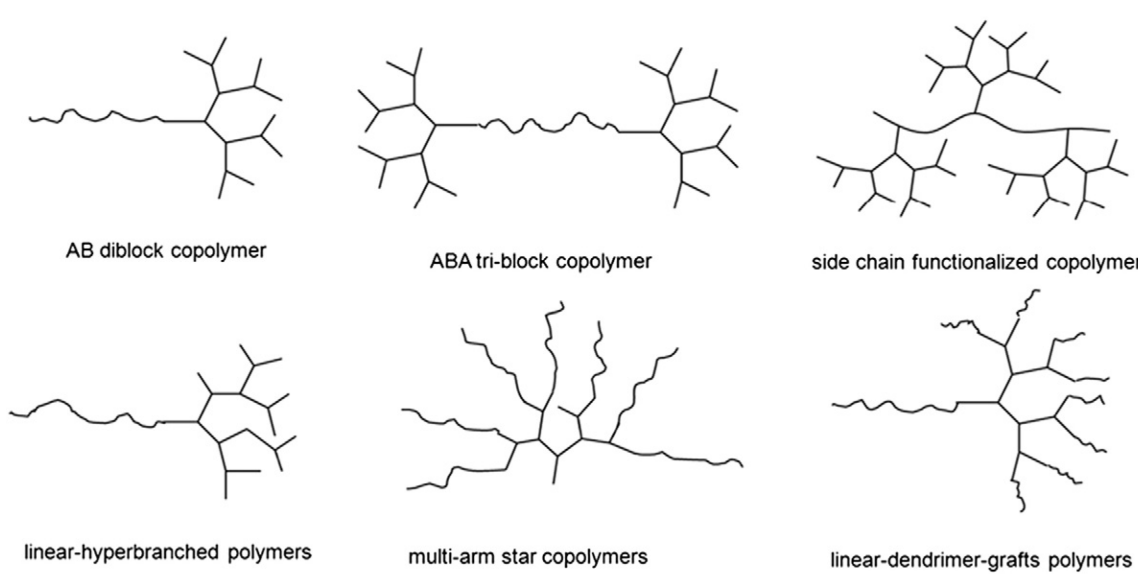

Fig 1. The six types of linear–dendritic block copolymers.