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Review

Amphiphilic block co-polymers: Preparation and application in nanodrug and gene delivery

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ABSTRACT

Self-assembly of amphiphilic block co-polymers composed of poly(ethylene oxide) (PEO) as the hydrophilic block and poly(ether)s, poly(amino acid)s, poly(ester)s and polypropyleneoxide (PPO) as the hydrophobic block can lead to the formation of nanoscopic structures of different morphologies. These structures have been the subject of extensive research in the past decade as artificial mimics of lipoproteins and viral vectors for drug and gene delivery. The aim of this review is to provide an overview of the synthesis of commonly used amphiphilic block co-polymers. It will also briefly go over some pharmaceutical applications of amphiphilic block co-polymers as "nanodelivery systems" for small molecules and gene therapeutics.

1. Introduction

Amphiphilic block co-polymers (ABCs) have been in use as pharmaceutical excipients in different forms for a long time and their application is experiencing rapid growth in modern pharmaceutical sciences [1–4]. Traditionally ABCs have been used as stabilizing agents in the formulation of coarse and colloidal dispersions and as gels as depot or bioavailable formulations. More recently evidence has been provided for the potential use of ABCs as safer replacements for low molecular weight surfactants in the solubilization of poorly soluble drugs and core/shell association colloids for nanoscale delivery systems [5–7].

The rapid development of ABC applications in the pharmaceutical sciences is primarily due to the chemical flexibility of their structure, which provides an opportunity for the design of versatile drug carriers. For instance, the size of both the hydrophilic and the hydrophobic parts can be varied at will to achieve polymers of varied hydrophilic–lipophilic balance (HLB); the molecular weight of the polymer can be varied within a wide range while maintaining a constant HLB and, more importantly, both the hydrophilic and hydrophobic parts can be functionalized.

Among different structures, ABCs with poly(ethylene oxide) (PEO) as their hydrophilic block and poly(amino acid)s ((PLAA)s), poly(ester)s, poly(amine)s or poly(amine ester)s as their hydrophobic block represent the most extensively researched polymers for constructing nanoscale delivery systems. This is largely due to the expected low immunogenicity, the biodegradability and the biocompatibility which may make them suitable for human administration. Methods of chemical synthesis of these block co-polymers have advanced tremendously and been optimized in recent decades. Among these methods, ring-opening polymerization (ROP) has been intensively explored and extensively used to synthesize PEOs, PEO–polyester conjugates and PEO–PLAA conjugates. Therefore, ROP polymerization technique has also been continuously refined in recent years to achieve tailored properties and controlled architectures of ABCs [8–10]. For example, several possible combinations of initiators and catalysts have been evaluated to achieve the desired polymer architecture and properties [11–15]. Enzyme-catalyzed ROP has emerged as one of the most promising tools to synthesize polyesters, avoiding the use of organometallic catalysts and having the appeal of a "green-chemistry" [16]. Easy synthesis, the potential for scaled up production and the chemical flexibility of these ABCs produced by ROP will eventually facilitate the application of ABCs as drug carriers.

The aim of this review is to provide an overview of the general synthesis and engineering of ABCs for use as nanodelivery systems. Specific nanostructures formed from ABCs and used for drug and gene delivery applications, e.g. polymeric micelles, polymeric

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vesicles, nanohydrogels and dendrimers, will also be briefly discussed. Advances in ABC based nanodelivery systems coincides with a better understanding of the disease-related mechanisms. This provides a golden opportunity for researchers in the field of polymer-based drug delivery. By taking advantage of the advances in polymer chemistry it will not only be possible to produce a number of sophisticated structures, but also to fine tune them for the delivery of specific therapeutics taking into account the pathophysiology path physiology of the disease, the biological rationale for the delivery approach and its proposed clinical application [17].

2. General synthesis of the most commonly used ABCs

ABCs made from PEO as the hydrophilic block and poly(propylene oxide) (PPO), PLAAs, poly(ester)s, polyamines or poly(amine ester)s as the hydrophobic block have been widely used for drug/gene delivery. The co-polymers can be prepared either by conjugation of separately synthesized blocks or by one-pot sequential polymerization using PEO as the microinitiator. The following section will review the methods of preparation of PEO and PEO-based block co-polymers.

2.1. Synthesis of heterobifunctional PEO

PEO is most commonly synthesized via anionic ROP of ethylene oxide (EO) in the presence of a hydroxide or alkoxide initiator [18,19]. The reaction takes place via nucleophilic attack on an EO methylene to open the ring and form the propagating species. Due to the stability of the propagating species, living anionic ring-opening polymerization of EO may be possible and the prepared PEO generally has a low polydispersity [20].

Heterofunctional PEO which has different functionalized end groups has been synthesized and extensively used in building ABCs for pharmaceutical and biomedical applications [21,22]. Two methods have been commonly used to synthesize heterofunctional PEOs (Fig. 1) [8]. The most direct one is ring-opening polymerization of EO with a heterobifunctional anionic initiator, which is followed by termination with another functional moiety (Fig. 1A) [22–34]. In this method, initiation and polymerization of EO by a heterobifunctional initiator proceeds in such a way that one of the functional groups reacts with EO while the other group remains intact. As a typical example, Kataoka's group showed that α-acetal-ω-hydroxyl-PEO (acetal-PEO-OH) could be synthesized by anionic ring-opening polymerization of EO in tetrahydrofuran (THF) using 3,3-diethoxypropanolate as the initiator and potassium naphthalene as the catalyst [35]. Thompson et al. synthesized α-maleimide-ω-hydroxyl-PEO (maleimide-PEO-OH) by polymerization of EO using a double metal cyanide complex catalyst and N-(2-hydroxyethyl)maleimide as the heterobifunctional initiator [8]. The second method involves derivatization of commercially available PEO possessing hydroxyl groups at both ends (HO-PEO-OH) or other homobifunctional PEOs (X-PEO-X) (Fig. 1B) [36–38]. Because the reactivity of hydroxyl groups at both ends of PEO is the same, this synthetic approach is complicated and involves several reaction steps and requires final separation of chemically similar polymers that differ only in their end groups, leading to a low yield. For instance, allyl-PEO-COOH was synthesized from PEO diolin four steps with a final yield of 35% [36].

2.2. Synthesis of PEO–PLAA block co-polymers

Amino acid-based polymers have been intensively explored as a potential source of new biomaterials [39]. ABCs of PEO–PLAA-based structures are in the front line of development for polymeric micellar delivery [1,5,39–43]. PEO–PLAA micellar delivery systems mostly use poly(L-aspartic acid) (P(L-Asp)), poly(L-glutamic acid) (P(L-Glu)), poly(L-lysine) (P(L-Lys)) and poly(L-histidine) (P(L-His)) or their derivatives as their core forming block (Fig. 2) [39,40,44–46]. The presence of carboxyl or amine groups not only makes these particular structures useful for chemical conjugation and electrostatic complexation of drugs and/or DNA to the PLAA block, but also eases the chemical modification of the micellar core for better micellar stability and/or drug incorporation/release. PEO–PLAAs can be obtained by either prior or subsequent addition of polyethylene glycol (PEGylation) to the PLAAs [47,48].

The most frequently used method for the synthesis of PLAAs is ROP of α-amino acid-N-carboxyanhydrides (NCAs) [49]. This method permits economical and convenient production of long polypeptide chains of PLAAs in good yield. NCA polymerization has been initiated using different protic or aprotic nucleophile or base initiators, with the most common being primary amines and alkoxide anions. The process is carried out in aprotic solvents such as

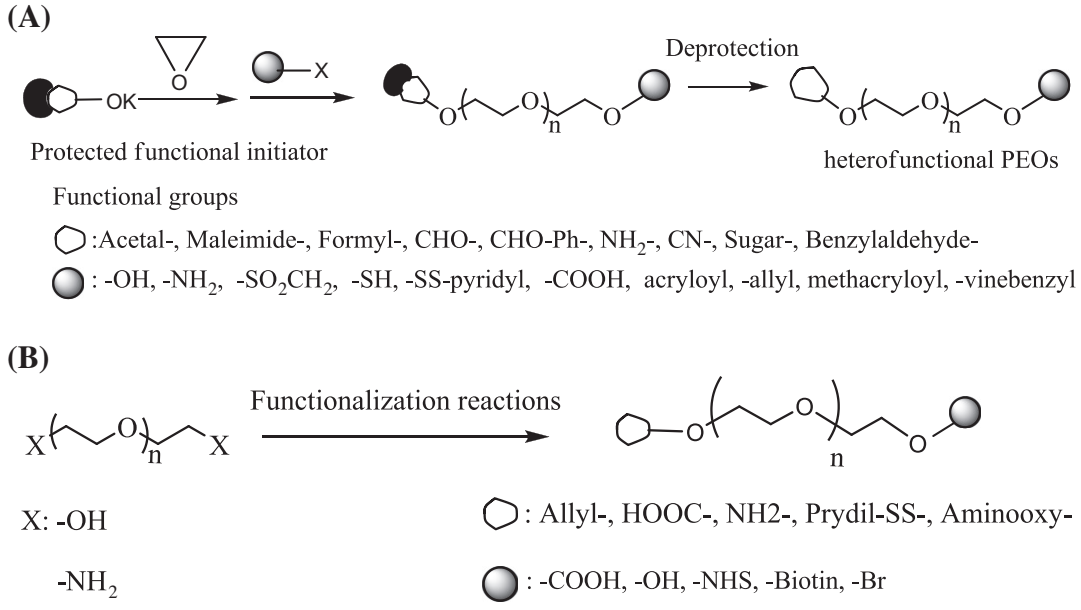

Fig. 1. Synthetic methods to produce heterobifunctional PEO oligomers. (A) Direct synthesis of heterobifunctional PEO. (B) End group modification of homobifunctional PEO.