



# Solubilization of poorly water-soluble compounds using amphiphilic phospholipid polymers with different molecular architectures



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## ABSTRACT

To achieve stable and effective solubilization of poorly water-soluble bioactive compounds, water-soluble and amphiphilic polymers composed of hydrophilic 2-methacryloyloxyethyl phosphorylcholine (MPC) units and hydrophobic *n*-butyl methacrylate (BMA) units were prepared. MPC polymers having different molecular architectures, such as random-type monomer unit sequences and block-type sequences, formed polymer aggregates when they were dissolved in aqueous media. The structure of the random-type polymer aggregate was loose and flexible. On the other hand, the block-type polymer formed polymeric micelles, which were composed of very stable hydrophobic poly(BMA) cores and hydrophilic poly(MPC) shells. The solubilization of a poorly water-soluble bioactive compound, paclitaxel (PTX), in the polymer aggregates was observed, however, solubilizing efficiency and stability were strongly depended on the polymer architecture; in other words, PTX stayed in the poly(BMA) core of the polymer micelle formed by the block-type polymer even when plasma protein was present in the aqueous medium. On the other hand, when the random-type polymer was used, PTX was transferred from the polymer aggregate to the protein. We conclude that water-soluble and amphiphilic MPC polymers are good candidates as solubilizers for poorly water-soluble bioactive compounds.

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## 1. Introduction

The preparation of safer and more effective injectable formulations for bioactive compounds is a key objective for pharmaceutical treatments. The bioactive compounds must be dissolved in a suitable medium, most likely an aqueous medium. However, there are many bioactive compounds with excellent therapeutic properties that are sometimes poorly water-soluble [1,2]. In general, the solubilities of these poorly water-soluble bioactive compounds can be enhanced using pharmaceutical solubilizers such as natural phospholipid assemblies, synthetic surface-active molecules, and water-soluble amphiphilic polymers [3–5].

As polymers composed of 2-methacryloyloxyethyl phosphorylcholine (MPC) units are well-known cytocompatible and tissue-compatible materials, they have been applied as surface coatings for implantable medical devices [6–13]. By controlling the chemical structure of the MPC polymer, water-soluble polymers can be obtained. For example, the MPC polymer prepared by the

conventional radical copolymerization of MPC with a hydrophobic methacrylate monomer, poly(MPC-*co*-*n*-butyl methacrylate) (PMB), composed of 80 mol% MPC units, is used in the pharmaceutical and cosmetic fields as a moisturizing component. In addition, water-soluble PMB composed of 30 mol% MPC units (PMB30r) is commercially available as a solubilizing test reagent for some pharmaceutical compounds [9,14,15]. Indeed, we have examined the solubilization of poorly water-soluble compounds using these MPC polymers. In the case of PMB30r, the anticancer drugs paclitaxel (PTX) and camptothecin are solubilized in aqueous media at high concentrations [15]. Moreover, we found that PMB30r can form soluble complexes with carbon nanotubes and transport them into fatty tissue without any significant adverse effect to the living system [16]. These properties are based on the formation of polymer aggregates through hydrophobic interactions among polymer chains and the lowering of polarity within these polymer aggregates. The amphiphilic characteristics of MPC polymers are important to understand in the context of the stable and effective solubilization of hydrophobic compounds.

Recent scientific progress in the radical polymerization field has achieved well-defined structural control of polymers [17]. We hypothesized that the architectures of MPC polymers also influence their amphiphilic characteristics, in other words the hydrophobic

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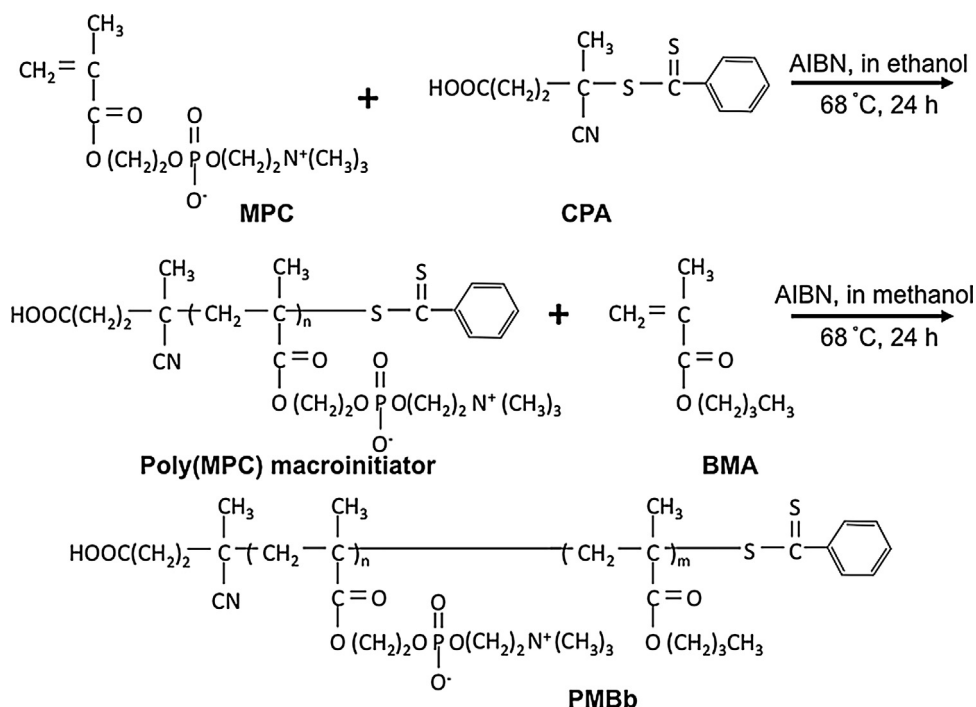


Fig. 1. Complete scheme for the synthesis of the block-type PMB (PMBb).

domain structures formed through polymer aggregation. Several researchers have reported the syntheses of water-soluble block-type MPC polymers by living polymerization processes [18–25]. These block-type MPC polymers form stable aggregates in aqueous media as polymer micelles. Thus, a comparison between random copolymers and block-type copolymers is useful for improving our understanding of the states of the hydrophobic domains formed in aqueous media.

In this study, we synthesized water-soluble amphiphilic random PMB and block-type PMB and analyzed their aggregation states. In addition, the solubilization and stabilization of poorly water-soluble PTX in these polymer aggregates is discussed.

## 2. Materials and methods

### 2.1. Materials

MPC and PMB30r (PUREBRIGHT® 50T) were obtained from NOF Corp. (Tokyo, Japan), where they were synthesized by previously described procedures [6,15,26]. The BMA and 2,2'-azobisisobutyronitrile (AIBN) were purchased from Kanto Chemical Co. (Tokyo, Japan). 4-Cyano-4-(phenylcarbonothioylthio)pentanoic acid (CPA) and paclitaxel (PTX) were purchased from Sigma-Aldrich (St Louis, MO, USA). Sodium 8-anilino-1-naphthalenesulfonate (ANS) and pyrene were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Fluorescence-dye-labeled PTX (PTX-F, Oregon-green 488-labeled) was purchased from Invitrogen (Carlsbad, CA, USA). All reagents were of extra pure grade and used without further purification.

### 2.2. Preparation of various PMBs

Random-type PMBs were synthesized by the conventional radical polymerization of MPC and BMA using AIBN as the radical initiator [6,26]. In summary, for PMB80r: MPC, BMA (mole ratio = 80:20, total monomer concentration = 0.50 mol/L), and AIBN (2.5 mmol/L) were dissolved in ethanol at room temperature, and

the solution was injected into a glass tube. Argon gas was bubbled through the solution for a few min to remove oxygen. The tubing was sealed and the polymerization was carried out at 68 °C for 24 h. The reaction mixture was poured into a large amount acetone/chloroform (50/50, vol/vol) to precipitate the formed polymer. The polymer was collected by filtration and dried under vacuum at room temperature overnight. The chemical structures of the polymers were identified by <sup>1</sup>H nuclear magnetic resonance spectroscopy (<sup>1</sup>H NMR, JEOL α-400, Tokyo, Japan) (see Supporting information Fig. S1 in the online version at DOI: [10.1016/j.colsurfb.2017.06.040](https://doi.org/10.1016/j.colsurfb.2017.06.040)). The random-type PMB (containing 80 mol% MPC units) obtained in this manner was designated as "PMB80r". PMB60r, containing 60 mol% MPC units, was also prepared in an analogous fashion.

Two kinds of block-type copolymers, composed of poly(MPC) and poly(BMA) segments, poly(MPC-*block*-BMA), were synthesized by a reversible addition fragmentation chain transfer (RAFT) polymerization technique [27,28]; the full synthetic scheme is shown in Fig. 1. Firstly, poly(MPC) with 120 MPC units (PMPC120) was synthesized using AIBN as an initiator and CPA as the chain transfer agent (CTA). Typically, MPC (0.50 mol/L), CPA (4.2 mmol/L), and AIBN (0.80 mmol/L) were dissolved in ethanol at room temperature. Polymerization was performed at 68 °C for 24 h. The formed poly(MPC) was precipitated by adding diethyl ether/chloroform (80/20, vol/vol). The poly(MPC) was dissolved in distilled water and dialyzed for 4 d. Finally, the solvent was removed by freeze-drying to obtain PMPC120 as a powder. Using the PMPC120 as a macroinitiator and AIBN as an initiator, block-type copolymers composed of poly(MPC) and poly(BMA) segments, were synthesized. In detail, for PMB80b, PMPC120, BMA (mole ratio = 1:30, [BMA] = 0.50 mol/L), and AIBN (3.3 mmol/L) were dissolved in ethanol at room temperature. Polymerization was performed at 68 °C for 24 h. The polymer was precipitated by the addition of diethyl ether, collected by filtration, and dried under vacuum overnight at room temperature. Two poly(MPC-*block*-BMA)s were prepared and these polymers are designated as "PMB80b" (80 mol% MPC units) and "PMB60b" (60 mol% MPC units). The outcomes of all PMB syntheses are summarized in Table 1. The chemical structures of PMPC120 and PMB60b were

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