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Synthesis of CO_2-philic amphiphilic block copolymers by RAFT polymerization and its application on forming drug-loaded micelles using $ScCO_2$ evaporation method

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ABSTRACT

Well-defined drug-loaded micelles are emerging as key nanoplatforms for cancer theranostic and biomedical application. As the basic building block, the CO_2-philic polymer has been demonstrated as a high-efficient candidate for the construction of drug-loaded micelles by using supercritical carbon dioxide ($ScCO_2$). Herein, the CO_2-philic polymer-poly vinyl acetate (PVAc) is successful *via* RAFT polymerization technology synthesized in this study. Moreover, the amphiphilic block copolymers, poly(vinyl acetate)-*b*-poly(ethylene glycol) methyl ether methacrylate (PVAc-*b*-PEGMA), is successfully synthesized and used for the preparation of paclitaxel-loaded micelles by solvent evaporation method. The parameters of the prepared micelles by using two solvents are compared. When $ScCO_2$ is used as the solvent, the average diameter, encapsulation efficiency (EE), drug loading efficiency (LC) is 476 nm, 38.1 ± 0.6%, 12.7 ± 0.2%, respectively. While ethanol is used as the solvent, the above three parameters are 48 nm, 30.6 ± 0.5%, and 10.2 ± 0.2%. In addition, *in vitro* drug release study reveals that the total drug release amount close to 80% from the prepared micelles within 120 h and the release rate is slow and continuous. These results indicate that the solvent evaporation method using the copolymers and $ScCO_2$ as the dispersed phase is a promising procedure for high-efficient fabrication of drug-loaded micelles.

1. Introduction

It is found that paclitaxel is one of the most famous anticancer drugs. Unfortunately, its poor water-solubility obstructs its clinical application [1–4]. To address this challenge, significant efforts have been made to develop novel drug delivery systems for enhancing its water-solubility, such as liposomes [5,6], nanoparticles [7,8], emulsions [9,10] and amphiphilic polymeric micelles [11]. Among them, amphiphilic polymeric micelles are gradually emerging as the most promising candidate for well-defined drug-loaded micelles [12–19].

Amphiphilic block copolymers have been paid much attention in recent years. A lot of them have been successfully synthesized and been widely used in different fields, such as drug carrier system, pharmaceutical applications, electronic materials, *etc* [20–24]. Among these applications, the self-assemble of amphiphilic block copolymers to form drug-loaded micelles is very important. The progress and applications of these micelles are reviewed in detail by a lot of researchers [25–29].

Solvent evaporation method is the most popular process for preparing drug-loaded micelles. The most commonly used solvents are ethanol, chloroform, or other organic solvents. However, the residual organic solvents in the micelles might cause serious side effects [30]. In order to prevent such disadvantage, we previously reported the method using supercritical carbon dioxide ($ScCO_2$) to replace organic solvent for the preparation of drug-loaded micelles [31].

During the organic solvent evaporation method, the formation of polymeric micelles is induced by self-assembly behavior of the amphiphilic block copolymers in the system, in which water acts as the continuous phase while organic solvent as the dispersed one. Similarly, for the system using $ScCO_2$ as the dispersed phase, novel amphiphilic block copolymers with a hydrophilic block and a CO_2-philic block should be designed. In this case, the self-assembly behavior of polymeric micelles is initiated while water acts as the continuous phase and $ScCO_2$ as the dispersed one.

As the CO_2-philic polymer, poly(vinyl acetate) (PVAc) is attracted much attention in recent years due to its unique biodegradability as well as the potential applications in coating, catalysis, and drug delivery system [32–37]. At the same time, due to its non-toxic and biocompatibility, poly(ethylene glycol) methyl ether methacrylate

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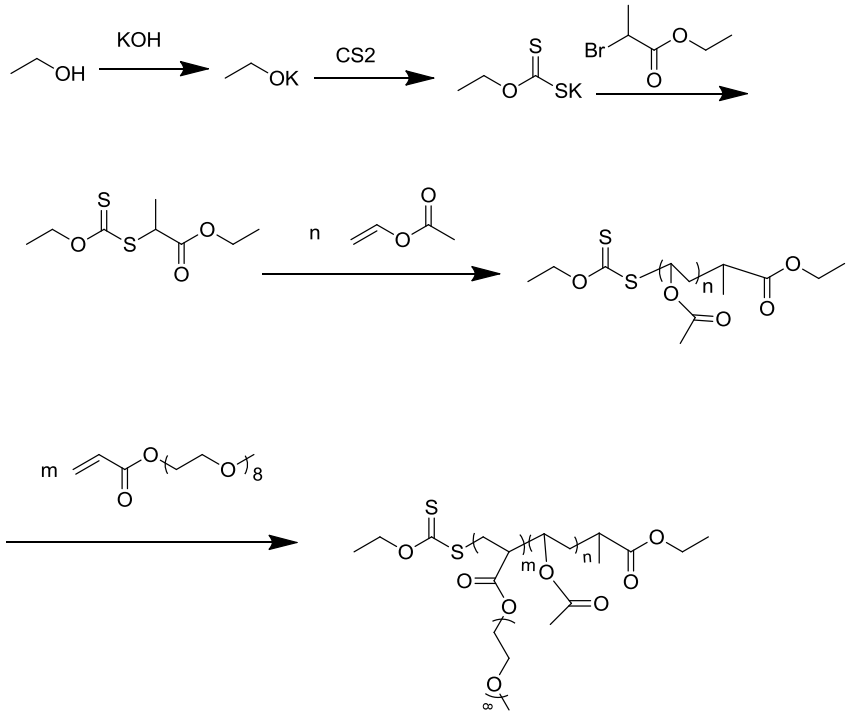

Scheme 1. Synthesis of PVAc-*b*-PEGMA.

(PEGMA) is widely used in drug delivery system as the hydrophilic block. Hence, by integration of the above advantages, the amphiphilic block copolymers with a hydrophilic block and a CO_2-philic block, poly (vinyl acetate)-*b*-poly(ethylene glycol) methyl ether methacrylate (PVAc-*b*-PEGMA), is designed and synthesized in this manuscript. The phase behavior of the copolymers in the water/$ScCO_2$ system is complicated. The solubility of the copolymers is depended on both PVAc block length and overall polymer molecular weight. The discussion about this topic is well concluded in the recent review [38]. Among the copolymers prepared in this study, PVAc block acts as the hydrophobic segment and aggregates in the core of the micelles to encapsulate drugs through the interaction between the micelles' hydrophobic core and the drugs, while PEGMA block acts as the hydrophilic segment and makes the micelles dissolve in water.

Recently, living free radical polymerization methods are widely used in the synthesis of well-defined block copolymers with controlled molecular weight and narrow molecular weight distribution. The most commonly used living free radical polymerization methods include reversible addition-fragmentation chain transfer radical polymerization (RAFT) [39], atom transfer radical polymerization (ATRP) [40,41], and nitroxide-mediated polymerization (NMP) [42]. Among them, RAFT is metal free and can be carried out with a wider range of monomers in various solvents [43,44]. Therefore, it is gradually considered as the efficient strategy for the synthesis of polymers with different structures [45–49]. Furthermore, it is reported that xanthate is beneficial to control radical polymerization of non-conjugated monomers like vinyl acetate [50].

In this paper, (S)-2-(ethyl propionate)-(O-ethyl xanthate) is synthesized and used as chain transfer agent for the synthesis of PVAc. After that, the amphiphilic block copolymers with a hydrophilic block and a CO_2-philic block, poly(vinyl acetate)-*b*-poly(ethylene glycol) methyl ether methacrylate (PVAc-*b*-PEGMA), is successfully synthesized. Moreover, the solvent evaporation method is employed for the preparation of paclitaxel-loaded micelles using ethanol and $ScCO_2$ as the solvent, respectively. The properties of the obtained micelles are characterized and discussed in detail.

2. Materials and methods

2.1. Materials

Vinyl acetate with a purity of 97% was purchased from Sinopharm Chemical Reagent Co. Ltd., China and used before passing through an alumina column to remove inhibitor. Potassium ethyl xanthogenate and poly(ethylene glycol) methyl ether methacrylate (PEGMA, Mn = 450) were purchased from Sigma-Aldrich and used as received. Paclitaxel with a purity of 99.8% was obtained from Jiangsu Yew Pharmaceutical Co. Ltd., China. Other reagents were commercially available and used as received.

2.2. Synthesis of VAc macroRAFT agent

The chain transfer agent, (S)-2-(Ethyl propionate)-(O-ethyl xanthate) is synthesized according to reference [51]. As a typical RAFT polymerization, vinyl acetate (8.600 g, 100 mmol), AIBN (0.033 g, 0.2 mmol) and the chain transfer agent, (S)-2-(ethyl propionate)-(O-ethyl xanthate) (0.222 g, 1 mmol) are added to a round-bottom flask with 20 mL ethanol as solvent. After the mixture is repeatedly degassed-and filled with dry nitrogen three times, the reaction is continued at 65 °C for 4 h and stopped by cooling the mixture using an ice bath. After that, the solvent is removed by a rotary evaporator. Then, the residual polymerization mixture is dissolved in tetrahydrofuran and precipitated from hexanes (200 mL). The product is purified by repeated dissolution in tetrahydrofuran, precipitation from hexane twice and finally drying under vacuum at room temperature.

2.3. Synthesis of poly(vinyl acetate)-b-poly(ethylene glycol) methyl ether methacrylate

VAc macroRAFT agent (0.131 g, Mn = 2120) and AIBN (0.003 g) are mixed with 7 mL 1,4-dioxane as solvent in a Schlenk tube, followed by adding poly(ethylene glycol) methyl ether methacrylate (PEGMA) (2.729 g, Mn = 450) as hydrophilic monomer. The mixture is reacted at 70 °C under nitrogen atmosphere for 24 h. Then the solution is cooled using an ice bath to stop the reaction. After that, the solvent is removed