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Multifunctional block copolymer nanocarriers for co-delivery of silver nanoparticles and curcumin: Synthesis and enhanced efficacy against tumor cells

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ABSTRACT

Functional multilayer polymeric micelles were obtained by self-assembly of a poly(ethylene oxide)-*b*-poly(*n*-butyl acrylate)-*b*-poly(acrylic acid) (PEO_{113}-*b*-$PnBA_{235}$-*b*-PAA_{14}) triblock terpolymer and exploited as template for the synthesis of silver nanoparticles and loading of anti-cancer agents. The terpolymer was synthesized by atom transfer radical polymerization of *n*-butyl acrylate and *tert*-butyl acrylate (tBA), initiated by a PEO-based macroinitiator. Then, PtBA blocks were converted into PAA by selective hydrolysis. PEO_{113}-*b*-$PnBA_{235}$-*b*-PAA_{14} terpolymer formed nano-sized spherical micelles in the concentration range from 1 to 10 mg mL^{-1} as confirmed by dynamic light scattering (DLS) and transmission electron microscopy (TEM). The presence of PAA chains in the middle micellar layer allowed loading of silver ions and subsequent UV-induced synthesis of silver nanoparticles within the micelles. After that, the anti-cancer drug curcumin was loaded in the hydrophobic PnBA micellar cores. The effect of combination of two anti-cancer agents, spontaneously released from the micelles, on the vitality of acute myeloid leukemia (HL-60), its multidrug-resistant subline HL-60/DOX and human urinary bladder carcinoma (EJ) cells was assessed. The *in vitro* experiments revealed enhanced efficacy in regard to the cytotoxic activity of silver nanoparticles and curcumin.

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1. Introduction

Polymeric micelles, defined as core-shell nanoparticles formed via self-assembly of amphiphilic block copolymers, have been extensively studied as convenient carriers of biologically active substances for a variety of medical applications [1]. They can be designed to possess a set of favorable properties including biocompatibility, longevity, high stability *in vitro* and *in vivo*, capacity to effectively solubilize poorly soluble drugs, controlled release profile of the drug, and ability to accumulate in the target zone based on the enhanced permeability and retention effect [2,3]. In particular, micellar nanocarriers have gained considerable interest in recent years for their ability to incorporate a number of anticancer drugs employed in

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cancer therapy [4]. There are examples of where different amphiphilic copolymer micelles have been used in clinical and pre-clinical treatment of tumors. Kim et al. exploited poly(ethylene glycol)-*b*-poly(D,L-lactide) (PEG-PDLL) micelles for delivery of paclitaxel in patients with advanced malignancies [5]. The poorly water soluble paclitaxel was physically entrapped in the hydrophobic PDLL core, while the hydrated PEG shell provided high *in vivo* stability of the system. Enhanced anti-tumor activity of doxorubicin (DOX) incorporated into micelles based on two nonionic poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) (PEO-*b*-PPO-*b*-PEO) copolymers, Pluronic L61 and Pluronic F127, was observed on several patients with advanced solid tumors (Ewing's sarcoma, carcinosarcoma, and oesophageal adenocarcinoma) [6]. A phase I clinical trial of a cisplatin-incorporated micellar formulation (PEG-*b*-poly(glutamic acid)) in patients with advanced solid tumors was also carried out [7]. The delayed and sustained release of cisplatin after *in vivo* administration contributed to the lower toxicity of the micellar formulation than pure cisplatin.

Despite the encouraging results obtained with the abovementioned block copolymer micellar formulations, presently, the efforts are focused on the development of systems with more diverse functions required for better performance at cellular and sub-cellular levels. Thus, the research on micellar carriers based on ABC triblock terpolymers or mixtures of AB and CD diblock copolymers have received increasing attention [8]. Compared to AB-type copolymer micelles, the ABC-type systems are worth investigating because the micelles then combine the intrinsic properties of three components rather than two, which increases their functionality and versatility. Usually, the self-assembly of multiblock terpolymers [9] or co-assembly of two different diblock copolymers [10,11] leads to the formation of multilayer micelles. Such micelles are promising candidates for the so called multi-drug therapy, referred to us as a simultaneous or sequential administration of two or more active substances with different mechanisms of action [12]. This strategy aims to suppress the drug resistance through different action mechanisms, minimize the amount of each drug and reduce the toxic side effects. For instance, Shi et al. reported that the co-delivery of the anticancer drug docetaxel and autophagy inhibitor chloroquine, encapsulated in complex micelles based on poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ε-caprolactone) and d-α-tocopheryl poly (ethylene glycol), enhanced the therapeutic effects against MCF-7 and MCF-7/ADR cells than either free drug or individually drug-loaded micelles [13]. The co-loading siRNA and doxorubicin in a multifunctional hierarchical nano-assembled carriers based on poly(ethylene glycol)-*b*-poly(glutamic acid) and poly(ε-caprolactone)-*b*-poly(ethylene imine) block copolymers, enabled simultaneously delivering siRNA and drug into the same cancer cells, yielding synergistic effect of RNA interference and chemotherapy in cancer [14].

Silver nanoparticles (AgNPs), in addition to their strong antimicrobial activity, have exhibited an anti-cancer effect [15]. It is suggested that AgNPs-mediated cytotoxicity originates primarily from the toxicity of silver nanoparticles itself, the release of silver ions and the generation of reactive oxygen species [16]. However, the use of pure AgNPs for cancer treatment is limited so far, because they may also damage the surrounding healthy tissue. Nevertheless, the surface modification with polymers is a promising way to decrease the apparent toxicity of AgNPs and increase their colloidal stability in biological media [17,18]. Moreover, hybrid core-shell particles, obtained by coating of AgNPs with a cross-linked poly(L-lysine) shell containing DOX, exhibited good biocompatibility before DOX release and induced cancer cell death upon release of the drug [19]. In spite of multiple advantages of such anti-cancer system, however, the possible synergism of AgNPs and DOX was not described. Recently, Locatelli et al. reported that the combination of alisertib and silver nanoparticles, incorporated in polymeric nanoparticles, caused tumor reduction in tumor-bearing mice [20]. It was concluded that the coexistence of two anti-cancer agents promoted synergistic effect. Since this phenomenon could have some advantages in cancer therapy, development and investigation of novel systems for multi-drug therapy based on AgNPs is expected to bring new alternatives to the therapeutics field.

The present work aims at evaluating the effect of combination of two anti-cancer agents, AgNPs and curcumin, loaded in PEO-*b*-PnBA-*b*-PAA triblock terpolymer micelles, on the vitality of acute myeloid leukemia (HL-60), its multidrug-resistant subline HL-60/DOX and human urinary bladder carcinoma (EJ) cells. To the best of our knowledge, this is the first study exploiting the capacity of functional multilayer polymeric micelles to act together as templates for synthesis of AgNPs and drug carriers. The system developed exhibited significantly higher cytotoxic effect on all types of cells studied than the individually drug or AgNPs-loaded micelles.

2. Materials and methods

2.1. Materials

Methoxy poly(ethylene glycol) (CH_3—PEO_{113}—OH, MW 5000, Fluka) was purified by precipitation in cold methanol (−40 °C), filtered, and dried under a vacuum at 40 °C overnight. *n*-Butyl acrylate and *tert*-butyl acrylate (supplied by BASF AG) were stirred overnight on calcium hydride (Merck, 95%) with Irganox 1010 inhibitor (CIBA Geigy) and distilled under a vacuum. CuBr (Aldrich, 98%) was stirred overnight in glacial acetic acid, filtered, and rinsed successively by acetic acid, ethanol, and ether to remove traces of $CuBr_2$. 2-Bromoisobutyryl bromide (Aldrich, 98%), triethylamine (TEA, Fluka, 99.5%), 1,1,4,7,10,10-hexamethyl triethylenetetraamine (HMTETA, Aldrich, 98%), N,N,N′,N′,N″-pentamethyldiethylenetriamine (PMDETA, Aldrich, 99%), ethyl methyl ketone (Merck, 99.8%), acetone (Sigma-Aldrich, 99.8%), tetrahydrofuran (THF, Sigma-Aldrich, 99.8%), methanol (Merck, 99.8%), 1,4-dioxane (Sigma-Aldrich, 99.5%), SiO_2 (63–200 μm, Merck), trifluoroacetic acid (Sigma-Aldrich, 99%), (4-benzoylbenzyl)trimethylammonium chloride (Sigma-Aldrich, 95%) and $AgNO_3$

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