SINGLE AND MULTIDRUG FILOMICELLES AS ANTICANCER DRUG DELIVERY SYSTEM

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Introduction

Polymeric micelles, in particular those prepared from polylactide-poly(ethylene glycol) (PLA-PEG) block copolymers, have been extensively studied as drug carrier because of many advantageous properties including bioresorbability, controlled drug release, ability to avoid reticuloendothelial system (RES) uptake, tumor targeting by enhanced permeability and retention (EPR) effect, etc [1]. Flexible worm-like "filomicelles" can be up to 8 μm long and in analogy to filoviruses – possess a long circulation time up to a week in the bloodstream because their unique visco-elastic properties and hydrodynamics could reduce interactions with the blood vessel walls [2]. The aim of this study was to evaluate the potential of bioresorbable PLA-PEG filomicelles for prolonged delivery of paclitaxel. Slow release of cytostatic drugs is very advantageous due to prolonged exposure of tumor cells to cytostatic over multiple cell cycles. This study aimed also to analyze the influence of drug-drug and drug-polymer interactions on drug loading and release properties of multidrug micelles. Simultaneous administration of two or more pharmacologically active agents with different mechanisms of action is recognized as more efficient compared to conventional therapy based on a single therapeutic agent [3]. Drug combination in anticancer treatment primarily aims to overcome tumor heterogeneity and multidrug resistance (MDR), and to achieve additive or more desirable synergistic anticancer efficacy without overlapping toxicity [3,4].

Materials and Methods

Micelles were prepared by co-solvent/evaporation method. Single drug loaded micelles were obtained with paclitaxel (Ptx) and multidrug micelles with mixture of Ptx and 17-AAG or Ptx, 17-AAG and rapamycine (Rap). The morphology of micelles was observed by TEM and AFM. NMR was applied for compositional and structural analyses of micelles in a solvated state. FTIR was used to evaluate interactions between particular drugs and between drugs and copolymer. The *in vitro* release of drugs from micelles was realized by dialysis method. *In vitro* drug release and degradation study was conducted at 37°C in phosphate buffered saline (PBS) at three different pH values (pH 7.4, pH 5.5 and pH 3.0). Quantitative assessment of paclitaxel was conducted by means HPLC.

Results and Discussion

The study revealed that using PLA-PEG copolymers with the same gross composition but with different PLA configurations results in formation of micelles with different morphologies. In fact, spherical micelles were obtained for poly(DL-lactide)-poly(ethylene glycol) (PDLLA-PEG), and filomicelles for poly(L-lactide)-poly(ethylene glycol) (PLLA-PEG). Therefore, polymer chain stereoregularity seems to strongly affect the micelle's morphology.

The release of paclitaxel from one drug loaded micelles is strongly dependent on the degradation of micelles. A biphasic drug release profile is observed for both PLLA-PEG and PDLLA-PEG micelles: slow release in the first phase and faster release in the second phase. Degradation is faster at acidic pH than at pH 7.4, and PLLA-PEG filomicelles degrade less rapidly than PDLLA-PEG spherical micelles, leading to various rates of drug release.

Ptx and 17-AAG present similar loading efficiencies in double loaded micelles probably due to interactions of drugs with each other and also with the copolymer. In contrast, unequal drug loading properties are observed for triple loaded micelles. Rapamycin shows very weak interactions with the copolymer, and displays the lowest loading efficiency. For the three drugs similar release profiles are observed: a strong burst followed by slower release. Nevertheless, Ptx release from micelles is significantly slower as compared to 17-AAG and Rap, probably due to interactions of NH and OH groups of Ptx with the carbonyl group of PLA.

Conclusions

Slow and sustained release of Ptx from filomicelles was revealed and correlation of this process with degradation. In fact, using long PLLA block provides slow degradation and thus leads to slow drug release from filomicelles. Faster degradation of PDLLA block leads to faster drug release from spherical micelles. The study reveals also the crucial importance of intermolecular interactions for drug loading and release properties.

Ptx-loaded micelles and multidrug micelles exhibit advantageous effect of prolonged drug release and cytotoxic activity against Caco-2 human colorectal adenocarcinoma cell line, which makes them a promising solution for drug delivery to solid tumors.

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