



FUNCTIONAL POLYLACTIDE MICELLES FOR TARGETED DELIVERY OF PACLITAXEL

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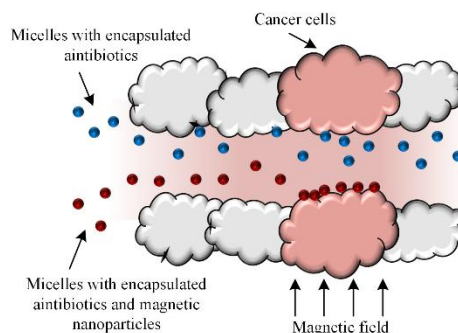
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Abstract

The aim of this work was to study the potential of magnetosensitive polylactide micelles (PLMs) for creating nanocontainers for targeted delivery of hydrophobic paclitaxel. After solubilization of paclitaxel and magnetic particles, the PLMs retain a size acceptable for use as a dosage form and demonstrate magnetosensitivity and colloid stability. The resulting nanosystems remain biodegradable. Thus, owing to the ability to include maghemite nanoparticles and hydrophobic drugs simultaneously, PLMs are promising for creating magnetically sensitive systems for targeted drug delivery.

Key words: poly(D,L-lactide)-b-(ethylene glycol) micelles, maghemite, paclitaxel, nanocontainer, targeted delivery.



Introduction

Minimization of non-specific side effects and enhancement of therapeutic activity of drugs by their targeted delivery to the tumor tissue are important problems of modern medicine [1]. One method to improve the efficiency of delivery of hydrophobic drugs to cancer cells is the use of nanocontainers such as micelles, which are typically composed of amphiphilic diblock copolymers [2, 3].

Polyesters are often used as a hydrophobic block, for example, polylactide (PLA), biodegradability and availability of which make it promising for use in medicine. The copolymerization of a lactide with hydrophilic poly(ethylene glycol) (PEG) affords an amphiphilic copolymer which is capable of self-organizing in an aqueous solution into micelles with a polyester core and a PEG shell [4, 5].

Since, as was shown earlier, such micelles are not suitable for passive delivery due to their small size (about 30 nm), it was proposed to modify them to enable active delivery [6]. Micelles can be modified, for example, by including magnetic nanoparticles, which will make the nanocontainers magnetically controllable. For example, maghemite ($\gamma\text{-Fe}_2\text{O}_3$) is used for this purpose. It has high residual magnetization and is used for biomedical purposes. Earlier the possibility of incorporating a hydrophobic antibiotic paclitaxel (PTX) and maghemite nanoparticles separately into PLMs was demonstrated [6]. It should be noted that PTX/PLMs and $\gamma\text{-Fe}_2\text{O}_3$ /PLMs were about 30 nm in size and therefore are suitable as containers for targeted drug delivery. It was shown that magnetically sensitive micelles can concentrate in the region of an applied magnetic field, but the ternary system containing both $\gamma\text{-Fe}_2\text{O}_3$ and an antibiotic still requires a comprehensive study.

Thus, the aim of this work was to study the possibility of

creating a nanocontainer based on PLA-PEG micelles with $\gamma\text{-Fe}_2\text{O}_3$ for targeted delivery of a hydrophobic antibiotic. In this communication, the magnetosensitivity of micelles containing PTX and $\gamma\text{-Fe}_2\text{O}_3$ ($\gamma\text{-Fe}_2\text{O}_3$ /PTX/PLMs), as well as the stability of such systems over time and the susceptibility of the loaded micelles to enzymatic hydrolysis are demonstrated.

Results and discussion

An aqueous solution of $\gamma\text{-Fe}_2\text{O}_3$ /PTX/PLMs was obtained by the film hydration and dispersion technique. The hydrodynamic diameter of the ternary micelles was found to be ~30 nm. Thus, the incorporation of both the antibiotic and magnetic particles did not significantly change the size of PLMs. The colloid stability of $\gamma\text{-Fe}_2\text{O}_3$ /PTX/PLMs was monitored for 24 h. The suspension was stable and did not undergo phase separation at least for 3 h. Then the slow precipitation occurred. However, the vigorous resuspending allowed for obtaining a stable suspension again. The application of a magnetic field to the freshly resuspended system resulted in distinct phase separation with concentration of micelles near the magnet (Fig. 1). After 30 min

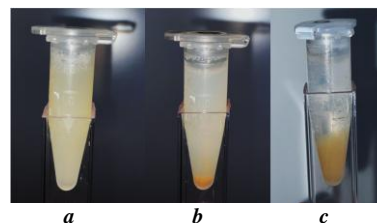


Figure 1. Micellar solution of $\gamma\text{-Fe}_2\text{O}_3$ /PTX/PLMs after ultrasonic dispersion (a), after 10 min of holding on the magnet (b), and after 20 min of holding above the neodymium magnet (c). The internal magnetic field was 160 ± 10 mT.

of the magnetic field induced separation, the supernatant was analyzed by light-scattering. No particles were detected in the supernatant. This reflects the modification of PLMs with γ -Fe₂O₃ and their resulting magnetic sensitivity.

In addition to the cooperative ultrasonic dispersion method, the PLM system with γ -Fe₂O₃ was obtained by mixing the pre-formed PLM and maghemite nanoparticles. In this case, in addition to the diameter of micelles, the individual maghemite nanoparticles subject to aggregation were registered in the system. Thus, it can be assumed that the method of cooperative ultrasonic dispersion affords colloidally stable maghemite nanoparticles encapsulated in PLMs. A plot of the relative intensity vs. the micelle diameter as well as the description of the system with the incorporated nanoparticles can be found in the Electronic supplementary information (ESI).

While biodegradable PLMs are known to withstand enzymatic hydrolysis for a certain time period that allows them to deliver a bioactive cargo prior to decomposition, the incorporation of both γ -Fe₂O₃ and PTX in the PLA core of micelles could violate the structure of the core and result in fast enzymatic hydrolysis. The addition of a PLA-specific enzyme, pancreatic lipase, was used to investigate the resistance of the ternary PLMs to hydrolysis. The micelles 30 nm in diameter were observed in a suspension even in 1 h after the enzyme addition. Hence, the micelles showed stability to hydrolysis for a time sufficient to be used in targeted delivery. On the other hand, after 24 h of incubation, the individual size of the micelles ceased to be recorded due to the enzymatic hydrolysis, demonstrating suitable biodegradation of the nanocontainer.

Experimental section

Polymer: poly(D,L-lactide)-b-(ethylene glycol methyl ether) diblock copolymer (PLA-PEG) with PEG M_n of 2000 and PLA M_n of 2000 (Sigma-Aldrich, USA) was used as received.

Chemicals: tetrahydrofuran (THF), Mohr's salt (Fe(NH₄)₂SO₄·5H₂O), sodium hypophosphite monohydrate, sodium hydroxide, sodium acetate, and trimethoxyaminomethane (Tris) from Reakhim (Russia), β -carboxymethyl cyclodextrin (β -CD), sulfosalicylic acid, and PTX from Sigma-Aldrich (USA) were used as received. Bidistilled water (deionized water) was used in all experiments. To hydrolyze the ester bonds in PLMs, an enzyme specific to PLA, pancreatic lipase, was used.

The hydrodynamic diameters of γ -Fe₂O₃/PTX/PLMs were determined in a thermostatic cell by DLS at a fixed scattering angle (90°) with a Brookhaven Zeta Plus instrument.

The magnetic flux density was measured with a WT10A Teslammeter (Weite Magnetic Technology, PRC).

The micelles based on the copolymer of lactide and ethylene glycol (PLMs) with encapsulated PTX and magnetic nanoparticles (γ -Fe₂O₃/PTX/PLMs) were synthesized using the method of ultrasonic dispersion of the polymer film in water described elsewhere [4]. A 20 mg sample of the copolymer was placed in a round-bottom flask and dissolved in 2 mL of THF. The solution of PTX and a weighed portion of maghemite were added to the PLA-PEG solution in THF prior to the evaporation of the solvent. Then THF was removed on a rotary evaporator, and the resulting film was dispersed in 2 mL of water. The

suspension was exposed to ultrasonication for 10 min with constant water cooling. A more detailed synthesis of the maghemite micelles and nanoparticles is presented in the ESI.

Conclusions

The ternary systems based on polylactide micelles with the incorporated antibiotic and magnetic nanoparticles were shown to have high magnetic sensitivity and resistance to the phase separation. At the same time, inclusion of both components (PTX and γ -Fe₂O₃) in the composition of PLA micelles resulted in the formation of particles that are resistant to enzymatic hydrolysis sufficient for targeted delivery, but then undergo enzymatic decomposition, which will facilitate the release of the antibiotic.

Hence, owing to the ability to include both maghemite nanoparticles and hydrophobic drugs simultaneously, the polylactide micelles are a promising object of research for creating magnetically sensitive systems for the targeted drug delivery.

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Electronic supplementary information

Electronic supplementary information (ESI) available online: PLA-PEG and PTX structures, relative intensity distribution, detailed experimental procedures. For ESI, see DOI: 10.32931/io2524a.

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