Prodrug Forming High Drug Loading Multifunctional Nanocapsules

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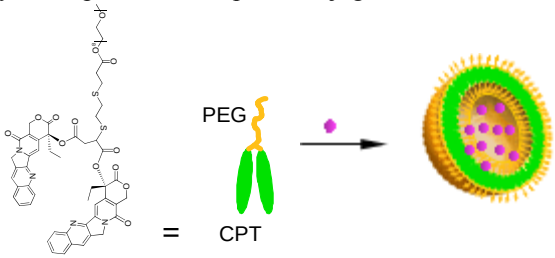
Statement of Purpose: Nanosized drug carriers have been extensively explored in drug delivery for cancer chemotherapy. They are typically inert and their only role is to make the vehicles. However, they are major components in drug-delivery systems, causing low drug loading capacity. In the nanoparticles or liposomes, the drug content is generally not greater than 10%.[1, 2] In polymer–drug conjugates, the drug content is generally only a few percent to keep the conjugates water-soluble.[3-5]



Scheme 1. Amphiphilic camptothecin (CPT) prodrug (PEG-DiCPT) and its self-assembly into nanocapsules to load other drugs (●)

Herein, we demonstrate a concept of a phospholipid-mimicking amphiphilic "prodrug", consisting of two CPT drug molecules and a short PEG chain (PEG-DiCPT) (Scheme 1). CPT is extremely hydrophobic and was thus used as the hydrophobic part. A very short nonionic PEG chain with only eight repeating units was selected as the water-soluble part to maximize the drug loading. Ester bonds were used as the linkers because they can easily be hydrolyzed by esterase. This amphiphilic phospholipid-like molecule formed liposome-like nanocapsules having two roles: As a nanocarrier of CPT, it achieved a loading of 58.5 wt% without premature drug release; As a nanocarrier it can be loaded with other anticancer drugs such as doxorubicin (DOX) for combination therapy.

Results

PEG-DiCPT formed nanosized liposome-like nanocapsules as observed by TEM(Fig. 1a). The size was 132 nm. The CPT content was 58.5 wt%, as calculated from the structure in Scheme 1. PEG-DiCPT hydrolyzed and thus slowly released CPT without the common burst release. However, in the presence of esterase, which is abundant in cytoplasm, PEG-DiCPT quickly hydrolyzed and released CPT (Fig. 1b).

The ability of the PEG-DiCPT nanocapsules to act as carriers for other drugs was demonstrated by loading and controlled releasing water-soluble doxorubicin-hydrogen chloride salt (DOX·HCl). DOX·HCl was loaded into the nanocapsules using a dialysis method with an efficiency of 85% and a content of 18.5%. The loaded DOX·HCl was released in a controlled manner from the nanocapsules (Figure 1c).

PEG-DiCPT showed similar cytotoxicity to both SKOV-3 and MCF-7 cancer cells when compared with free CPT (Fig. 2). PEG-DiCPT/DOX·HCl showed a higher cytotoxicity than PEG-DiCPT, free CPT or free DOX to MCF-7 cells and SKOV-3 cells.

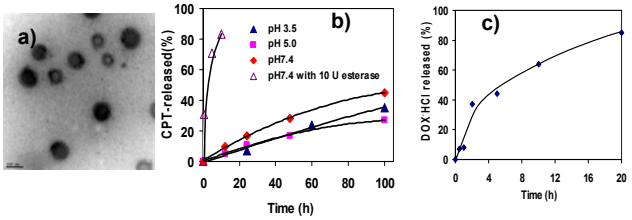


Figure 1. The PEG-DiCPT-formed vesicles observed TEM) (scale bar of 100 nm (a); the CPT-release kinetics from the vesicles (b); the DOX-release in PBS at 37 °C from the vesicles loaded with 18.5% DOX·HCl (c).

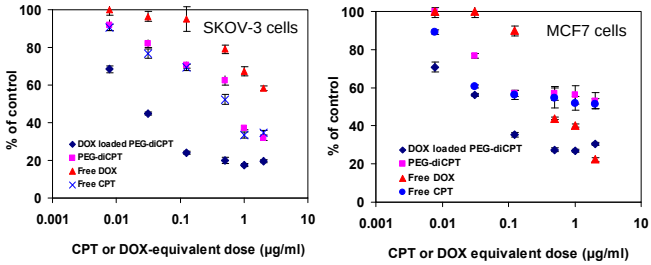


Figure 2. In vitro cytotoxicity of CPT, PEG-DiCPT, DOX·HCl, and PEG-DiCPT/DOX·HCl to SKOV-3 ovarian cancer cells and MCF-7 breast cancer cells determined by MTT assay. Cells were cultured with the treatments for 24 h followed by 24 h postculture.

In conclusion, we demonstrated a new concept employing the drug molecules themselves as components of nanocarriers to substantially increase the drug loading content, minimize the use of inactive materials, and suppress the premature drug burst release.

Acknowledgements. We thank the National Science Fund for Distinguished Young Scholars (50888001) and the National Basic Research Program (973 Program) (2009CB526403) of China, and the National Science Foundation of USA (DMR-0705298) for their financial support.

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