



Delivery of doxorubicin and paclitaxel from double-layered microparticles: The effects of layer thickness and dual-drug vs. single-drug loading

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ABSTRACT

Double-layered microparticles composed of poly(D,L-lactic-co-glycolic acid, 50:50) (PLGA) and poly(L-lactic acid) (PLLA) were loaded with doxorubicin HCl (DOX) and paclitaxel (PCTX) through a solvent evaporation technique. DOX was localized in the PLGA shell, while PCTX was localized in the PLLA core. The aim of this study was to investigate how altering layer thickness of dual-drug, double-layered microparticles can influence drug release kinetics and their antitumor capabilities, and against single-drug microparticles. PCTX-loaded double-layered microparticles with denser shells retarded the initial release of PCTX, as compared with dual-drug-loaded microparticles. The DOX release from both DOX-loaded and dual-drug-loaded microparticles were observed to be similar with an initial burst. Through specific tailoring of layer thicknesses, a suppressed initial burst of DOX and a sustained co-delivery of two drugs can be achieved over 2 months. Viability studies using spheroids of MCF-7 cells showed that controlled co-delivery of PCTX and DOX from dual-drug-loaded double-layered microparticles were better in reducing spheroid growth rate. This study provides mechanistic insights into how by tuning the layer thickness of double-layered microparticles the release kinetics of two drugs can be controlled, and how co-delivery can potentially achieve better anticancer effects.

Statement of Significance

While the release of multiple drugs has been reported to achieve successful apoptosis and minimize drug resistance, most conventional particulate systems can only deliver a single drug at a time. Recently, although a number of formulations (e.g. micellar nanoparticles, liposomes) have been successful in delivering two or more anticancer agents, sustained co-delivery of these agents remains inadequate due to the complex agent loading processes and rapid release of hydrophilic agents. Therefore, the present work reports the multilayered particulate system that simultaneously hosts different drugs, while being able to tune their individual release over months. We believe that our findings would be of interest to the readers of Acta Biomaterialia because the proposed system could open a new avenue on how two drugs can be released, through rate-controlling carriers, for combination chemotherapy.

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1. Introduction

Chemotherapy is an integral aspect of cancer treatment, both in the early as well as in the advanced stages. First-line chemotherapy necessitates the use of different drugs, either concurrently or

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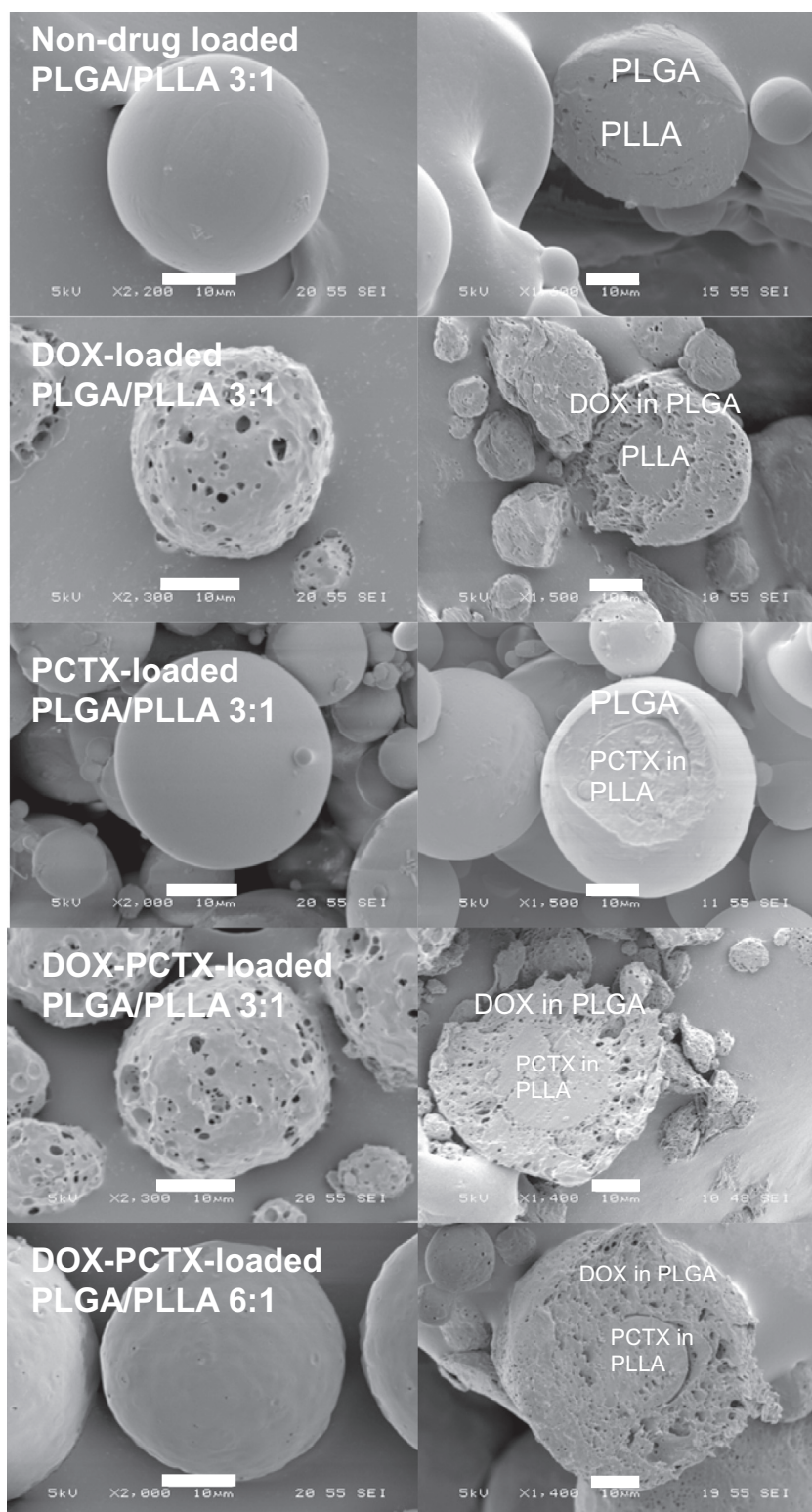


Fig. 1. Internal and external structure of double-layered PLGA/PLLA microparticles. (Row 1: non-drug loaded PLGA/PLLA 3:1, Row 2: DOX-loaded PLGA/PLLA 3:1, Row 3: PCTX-loaded PLGA/PLLA 3:1, Row 4: DOX-PCTX-loaded PLGA/PLLA 3:1, Row 5: DOX-PCTX-loaded PLGA/PLLA 6:1). Scale bar = 10 μm.

sequentially, with regimens lasting for as long as 3–6 months. However, such a treatment regimen would often demand high parenteral dosage and this is frequently associated with systemic toxicity [1,2].

Doxorubicin hydrochloride (DOX) and paclitaxel (PCTX) are two of the most widely used drugs for cancer chemotherapy [3,4]. At

present, few drug delivery systems for cancer therapy using these drugs are commercially available. Those commercially available include Doxil®, Caelyx® and Myocet® – DOX-loaded liposomes. However, issues of drug leakage and aggregation, which can affect therapeutic efficacy, and difficulties with sterilization have not been resolved. The phospholipids are thermo-labile and thus

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