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Pluronic-based functional polymeric mixed micelles for co-delivery of doxorubicin and paclitaxel to multidrug resistant tumor

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ABSTRACT

Although doxorubicin (DOX) and paclitaxel (PTX) are widely used in clinic as chemotherapeutics, both drug substances are found to be glycoprotein P (P-gp) substrates which are liable to develop the multidrug resistance (MDR). Additionally, the use of single chemotherapeutic drug has known limitations such as high toxicity profile due to the relatively high doses and limited regimen of clinical application. To this end, Pluronic P105–DOX conjugate was successfully designed and developed which can be further used as a hydrophobic core to entrap another anti-cancer drug PTX with Pluronic F127 to form the dual drug-loaded mixed micelles (PF–DP) in our study, which would offer great advantages over conventional micelles, including easy fabrication, high loading capacity, and co-delivery of hydrophilic DOX and hydrophobic PTX to achieve synergistic effect of these two drug substances. Results showed that PF–DP possessed a good polydispersity and sustained release profile for both DOX and PTX in vitro. Studies on cellular uptake demonstrated both anti-cancer drugs in PF–DP can effectively accumulate in MDR cancer cells. Furthermore, in vitro cytotoxicity, cell apoptosis and cell cycle arrest studies indicated that PF–DP had better antitumor efficacy in MDR cancer cells compared to those of single-drug loaded micelles. It was also found that PF–DP can suppress the growth of tumor cells more efficiently than single drug formulations at the equivalent drug concentrations, suggesting synergistic effect could be achieved. More importantly, a much stronger antitumor efficacy in MCF-7/ADR tumor-bearing mice was observed in PF–DP group than that of combined administration of free DOX and PTX. Collectively, the dual drug-loaded Pluronic-based functional mixed micelles developed in this study might be a potential nano-drug delivery system for MDR cancer chemotherapy.

1. Introduction

Chemotherapy is far from perfect due to the undesirable side effects, low bioavailability as well as emergence and development of drug resistance. As reported, multidrug resistance could significantly limit the penetration of anticancer drugs into tumor issues, leading to the poor concentration of the anticancer drugs in the tumor and the failure of chemotherapy (Hirsch et al., 2009; Jain, 2012; Minchinton and Tannock, 2006). To overcome these limitations, a variety of effective advanced drug delivery systems have been designed using different types of biocompatible nanomaterials. One promising pharmaceutical strategy is the polymeric nanomicelle system which has been tested in several clinical trials such as doxorubicin-loaded micelles (NK911), paclitaxel-loaded polymeric micelles (NK105), epirubicin-loaded micelles (NC-6300) and platinum drug-loaded polymeric micelles (Batrakova et al., 2005; Cabral and Kataoka, 2014; Kabanov et al., 2002). Polymeric micelles (usually with small particle size less than 100 nm) exhibit many advantages over other drug delivery systems such as targeting ability, long circulation and easy production (Torchilin, 2001). Additionally, the entrapped anticancer drugs will be protected from inactivation in biological media due to the specific core–shell structure of the polymeric micelle system. Collectively, polymeric micelles have been considered to be an excellent nano-drug delivery system for chemotherapy (Deng et al., 2012; Kataoka et al., 2012).

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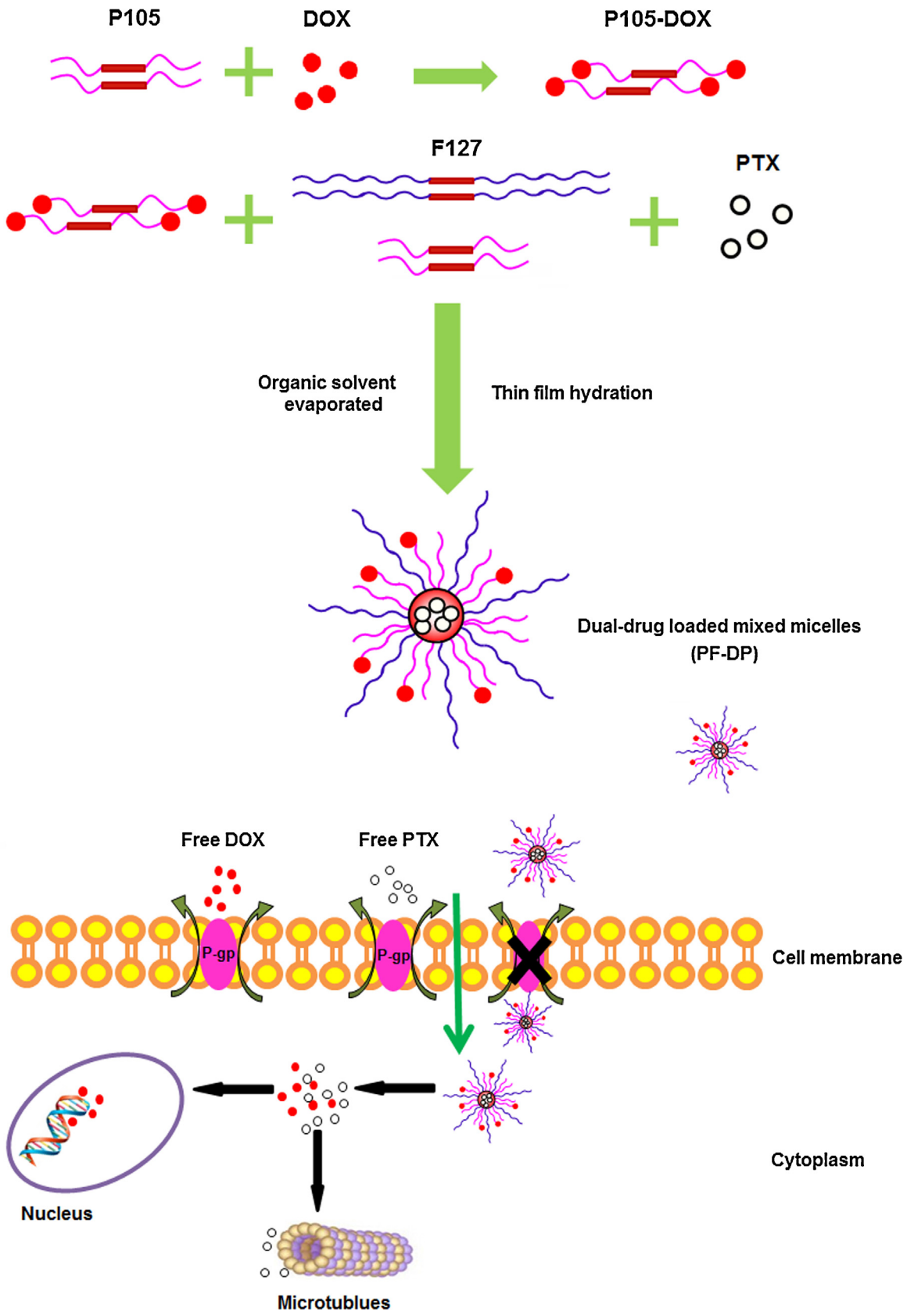

Fig. 1. Schematic illustration of dual drug (DOX and PTX)-loaded mixed micelles in an attempt to achieve the synergistic effect and MDR reversal capacity.