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Polymeric Micelles Based on Block Copolymer α-Tocopherol Succinate-g-Carboxymethyl Chitosan for Tamoxifen Delivery

Authors : Sunil K. Jena, Sanjaya K. Samal, Mahesh Chand, Abhay T. Sangamwar

Abstract : Tamoxifen (TMX) and its analogues are approved as a first line therapy for the treatment of estrogen receptor-positive tumors. However, clinical development of TMX has been hampered by its low bioavailability and severe hepatotoxicity. Herein, we attempt to design a new drug delivery vehicle that could enhance the pharmacokinetic performance of TMX. Initially, high-molecular weight carboxymethyl chitosan was hydrolyzed to low-molecular weight carboxymethyl chitosan (LMW CMC) with hydrogen peroxide under the catalysis of phosphotungstic acid. Amphiphilic block copolymers of LMW CMC were synthesized via amidation reaction between the carboxyl group of α-tocopherol succinate (TS) and an amine group of LMW CMC. These amphiphilic block copolymers were self-assembled to nanosize core-shell-structural micelles in the aqueous medium. The critical micelle concentration (CMC) decreased with the increasing substitution of TS on LMW CMC, which ranged from 1.58 × 10-6 to 7.94 × 10-8 g/mL. Maximum TMX loading up to 8.08 ± 0.98% was achieved with Cmc-TS4.5 (TMX/Cmc-TS4.5 with 1:8 weight ratio). Both blank and TMX-loaded polymeric micelles (TMX-PM) of Cmc-TS4.5 exhibits spherical shape with the particle size below 200 nm. TMX-PM has been found to be stable in the gastrointestinal conditions and released only 44.5% of the total drug content by the first 72 h in simulated gastric fluid (SGF), pH 1.2. However, the presence of pepsin does not significantly increased the TMX release in SGF, pH 1.2, released only about 46.2% by the first 72 h suggesting its inability to cleave the peptide bond. In contrast, the release of TMX from TMX-PM4.5 in SIF, pH 6.8 (without pancreatin) was slow and sustained, released only about 10.43% of the total drug content within the first 30 min and nearly about 12.41% by the first 72 h. The presence of pancreatin in SIF, pH 6.8 led to an improvement in drug release. About 28.09% of incorporated TMX was released in the presence of pancreatin in 72 h. A cytotoxicity study demonstrated that TMX-PM exhibited time-delayed cytotoxicity in human MCF-7 breast cancer cells. Pharmacokinetic studies on Sprague-Dawley rats revealed a remarkable increase in oral bioavailability (1.87-fold) with significant ($p < 0.0001$) enhancement in AUC0-72 h, t1/2 and MRT of TMX-PM4.5 than that of TMX-suspension. Thus, the results suggested that CMC-TS micelles are a promising carrier for TMX delivery.

Keywords : carboxymethyl chitosan, d-α-tocopherol succinate, pharmacokinetic, polymeric micelles, tamoxifen
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