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DHA and pGPMA Dual Modified pH Sensitive Polymeric Micelles for Target Treatment of Liver Cancer

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Abstract

In clinical therapy, the poor prognosis of hepatocellular carcinoma (HCC) is mainly attributed to the failure of chemotherapeutical agents to accumulate in tumor as well as lack of potency of tumor penetration. In this work, we developed actively tumor-targeting micelles with pH-sensitive linker as a novel nanocarrier for HCC therapy. These micelles comprised of biodegradable PEG-pAsp polymers, in which PTX can be covalently conjugated to pAsp via an acid-labile acetal bond to form pH-responsive structures. In vitro drug release studies showed that these structures were stable in physiological condition whereas collapsed once internalized into cells due to the mildly acidic environment in endo/lysosomes, resulting in facilitated intracellular PTX release. In addition, dehydroascorbic acid (DHA) and guanidinopropyl methacrylamide polymers (pGPMA) were decorated on the surface of micelles to achieve specific tumor accumulation and tumor penetration. Cellular uptake and in vivo imaging studies proved that these micelles had remarkable targeting property toward hepatocarcinoma cells and tumor. Enhanced anti-HCC efficacy of the micelles was also confirmed both in vitro and in vivo. Therefore, this micellar system may be a potential platform of chemotherapeutics delivery for HCC therapy.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the second leading cause of cancer related mortality.[1-2] Because incubation period for HCC is very long, most of patients are in the intermediate or advanced stage when first diagnosed. In consideration of the great difficulty for surgical operation, chemotherapy is a significant approach for most of tumor sufferers.[3-4]

Paclitaxel (PTX) is a widely used chemotherapeutic drug against an extensive range of solid tumors. However, it has been extremely limited in clinical applications due to its slightly solubility in water.[5] A common formulation of PTX is Taxol, which comprises of Cremophor EL (polyethoxylated castor oil) and ethanol (1:1; v/v). Although this formulation is able to increase the solubility and bioavailability of paclitaxel (PTX), the relatively large amount of Cremophor EL has been demonstrated to have serious side effects, including severe hypersensitivity reactions, myelosuppression, neurotoxicity, and red blood cells lysis.[6-8]

Nowadays, polymeric micelles have extensively been applied in cancer therapy in the aim of improving solubility and bioavailability of hydrophobic