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Tuning the pharmacokinetics and efficacy of irinotecan (IRI) loaded gelatin nanoparticles through folate conjugation

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ABSTRACT

Gelatin based nanocarriers have major limitation of shorter circulation half-life ($t_{1/2}$). Present study addressed this issue by conjugating gelatin with folate followed by nanoprecipitation in presence of polysorbate 80 to form folate attached gelatin nanoparticles (GNP-F). The folic acid was conjugated with gelatin through the formation of amide linkage with a maximum conjugation yield of ~69%. Cryo-SEM analysis indicated that unconjugated gelatin nanoparticles (GNP) and GNP-F were spherical of nearly identical size of ~200 nm. The irinotecan (IRI)-loading efficiency estimated for IRI-GNP and IRI-GNP-F was 6.6 ± 0.42% and 11.2 ± 0.73% respectively and both formulations showed faster release of IRI at acidic pH (~5) than at physiological pH (~7). Further IRI-GNP-F demonstrated significantly higher cytotoxicity in folate receptor (FR)-positive HeLa cells than the unconjugated IRI-GNP nanoparticles confirming active targeting. Subsequently the antitumor activity of above formulations in FR-positive fibrosarcoma (syngeneic) tumor-bearing mice followed the order of IRI-GNP-F > IRI-GNP > free IRI. The pharmacokinetic evaluation of IRI-GNP and IRI-GNP-F revealed that encapsulation of IRI within GNP without folate improved its plasma maximum concentration (C_{max}). However, folate conjugation of GNP remarkably improved the $t_{1/2}$ of IRI. Taken together, folate as a targeting ligand modulates the pharmacokinetic property of IRI loaded GNP to favor active verses passive targeting.

1. Introduction

The objective of cancer treatment is to achieve maximum therapeutic efficacy of chemotherapeutic drugs with minimum side effects (Sui and Shen, 2011; Herrero and Medarde, 2015). However, it is possible only if chemotherapeutic drugs are selectively delivered within tumor cells. Unfortunately, none of the chemotherapeutic drug available in market is cancer cell specific and this underlines the need of a drug delivery system (Dasari and Tchounwou, 2014; Fujita et al., 2015). Nanotechnology has contributed immensely in the development of drug delivery systems that not only selectively deliver chemotherapeutic drugs to cancer cells but can also improve their solubility as well as biological half-life (Akhter et al., 2013; Din et al., 2017; Iqbal et al., 2018). Initial studies were focused to design nanomaterials which can exploit enhanced permeability and retention (EPR) arising due to leaky vasculatures surrounding tumor tissue to selectively deliver chemotherapeutic drugs into cancer cells. This method of achieving tumor selectively was referred as passive targeting (Greish, 2010; Prabhakar et al., 2013; Golombek et al., 2018). In the last two decades, a considerable progress has been made towards understanding the physiochemical parameters such as shape, surface charge and size of nanomaterials facilitating EPR and this has paved the way for the successful translation of a number of drug delivery system based on passive targeting approach into clinics (Natfji et al., 2017; Das et al., 2019). As of today, around 15 such nano-formulations have been approved by FDA for clinical use (Ventola, 2017). However recent clinical studies have revealed that EPR is a heterogeneous process as tumor microenvironment controlling EPR such as vascular volume, perfusion, permeability, penetration, and retention vary significantly not only from patient to patient but also between tumors of different tissue origins within the same patient (Zhang et al., 2017; Park et al., 2019; Maeda et al., 2009). Further, it is found that rapidly growing and highly

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