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5-Fu inclusion complex capped gold nanoparticles for breast cancer therapy

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ABSTRACT

We have attempted to prolong the circulation time and increase the solubility of 5-Fluorouracil by complexing it with cyclodextrin and then further conjugating onto the gold nanoparticle to form 5Fu ICAu. The ^{1}H NMR and molecular docking studies suggested that 5-Fu was included within the 2HP-β-CD cavity and H-5 proton probably serves as the binding site for stabilization of the inclusion complex. The 5Fu-ICAu showed higher cell inhibition rate when studied on MDA-MB-231 and MCF-7 breast cancer cell lines due to the enhanced permeability and retention (EPR) effect by allowing the selective accumulation of nanoparticles at tumor site. This unique system can serve as a novel nanocarrier for delivery of hydrophobic drugs.

1. Introduction

Oral drug delivery is still considered as the safest route associated with patient convenience, compliance and lower costs than other methods. However, several drugs remain poorly available when administered orally, as they suffer from poor solubility, low permeability, low stability and risk of toxicity, especially in the gut [1,2]. In order to minimize these drawbacks, specific polymeric drug delivery systems have been studied for poorly absorbed drugs like cyclosporin-A [3], 5-Fluorouridine,[4] gemcitabine [5] and insulin [6].

Anticancer drug 5-Fluorouracil (5-Fu) is an analog of uracil and is widely used for the treatment of breast, gastrointestinal tract, pancreas, head, and ovarian cancers. The 5-Fu exerts its anticancer effect through the inhibition of nucleotide synthetic enzyme thymidylate synthase and misincorporation of fluoronucleotides into RNA and DNA [7]. In this way, it can inhibit tumor cell growth by arresting malignant cells in the S phase and forcing them to apoptosis. However, it also exhibits several undesirable side effects such as diarrhea, dehydration, abdominal pain, nausea and stomatitis [8]. A great deal of research has been carried out on site-specific delivery to reduce the systemic side effects of therapy. To prolong the circulation time of 5-Fu and control delivery, researchers have attempted to modify its delivery by the use of liposome vesicles embedded in a chitosan matrix [9]. However, this approach was only suitable for topical applications, similar to Simeonova *et al.* (2003) study, where the use of poly (butyl cyanoacrylate) nanoparticles for topical treatment of skin lesions was demonstrated [10]. In order to improve the cancer-targeting properties of 5-Fu, a novel pH-responsive drug delivery system sensitive to the acidic pH of solid tumours was synthesized by a diafiltration method [11]. Arica *et al.* (2002) reported the encapsulation of 5-Fu within alginate beads [12] whereas Martini *et al.* (1995) designed a 5-Fu delivery system based on poly (ε-caprolactone) nanoparticles for the treatment of breast cancer [13]. On the other hand, Duan *et al.* (2007) reported the preparation of spherical poly (lactic acid-4-hydroxy proline-polyethylene glycol) nanoparticles for the delivery of 5-Fu [14]. Another pH-sensitive TPP cross-linked 5-Fu encapsulated chitosan nanoparticles was demonstrated for tumor localized drug delivery applications [15]. Along with nanoparticles, dendrimers have also been used as a nanocarrier for their high encapsulation efficiency and tumor targeting for delivery of 5-Fu [16]. Recently, 5-Fluorouracil-1-acetic acid was conjugated with β-CD through an ester or amide linkage, for the delivery of 5-Fu against colon-specific therapy [17].

Even though several strategies have been developed for the administration of 5-Fu with increased solubility and therapeutic

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