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Hyaluronic acid embedded cellulose acetate phthlate core/shell nanoparticulate carrier of 5-fluorouracil

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ABSTRACT

Aim of this research was to prepare hyaluronic acid-modified-cellulose acetate phthalate (HAC) core shell nanoparticles (NPs) of 5-fluorouracil (5-FU). HAC copolymer was synthesized and confirmed by fourier transform infrared (FTIR) and nuclear magnetic resonance (NMR) spectroscopy. HAC NPs with 5-FU were prepared using HAC copolymer and compared with 5-FU loaded cellulose acetate phthalate (CAP) NPs. NPs were characterized by atomic force microscopy (AFM), particle size, zeta potential, polydispersity index, entrapment efficiency, in-vitro release, differential scanning calorimetry (DSC) and X-ray diffraction (XRD). HAC NPs were found slower release (97.30% in 48 h) than (99.25% in 8 h) CAP NPs. In cytotoxicity studies, showed great cytotoxic potential of 5-FU loaded HAC NPs in A549, MDA-MD-435 and SK-OV-3 cancer cellline. HAC NPs showing least hemolytic than CAP NPs and 5-FU. Area under curve (AUC), maximum plasma concentration (C_{max}), mean residence time (MRT) and time to reach maximum plasma concentration T_{max}), were observed 4398.1 ± 7.90 μg h/mL, 145.45 ± 2.25 μg/L, 45.74 ± 0.25 h, 72 ± 0.50 h, respectively of HAC NPs and 119.92 ± 1.78 μg h/mL, 46.38 ± 3.42 μg/L, 1.2 ± 0.25 h, 0.5 ± 0.02 h were observed in plain 5-FU solution. In conclusion, HAC NPs is effective deliver carrier of 5-FU for lung cancer.

1. Introduction

After heart and infectious diseases, cancer is currently leading cause of death in the world [1]. Researchers have vigorously searched for proper treatment to eradicate this disease but precisely the treatment was not found to be adequate for the said disease. [2]. While the needs of the effective and safe therapeutics are still desired, the precise and useful visualization of anti-cancer drugs following their administration can play an essential role to formulate effective treatment plans [3].

Ultimate cancer therapeutics is desired for successful cancer management. Over the past few decades conventional treatment options such as chemotherapy and radiation have experienced many advances in cancer treatment with lot of limitations and side effect. Parentally administering potent anticancer bioactive often results intense side effects due to action of the drugs on non target sites. With such nonspecific drug action, the concentration of drug rendered available at the tumor site itself is low on the other hand drug entering into a healthy tissue leads to produce-toxicity and ultimately the effective dose became an ineffective dose. To improve this complexity, researchers have been paying attention on fabrication of tumor-specific drugs or delivery systems that can selectively localize existing agents to the tumor sites. Recent advances in nanotechnology promises further developments in target-specific drug delivery systems [4].

Nanoparticles are excellent tumor-targeting carriers due to their unique inherent property. Almost all tumors have poor lymphatic drainage and fenestrated vasculature, resulting in an enhanced permeability and retention (EPR) effect [5], which allows nanoparticles to accumulate specifically at the tumor site. In addition, nanoparticles will also help to avoid uptake of anticancer bioactive by the reticuloendothelial system [6] and mononuclear phagocytes [7]. Altogether, these results in the property of nanoparticles to circulate for prolonged periods of time, accumulate drugs at the tumor mass because they specifically extravasate through the fenestrated capillaries which allow them to eventually reach the tumor vasculature as guided by the EPR effect [8]. Passive tumor-targeting properties by the EPR effect and intratumoral localisation of nanoparticles can be achieved by conjugation of the particle with tumor-specific recognition of small molecules, such as folic acid [9], peptide [10], antibodies or lectins [11] and glycosaminoglycans [12,13] known as active targeting.

HA occurs naturally in all living organisms and principally a carbohydrate, more specifically a mucopolysaccharides. It con-

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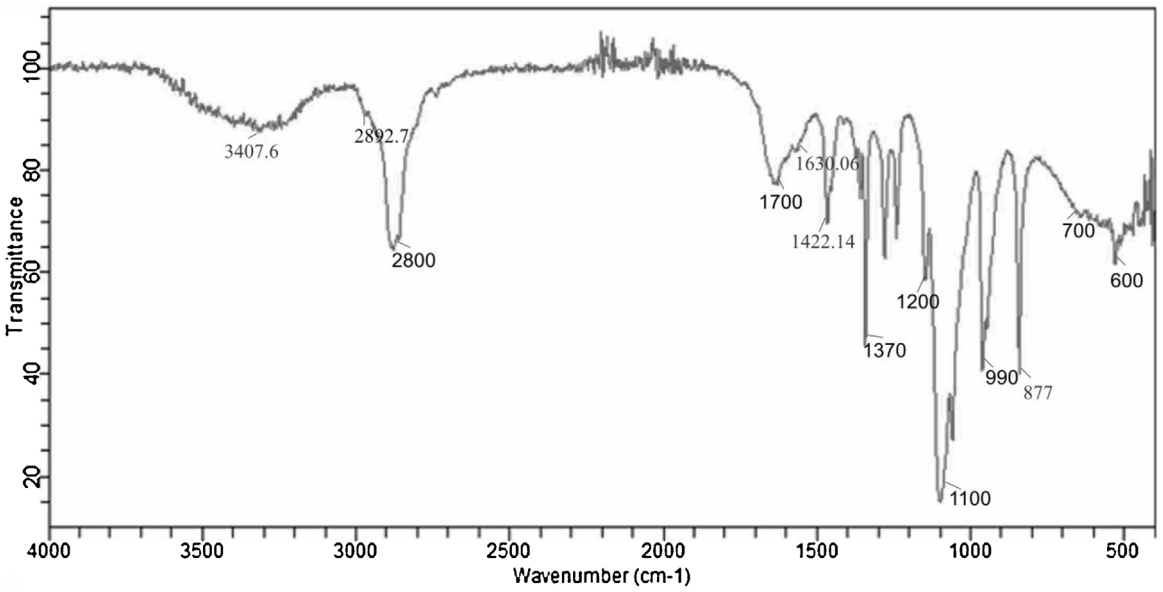

Fig. 1. FTIR spectra of HA–ADH–CAP (HAC) copolymers.

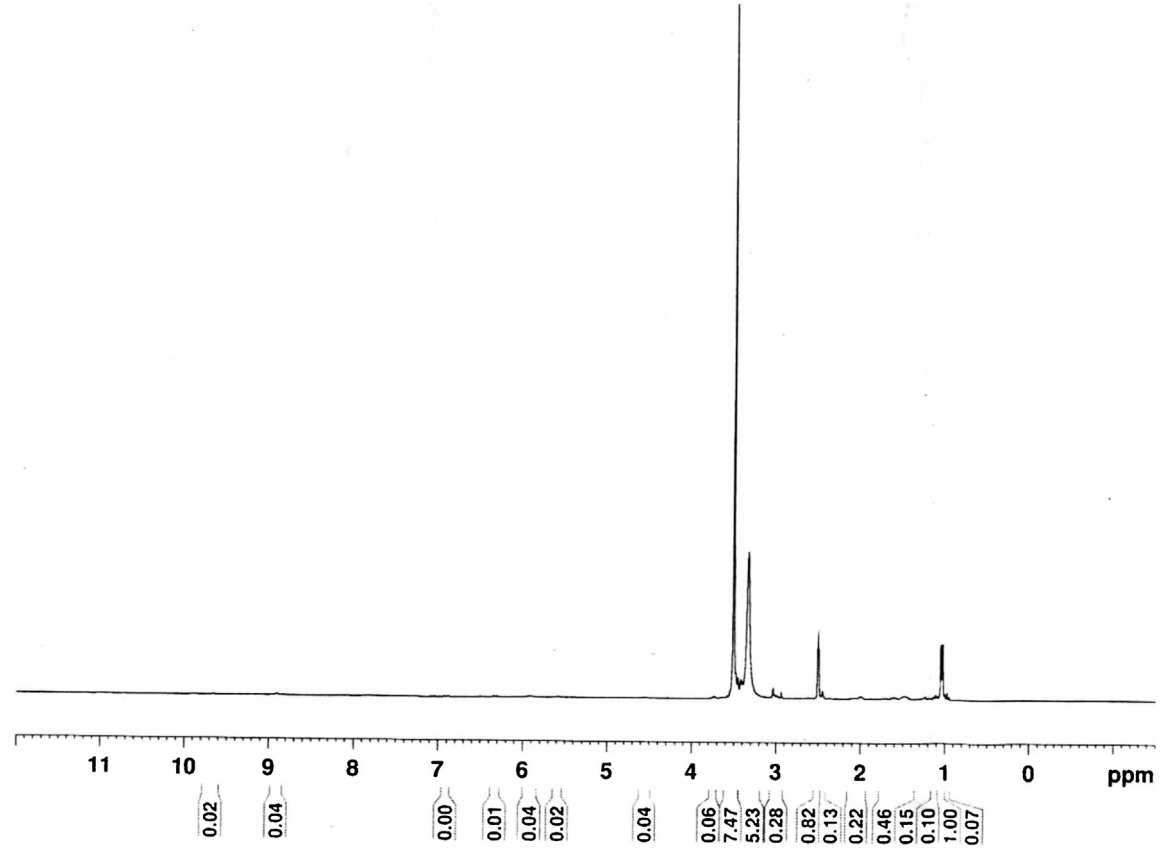

Fig. 2. NMR spectra of HA–ADH–CAP (HAC) copolymers.

tains thousands of carbohydrates sugars molecule. HA consists of a repeating disaccharide structure [→(3)-β-D-GlcNAc-(1 → 4)-β-D-GlcA-(1)→] and it is generally a linear polyanion in nature. HA, is a high molecular weight glycosaminoglycan composed of disaccharide repeats of *N*-acetylglucosamine and glucuronic acid and considered as an extracellular matrix component. HA is conserved throughout all mammals, suggesting that it is a biomolecule of considerable importance [14]. In the human body, HA occurs in the salt form, hyaluronate, and is found in high concentrations in several soft connective tissues, including vitreous humor synovial fluid umbilical cord and skin.

CAP is a cellulose derivative synthesized for common uses in various controlled and sustained drug delivery applications. CAP is white free flowing powder and colorless flakes, it is hygroscopic in