MESOPOROUS AND BIOCOMPATIBLE CHITOSAN/ALGINATE CORE-SHELLED NANOPARTICLES TO CARRYING ACTIVE ENZYMES FOR CANCER THERAPY

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ABSTRACT

In this work, we propose the employment of chitosan/alginate core-shelled mesoporous nanoparticles to serve as enzyme-controlled cancer drug carriers, as shown in Fig. 1. Enzymes are caged and protected inside the nanoparticles for digesting non-toxic pre-drug into cancer drug and then released into tumor cite by diffusion. According to enhanced permeability and retention effect (EPR effect), nanoparticles tend to accumulate in tumor tissue more than normal tissue.[1] The nanoparticles were fabricated by alginate particles electrospraying in corporate with mesoporous chitosan coating.

Introduction

Cancer is the first leading cause of death in developed countries and the second one in developing countries, accounting for around 13% of all deaths in 2008. Conventional cancer therapy, chemotherapy, the agents are distributed non-specifically where they affect both normal and cancerous cells. Nanoparticles drug delivery carriers, by using both passive and active targeting strategies, can enhance the intracellular concentration of drugs in cancer cells while avoiding toxicity in normal cells. In previous researches, nanoparticles drug delivery carriers focus more on directly chemo drug carrying and delivering, however, the leakage of drug during circulation and unwanted organ/tissue targeting/accumulating pose serious side effects on the therapy [2]. Therefore, instead of carrying cancer drug directly, by carrying enzymes for non-toxic pre-drug digestion in demand may solve the aforementioned issues. However, to design an active enzyme carrier needs to consider not only the protection the activity of enzyme, but also the drug releasing efficiency and biodegradability [3]. In this study, alginate-based nanoparticles was employed to carry enzyme for its good biocompatibility and diffusivity. To enhance the protection of the enzyme being attacked from immune system including macrophage and antibodies but not deteriorate the drug diffusion properties too much, chitosan with mesoporous were selected to coating on the alginate particle surface. Most importantly, the fabrication processes designed in this study are both aqueous base with enzyme compatibility.

Experimental

The materials used in this paper are 1wt% alginate dissolved in phosphate buffered saline, 2wt% chitosan dissolved in 1wt% acetic acid aqueous solution and 0.1M calcium chloride aqueous solution. As shown in Fig. 2, the alginate/enzyme nanoparticles were fabricated by electrospraying into calcium chloride solution[4], and then immersed in chitosan solution for chitosan coating by electrostatic attraction [5].

Figure 1:  Schematic of process.
RESULTS AND DISCUSSION

Experiment results illustrated the detail structures of the chitosan/alginate core-shell nanoparticles, and characterizing the permeable molecule size and efficiency. As shown in Fig. 3, the SEM and TEM images illustrate the structures of the nanoparticles with sizes between 200 and 400 nm as well as thickness of the chitosan layer of 7 nm on 300 nm nanoparticle and 10 nm on 200 nm nanoparticle for 30 and 60 minutes immersion time, respectively. The relationship between the particle size and alginate flow rate (80–250 µl/hr) is shown in Fig. 4. To characterize the alginate/chitosan nanoparticle’s permeable molecule size, we scaled up the particle size to micron scale (50–100 µm) and employed IgG (~5 nm in diameter with fluorescence dye conjugated) and R6G (~0.4 nm in diameter) for diffusion testing. As shown in Fig. 5, the optical microscopy, fluorescence microscopy, and the confocal microscopy images show the results of the particles immersion in R6G and IgG for 5 minutes and 1 hr, respectively, demonstrating the mesopores on chitosan shell can block out IgG while allow R6G rapidly diffusing in, capable for enzyme carriage/protection and drug intaking/releasing.
Figure 5: The images show R6G and IgG with (a)(d)OM, (b)(e)fluorescence microscope and (c)(f)confocal microscope respectively.

CONCLUSION

The confocal microscopy results demonstrate alginate/chitosan mesoporous nanoparticles fabricated in this study have ability to encapsulate enzyme and let drug diffuse in. And the size of nanoparticles can control in nano-scale. That means nanoparticles designed in this study have the predictable application for enzyme-activated cancer therapy.

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