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Synthesis of Magnetic $Co_{0.5}Zn_{0.5}Fe_2O_4$-Chitosan Nanoparticles as pH Responsive Drug Delivery System[1]

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Abstract—Chitosan magnetic nanoparticles can be used as drugs carriers. Unlike the traditional particles, the novel magnetic $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles were highly biodegradable. Such nanoparticles with core-shell structure were prepared efficiently. Transmission and scanning electron microscopies exhibited magnetic $Co_{0.5}Zn_{0.5}Fe_2O_4$ particles being encapsulated by spherical chitosan nanoparticles. Size of $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles was below 100 nm. Those particles were characterized by saturated magnetization ca 80 emu/g and superparamagnetism. Release of bovine serum alumin entrapped in the particles was pH dependent.

Keywords: chitosan, $Co_{0.5}Zn_{0.5}Fe_2O_4$, bovine serum albumin, controlled release

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INTRODUCTION

Chitosan has emerged as promising biopolymer in the synthesis of hydrogels to be used in advanced drug delivery systems [1–3]. There are some disadvantages associated with chitosan, for instance low solubility of at physiological pH 7.4, which limits its use as absorption enhancer in nasal or peroral delivery systems [4–8]. Chitosan based drugs delivery systems have high swelling capacity in aqueous environment, leading to rapid release of drugs. Such limitations led to development of chemically modified chitosan derivatives. Due to rapid development of nanotechnology magnetic nanoparticles are being widely studied [9–13].

In this paper, magnetic $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles were obtained using $Co_{0.5}Zn_{0.5}Fe_2O_4$ as a core and chitosan as a polymeric shell. The size, structure and magnetic properties of the magnetic nanoparticles were characterized by TEM, SEM, XRD and vibrating sample magnetometry. Binding of chitosan to magnetic nanoparticles was confirmed by FT-IR spectrophotometry. The effect of pH on swelling rate as well as drug release was studied.

[1] The text was submitted by the authors in English.

EXPERIMENTAL

Reagents. Chitosan (M_w = 1.0 × 10^5, deacetylating degree 95.5%) was purchased from YuHuan Chemical Company, China. All other reagent grade chemicals were purchased from Kemel Chemical Reagent Co. Ltd. Deionized water was re-deionized (electrical resistivity ≥ 18.9 MΩ cm, 25°C) and deoxygenated by boiling for 1 h before use.

Synthesis of magnetite. $Co_{0.5}Zn_{0.5}Fe_2O_4$ was prepared without an additional stabilizer. In a typical synthesis an aqueous mixture of $Co(NO_3)_2$, $Zn(NO_3)_2$, and $Fe(NO_3)_3$ was loaded into the three-necks flask in the stoichiometric ratio that corresponded the formula of $Co_{0.5}Zn_{0.5}Fe_2O_4$. The mixture was stirred at 70°C. NaOH solution (0.1 mol/L) was added to adjust pH to 12, this was followed by refluxing for 1 h. Light black sedimentation appeared and crystal growth was progressing for 2 h with constant stirring to give a stable water-based suspension. The products were isolated from the solvent by an external magnetic field, dispersed again in deionized water and dried in the oven at room temperature.

Preparation of magnetic chitosan nanoparticles. $Co_{0.5}Zn_{0.5}Fe_2O_4$, 0.5 g, magnetic particles was quickly added into the 40mL acetic acid solution (5% v/v)

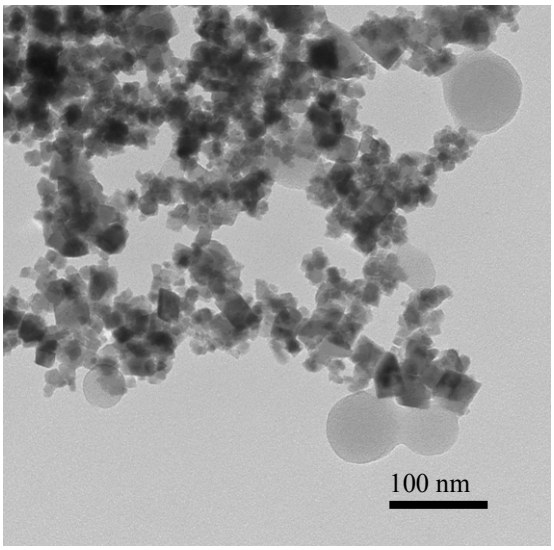
which contained 2.0 g of chitosan. The solution was placed in the ultrasonic reactor for 10 min to disperse chitosan and magnetic particles uniformly at frequency of ultrasonic 22 kHz and power 1000 W. This was followed by addition of 40 mL of liquid paraffin and 10 drops of Span-80 and the solution was placed in the ultrasonic reactor for 30 minutes (ultrasonic frequency 22 kHz and power 500 W). For achieving better magnetic properties of $Co_{0.5}Zn_{0.5}Fe_2O_4$ the reaction system was stored at 60°C for 5 h in a water bath. The cross-linked magnetic chitosan nanoparticles were formed upon adding 2.0 mL of glutaraldehyde and maintaining the same conditions for 5 h. The prepared nanoparticles were concentrated by centrifugation (8000 rpm for 1 h), rinsed with ethanol and deionized water repeatedly and freeze dried for 24 h.

Characterizations of magnetic chitosan nanoparticles. X-ray power diffraction (XRD) measurement was performed by a Bruker D8 diffractometer with monochromatized CuK_α radiation (λ = 1.5426 Å), 40 kV, 30 mA. $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles were characterized by FT-IR (IR Prestige-21, Shimadzu Inc.) and measured by transmission electron microscopy (TEM, H-7650, Hitachi Inc.). The sample for TEM analysis was obtained by placing a drop of nanoparticles dispersed onto a copper micro-grid and evaporated at 20°C. The surface of the magnetic particles was studied by the scanning electron microscope (SEM, Kyky-2800, Kyky technology Co., Ltd). The elemental analysis was performed by an elemental analyzer (Vario EL III, Elementar Inc.). Magnetic measurements were done by a vibrating sample magnetometer (VSM, PPMS-9, Quantum Design).

Dissolution tests in vitro. $Co_{0.5}Mn_{0.5}Fe_2O_4$-chitosan nanoparticles samples (0.5 ± 0.001 g) were accurately weighed and immersed in bovine serum albumin solution (BSA, 0.5 wt %) and stored at 0°C for 25 h. The swollen particles loaded with a drug were placed in a vacuum oven and dried at 37°C. The kinetics of drug release was recorded using a Distek TM dissolution 2100A paddle system (500 rpm, 37 ± 0.5°C). The concentration of BSA in the samples was calculated based on average calibration curves (n = 6).

RESULTS AND DISCUSSION

FT-IR. The band of $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles at 1635.5 cm^{-1} was attributed to the Schiff base and indicated that glutaraldehyde participated in the cross-linking process. The band at 580.5 cm^{-1} was characteristic to magnetic $Co_{0.5}Zn_{0.5}Fe_2O_4$ particles and indicated crosslinking between those and chitosan. So, $Co_{0.5}Zn_{0.5}Fe_2O_4$ magnetic particles were efficiently wrapped by chitosan particles.



TEM micrographs for the $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles.

XRD results. All diffraction peaks exhibited presence of $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles. XRD data of the magnetic chitosan particles and pure $Co_{0.5}Zn_{0.5}Fe_2O_4$ particles were almost identical. The magnetic chitosan particles were binding with $Co_{0.5}Zn_{0.5}Fe_2O_4$.

TEM. Size of the $Co_{0.5}Zn_{0.5}Fe_2O_4$ particles was between 10 and 30 nm. All magnetic chitosan particles had size below 100 nm (see figure).

SEM. $Co_{0.5}Zn_{0.5}Fe_2O_4$ particles were about 20 nm and had spinel crystal structure. Diameter of the magnetic chitosan particles was about 20 nm and the form varied from spinel structure to egg-type shape. The surface of magnetic CS particle was tightly wrapped and did not exhibit $Co_{0.5}Zn_{0.5}Fe_2O_4$ particles indicating that the $Co_{0.5}Zn_{0.5}Fe_2O_4$ particles were wrapped by chitosan efficiently.

Elemental analysis. The ratio of atoms Fe, Co, Zn was about 4 : 1 : 1 and it indicated that $Co_{0.5}Zn_{0.5}Fe_2O_4$ magnetic particles were encapsulated by chitosan particles (see the table).

Elemantal analysis of magnetic chitosan particles

Element, %	C	O	N	Co	Zn	Fe
Content	54.37	28.41	2.23	2.59	2.58	9.82

Magnetization tests. Magnetization of pure $Co_{0.5}Zn_{0.5}Fe_2O_4$ particles (130 emu/g) was higher than that of magnetic $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles (80 emu/g). Both types of particles exhibited characteristics of superparamagnetism.

$Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles had high solubility and dispersibility in water and would not aggregate or precipitate for one month. When subjected to a strong magnetic field, the particles could be completely separated from the solution within seconds.

Drug release from $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nano-particles at different pH. The drug loading rates were 8.001×10^{-5}, 7.487×10^{-5}, and 8.568×10^{-5} g/g, after immersing in 0.5% bovine serum albumin solution for 34 h at room temperature. At pH 1.0 the system rapidly disintegrated, whereas at pH 7.4 and 9.18 aqueous solutions remained intact. That was attributed to a hydrophobic barrier limiting access of water and dissolution of the drug. The composite membrane was tested as a carrier for colonic drug delivery and its function was pH dependent.

CONCLUSIONS

In summary, $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles with optimum core/shell structure and magnetically responsive properties were constructed. $Co_{0.5}Zn_{0.5}Fe_2O_4$-chitosan nanoparticles exhibited a certain potential as pH dependent drug delivery systems.

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