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Preparation and characterization of polymer nanocomposites coated magnetic nanoparticles for drug delivery applications

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ABSTRACT

In the present research work, the anticancer drug 'curcumin' is loaded with Chitosan (CS)-polyethylene glycol (PEG)-polyvinylpyrrolidone (PVP) (CS-PEG-PVP) polymer nanocomposites coated with superparamagnetic iron oxide (Fe_3O_4) nanoparticles. The system can be used for targeted and controlled drug delivery of anticancer drugs with reduced side effects and greater efficiency. The prepared nanoparticles were characterized by Fourier transmission infrared spectroscopy (FTIR), vibrating sample magnetometry (VSM), scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Curcumin drug loaded Fe_3O_4-CS, Fe_3O_4-CS-PEG and Fe_3O_4-CS-PEG-PVP nanoparticles exhibited the mean particle size in the range of 183–390 nm with a zeta potential value of 26–41 mV as measured using Malvern Zetasizer.

The encapsulation efficiency, loading capacity and in-vitro drug release behavior of curcumin drug loaded Fe_3O_4-CS, Fe_3O_4-CS-PEG and Fe_3O_4-CS-PEG-PVP nanoparticles were studied using UV spectrophotometer. Besides, the cytotoxicity of the prepared nanoparticles using MTT assay was also studied. The curcumin drug release was examined at different pH medium and it was proved that the drug release depends upon the pH medium in addition to the nature of matrix.

1. Introduction

In the recent past, many researchers' attention has been towards Superparamagnetic iron oxide nanoparticles (SPIOs, Fe_3O_4 nanoparticles (NPs)), which was due to their distinctive characteristics. It has been broadly used in biomedical applications such as MRI contrast enhancement agents, hyperthermia treatment and drug delivery system, which is due to the better biocompatibility, special magnetic properties, chemical stability, targeting ability and biological degradability [1]. A number of side effects were identified in the conventional oral delivery and injection of drug, but the usage of SPIONs were found to be better carriers for drug delivery in the target location.

Curcumin exhibits immense biological properties like antioxidant [2], anti-inflammatory [3], antibacterial [4], and anticancer activities [5], particularly against colorectal cancer [6–8]. But, it has very poor water-solubility, instability and short half-life in vivo metabolism resulting in limited clinical application. Recent research suggests that to increase the water solubility and bioavailability of Cur, various carriers were put to trial to encapsulate the drug in polymeric micelles [9], solid lipid nanoparticles [10], polymeric nanoparticles [11], biodegradable microspheres [12], phospholipids [13], cyclodextrin [14], hydrogel [15] and liposomes [16].

Modification of the surface of Fe_3O_4 nanoparticles with different types of biopolymers was done to meet the rising needs of the biomedical applications. Numerous natural polymers like PEG, chitosan, starch, and PVA have been used as potential applicants for surface coating purposes [17]. The polymer coatings reduce the aggregation problem of uncoated Fe_3O_4 and lower toxicity. Using the external magnetic field, these kinds of composites were able to effectively deliver DNA, RNA and other relatively small therapeutic molecules to target tissues [18]. Chitosan is a cationic polysaccharide obtained from partial deacetylation of chitin, which is a copolymer consisting of 2-amino-2-deoxy-D-glucose and 2-acetamido-2-deoxy-D-glucose units with β-(1–4) linkages.

Fe_3O_4 nanoparticles, when coated with chitosan displays high biocompatibility, low toxicity and ability to interact with biomolecules such as polypeptides, DNA, and antibodies [19]. Polyethylene glycol (PEG) is often employed in a wide range of medical applications. Also it is very popular for its special features like long polymeric chains, which are soluble in water and nontoxic in the blood. They also act as lubricants and binders as well as antibacterial agents [20]. Polyvinylpyrrolidone (PVP), a water-soluble polymer with amphiphilic character, also possesses outstanding features such as solubility, film and complex formation, adhesive

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and bonding power and toxicological harmlessness. This has led to an extensive investigation for varied prospective applications in the fields of cosmetics, pharmaceutical, medicine and industrial production [21,22].

In the present study, we have investigated the synthesis and characterization of curcumin loaded Fe_3O_4-CS, Fe_3O_4-CS-PEG and Fe_3O_4-CS-PEG-PVP nanoparticles as a possible and potential drug carrier for targeted drug delivery. Furthermore, the drug release properties of the nanoparticles were investigated.

2. Materials and methods

2.1. Materials

Ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$, purity > 99%), ferrous chloride tetrahydrate ($FeCl_2 \cdot 4H_2O$, purity > 99%), ammonium hydroxide (25 wt%), polyethyleneglycol-2000 (PEG), polyvinylpyrrolidone (PVP, MW: 10,000), chitosan (MW = 60–90 kDa; degree of deacetylation 85%), sodium tripolyphosphate (TPP), phosphate buffered saline (PBS), Curcumin (≥ 94%), 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Caco-2 and HCT-116 cells were purchased from National Center for Cell Sciences (NCCS), Pune, India. All chemicals were used directly without further purification.

2.2. Preparation of super paramagnetic Fe_3O_4 nanoparticle

Fe_3O_4 nanoparticles were prepared by co-precipitation method according to the following procedure. In a typical experiment, 0.6 g of $FeCl_2 \cdot 4H_2O$ and 0.82 g of $FeCl_3 \cdot 6H_2O$ were dissolved in 10 mL of deionized water in a flask. The mixture was vigorously stirred at room temperature (25 °C) for 15 min to obtain a homogeneous dark orange solution. Then, 2.5 mL ammonium hydroxide (28%) was added dropwise to the above solution under vigorous stirring. During the process, the pH was maintained at about 10 and the solution became dark orange to black after base addition. 30 min later, this solution was kept at 80 °C for 45 min with vigorous stirring. Then the solution was cooled to room temperature, and the resulting products were isolated from reaction system by magnetic separation and washed several times with distilled water to remove excess ammonia. Finally, the magnetic Fe_3O_4 nanoparticles were obtained after being dried in a vacuum oven at room temperature for 24 h.

2.3. Preparation of superparamagnetic CS with curcumin (Fe_3O_4-CS-Cur)

The previously reported procedure was followed in the preparation of CS nanoparticles [23]. Briefly, CS (4 mg/mL) and 5 mg of Fe_3O_4 were first dissolved in a 1% aqueous acetic acid solution and curcumin (Cur) (5–20 mg) was dissolved separately in ethanol and prepared at different concentrations (10%, 20%, 30%, 40%, and 50%, using 4, 8, 12, 16, and 20 mg of drug, respectively). Then, the different concentrations of the drug solution was added to 10 mL of the magnetic chitosan solution under magnetic stirring (1000 rpm) at room temperature to obtain magnetic chitosan drug solution. The magnetic chitosan drug solution was added drop wise (using a disposable syringe with a 22-gauge needle) into 4 mL of the TPP solution (2 mg/mL) under magnetic stirring (~200 rpm) at room temperature. Magnetic CS nanoparticles was formed suddenly. The magnetic CS nanoparticle suspension was stirred at 25 °C for 90 min for further cross-linking of the nanoparticles. Finally, the magnetic CS nanoparticles were collected by centrifugation at 1500 rpm and dried in vacuum oven at 40 °C for 24 h.

2.4. Preparation of the Fe_3O_4-CS-Cur-PEG and Fe_3O_4-CS-Cur-PEG-PVP nanoparticles

The various percentage of encapsulated Fe_3O_4-CS-Cur in the PEG and PVP solutions were prepared by a method described in our previous report [24] as follows. First, 10% of PEG solution was prepared in water. Then, the solution was gradually added to a correct portion of the Fe_3O_4-CS-Cur nanoparticles under constant magnetic stirring at room temperature for 1 h. The resulting encapsulated nanocomposites (Fe_3O_4-CS-Cur-PEG) were collected by centrifugation at 1500 rpm and freeze-dried at −30 °C for 20 h. Similarly, PVP (20 mg) was dissolved in water and gradually added to Fe_3O_4-CS-Cur-PEG nanocomposites under constant magnetic stirring at room temperature for 1 h. Lastly, the resulting encapsulated nanocomposites (Fe_3O_4-CS-Cur-PEG-PVP) were collected by centrifugation at 1500 rpm and freeze-dried at −30 °C for 20 h.

2.5. Particle size analysis

Drug loaded nanoparticles were characterized for the particle size, size distribution and zeta potential using Zetasizer (Malvern Instruments, UK).

2.6. Scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FT-IR) analysis

Morphological characteristics of the freshly prepared (Fe_3O_4-CS-Cur, Fe_3O_4-CS-Cur-PEG and Fe_3O_4-CS-Cur-PEG-PVP) nanocomposites were analyzed using scanning electron microscopy (SEM-Hitachi-S-2700), FT-IR spectrum was taken to study the interaction the between nanoparticles and drug using Perkin Elmer spectrum RXI. Concisely KBr pellets were prepared by quietly mixing 1 mg of the sample with 200 mg of KBr. Fourier Transform Infrared spectroscopy (400–4000 cm^{-1}) was performed with a resolution of 2 cm^{-1}.

2.7. TEM analysis

The morphology and nanostructure of the prepared (Fe_3O_4-CS-Cur, Fe_3O_4-CS-Cur-PEG and Fe_3O_4-CS-Cur-PEG-PVP) nanocomposites were investigated by transmission electron microscopy (TEM, Hitachi H-600-II) operating at 200 kV. To prepare samples for TEM, a drop of the aqueous suspension of nanoparticles is placed onto amorphous carbon coated copper grids and the samples were dried at an ambient temperature.

2.8. Vibrating sample magnetometry (VSM) analysis

The magnetic properties of the CS, PEG, and PVP coated and uncoated nanoparticles were studied by using vibrating sample magnetometer (VSM) (Lake Shore, USA) at room temperature. Zero-field cooled (ZFC) and field cooled (FC) thermomagnetic curves were recorded under an applied magnetic field of $H = 3.95$ kA/m. To obtain ZFC data, the samples were cooled in zero field from room temperature of 300 K, and then the magnetization was measured with an increasing temperature under the applied constant magnetic field of 3.95 kA/m. For FC data, the process was repeated under the same magnetic field applied both while cooling and heating of the sample.

2.9. Evaluation of encapsulation efficiency (EE) and loading capacity (LC)

The suspensions of the drug-loaded nanoparticles was centrifuged in a cooling centrifuge at 20,000 rpm at 30 °C for 40 min