Abstract

Introduction: 5-Fluorouracil is the main drug used in colorectal cancer treatment. Due to its non-specific effect on healthy cells, 5-FU is associated with multiple side effects. A possible solution to overcome the adverse side effects of the drug, is to load the drug in targeted nanoparticles. In the present study, iron oxide (Fe_3O_4) nanoparticles with polylactic acid-hyaluronic acid copolymer (PLA-HA) coating were synthesized to encapsulate 5-flourouracil. Physicochemical properties, drug release pattern, toxicity and efficiency of nanoparticles in drug delivery to colorectal cancer cell lines (HCT116) were then evaluated.

Methods: Fe_3O_4 nanoparticles were prepared by green biosynthesis method. Fourier transform infrared spectroscopy (FT-IR) and Ultraviolet–visible spectroscopy (UV-Vis) was used to confirm the synthesis of iron oxide nanoparticles. PLA-HA copolymer was synthesized by conjugation of NH2-HA and acrylate-PLA. PLA-HA/Fe_3O_4/5-FU and PLA/Fe_3O_4/5-FU nanoparticles were prepared by solvent diffusion method. The size and zeta potential of nanoparticles were determined by dynamic light scattering (DLS) method. Morphological properties and shape of the nanoparticles were studied using transmission electron microscopy (TEM) imaging. Also, the magnetic properties of the nanoparticles were evaluated by vibrational sample magnetometer (VSM). The encapsulation efficiency of 5-FU in nanoparticles was also determined through measuring the amount of free drug present in the final supernatant of the synthesis process by spectrophotometry. The drug release pattern was investigated by incubating nanoparticles in phosphate buffer solution (PBS) with acidic and neutral pH (respectively, pH 6 and 7.4). Finally, the toxicity and efficacy of prepared nanocarriers in drug delivery to colorectal cancer cell line (HCT116) were evaluated using MTT assay on cells treated with different concentrations of drug-free nanoparticles and drug-loaded nanoparticles.

Results and discussion: The synthesis of iron oxide nanoparticles was confirmed by FT-IR and UV-vis spectra. The synthesized PLA-HA/Fe_3O_4/5-FU nanoparticles had a spherical shape with an average size of 235 nm and a zeta potential of -18 mV. The results of VSM analysis demonstrated that the nanoparticles had superparamagnetic properties. The results of spectrophotometric analysis showed that the encapsulation efficiency of 5-FU in nanoparticles was 42 percent. The nanoparticles followed a burst and sustained release pattern at neutral and acidic pH. Also, it was found that the drug is released more readily at acidic pH. Due to the lower pH of tumor tissue compared to healthy tissue, this property may reduce the side effects of the drug. MTT assay results indicate proper biocompatibility of drug-free nanocarriers and their low toxicity. It was also observed that PLA-HA/Fe_3O_4/5-FU nanoparticles significantly reduced the HCT116 cells viability compared to PLA/Fe_3O_4/5-FU nanoparticles. This phenomenon is probably due to the specific interaction of hyaluronic acid with CD_{44} receptors, which are overexpressed on the surface of cancer cells. Due to its acceptable properties, PLA-HA/Fe_3O_4 nanoparticles have the potential for further research to be used as a targeted drug delivery system.

Keywords: 5-fluorouracil (5-FU), targeted drug delivery, polylactic acid, hyaluronic acid, magnetic nanoparticles.