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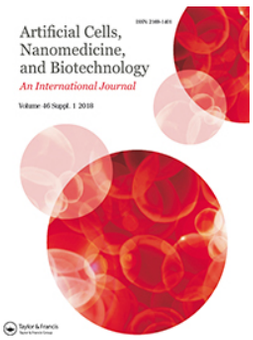

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Synthesis, characterization and *in vitro* evaluation of magnetic nanoparticles modified with PCL–PEG–PCL for controlled delivery of 5FU

Nahideh Asadi[a,b], Nasim Annabi[c,d,e], Ebrahim Mostafavi[e], Maryam Anzabi[f,g], Rovshan Khalilov[h,i], Siamak Saghfi[h,i], Masoud Mehrizadeh[j] and Abolfazl Akbarzadeh[a,e,h,k]

[a]Tuberculosis and Lung Disease Research Center of Tabriz, Tabriz University of Medical Sciences, Tabriz, Iran; [b]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran; [c]Biomaterials Innovation Research Center, Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, USA; [d]Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, USA; [e]Department of Chemical Engineering, Northeastern University, Boston, MA, USA; [f]Center of Functionally Integrative Neuroscience (CFIN) and MINDLab, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; [g]Department of Radiology, Neurovascular Research Laboratory, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA; [h]Joint Ukrainian-Azerbaijan International Research and Education Center of Nanobiotechnology and Functional Nanosystems, Drohobych Ukraine & Baku, Azerbaijan; [i]Department of Plant Physiology, Faculty of Biology, Baku State University, Baku, Azerbaijan Republic; [j]Department of Petroleum engineering, School of engineering and Applied Sciences, Khazar University, Baku, Azerbaijan; [k]Universal Scientific Education and Research Network (USERN), Tabriz, Iran

ABSTRACT

Magnetic nanoparticles have properties that cause to apply them in cancer therapy and vehicles for the delivery of drugs such as 5FU, especially when they are modified with biocompatible copolymers. The aim of this study is to modify superparamagnetic iron oxide nanoparticles (SPIONPs) with PCL–PEG–PCL copolymers and then utilization of these nanoparticles for encapsulation of anticancer drug 5FU. The ring-opening polymerization (ROP) was used for the synthesis of PCL–PEG–PCL copolymer by ε-caprolactone (PCL) and polyethylene glycol (PEG2000). We used the double emulsion method (water/oil/water) to prepare 5FU-encapsulated Fe_3O_4 magnetic nanoparticles modified with PCL–PEG–PCL copolymer. Chemical structure and magnetic properties of 5FU-loaded magnetic-polymer nanoparticles were investigated systematically by employing FT-IR, XRD, VSM and SEM techniques. *In vitro* release profile of 5FU-loaded NPs was also determined. The results showed that the encapsulation efficiency value for nanoparticles were 90%. Moreover, the release of 5FU is significantly higher at pH 5.8 compared to pH 7.4. Therefore, these nanoparticles have sustained release and can apply for cancer therapy.

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Magnetic nanoparticles; PCL–PEG;5FU

Introduction

Drug delivery systems have some drawbacks. For example, oral drug delivery systems that are extremely important to the field of medicine, because the largest part of the common illnesses is treated by oral rout of medication, they have some defects such as low solubility in aqueous solutions and low penetration across intestinal membranes [1]. The gastrointestinal system has problems for protein drug delivery. Also cancer chemotherapeutics due to their nonselective activity are less effective to cure tumours so resulting in dose limiting side effects [2,3].

Drug delivery systems have modified with new therapeutic molecules such as nucleic acids, peptides and others to improve themselves. Moreover, some of these systems give a stable concentration of drug in the bloodstream for a long period of time that is attractive for the treatment of some diseases, and there is factual evidence of patients' indicating improvement during this treatment [4]. Drug delivery with controlled rate, sustain release and targeted delivery are other very attractive ways and have been pursued remarkably [5,6].

Recent progresses in the applying of carriers for sustain and target drug delivery, micro- and nano-systems [7,8], biorecognizable structures, micro-needles for transdermal drug delivery lead to improve permeability and flexibility of these polymeric materials. In the smart drug delivery systems, micro- and nanoparticles can hold and release diverse active agents on demand [9]. The main purposes of nanoparticles in a drug delivery system are controlling: surface properties, particle size and release of pharmacologically active ingredients in the way to get the drug at the targeted site in the optimal rate and dose procedure [10,11]. Systems based on drug delivery can provide improved efficacy and decreased toxicity for anticancer agents. Long blood circulation result in carriers can use the "enhanced permeability and retention" (EPR) effect for special extravasation from tumour vessels [12]. Drug-loaded nanoparticles transport therapeutics to tumour sites undergo a multistep process to achieve their therapeutic target, launch with extravasation from leaky tumour vessels [13] (see Figure 1).

Various nanosystems have been studied as drug delivery systems such as polymeric micelles, polymeric nanoparticles,

CONTACT Abolfazl Akbarzadeh akbarzadehab@tbzmed.ac.ir Tuberculosis and Lung Disease Research Center of Tabriz, Tabriz University of Medical Sciences, Tabriz, Iran

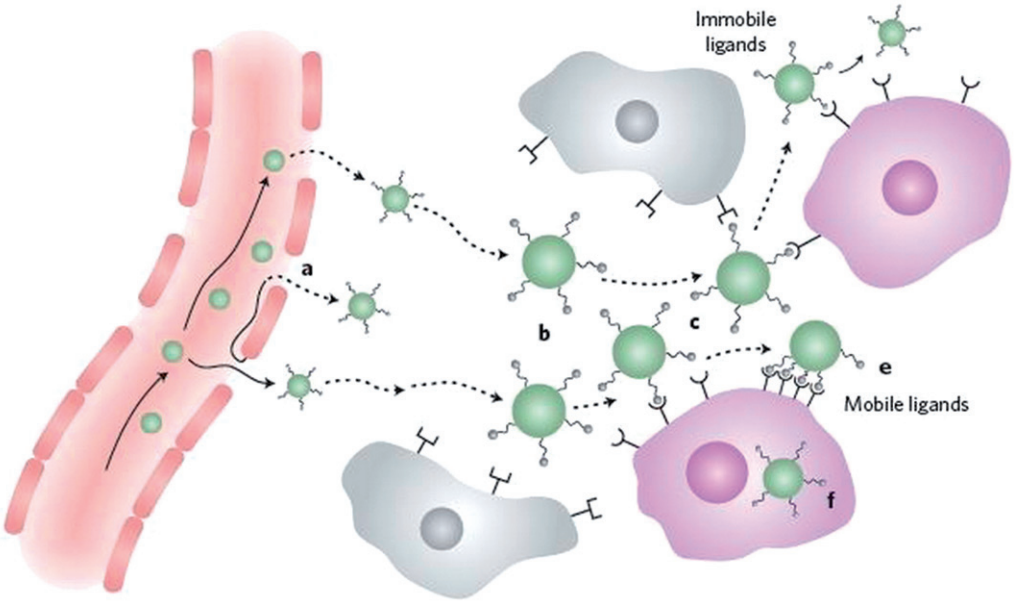
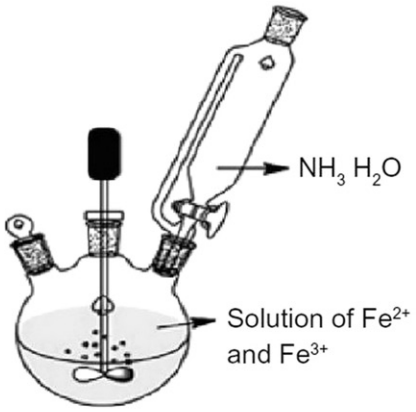


Figure 1. Image of multivalent targeting in nanoparticle drug delivery [13].

nanogels, nanocapsules, fullerenes, solid lipid nanoparticles (SLN), nanoliposomes, dendrimers, quantum dots and metal nanoparticles [6,14]. Magnetic nanoparticles (MNPs) have received much attention due to their unique physical properties, biocompatibility, magnetic susceptibility, stability and their role in the cellular and molecular level of biological interactions. In addition, MNPs are easily controlled by an exterior magnetic field application, which offer the releasing of the anticancer agent at an exact rate and at a specific site, overcoming the problems of conformist techniques for diagnosis and therapy. These properties cause the magnetic nanoparticles be suitable in biomedical fields, such as, drug delivery, hyperthermia treatment [15–17].

Polymeric nanoparticles have benefits for drug delivery such as encapsulation of bioactive molecules and protection them from enzymatic and hydrolytic degradation [6,18–21]. Therapeutically polymeric nanoparticles that used are composed of biocompatible or biodegradable materials, like poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL), alginic acid, chitosan and gelatin [22–26]. Specially, amphiphilic, thermosensitive ones for example BAB and ABA tri-block or AB di-block consisting of hydrophobic (B) and hydrophilic (A) blocks have been researched more than other smart systems because of their *in situ* gel-forming properties at body temperature [27–29]. Polycaprolactone (PCL) is a hydrophobic, biodegradable, semi-crystalline polymer. The suitable solubility of this polymer, its low melting point and amazing blend-compatibility have encouraged wide studies into its possible uses in the biomedical field like packaging, medical implant, and controlled drug delivery [30,31].

The purpose of this work was to evaluate the magnetic-PCL–PEG–PCL nanoparticles as anticancer drug carriers. Firstly, Fe_3O_4 magnetic nanoparticles were prepared and then the PCL_{1000}–PEG_{2000}–PCL_{1000} triblock copolymer was synthesized with ring opening polymerization by ε-caprolactone and PEG and stannous octoate as catalyst [32]. Then, 5FU was encapsulated in Fe_3O_4–PCL–PEG–PCL nanoparticles by the double emulsion method (w/o/w). The physicochemical properties of nanoparticles and *in vitro* release of 5FU were characterized [33–38].



$$2\,FeCl_3 + FeCl_2 + 4\,H_2O + 8\,NH_3 \rightarrow Fe_3O_4 + 8\,NH_4Cl$$

Figure 2. Preparation of magnetic nanoparticles.

Experimental section

Materials and methods

Ferric chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), ferrous chloride tetrahydrate ($FeCl_2{\cdot}4H_2O$) and ammonium hydroxide (32 wt.%) were purchased from Fluka (Buchs, Switzerland). ε-Caprolactone (ε-Cl)), stannous octoate ($Sn(Oct)_2$) and polyethylene glycol (PEG) (molecular weight 2000) were purchased from Sigma Aldrich (St. Louis, MO). Infrared spectra were recorded with BRUKER series FTIR. The magnetic property was measured on a vibrating sample magnetometer (Meghnatis Daghigh Kavir, Iran) at a maximum magnetic field of 10 kOe at room temperature [39]. X-ray diffraction and scanning electron microscopy (SEM) measurements were conducted using VEGA and TESCAN, respectively. The drug

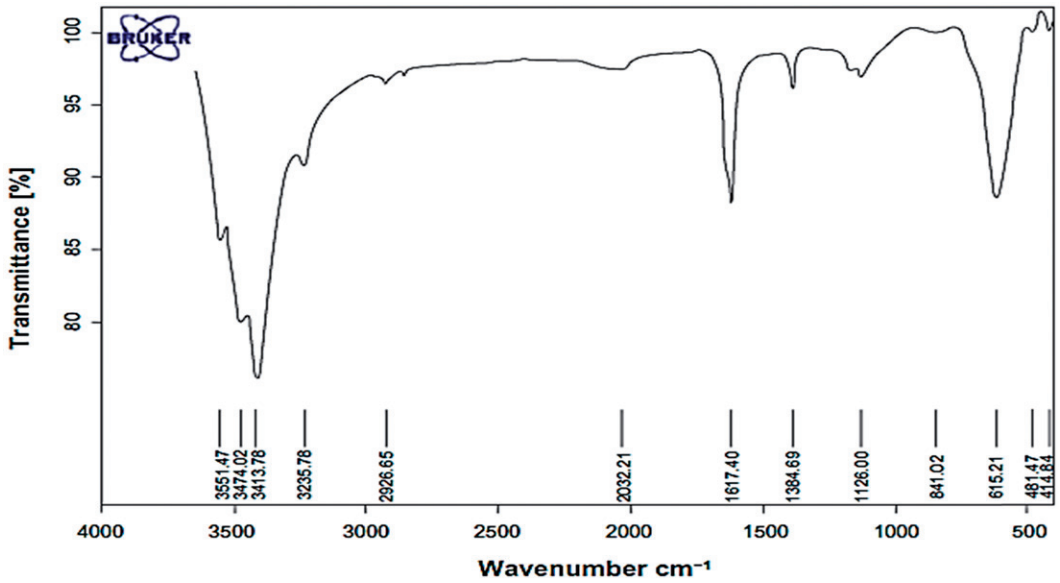


Figure 3. Fourier transform infrared spectra of magnetic nanoparticles.

encapsulation efficiency and release profile were determined by an ultra violet visible spectrometer (Shimadzu, Tokyo, Japan).

Preparation of superparamagnetic nanoparticles

Chemical coprecipitation method was used for the synthesis of magnetic nanoparticles [40]. Giving to this method, 0.7418 g of $FeCl_2{\cdot}4H_2O$ (4 mmol) and 0.2242 g of $FeCl_3{\cdot}6H_2O$ (7 mmol) were dissolved in 10 ml of deionized water, such that the ratio of Fe^{2+}/Fe^{3+} was 1.75:1, respectively. This solution was stirred under nitrogen at 85 °C for 1 h. In the next step, 22.5 ml $NH_3{\cdot}H_2O$ (25%) was added into the solution quickly, stirred under nitrogen for 1 h, and then cooled at room temperature. Finally, the precipitated particles were washed three times with water and dried under vacuum at 70 °C (see Figure 2).

Synthesis of (PCL_{1000}–PEG_{2000}–PCL_{1000}) triblock copolymer

PCL_{1000}–PEG_{2000}–PCL_{1000} copolymer was prepared by ring opening polymerization. $Sn(Oct)_2$ was a catalyst of reaction. A 7.4 g of ε-caproate lactone and 5 g of polyethylene glycol with a molecular weight of 2000 (PEG_{2000}) were weighed and in a bottleneck flask were heated to 120 °C under a nitrogen atmosphere to complete melting. Then 1 ml of 0.05% (w/w) stannous octoate was added and the temperature was raised to 130 °C. This temperature was continued for 2 h. The polymerization was carried out under vacuum [41].

Preparation of 5FU encapsulated Fe_3O_4 magnetic nanoparticles modified with PCL–PEG–PCL copolymer

We used double emulsion method (water/oil/water) for encapsulation of 5FU in Fe_3O_4–PCL–PEG–PCL modified nanoparticles. Firstly, an aqueous solution of 5FU (2.5 mg/2.5 ml) was added to dichloromethane, that 120 mg of the PCL–PEG–PCL copolymer and 5 mg of the Fe_3O_4 nanoparticles had been dissolved in it, using a sonication at 20,000 rpm for 25 s, the w/o emulsion was created. Then w/o emulsion was added to a 50 ml aqueous solution of PVA (polyvinyl alcohol) 0.5% and the mixture was sonicated at 70,000 rpm for 2 min to make w/o/w emulsion. The w/o/w emulsion was stirred at room temperature to evaporate the organic phase (Heidolph Instruments, Hei-VAP Series, Schwabach, Germany). In order to purify the nanoparticles, two cycles of centrifugation (10,000 rpm for 1 h in a Biofuge 28 RS, Heraeus centrifuge) was used. Then the precipitate and solution were separated. Nanoparticles was dried by freeze-drying and supernatant solution was used to measure the concentration of encapsulated drug. Finally, the nanoparticles were filtered through a 1.2 mm filter (Millipore, Bedford, MA). To determine the encapsulation efficiency of 5FU in modified Fe_3O_4 magnetic nanoparticles, nanoparticles were disintegrated in dichloromethane [42]. The 5FU concentration was determined by spectrophotometer at 266 nm. Drug encapsulation efficiency was obtained with the following equation:

$$\text{Encapsulation efficiency } (\%) = (\text{Drug total} - \text{Drug supernatant})/\text{Drug total} \times 100$$

Nanoparticle characterization

FTIR spectrophotometer (BRUKER series) was used for recording infrared spectra. For this purpose, the samples and KBr were pressed to form a tablet. In order to analysis the crystal structure of the Fe_3O_4 magnetic nanoparticles, power X-ray diffraction (Rigaku D/MAX-2400 X-ray diffractometer) was applied. The magnetization curves of the samples were measured by vibrating sample magnetometry at room temperature. To determine the size and morphology of the nanoparticles, SEM was used by VEGA/TESCAN.

In vitro *drug release profile study*

For this purpose, 3 mg of 5FU-encapsulated modified magnetic nanoparticles was dispersed in 30 ml of phosphate buffered solution (pH 7.4). Samples were incubated in 37 °C.

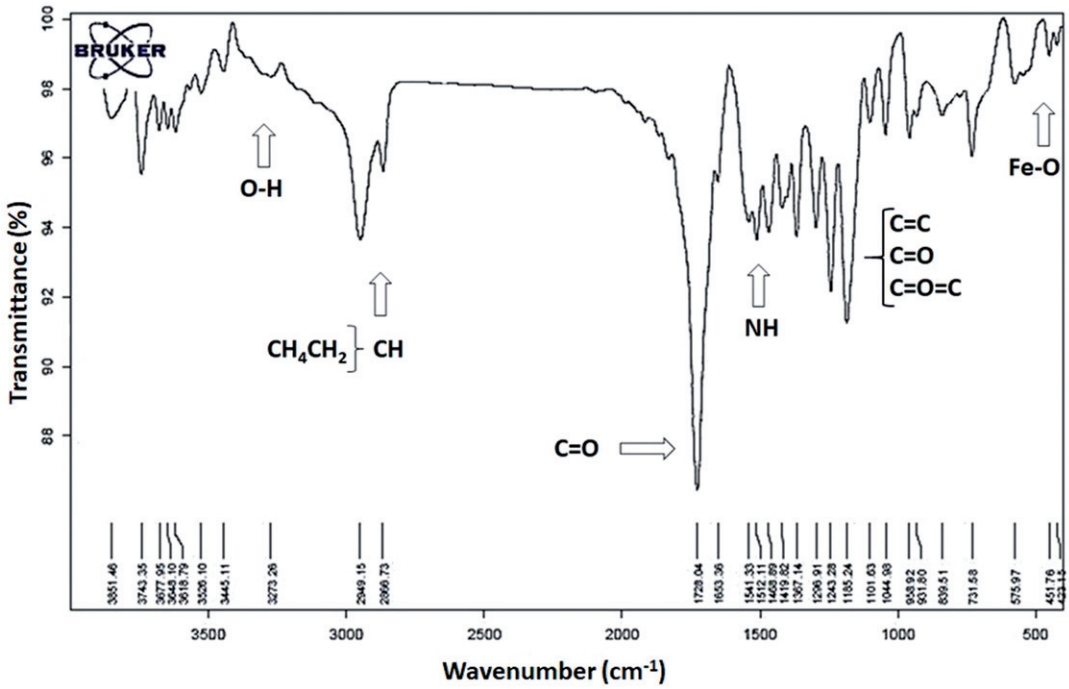


Figure 4. Fourier transform infrared spectra of 5FU encapsulated Fe_3O_4 magnetic nanoparticles modified with PCL–PEG–PCL copolymer.

In determined time intervals, 3 ml of samples were removed and analyzed with ultraviolet spectrofluorometry (Shimadzu, Tokyo, Japan) and same volume of fresh phosphate-buffered solution was reconstituted. The samples were analyzed with ultraviolet spectrofluorometry to calculate the amount of released 5FU (λ_{ex} 470 nm and λ_{em} 585 nm). To investigate the effect of pH on drug release, the test was repeated in acidic acetate buffer solution (pH =8.5) and at temperature 40 °C.

Results and discussion

Characterization of nanoparticles

The encapsulation efficiency value achieved for 5FU was:

$$\text{EE\%} = (\text{Drug total} - \text{Drug supernatant})/\text{Drug total} \times 100$$

$$\text{EE } \% = [(5 - 0.382)/5] \times 100 = 90\%$$

FTIR spectroscopy

The structure confirmation of Fe_3O_4 and PCL–PEG–PCL copolymer was studied by FTIR spectroscopy. From the infrared spectra shown in Figure 3, the absorption peaks at 580 cm^{-1} belonged to the stretching vibration mode of Fe–O bonds in Fe_3O_4, 3402 cm^{-1} belonged to free hydroxyl group (OH) of Fe_3O_4. The peaks at 2869 cm^{-1} and 2950 cm^{-1} are due to C–H stretch. Absorption at 933 cm^{-1} and 1247 cm^{-1} belonged to C–O stretch. 1750–1765 cm^{-1} is assigned to C = O, 1090–1300 cm^{-1} assigned to C–C, C–O and 1085–1150 cm^{-1} is due to polyethylene glycol ether band (see Figures 4 and 5).

X-ray diffraction patterns

The X-ray diffraction was used to study the crystal structure of the Fe_3O_4 nanoparticles. This provides patterns for pure Fe_3O_4 magnetic nanoparticles and 5FU-encapsulated modified magnetic nanoparticles. The characteristic diffraction peaks are indicated, respectively, by their indices (2 2 0), (3 1 1), (4 0 0), (4 2 2), (5 1 1) and (4 4 0), which could be well indexed to the inverse cubic spinel structure of Fe_3O_4 (JCPDS card 85-1436). Characteristic diffraction peaks were also observed for 5FU-encapsulated Fe_3O_4 magnetic nanoparticles modified with PCL–PEG–PCL copolymer. This determines that modification of the Fe_3O_4 nanoparticles did not lead to any crystal phase change. The average crystallite size D was about 10 nm and obtained from the Sherrer equation $D_{k\lambda} = 0.9\lambda$ (βCosθ) where K is the constant, λ is the X-ray wavelength and β is the peak width of half-maximum (see Figures 6 and 7).

Magnetic properties

The magnetic properties of Fe_3O_4 nanoparticles were determined with VSM at room temperature. Figure 8 displays the hysteresis loops of the samples. For 5FU-encapsulated Fe_3O_4 magnetic nanoparticles modified with copolymer, the saturation magnetization is 18 emu/g, which is less than the pure Fe_3O_4 nanoparticles (61 emu/g). This difference recommends that a large amount of copolymer modified magnetic nanoparticles and 5FU. It is possible to separate 5FU-encapsulated modified Fe_3O_4 nanoparticles from the reaction medium by using a magnetic field. This is due to the large saturation magnetization. In addition, there was no hysteresis in the magnetization, with both remanence and coercivity being zero, indicating that these magnetic nanoparticles have superparamagnetic properties [43].

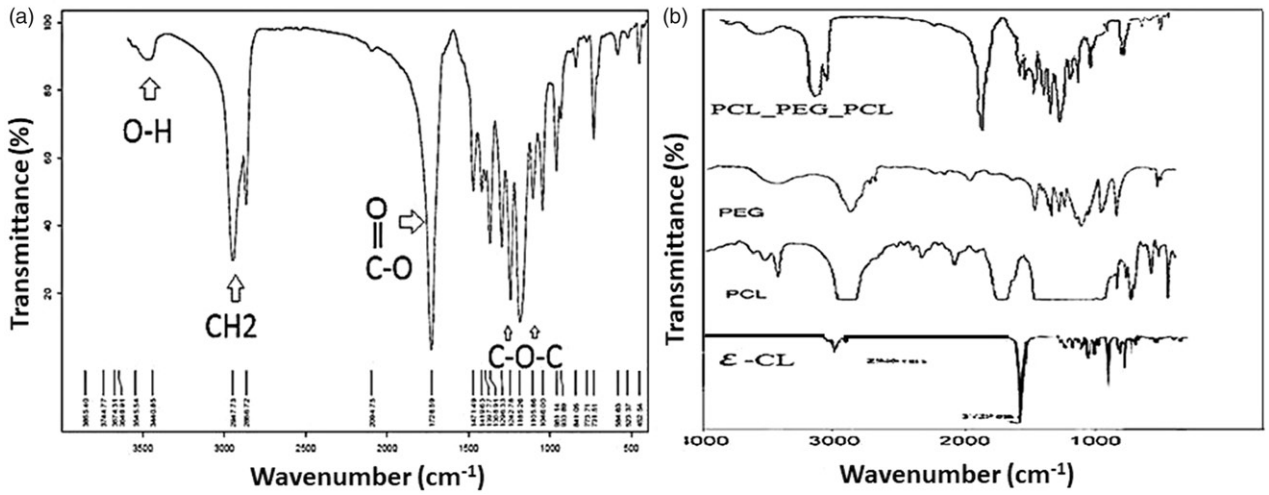


Figure 5. (a) Fourier transform infrared spectra of PCL–PEG–PCL copolymer. (b) Comparative Fourier transform infrared spectra of synthesized copolymer (PCL–PEG–PCL) with FT-IR spectra of its polymers.

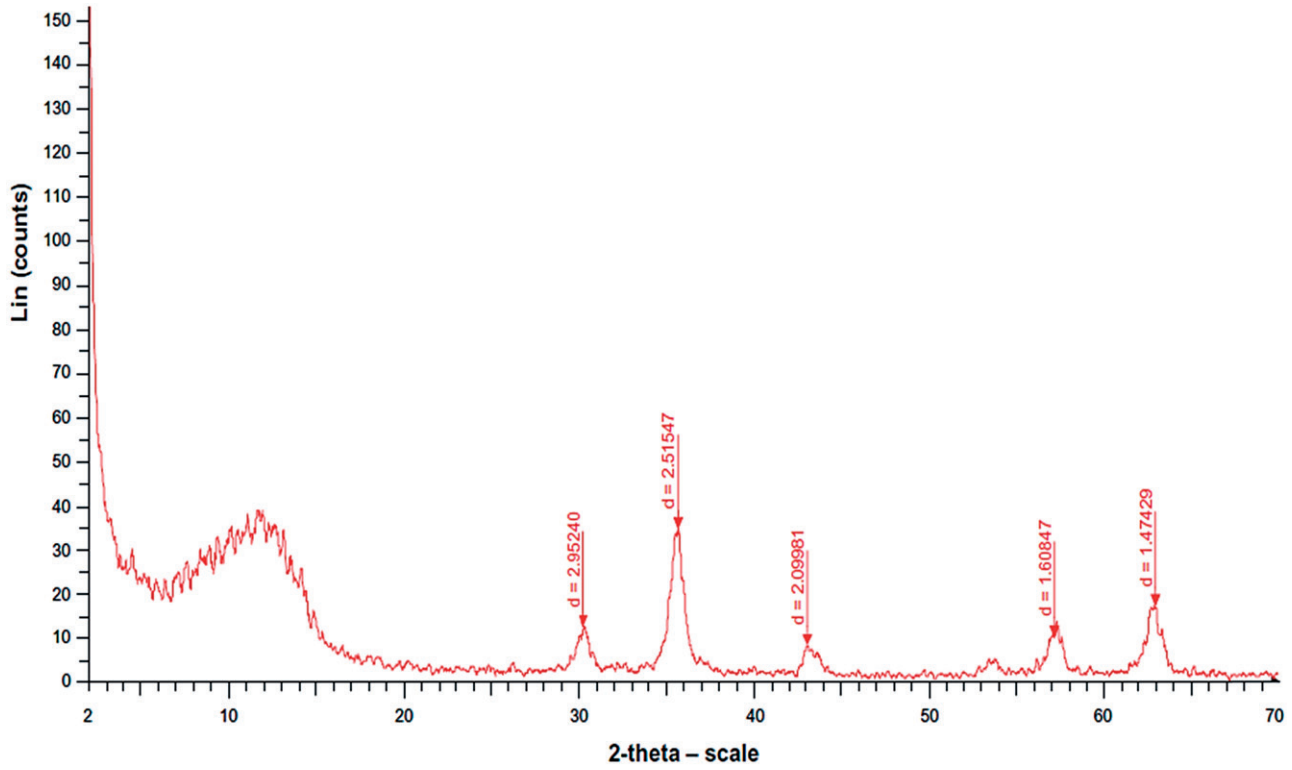


Figure 6. XRD spectra of Fe_3O_4 magnetic nanoparticles.

SEM analysis

The size and surface morphology of the nanoparticles was observed by SEM. Figure 9(a,b) shows micrographs of pure Fe_3O_4 nanoparticles and 5FU-encapsulated Fe_3O_4 modified nanoparticles, respectively. As it can be seen, the photograph demonstrates that nanoparticles are well aggregated, which was due to the nanosize of the Fe_3O_4 of about 10 nm. After modification of magnetic nanoparticles with PCL–PEG–PCL copolymer and encapsulation of 5FU, the size of the particles changed, and dispersion of the particles was greatly improved (Figure 9(b)), which can be due the electrostatic repulsion force and steric hindrance between the copolymer chains on the encapsulated Fe_3O_4 nanoparticles.

In vitro *drug release profile*

The release profiles of 5FU were achieved by the ratio of 5FU release with respect to the total amount of 5FU encapsulated. Releasing 5FU from nanoparticles has two phases: burst release in initial and sustain release after 12 h. A major amount of drug released within 12 h. This was 33.1% for Fe_3O_4 magnetic nanoparticles modified with PCL–PEG–PCL (Figure 10). The total release amount of 5FU over 2 days was 81.4% from Fe_3O_4–PCL–PEG–PCL. The 5FU release rate from the Fe_3O_4–PCL–PEG–PCL nanoparticles was also pH-dependent and improved at pH 5.8. In a drug releasing, several processes are involvement, containing distribution through the polymer matrix, release by polymer degradation, and

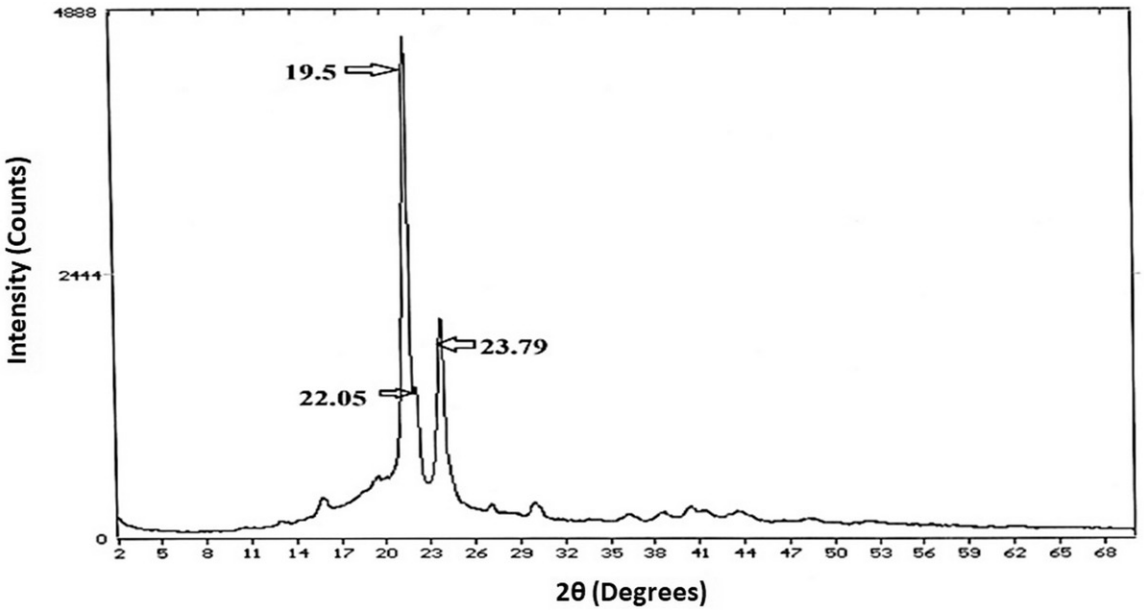


Figure 7. XRD spectra of PCL_{1000}–PEG_{2000}–PCL_{1000} copolymer.

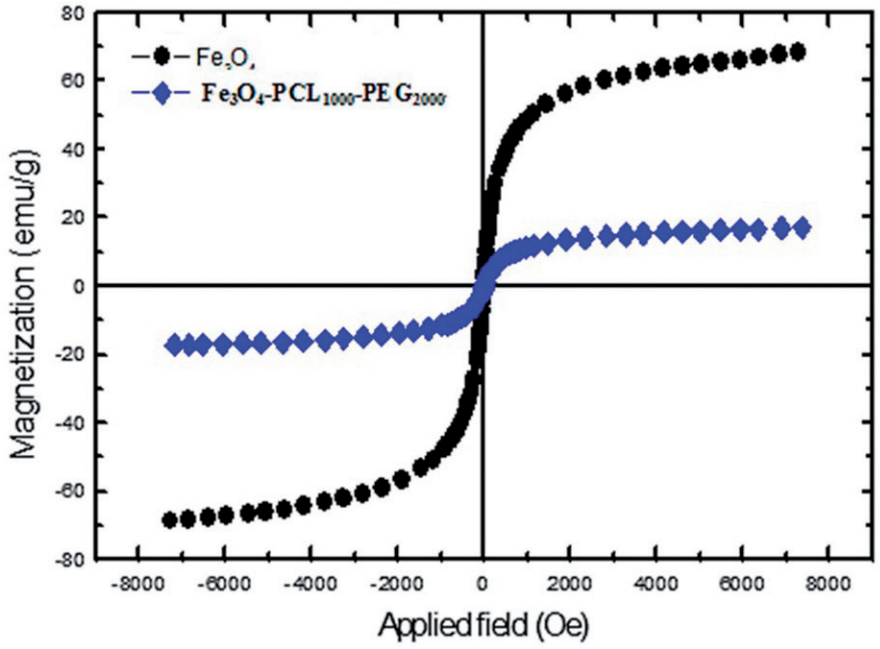


Figure 8. Magnetic behaviour of magnetic nanoparticles.

solubilization and diffusion through microchannels that exist in the polymer matrix or are formed by erosion [44,45]).

Conclusion

Nanotechnology-based drug delivery can modify cancer treatment by improving distribution and accumulation of several drugs in the disease sites. Targeted drug delivery in cancer by hyperthermia *via* magnetic nanoparticles has functional characteristics such as small size, low toxicity, high stability, simple purification and sterilization [46–49]. In this work, we encapsulated 5FU in an improved and less-toxic carrier. In order to minimize undesired uptake or interactions in unusual sites, a biodegradable nanocarrier based on magnetic nanoparticles and copolymer has been developed for 5FU. Quantity and location of drug release are controlled by the PCL–PEG–PCL-coated magnetic nanoparticles and pH. This nanosystem can be used for targeting a wide variety of solid tumours. There are some parameters that effect on encapsulation efficiency such as copolymer concentration in organic solution, volume of the outer aqueous phase, volume of the internal aqueous phase, 5FU concentration in the inner aqueous phase, the first and second homogenized speed and time. The encapsulation efficiency (EE) was 90%. It is indicated that the 5FU-encapsulated Fe_3O_4–PCL–PEG–PCL nanoparticles have pH sensitive property and can be used for targeting extracellular pH of cancer cells and could be an effective carrier for anticancer drugs delivery.

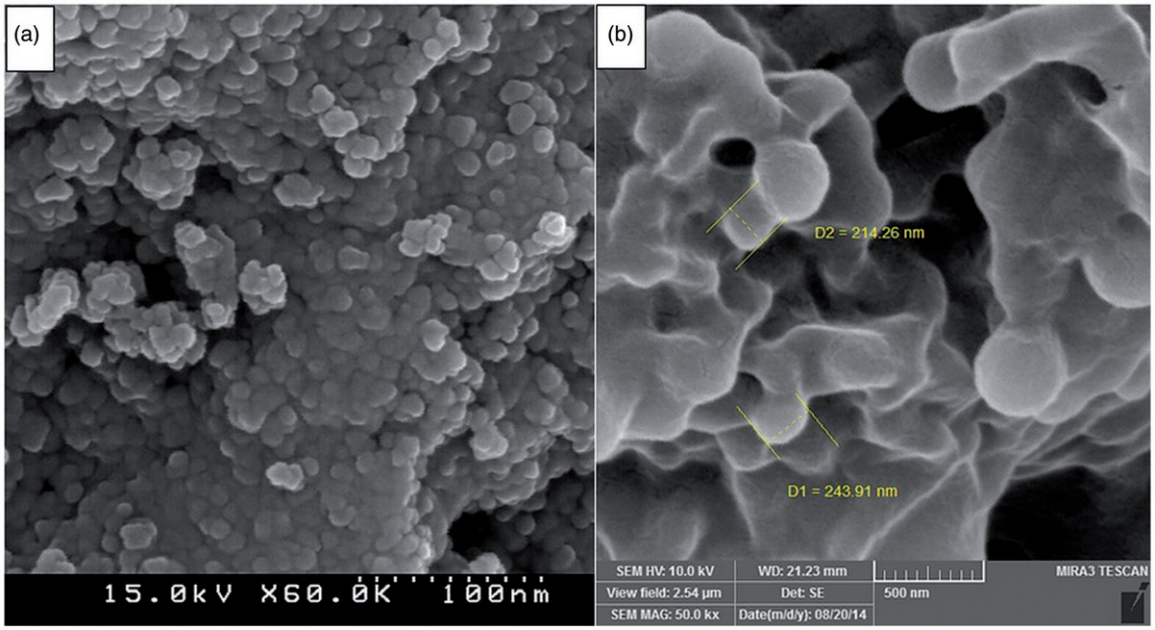


Figure 9. (a) SEM image of Fe_3O_4 nanoparticles and (b) 5FU-encapsulated Fe_3O_4 magnetic nanoparticles modified with PCL–PEG–PCL copolymer.

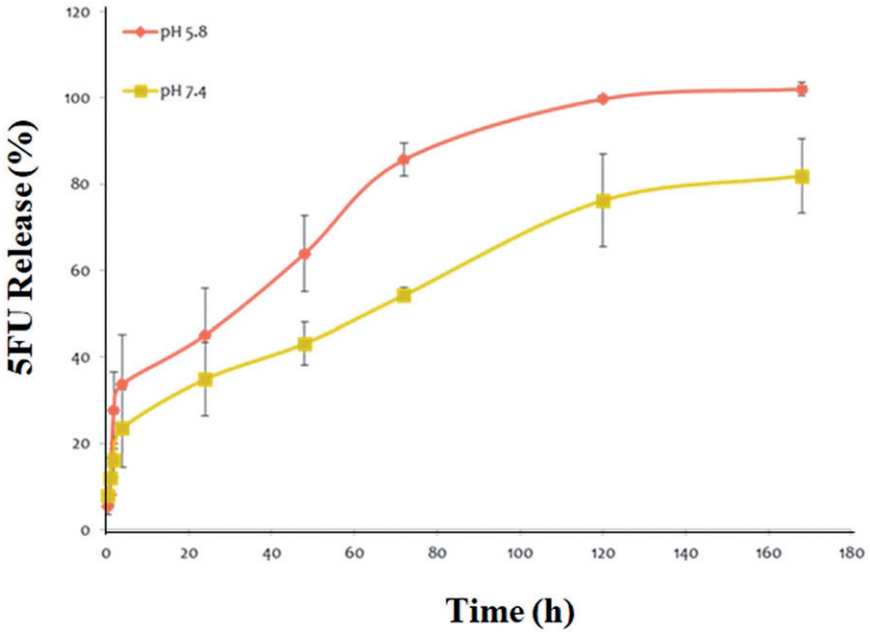


Figure 10. *In vitro* release experiment.

Overall, modification of the magnetic nanoparticles could be possible useful for drug delivery systems. Our results explain that Fe_3O_4 magnetic nanoparticles modified with PCL–PEG–PCL could be a valuable carrier for drug delivery.

Disclosure statement

No potential conflict of interest was reported by the authors.

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