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Synthesis and Physicochemical Characterization of Biodegradable PLGA-based Magnetic Nanoparticles Containing Amoxicilin

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The purposes of this research were to synthesize amoxicillin-carrying magnetic nanoparticles. Magnetic nanoparticles were prepared by a chemical precipitation of ferric and ferrous chloride salts in the presence of a strong basic solution. PLGA and PLGA-PEG copolymers were prepared by ring opening polymerization of lactide (LA) and glycolide (GA) (mole ratio of LA: GA 3:1) with or without polyethylene glycol (PEG). Amoxicillin loaded magnetic PLGA and PLGA-PEG nanoparticles were prepared by an emulsion-evaporation process (o/w). Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) photomicrographs showed that the magnetic nanoparticles have the mean diameter within the range of 65-260 nm also they were almost spherical in shape. Magnetic nanoparticles prepared with PLGA showed more efficient entrapment (90%) as compared with PLGA-PEG (48-52%) nanoparticles. *In-vitro* release of amoxicillin from magnetic PLGA nanoparticles showed that 78% of drug was released over 24 hours. The amount of amoxicillin released from PLGA-PEG s was higher than PLGA.

Key Words : Magnetic nanoparticles, PLGA, PLGA-PEG, Amoxicillin, Drug release

Introduction

Magnetic drug delivery by particulate carriers is a very efficient way of delivering drug to a localized diseases site at the gastrointestinal (GI) tract.[1,2] The speed of travel through the stomach and intestines can be slowed down at specific positions by an external magnet, thus changing the timing and/or extent of drug absorption in stomach or intestines. Regarding biomedical applications, the iron oxides magnetite (Fe_3O_4) and maghemite (Fe_2O_3) are amongst the most studied magnetic particles to date, because of their generally appropriate magnetic properties and biological compatibility. These magnetite particles dissolve in acid media and proper protection against gastric dissolution is an essential step to enable their use for local drug delivery in the GI tract. Furthermore some drug are unstable in low pH thus protecting compounds from gastric environment is a key issue in pharmaceutical technology. A number of different approaches have been proposed so far, including coating with pH-sensitive polymers, time dependent delivery systems, and the use of biodegradable polymers.[3]

Magnetic nanoparticles (MNPs) can be used to enhance the specific accumulation of nanoparticles within diseased tissue. By integrating therapeutic agents, these multifunctional MNPs can serve firmly as a vehicle for drug delivery. The advantage of these MNPs, is their high surface area-to-volume ratios allowing for a large number of therapeutic molecules to be attached to individual nanoparticles. Also, while utilizing an active targeting strategy for specific delivery, the magnetic properties of the nanoparticle may be used to give imaging modality for monitoring of drug delivery through MRI,[4] or a substitute source of treatment through magnetic fluid hyperthermia (MFH) therapy. Recently developed drug capsule is based on the heating effect of a magnetic absorber (iron oxide) in an irregular magnetic field caused by hysteresis losses.[5]

Helicobacter pylori (H. pylori) are spiral-shaped gram-negative bacteria with polar flagella that live near the surface of human gastric mucosa. It is the only known organism capable of colonizing the harsh environment of the human stomach, and is the most common chronic bacterial infection. For effective treatment of H. pylori, stability of the drug in the low pH of gastric fluid, and a minimum residence time of the antibiotic in the stomach are required.[6-9]

Some antibacterial agents such as amoxicillin and tetracycline have low minimum inhibitory concentration (MIC) values against H. pylori in culture. However, single antibiotic therapy is not effective in the eradication of H. pylori infection *in vivo*, due to the low concentration of the antibiotic reaching the bacteria under the mucosa and the short residence time of the drug on the site of the infection. One possible way to achieving both requirements is the magnetic vectorization of antibiotic in polymerized magnetic particles, with low-gastric dissolution rate.[3] By combining the biodegradability of the aforementioned polyester particles with the super paramagnetic properties of magnetite nanocrystals one can prepare a magnetically responsive drug delivery system which can be simultaneously used for diagnostic applications.[10] The super paramagnetic properties conferred by magnetic nanocrystals encapsulated into biodegradable particles allow them to be accumulated in a specific part of the body by applying an external magnetic field and release there a previously loaded active pharmaceutical ingredient.[11]

Magnetic delivery of antibiotics for treatment of H. pylori has been studied. In one approach the dosage form containing a small internal magnet, and a magnet placed on the abdomen over the position of the stomach has been use.[12] Magnetic tablet containing 50% w/w ultra ferrite with hydroxypropylcellulose and cinnarizine has also been prepared. In beagle dogs, the tablet remained in the stomach for 8 h by the application of a magnetic field (1000 to 2600 G).[13] A method for determining the gastrointestinal transit of magnetic dosage forms under the influence of an extracorporeal magnet,using a pH-telemetering capsule (Heidelberg capsule) has been developed. Smallmagnets were attached to the capsule and administered tohumans. Using an extracorporeal magnet, gastric residencetime of the dosage form was > 6 h compared with 2.5 h control.[14]

In present work, we have reported the synthesis, characterization and drug release behavior of amoxicillin-loaded magnetic poly (lactide-*co*-glycolide) (PLGA) and poly (lactide-*co*-glycolide)-polyethylene glycol (PLGA-PEG) biodegradable nanoparticles. Different ratios of lactide and glycolide were employed to obtain a suitable copolymer composition with high drug encapsulation efficiency.

Experimental Procedures

Materials and Methods. DL-Lactide (LA), ferric and ferrous chloride salts were obtained from sigma (St. Louis, MO, USA).

Glycolide (GA) purchased from Purac (Holland). Poly ethylene glycol (PEG, Mw 2000 & 4000), dichloromethane (DCM) and ammonium hydroxide $NH_3{\cdot}H_2O$ (30% w/v) were obtained from Merck chemical co. (Germany). Poly vinyl alcohol (PVA, Mw 10000), and stannous octoate (SnOct) from Sigma Chemical Co. (St. Louis, MO, USA). Amoxicillin was provided by Dana Pharmaceutical co. (Tabriz, Iran).

Synthesis of Poly (lactide-*co*-glycolide) copolymer (PLGA). Poly (lactide-*co*-glycolide) copolymer (PLGA) was prepared by a ring opening polymerization method.[11,12] Briefly, lactid (0.684 mol) and glycolide (0.838 mol) were mixed in a three necked flask equipped with N_2 outlet heated while stirring to 140 °C under nitrogen atmosphere followed by addition of SnOct (0.05% w/w). After 15 minutes the brown viscous mixture reacted further at 140 °C for 10 h. After cooling, the mixture was dissolved in chloroform and the solvent was separated. Some diethyl ethers purred in organic polymer solution and residue polymer was collected.

Synthesis of Tri-block Poly (lactide-*co*-glycolide)-polyethylene Glycol Copolymer (PLGA-PEG). Lactide, glycolide and PEG (average molecular weight of 2000 and 4000) were mixed in a three necked flask equipped with N_2 outlet (according to Table 2). Temperature of the reaction was raised to 140 °C. Then stannous octoate (0.05% w/w) was added. The mixture was stirred under N_2 atmosphere at 140 °C for 10 h. After 10 h the reaction was stopped and the flask was cooled down to room temperature. The residue was dissolved in dichloromethane (50 mL). The polymer solution was precipitated in a large amount of cold chloroform.[15,16] The structures of copolymers were characterized by FT-IR, ^{13}C-NMR and ^{1}H-NMR.

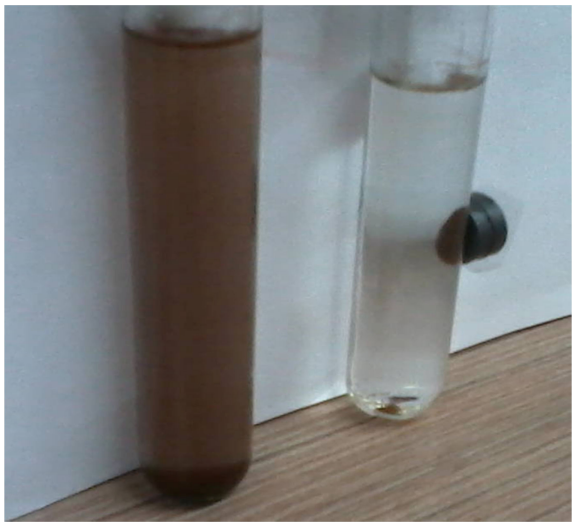

Figure 1. Magnetic nanoparticle suspensions attached to a magnet.

Synthesis of Superparamagnetic Magnetite Nanoparticles. Super paramagnetic magnetite NPs were prepared *via* improved chemical coprecipitation method.[17] According to this method, 3.1736 g of $FeCl_2{\cdot}4H_2O$ (0.016 mol) and 7.5684 g of $FeCl_3{\cdot}6H_2O$ (0.028 mol) were dissolved in 320 mL of deionized water. The mixed solution was stirred under N_2 at 80 °C for 1 h. Then, 40 mL of $NH_3{\cdot}H_2O$ (30% w/v) was injected into the mixture rapidly, stirred under N_2 for another 1 h and then cooled to room temperature. The precipitated particles were washed five times with hot water and separated by magnetic decantation according to Figure 1.

Characterization of Poly (lactide-*co*-glycolide) (PLGA) and PLGA-PEG.

Study of Thermal Properties: Glass transition temperature (Tg) was determined using differential scanning calorimetric measurements (DSC7 Perkin Elemer, Waltham, USA). All measurements were conducted in crimped nonhermetioc aluminium pans by heating the samples at a rate of 10 °C/min from 20 to 180 °C, with an empty crimped aluminum pan used as reference. T_g was considered at the mid-point temperature of the endothermic drift in the heating curve. All DSC tests were carried out under a 2 mL/min flow of nitrogen to prevent oxidation.[18]

Determine of Average Molecular Weight and Polydispersity Index: The molecular weight and molecular weight distribution (polydispersity index, Mw/Mn) of copolymers were determined by gel permeation chromatography (GPC, waters 515 HPLC pump, USA), that is equipped with a refractive index detector, using a series of high-resolution columns (waters, styragel HR4E 7.8 mm × 300 mm and styragel HR3E 7.8 × 300 mm) and tetrahydrofuran (THF) as a mobile phase. Tetrahydrofuran was used as eluent at 45 °C and polystyrene standards (polymer laboratories, Inc. USA). Total time for analyzing of samples which were injected after dissolving in THF solvent was 10-15 minutes.

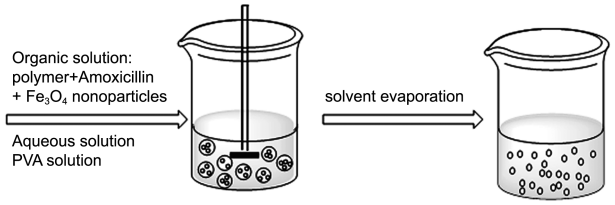

Figure 2. Scheme of emulsification-solvent evaporation method for preparation of amoxicillin-loaded magnetic nanoparticles.

Fourier Transforms Infrared Spectroscopy: FT-IR spectra obtained by FT-IR spectrophotometer (Shimadzu 8400, Kyoto Japan) for blank and drug loaded nanoparticles using KBr discs.

^{1}H- NMR Spectroscopy: The chemical structures of the copolymers were determined by ^{1}H-NMR (Bruker spectra spin 400 MHz, Leipzig, Germany).

Preparation of Magnetic PLGA Nanoparticles Containing Amoxicillin. Amoxicillin-loaded magnetic PLGA nanoparticles were prepared according to the method reported in the literature with slight modification.[19] Briefly, 500 mg magnetic NPs were dispersed into DCM solution containing (1 g PLGA and100 mg amoxicillin in 20 mL DCM) to form a stable magnetite oily suspension, the oily suspension was added into a 60 mL aqueous PVA solution containing (1% w/v) and homogenized (Edmund Buhler HO 4AP homogenizer 10000 rpm 3 × 10 s, Germany) at room temperature. The organic phase was removed using a rotary evaporator under a reduced pressure (Heidolph, Germany).

Drug Loading Determination. A certain amount of drug-loaded nanoparticles were ground to powder. About 200 mg was accurately weighed and transferred into a 100-mL flask with distilled water to the volume of 90 mL. The suspension was sonicated in a water bath and then filtered through a 0.45 μm membrane filter. The amount of drug in the solution was determined by UV-vis. Spectrophotometer (UV Shimadzu 160) at 272 nm. Loading capacity was expressed in term of entrapment efficiency (EE %) as follows :

$$EE\% = \frac{\text{Amount of loaded amoxicillin in nanoparticles}}{\text{Amount of drug used in formulation}} \times 100$$

Determination of Particle Size and Morphology of the Drug-loaded Nanoparticl. The size and morphology of the polymeric nanoparticles was observed using a transmission electron microscopy (TEM) and scanning electron microscopy (SEM, Leo Electron Microscopy Ltd, Cambridge, UK). For transmission electron microscopy (TEM), a drop of drug loaded nanoparticle suspension in aqueous solution was placed on a carbon film coated on a copper grid for TEM and freeze-dried. Observation was performed at 80 kV using LEO 906 TEM (Zeiss, Germany). For the scanning electron microscopy (SEM), the lyophilized nanoparticles were placed on a double stick tape over aluminum stubs to get a uniform layer of particles. Samples were then gold-coated using a sputter gold coater. Gold coated particle samples were cooled over liquid nitrogen prior to SEM observations to avoid their melting under high magnification due to the electron beam exposure. Prior to examination, samples were prepared on aluminum stubs and coated with gold under argon atmosphere by means of a sputter coater.[20]

***In-vitro* Drug Release Test.** The *in vitro* release of amoxicillin from magnetic nanoparticles was carried out at 37 °C in buffered solutions (pH 1 and 7.4 for simulation of stomach and intestine pH, respectively). In each experiment, 100 mg polymer was taken in 20 mL buffer solution. The beakers were placed in a shaker incubator maintained at 37 °C. At predetermined time intervals, 3 mL of samples were removed from the external buffer solution and were replaced with fresh buffer solution. The amoxicillin released into the medium was analyzed using an UV-Vis spectrophotometric method at 272 nm.

Results

Synthesis of Magnetic Iron Oxide Nanoparticles. Magnetite is prepared by adding a base to an aqueous mixture of Fe^{2+} and Fe^{3+} chloride at a 1:2 molar ratio. The precipitated magnetite is black in color. The chemical reaction of Fe_3O_4 precipitation is given in Figure 3. The overall reaction may be written as follows:

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \rightarrow Fe_3O_4 + 4H_2O \quad (1)$$

According to the thermodynamics of this reaction, a complete precipitation of Fe_3O_4 should be expected between pH 9 and 14, while maintaining a molar ratio of Fe^{3+}:Fe^{2+} is 2:1 under a non-oxidizing oxygen free environment. Otherwise, Fe_3O_4 might also be oxidized as:

$$Fe_3O_4 + 0.25O_2 + 4.5H_2O \rightarrow 3Fe(OH)_3^- \quad (2)$$

Characterization of Copolymers. PLGA and PLGA-PEG block copolymers were synthesized by ring opening polymerization method according to Table 1.

The chemical composition of the copolymers was determined with ^{1}H-NMR and ^{13}C-NMR by integrating the signals pertaining to each monomer. As an example, Figure 4 shows ^{1}H-NMR spectrum of the PLGA (a) and PLGA-PEG (b). The multiplets at 5.3 and 4.8 ppm correspond to the lactide CH and the glycolide CH_2, respectively and the peak at 1.6

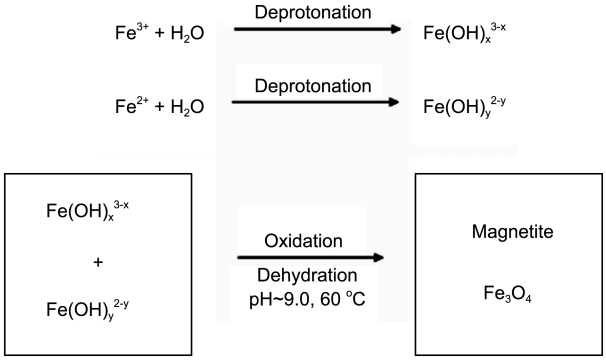

Figure 3. Scheme showing the reaction mechanism of magnetite particle formation from an aqueous mixture of ferrous and ferric chloride by addition of a base.

Table 1. Conditions used for preparation of PLGA and PLGA-PEG*

Sample code	PEG (Mw)	PEG (wt %)	Polymerization yield (%)	Average molecular weight Mw	Mn	Mw/Mn
PLGA	-	0	74.5	5845	4175	1.4
$PLGA\text{-}PEG_{2000,5}$	2000	5	63.2	6813	3785	1.8
$PLGA\text{-}PEG_{2000,10}$	2000	10	51.5	4513	2149	2.1
$PLGA\text{-}PEG_{4000,5}$	4000	5	42.6	9343	3737	2.5
$PLGA\text{-}PEG_{4000,10}$	4000	10	38.3	4218	1507	2.8

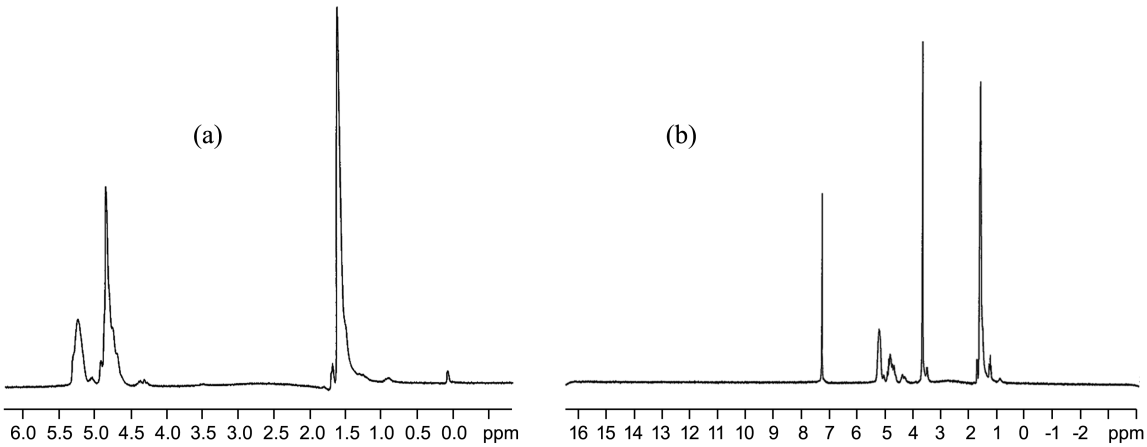

Figure 4. ^{1}H-NMR spectrum of Poly (lactide-*co*-glycolide)-polyethylene glycol with different compositions (a) PLGA and (b) PLGA-PEG.

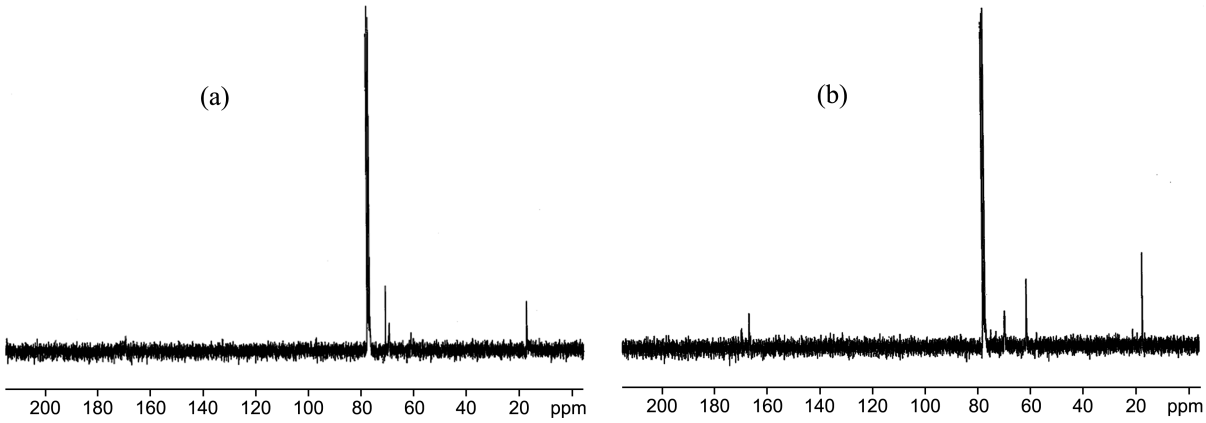

Figure 5. ^{13}C-NMR spectrum of Poly (lactide-*co*-glycolide)-polyethylene glycol with different compositions (a) PLGA polymer, (b) PLGA-PEG NPs.

corresponds to lactide CH_3 and the large peak at 3.6 ppm corresponds to the methylene groups of PEG.

Figure 5 shows the ^{13}C-NMR spectrum of PLGA (a) and PLGA-PEG (b). ^{13}C-NMR analysis revealed the presence of three sets of peaks. The first corresponds to carboxylic and carbonyl bonds (168.9 ppm), the second one (71.1-63.5 ppm) corresponds to CH bonds in lactic acid and CH_2 in glycolic acid and the third one corresponds to methylen groups of the d,l-lactic acid repeated units (18.2 ppm). On the contrary, ^{13}C-NMR analysis of PLGA-PEG (b), revealed a marked increase in the intensity of the first peak (171.6-169.1 ppm), with a significant inversion in the intensity of the second set of peaks that is even noticeable at the lower proportion at which PEG derivative was used (5% with respect to PLGA).

Fourier Transforms Infrared Spectroscopy. The Fourier transforms infrared (FT-IR) spectra of the PLGA (a), PLGA-PEG (b), amoxicillin (c), amoxicillin loaded PLGA magnetic nanoparticles (d) and amoxicillin loaded PLGA-PEG magnetic nanoparticles (e) are shown in Figure 6. Prominent peak at 1765-1750 cm^{-1} corresponded to (C=O bonds) and C-C-O bonds was observed at 1300-1090 cm^{-1} and eteric bonds (C-O-C) appears at 1085-1190 cm^{-1}. The carboxylic acid end groups of the polymer were observed at 3000-3100 cm^{-1}. The bond at 2950 cm^{-1} clearly indicates the presence of (ethylene glycol) (C-H). FT-IR spectrum of amoxicillin

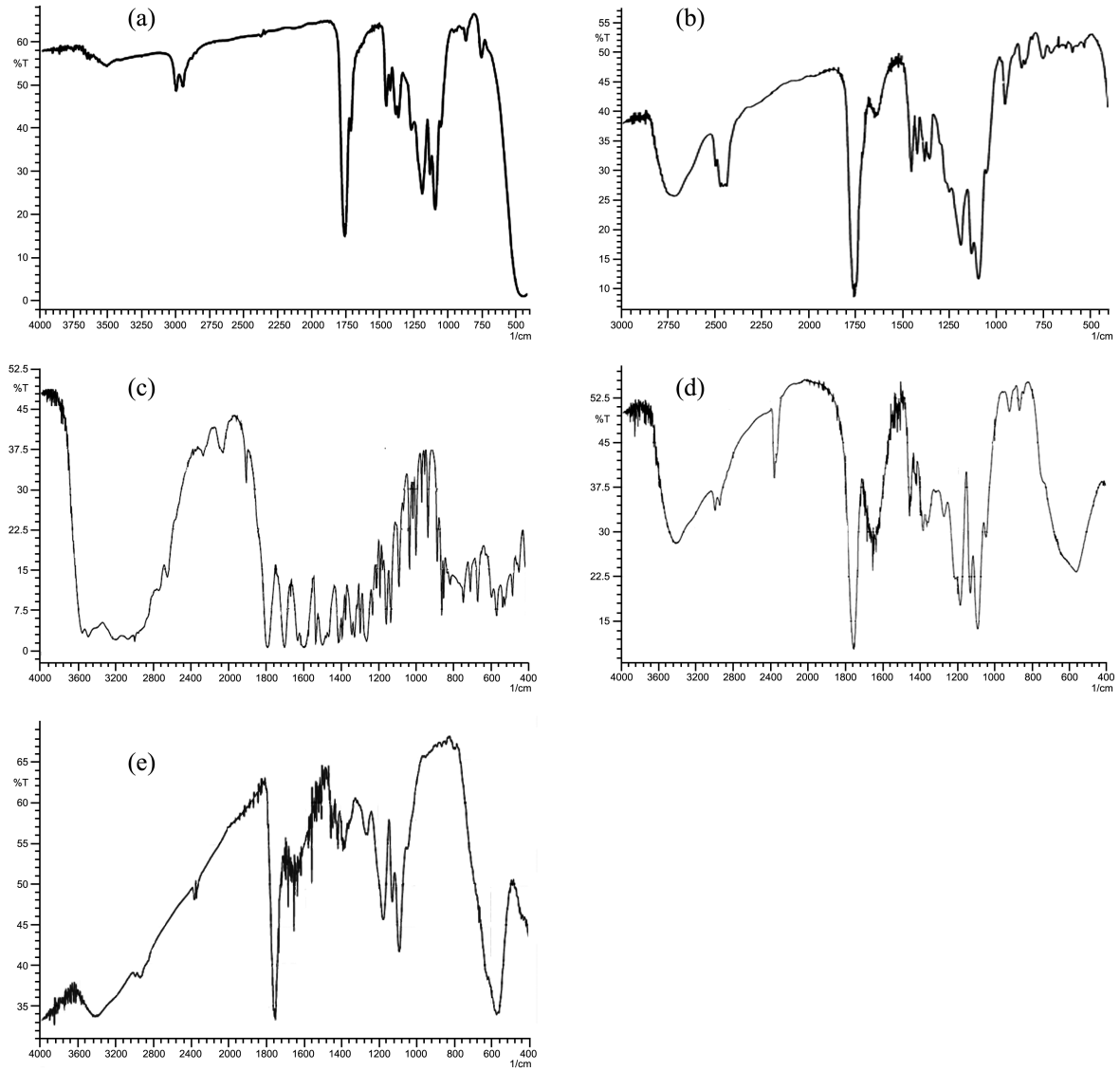

Figure 6. FT-IR spectrum of (a) PLGA, (b) PLGA-PEG, (c) amoxicillin, (d) PLGA containing amoxicillin and Fe_3O_4 (e) PLGA-PEG with drug and Fe_3O_4.

showed characteristic peaks of amide I and amide III at 1653 and 1322 cm^{-1}. The presence of absorption bond at 1760-1730 corresponded to betalactam ring. FT-IR spectrum of amoxicillin loaded PLGA and PLGA-PEG magnetic nanoparticles are shown in Figure 5(d, e), the presence of absorption bond at 580 cm^{-1} is attributed to the Fe-O and peak at 3400 cm^{-1} corresponded to –OH vibrations of Fe_3O_4 NPs.

Thermal Properties of PLGA Copolymer. Thermal properties of PLGA copolymers were determined by differential scanning calorimetry (DSC). Thermogram analysis of glass transition temperature of PLGA and PLGA-PEG copolymers are shown in Figure 7. PLGA exhibited transition temperature (*T*g) about 48 °C. However, the incorporation of PEG chains caused a slight decrease in the *T*g values of PLGA-PEG derivatives (about 45.5 °C for both PEG_{2000} and PEG_{4000}). The plasticizing effect of PEG segments is based on the reduction of the attractive forces among the polymer chains.

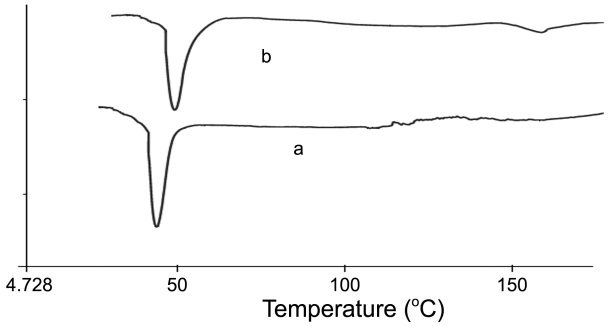

Figure 7. DSC termograms of copolymers; (a) PLGA-PEG (b) PLGA.

Physicochemical Characterization of Synthesized Nanoparticles. Amoxicillin-loaded magnetic PLGA-based nanoparticles were prepared by a double emulsion-solvent evaporation method in the presence of magnetic Fe_3O_4 nanoparticles. Physicochemical characteristics of amoxicillin-

Table 2. Physical characteristics of synthesized polymers*

Formulation no.	Polymer type	Encaosulation efficiency (%)	Particle size (nm)	Release % after 24 h (pH 7.4)	Release % after 24 h (pH 1)
F1	PLGA	90 ± 14	260 ± 25	62	78
F2	PLGA-$PEG_{2000,5}$	52 ± 9.5	65 ± 14	68	90
F3	PLGA-$PEG_{4000,5}$	48 ± 6.5	86 ± 11	64	84

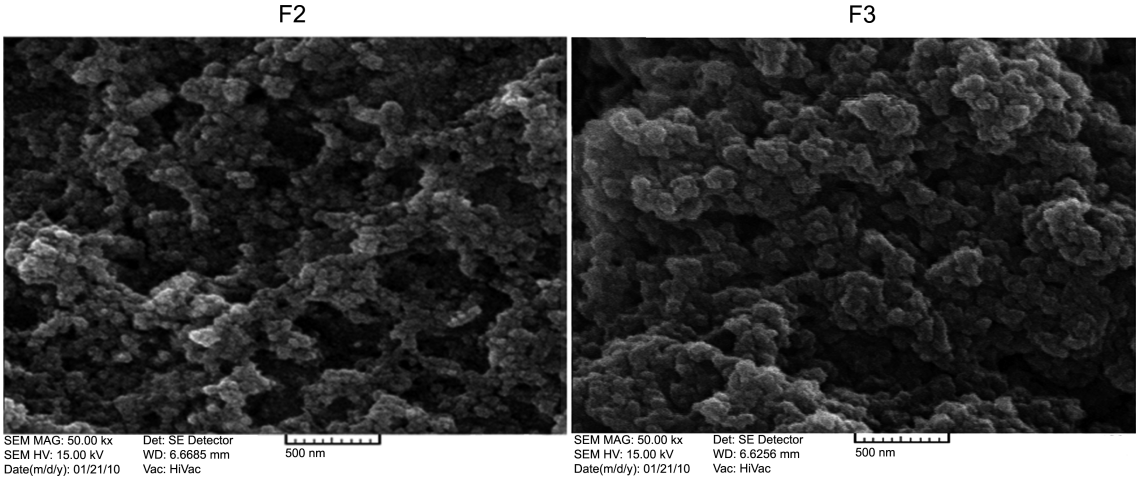

Figure 8. SEM of magnetic PLGA nanoparticles (F1), PLGA-$PEG_{2000,5}$ nanoparticles (F2), PLGA-$PEG_{4000,5}$ nanoparticles (F3).

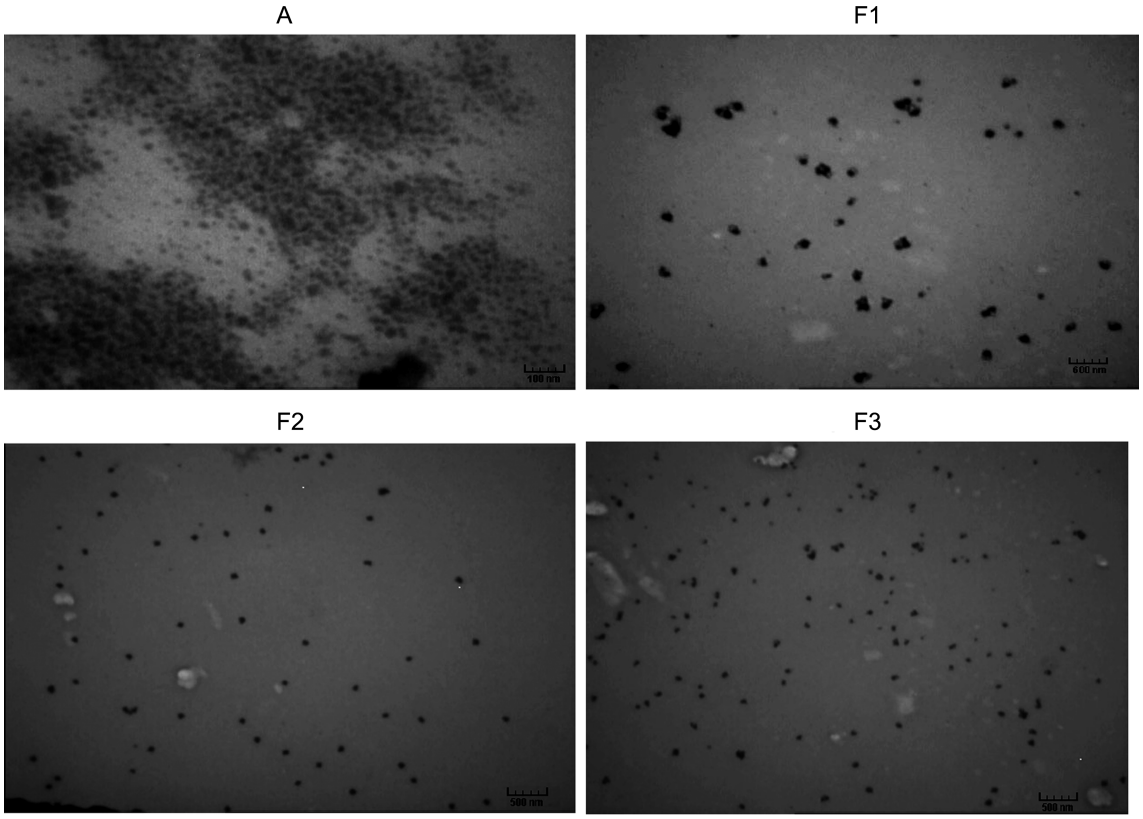

Figure 9. TEM pictures of Fe_3O_4 magnetic nanoparticles (A), magnetic PLGA nanoparticles (F1), PLGA-$PEG_{2000,5}$ nanoparticles (F2), PLGA-$PEG_{4000,5}$ nanoparticles (F3).

loaded nanoparticles are shown in Table 2. In this table the mean particle size and encapsulation efficiency of the samples were listed along with the polymer type and the drug release % after 24 h. Figure 8 and Figure 9 shows the

SEM and TEM micrographs of the magnetic PLGA-based nanoparticles. SEM and TEM micrographs of all drug-loaded magnetic nanoparticles revealed relatively spherical morphology. The average particle size of samples was 65-260 nm. In comparision with PLGA-PEG nanoparticle, amoxicillin-loaded PLGA nanoparticles showed higher encapsulation efficiency (about 90%). The smallest particles were obtained with PLGA-$PEG_{2000,5}$.

1 g polymer, 100 mg amoxicillin in 20 mL DCM and 500 mg magnetic nanoparticles were used for all formulations.

The copolymer composition and molecular weight would critically affect the physical and chemical properties of the nanosized magnetic particles. In order to prevent them from possible oxidation in air as well as from agglomeration, Fe_3O_4 nanoparticles produced by reaction (1) are usually coated with organic or inorganic molecules during the precipitation process. To control the reaction kinetics, which is strongly related with the oxidation speed of iron species, the synthesis of particles must be done in an oxygen-free environment by passing N_2 gas. Bubbling nitrogen gas through the solution not only protects critical oxidation of the magnetite but also reduces the particle size when compared with methods without removing the oxygen.[21]

Drug Loading Efficiency. As shown in Table 2 the encapsulation efficiency and particle size of drug-loaded nanoparticles were depended on polymer composition. The loading efficiency of PLGA nanoparticles was higher than PLGA-PEG magnetic nanoparticles (according to Table 2). About 90% of the incubated drug was loaded into the PLGA-coated magnetic nanoparticles, which was higher than other studies.[22]

***In vitro* Release of Amoxicillin from Nanoparticles.** The release behavior of the nanoparticles was studied for F2 formulation which had smaller particle size and compared with formulation F1 (PLGA). Release studies were carried out for 24 hours in phosphate buffer solutions (pH 1 and pH 7.4) at 37 °C.

The percentage of amoxicillin release from PLGA nanoparticles (formulation F1) is shown in Figure 10. Burst release of amoxicillin was observed in both pH medium for the initial 1 h. About 59% of amoxicillin entrapped in the

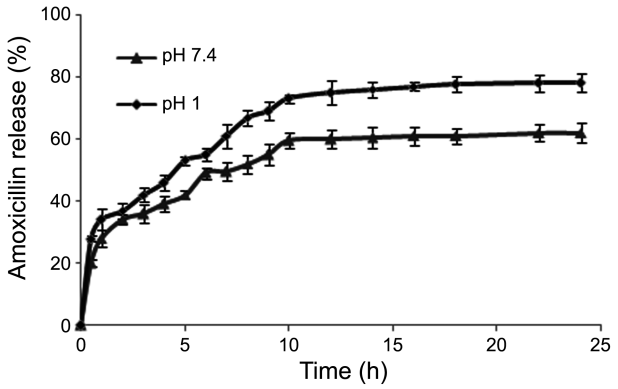

Figure 10. Amoxicillin release curves from PLGA coated magnetic nanoparticles in different mediums: pH 7.4 phosphate mediums and pH 1.0 hydrochloric acid.

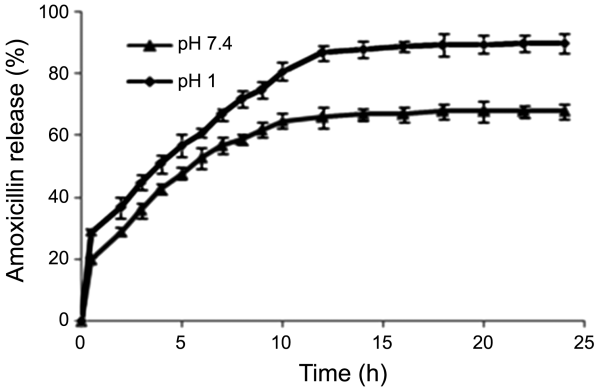

Figure 11. Amoxicillin release curves from PLGA-$PEG_{2000,5}$ coated magnetic nanoparticles in different mediums: pH 7.4 phosphate mediums and pH 1.0 hydrochloric acid.

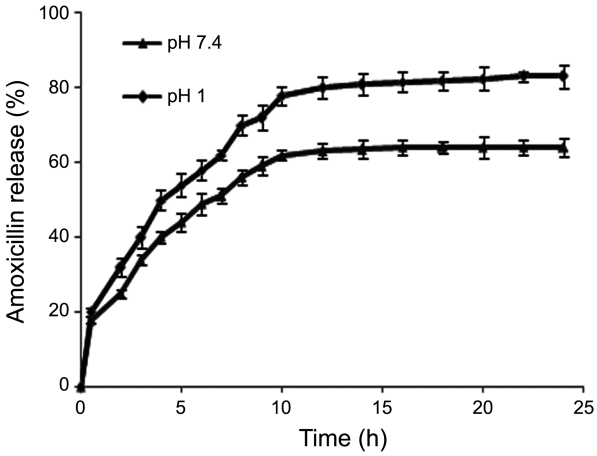

Figure 12. Amoxicillin release curves from PLGA-$PEG_{4000,5}$ coated magnetic nanoparticles in different mediums: pH 7.4 phosphate mediums and pH 1.0 hydrochloric acid.

polymer coated magnetic nanoparticles was released in 4 hours in the pH 1 medium, while in phosphate buffer solution at pH 7.4, no more than 40% was released.

The percentage of amoxicillin release from PLGA-PEG nanoparticles (formulation F2 and F4) are shown in Figure 11 and Figure 12. As shown in Figure 8 and Figure 9 the amount of amoxicillin released from PLGA-PEGs were higher than PLGA because of the more hydrophilic character of these copolymers. The amount of released drug from PLGA-$PEG_{2000,5}$ was higher than PLGA-$PEG_{4000,5}$. Release profile from the magnetic nanoparticles shows that drug releases is pH dependent. As shown in Figures 7-9 in *vitro* amoxicillin release amount were higher in pH 1 than in pH 7.4 phosphate buffer solution.

Conclusion

Drug-loaded magnetic nanoparticles were synthesized using magnetite Fe_3O_4 and poly (lactide-*co*-glycolide) (PLGA) or poly (lactide-*co*-glycolide) -polyethylene glycol (PLGA-PEG) for the purpose of targeted antibiotic delivery. The prepared nanoparticles were evaluated to assess the various

parameters such as drug content analysis, particle size analysis (TEM and SEM Analysis), and *in-vitro* drug release studies. The cumulative percentage drug release from PLGA, PLGA-$PEG_{2000,5}$ and PLGA-$PEG_{4000,5}$ formulations were found to be 78%, 90% and 84% respectively. By observing the *in-vitro* drug release results of all formulation, PLGA-$PEG_{2000,5}$ formulation was found to be the best formulation with relatively high drug loading efficiency, smaller particle size and higher cumulative percentage drug release. The prepared nanoparticles released the drug in a controlled manner. Also the polymer used was nontoxic, biocompatible and act as a good carrier of the antibiotic drug. As the amoxicillin has a short biological half life, these magnetic PLGA-based nanoparticles could be used in the controlled released oral formulation of antibiotic drugs. Magnetic PLGA nanoparticles developed in this study may serve as a potential device for the delivery of antibiotic drug in which the primary target is the stomach or the upper small intestine, because release curves show that drug releases rate in pH 1 were significantly higher than in pH 7.4.

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