

RESEARCH PAPER

Core-shell magnetic pH-responsive vehicle for delivery of poorly water-soluble rosuvastatin

Mitra Amoli-Diva¹, Kamyar Pourghazi^{2,3*}

¹Department of Chemistry, Payam Noor University (PNU), Tehran, Iran

²Department of Chemistry, Karazmi (Tarbiat Moalem) University, Tehran, Iran

³Department of Research and Development, Darupakhsh Pharmaceutical Co., Tehran, Iran

ABSTRACT

Objective(s): Development of an oral sustained-controlled release vehicle which, slowly releases the drug and maintains an effective drug concentration for a long time is aimed.

Materials and Methods: A biodegradable magnetic polymeric drug delivery vehicle, using superparamagnetic iron oxide nanoparticles encapsulating by polyvinylpyrrolidone-block-polyethylene glycol-block-poly methacrylic acid (PVP-PEG-PMAA) was developed for targeted and controlled delivery of rosuvastatin. The carrier was characterized by TEM, XRD, and FT-IR techniques.

Results: A typical carrier has about a 9 nm magnetite core, about 20 nm mean diameter with a narrow size distribution. The loading efficiency and pH-controlled release properties of the carrier were examined using a hydrophobic model drug rosuvastatin. Maximum loading efficiency of about 96% and a release amount of 90% of 12 hours were achieved at 37 °C in pH 1.2. While in pH 5.5 and 7.2, release amount of 25% and 37% were obtained respectively.

Conclusion: The results indicate that the prepared pH-responsive polymer which covalently coated around magnetic nanoparticles is an efficient carrier with good loading capacity and controlled-release property.

Keywords: Drug delivery, Magnetic nanoparticles, Nano-carrier, pH-responsive polymer, Rosuvastatin

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INTRODUCTION

Among the various routes of drug delivery, oral route is perhaps the most preferred by the patient. Today, there is a growing interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time [1] because some drugs easily absorb from the gastrointestinal tract or have short half-lives eliminates quickly from the systemic circulation.

Thus, frequent dosing is required to achieve suitable therapeutic activity of them. For this reason, development of oral sustained-controlled release formulations is necessary to release

the drug slowly and maintain an effective drug concentration for a long time. Such a drug delivery system would be retained in the stomach after oral administration and release the drug in a controlled manner so that the drug could be supplied continuously to its absorption sites [2].

Various approaches have been proposed to increase gastric residence of drug delivery systems or increase maintenance time of delivery vehicles such as raft forming systems [3], mucoadhesion or bioadhesion systems [4], and magnetic systems [5, 6].

Today, magnetic nanoparticles (MNPs) with supermagnetism property and high surface to volume ratio have widespread applications in many areas such as biology, pharmacy and diagnostics [7-9]. They can separate from the

* Corresponding Author Email: kmrpourghazi@gmail.com

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solution using an external magnetic field and re-disperse when the magnetic field withdraws. This feature is essential in biomedical applications, because MNPs do not retain their magnetism after removal of the external magnetic field, and thus maintain their colloidal stability and prevent clogging of the vessels and capillaries [10]. Therefore, they have potential to revolutionize current diagnostic and therapeutic techniques. This material is one of FDA-approved materials used in vivo and has been utilized in magnetic separation of biological entities, hyperthermia treatment, magnetic resonance imaging (MRI), and drug delivery [11]. But, it is noticeable that MNPs designed for biomedical applications are required to form a non-toxic aqueous dispersion of nanoparticles with a narrow size distribution, good colloidal stability under physiological conditions, and prolonged circulation in the bloodstream [10]. However, when MNPs are administered intravenously, they tend to agglomerate through Van der Waals attractions [12], adsorb plasma proteins and consequently, form large aggregates that are quickly cleared from the bloodstream by macrophages in organs of the reticuloendothelial system (RES), namely lungs, liver, and spleen [13]. To overcome this problem, they are often encapsulated in a biocompatible polymeric matrix, which enables the attachment of an anticancer drug by chemically binding to the polymer, direct entrapment on the particle, or by dispersion in the polymeric matrix [10]. Our important technology in this study is surface modification using biocompatible polymers, namely poly ethylene glycol (PEG), poly methacrylic acid (PMAA) and polyvinylpyrrolidone (PVP).

On the other hand, a great challenge that researchers have to confront with is the effective clinical application of hydrophobic agents, because of the poor solubility of most therapeutic drugs for treatment in aqueous media [14, 15]. Rosuvastatin is a synthetic lipid lowering agent which is used in hypercholesterolemia. It is a selective and competitive inhibitor of HMG-CoA reductase [16]. It inhibits the enzyme 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme that converts HMG-CoA to mevalonate, a precursor of cholesterol, and thereby checks the synthesis of cholesterol. It is used in the treatment of hyper-cholesterolemia and dyslipidemia. Also, drug is reported to be unstable in acidic pH. Thus, a formulation with

a high degree of oral absorption and extended delivery potential would be highly desirable for this drug.

In the present investigation, we report the development of a multifunctional polymeric drug delivery system aiming to deliver hydrophobic drug. This drug delivery system is consisting of Fe_3O_4 nanoparticles grafted polyvinylpyrrolidone-block-polyethylene glycol-block-poly methacrylic acid (PVP-PEG-PMAA). The prepared carrier was characterized by transmission electron microscopy (TEM), X-Ray diffraction (XRD), and Fourier transformation infrared spectroscopy (FT-IR) techniques. Rosuvastatin was used as a model drug in our tests and the carrier was examined for loading efficiency and sustained release, which are important profiles for successful and efficient drug delivery. Finally, the possible mechanism for delivery of rosuvastatin was discussed. The results revealed that the use of pH-responsive polymer coated MNPs as the carrier might be a promising strategy for the dosing of hydrophobic drugs.

MATERIALS AND METHODS

Chemicals and reagents

All chemicals and reagents were of analytical grade and used without further purification. Polyethylene glycol (PEG), ferric chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$), ferrous chloride tetrahydrate ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$), aqueous ammonia (25% w/w), 3-aminopropyl triethoxy silane (APTS), methanol, acetic acid, sodium acetate trihydrate ($\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$), sodium hydroxide, potassium hydrogen phosphate, glycerol, hydrochloric acid, potassium chloride, methacrylic acid (MAA), and ethylene glycol dimethacrylate (EGDMA) were purchased from Merck Company (Darmstadt, Germany). Polyvinylpyrrolidone (PVP, Mw = 40000) was purchased from Rahavard Tamin Chemical Co. (Saveh, Iran) and 2, 2'-azobis isobutyronitrile (AIBN) was purchased from ACROSS (Geel, Belgium). Rosuvastatin standard was received from faculty of pharmacy, Tehran University, Iran and deionized water was used throughout the experiments.

Synthesis of APTS coated MNPs

The MNPs were prepared via a simple chemical co-precipitation method as reported in the literature [17] with slight modifications. Briefly, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (5.8 g) and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (2.1 g) were dissolved in 100 mL deionized water under

nitrogen atmosphere with vigorous stirring at 85 °C. Then, ammonia solution (20 mL, 25% w/w) was added to the solution. The color of the solution turned immediately to black. The suspension was stirred for 15 min and then, washed with deionized water (200 mL, three times) and 0.02 M sodium chloride (100 mL, once). Functionalization of MNPs was carried out by exploiting the chemistry of silane molecules, according to the procedure previously reported [12]. Typically, 40 mL of aqueous solution of APTS (10 % v/v) was added to the above precipitate was followed by glycerol (30 mL). The suspension was stirred at 90 °C for 2 h under nitrogen atmosphere. After cooling down to room temperature, the suspension was washed sequentially with deionized water (3×150 mL) methanol (2×100 mL) and deionized water (3×150 mL). Finally the APTS coated MNPs were dried in an oven at 50 °C.

Synthesis of magnetic nano-carrier

The polymeric PVP-PEG-PMAA layer on the surface of MNPs was synthesized via radical polymerization procedure. First, 40 mg of PVP, 40 mg of PEG, 1.5 mL of MAA (0.4 mM), 1.5 mL of EGDMA (0.4 mM) as the cross-linker, 30 mg of AIBN as the initiator and 30 mg of APTS coated MNPs were added to 12 mL of methanol in a 50 mL conical flask. The solution was bubbled with nitrogen gas and continuously stirred under a nitrogen atmosphere for 15 min. Next, the mixture was placed in a water bath for 8 h at 70 °C with vigorous stirring. Finally, the suspension was allowed to cooling down to the room temperature, centrifuged at 3000 rpm for 20 min and sequentially washed with 250 mL of deionized water (twice), 100 mL of methanol (twice) and 200 mL of deionized water (three times) under centrifugation to thoroughly remove non-reacted monomers and reagents followed spectrophotometrically (UV-240 Shimadzu, Tokyo, Japan). Finally the carrier was dried in vacuum oven at 50 °C for 24 h. The product was denoted as the nano-carrier.

Characterization

The particle size and morphology of APTS coated MNPs and the nano-carrier were evaluated using Phillips CM120 and EM2085 transmission electron microscopes (Amsterdam, Netherlands) with an accelerating voltage of 100 kV. Images were obtained by placing 50 µL of modified MNPs

or nano-carrier suspension (2 mg mL⁻¹) in deionized water on 300 mesh carbon-coated TEM copper grids and the average size of the nanoparticles was measured based on more than 350 particles from the TEM images. Phase characterization of APTS coated MNPs was performed using Phillips PW-1800 (Amsterdam, Netherlands) X-Ray diffractometer by Cu-Kα radiation wavelength of 1.540598 Å, current of 40 mA, step size of 0.1° 2θ, and matching peak positions to the Joint Committee on Powder Diffraction Standards (JCPDS) card file No.79-0418. The sample was mounted on a glass slide and measurements were performed range from 10° to 80°. Chemical interactions of APTS and PVP-PEG-PMAA polymer with MNPs were studied by Perkin Elmer Spectrum one Bv5.3.0 (Waltham, MA, USA) Fourier transform infrared spectroscopy in the range of 400-4000 cm⁻¹ for samples dispersed in KBr pellets.

Swelling studies

The swelling behavior of the nano-carrier was measured gravimetrically in different buffered solutions with pH in the range of 1.2-9 according to procedure described previously [18-20]. After soaking into each pH, the particles were allowed to swell for approximately 72 h to reach a swelling equilibrium. After this time, the excess water was removed with a filter paper and the samples were weighed. Average value of three measurements was taken for each sample and the swelling ratio was calculated using the following equation:

$$\text{Swelling ratio} = (W_s - W_d) / W_d$$

Where W_s is weight of swollen carrier and W_d is weight of the carrier before swelling.

Drug loading and release studies

The dried nano-carrier (500 mg) was transferred to a 100 mL beaker containing 50 mL of 40 µg mL⁻¹ of rosuvastatin. The solution was left to equilibrate for 24 h to ensure that the hybrid hydrogel reached equilibrium. Different concentrations of rosuvastatin were applied and un-loaded drug concentration in supernatant was measured spectrophotometrically at 238 nm. Appropriate dilution performed to ensure the absorbance was in the linearity range of Beer's law. Drug loading percentage was calculated using following equations [21]:

$$\text{Drug loading (\%)} = (W_{\text{Drug loaded}}) / (W_{\text{Total drug}}) \times 100$$

Where $W_{\text{Drug loaded}}$ is weight of rosuvastatin loaded to the carrier and $W_{\text{Total drug}}$ is total weight of

rosuvastatin. Then, drug-loaded carrier was washed three times with deionized water to remove unbounded or free drug and used for release experiments.

In-vitro release experiments were performed in simulated body conditions according to refs [22, 23] with slight modifications. Three buffered solutions with pH 1.2, 5.5 and 7.2 were used for release medium and the temperature was precisely controlled at 37 ± 0.1 °C. Then, 500 mg of rosuvastatin loaded nano-carrier was immersed into 25 mL of each buffered solution with magnetic stirring. At predetermined time intervals, stirring was canceled and the carrier was sedimented by centrifugation for 1 min. Then, 5 mL of the supernatant (release medium) was removed and the same volume of fresh buffer solution was replaced to compensate the decreased volume.

The withdrawn solution was analyzed spectrophotometrically to determine the cumulative drug released. In addition, effect of MAA concentration and MNPs content on the rosuvastatin release of the carrier was also investigated. Each measurement was performed in triplicates.

Mechanism of rosuvastatin release

To characterize the mechanism of drug release, Korsmeyer-Peppas model was used which describes drug release from a polymeric system. In this model, first 60% drug release data were fitted to Korsmeyer-Peppas equation of $M_t / M_\infty = Kt^n$ in which, M_t represents a fraction of drug released in time t , M_∞ is the amount of drug released after an infinite time, K represent a release rate constant incorporating structural and geometric characteristics of the carrier and n is release exponent.

The value of n is related to geometrical shape of carrier and used to characterize the type of release mechanism [17, 24]. In the case of spheres, the value of $n < 0.43$ corresponds to drug release from the polymer matrix by Fickian diffusion [25]. Similarly, the value of " n " in the range of 0.43-0.85 indicates diffusion controlled as well as swelling controlled drug release.

The $n > 0.85$ exhibits swelling controlled drug release, attributed to the polymer relaxation during swelling process.

RESULTS AND DISCUSSION

MNPs can be incorporated into polymer matrix by mixing them with a preformed polymer or by

adding MNPs during the polymerization process. In this way the hybrid polymer can be manipulated by an external magnetic force and deliver a large quantity of the drug. This strategy of incorporation has the limitation that the MNPs are only physically incorporated within the polymer. The consequence of such a physical incorporation is that a continuous release of MNPs from the matrix to human environment may occur, cause some potential effects of accumulation and perhaps toxicity for tissue to which the carrier is applied [26]. In this work, the MNPs were modified with APTS to form covalent bonds between hydroxyl groups present on the surface of the MNPs and the ethoxy groups of APTS [12]. The silanized MNPs present free amino groups on the surface to prevent MNP aggregation and allow the formation of amidic groups with the carboxylic groups of PMAA. So, synthesis of the polymeric nano-carrier involves the formation of an amide bond between the carboxylic groups of the PMAA and the primary amines of the APTS modified MNPs.

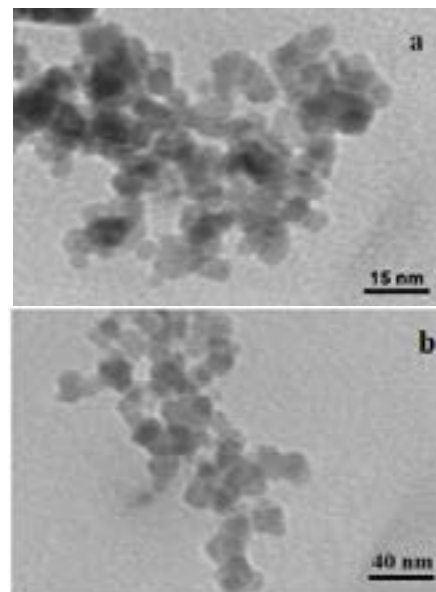


Fig. 1. TEM images of (a) APTS coated MNPs and (b) magnetic nano-carrier

Characterization

The size of a drug carrier is an important physicochemical parameter in developing an appropriate drug delivery system. Drug carriers designed for in vivo usage should be in the range of 10-100 nm to prevent elimination by the kidneys (<10 nm) and recognition RES (>100 nm). In this

study, we synthesized PVP-PEG-PMAA coated magnetic nanoparticles with a narrow particle size distribution. The TEM images of APTS-modified MNPs and the nano-carrier were shown in Fig. 1. The images reveal that silane modified MNPs has average size of 9 ± 2 nm. In absence of MNPs in polymerization reaction, polymeric nanoparticles tend to produce with larger size and they have not uniform shape with diameters in the range of 15-40 nm (results not shown here). After coating of MNPs with polymeric shell, its average size increases to 20 ± 3 nm.

Fig. 2 shows the XRD pattern of the prepared APTS-modified MNPs. Diffraction peaks at peak position (2θ) of 30.12, 35.57, 43.12, 53.51, 57.22 and 62.79 corresponding to 220, 311, 400, 422, 511 and 440 crystal planes of pure Fe_3O_4 nanoparticles respectively. It reveals that the prepared MNPs have cubic spinel structure according to the standard XRD data cards of Fe_3O_4 crystal (JCPDS

[17]). The results indicate that the modification with APTS did not change the crystal structure of MNPs.

FT-IR is a powerful technique for the characterization of various nanomaterials because of providing fingerprint vibration and rotation information. Fig. 3 represents FT-IR spectra of APTS coated MNPs and magnetic nano-carrier. The characteristic absorption band of Fe_3O_4 nanoparticles which occurs due to the stretching vibration of Fe-O bond was observed at about 580 cm^{-1} [27, 28]. This band is also present in the nano-carrier spectrum confirming the presence of MNPs in the structure of the carrier. The absorption band at 1039 cm^{-1} corresponds to the stretching vibration of Si-O band and the vibration of Fe-O-Si band at 587 cm^{-1} overlaps with Fe-O peak of MNPs and therefore cannot be distinguishable. Furthermore, the existence of two absorption bands at 3373 and 1632 cm^{-1} which are due to

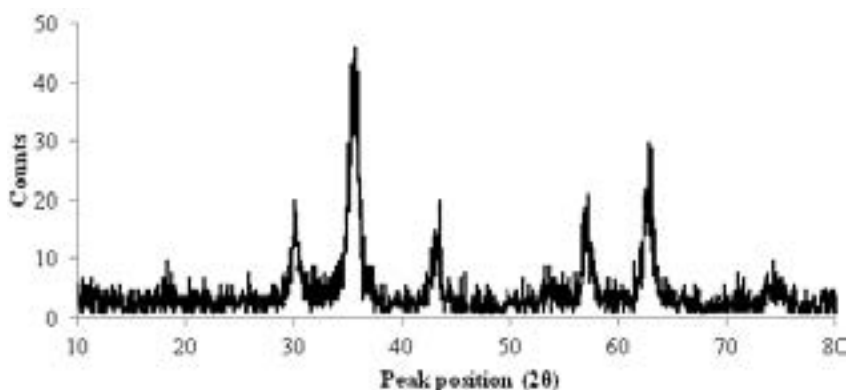


Fig. 2. The XRD pattern of the prepared APTS-modified Fe_3O_4

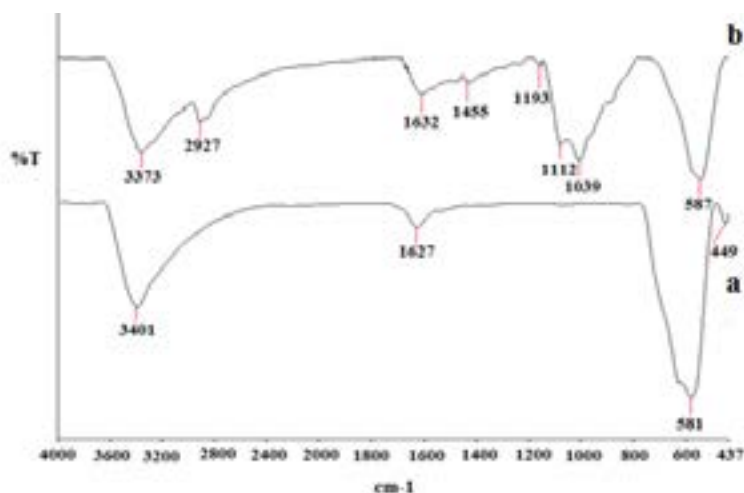


Fig. 3. FT-IR spectra of (a) APTS coated MNPs (b) magnetic nano-carrier

the N-H stretching and NH_2 bending modes of free NH_2 groups respectively, confirm the coating of MNPs with APTS [29]. These bands were also appearing in the nano-carrier spectrum. Although a broad absorption band at $\sim 3400 \text{ cm}^{-1}$ can be attributed to the OH groups of polymeric layer. On the other hand, the $\sim 1670 \text{ cm}^{-1}$ absorption band is typical of the ester/acid asymmetric stretching vibration of carbonyl groups in the nano-carrier. Furthermore, a vibrational peak at about 2953 cm^{-1} is corresponding to asymmetric stretching of -CH in the structure of the polymer [30] and the intense characteristic band at 1373 cm^{-1} is attributed to bending of -CH groups in polymeric layer.

Swelling studies

Swelling behavior is a critical parameter affecting release characteristics of a pH responsive polymeric-based drug carrier. Fig. 4 represents swelling ratio of the prepared nano-carrier in different pH. As can be seen, the maximum swelling occurs in buffered solution with pH 8 and then, it remains constant. As reported in the literature, the pK_a of PMAA is about 7.0 [31]. So, in pH values lower than the pK_a , most carboxylic acid groups in the polymeric shell are in the form of COOH. Thus, the hydrogen bonds between COOH groups in PMAA together and with carbonyl groups in PVP led to the polymer-polymer interactions. As a result, the flexibility of the polymeric chain and therefore, swelling ratio of the polymer strongly decreases. As pH value rises above the pK_a , the carboxyl groups ionize and effectively increase the concentration of free ions inside the polymeric shell. Therefore,

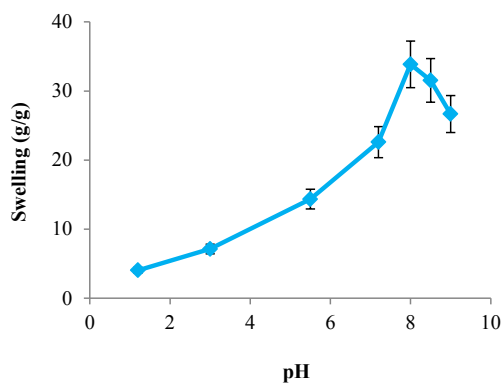


Fig. 4. The swelling behavior of the prepared nano-carrier in different pH. The results are average of three replicates measurement

the polymer tends to expand and minimize the repulsion between ionized carboxylic groups led to swelling. The reasons for the swelling-loss in the highly basic solutions are: crating a shielding effect in which high ionic strength of the buffered solution caused fewer acid side groups to become ionize, decreasing the electrostatic repulsion and the swelling ratio [32] and charge screening effect of excess Na^+ in the swelling media, which shields the carboxylate anions and prevents effective anion-anion repulsion [33].

Loading efficiency and release studies

The rosuvastatin loading efficiency was determined by varying the weight ratio of the carrier to the drug.

Obtained results were summarized in Table 1. For the nano-carrier to drug weight ratio of 2.5:1, the loading efficiency is above 96% and when the ratio increases, a decrease in loading efficiency occurs.

To investigate the effect of loading (%) on the rosuvastatin release, drug loaded magnetic nano-carrier with different loadings (%) were left in buffered solutions with pH 1.2 and allowed to release the entrapped drug.

The obtained results revealed that the amount of rosuvastatin release increases with decreasing the weight ratio of carrier to drug.

Similar results were reported previously by other authors [34-36].

In order to investigate the potential of using magnetic nano-carrier as a drug carrier, its time dependent drug release behavior was evaluated in three different buffered solutions with pH 1.2, 5.5 and 7.2 at 37°C and its in-vitro release profile was represented in Fig. 5.

In these experiments, conditions were maintained by regularly replacing the incubation medium and each point was performed three times to calculate an average value. Based on the UV-Vis spectra, quick release (about 60% of the drug in 2.5 h) was observed for the nano-carrier.

Table 1. Loading characteristics of the magnetic nano-carrier

Sample	Weight ratio (nano-carrier:drug)	%Loading efficiency (mean \pm RSD)
Loading S1	2.5:1	96 \pm 3
Loading S2	10:1	88 \pm 2
Loading S3	25:1	79 \pm 3

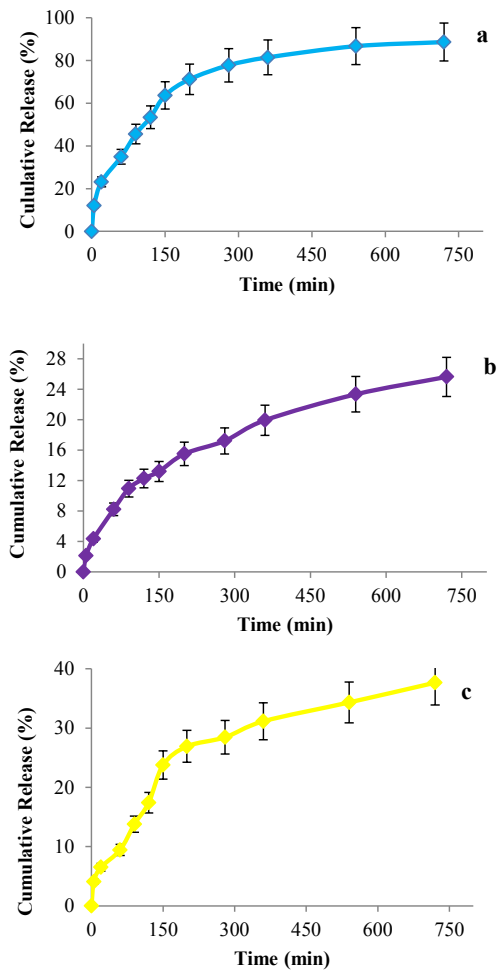


Fig. 5. Rosuvastatin release profiles of magnetic nano-carrier in different pH (a) pH=1.2, (b) pH=5.5 and (c) pH=7.2

In the following stage, a sustained release pattern is confirmed by the slight change of UV-Vis spectra and finally, 87% of the cumulative release amount was occurred in 12 h. Similarly, about 18% and 34% of loading drug was released in t 12 h at pH 5.5 and 7.2, respectively. Meanwhile, all the drug loaded batches show a biphasic release pattern within the first 2.5 h and a prolonged release manner over a period of 12 h. The burst release of the drug is associated with the drug molecules entrapped in the surface layer of the particles and progressively dissolved when it comes in contact with the release medium [37]. Because of the magnetic orientation role of MNPs, the magnetic drug nano-carrier could be transported by applying an external magnetic field and maintained the concentration of the drug for prolonged durations.

When the pH value increases from 1.2 to 7.2

(above pK_a of MAA), the carboxylic acid groups in the polymer chain dissociate and repulsion between similar negative charges may causes expansion of the polymer which can form a gel that slows release rate.

Effect of MNPs amount on rosuvastatin release

The effect of MNPs content on the release of rosuvastatin was investigated by adding different amount of MNPs ranging between 0 to 100 mg to the polymerization reaction. It was observed that the amount of rosuvastatin release from magnetic nano-carrier decreases with increasing MNPs amount (Fig. 6a) due to the decrease in polymer content of the prepared carriers. Furthermore, considering the amount of released rosuvastatin (release profiles not shown here) reveals that most of the loaded rosuvastatin was released immediately at primary release time and this trend increases with increasing the amount of MNPs which can due to the physical adsorption of the drug onto the surface of magnetic nano-carrier and confirms the low pore density of the carrier. On the other hand, the results revealed that the carrier should have at least 30 mg of MNPs to have enough magnetization and this amount was used in production of the selected magnetic nano-carrier.

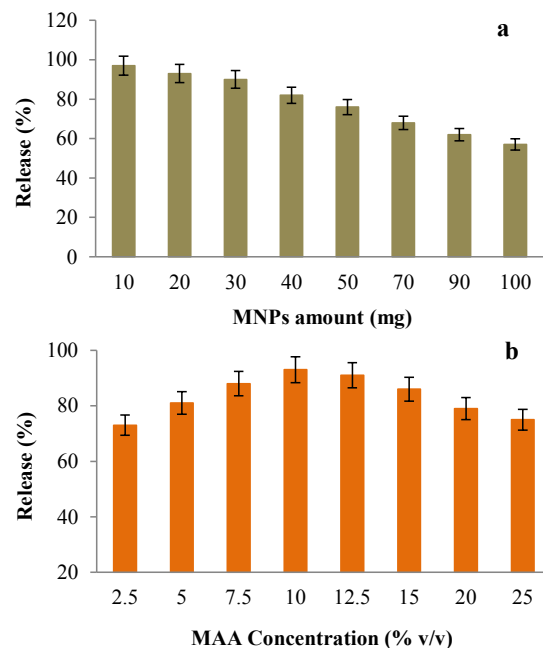


Fig. 6. Effect of (a) MNPs content and (b) amount of MAA monomer on the rosuvastatin release in pH 1.2 at 37 °C

Effect of MAA concentration on rosuvastatin release

To investigate the effect of carboxylic amount on the rosuvastatin release, different amounts of MAA in the range of 2.5-25 % (v/v) were used during the polymerization process while the other reagents were constant. Variation in the amount of MAA amount can alter chemical structure of the prepared polymer through variation in the amount of functional carboxylic acid groups. The results were shown in Fig. 6b. From the figure, an increase in rosuvastatin release was observed up

to 10 % (v/v) of MAA monomer and then release rate was decreased. Increase in carboxylic group content of the polymer can produce greater hydrodynamic free volumes and more porosity which increase diffusional passes. A decrease after that can probably due to the decrease in free volume accessible for drug molecules because of largely crowded polymeric chain on the thin layer coated to the MNPs. Based on the results, 10% (v/v) of MAA was added as the optimum amount in polymerization reaction medium.

Drug release mechanism

From the results obtained in previous section, it seems that rosuvastatin loading was a result of swelling of the carrier by the drug solution and consequently its release is closely related with deswelling of the carrier. So, in order to investigate release mechanism precisely, the obtained release data were fitted to the Korsmeyer-Peppas equation. It's worth noting that the drug release profile in all three buffered solutions fit well with the model, which gains an insight into the nano-carrier release mechanism. Fig. 7a-c illustrates the linear fit of in vitro release. A plot of cumulative drug release (%) in logarithmic scale, given as $\log M_t/M_\infty \times 100$ against $\log t$ at pH 1.2, 5.5 and 7.2, revealed linear fit with $R^2=0.998, 0.996$ and 0.996 respectively. The factor "n" is determined from the slope of the fit curves as 0.52, 0.55 and 0.54 respectively. The results confirm the non-Fickian transport of drug release attributed to the combination of diffusion as well as swelling controlled release.

CONCLUSION

A novel magnetic APTS-modified Fe_3O_4 nanoparticles coated by a pH responsive polymer (PVP-PEG-PMAA) was successfully designed and synthesized as a drug carrier and hydrophobic rosuvastatin was selected as a model drug to study its loading and release characteristics, and release mechanism. The pH-sensitive property of the polymeric shell enables the carrier to control rosuvastatin release in different pH. Furthermore, since Food or drug stay in the stomach only for a short period of time, the prepared vehicle can increase gastric residence of the drug and maintenance time of the drug carrier. The results indicate that the prepared magnetic nano-carrier has potential application for targeted and controlled rosuvastatin release and encourage us

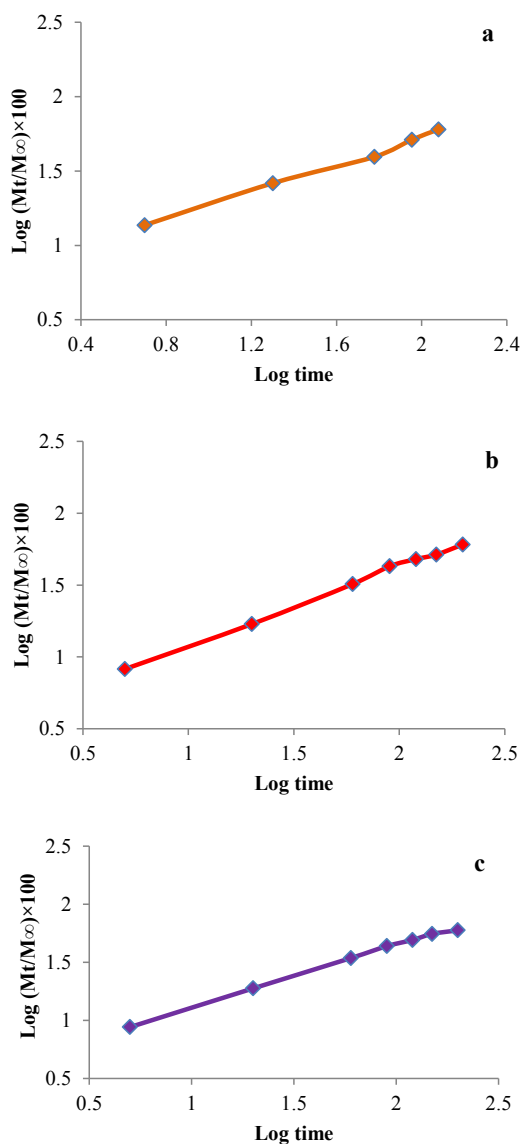


Fig. 7. The linear fit of Korsmeyer-Peppas equation for in vitro release profile of rosuvastatin in (a) pH=1.2, (b) pH=5.5 and (c) pH=7.2

to deep considering the interactions of polymer with other similar structural drugs to provide precise design of the nano-carrier with desirable properties and release characteristics.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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