RESEARCH ARTICLE

Magnetic nanoparticles grafted pH-responsive poly (methacrylic acid-co-acrylic acid)-grafted polyvinylpyrrolidone as a nano-carrier for oral controlled delivery of atorvastatin

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ABSTRACT

Objective(s): Researchers have intended to reformulate drugs so that they may be more safely used in human body. Polymer science and nanotechnology have great roles in this field. The aim of this paper is to introduce an efficient drug delivery vehicle which can perform both targeted and controlled antibiotic release using magnetic nanoparticles grafted pH-responsive polymer.

Methods: Fe_3O_4 nanoparticles were prepared via a simple co-precipitation method and coated with APTS. Then, it was used as a core in synthesis of a core-shell pH-responsive polymer. After that, atorvastatin was loaded into the carrier and its release rate, kinetic and mechanism were investigated.

Results: The results revealed that cumulative release of the drug from nano carrier was 78% at pH 1.2 while in pH 5.5 and 7.2, the drug release was only about 5 and 31% respectively. Effect of different parameters on the atorvastatin release such as amounts of MAA monomer, EGDMA as cross-linker, AIBN as initiator, and MNPs were also studied. Furthermore, release kinetics and mechanism investigation along with the swelling behavior studies of plain polymer reveal Fickian pattern and diffusion controlled mechanism.

Conclusions: The results indicate that the prepared nano-carrier can be serving as a suitable candidate for controlled delivery of the drugs.

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INTRODUCTION

Polymers with environmentally responsive behavior can be considered as bio-devices and their development is central to emerging smart applications in biology and medicine1. Synthetic or modified biological materials that can undergo conformational or phase changes in response to variations in pH and temperature are of special interest. Polymers of these types have been extensively studied in biomedical field because these two factors can be easily controlled and are applicable both in vitro and in vivo conditions [1-4].Variations in pH occur at different body organs such as gastro-intestinal track and blood vessels and this can be suitable base for pH-responsive drug release. Polymers with pH-responsive properties are usually composed of a polymeric back-bone with ionic pedant groups. In suitable release medium these pedant groups can ionize and develop desirable changes on the polymer network [5]. On the other hand, polyvinylpyrrolidone (PVP) is a biocompatible polymer which has been widely used in pharmaceutical industry [6-8]. This compound was used to provide adequate drug release in gastric environments (low pH) [9,10].

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Incorporation of ionizable monomers into PVP backbone enables better phase transition and solubility changes dependent on the pH [11]. Two frequently used ionizable monomers are acrylic acid (AAc) and methacrylic acid (MAA) which have been extensively investigated for therapeutic use on account for their ability to swell reversibly with changes in pH [12]. In addition, low cost of acrylic polymers and their adhesion to biological surface when partially protonated have also contributed to making this class of polymers of long-standing interests in pharmaceutical applications [13,14].

Today, Fe_3O_4 nanoparticles (MNPs) with supermagnetism properties have widespread applications many areas such as biology pharmacy and diagnostics [15-18] because they can separate from the solution using an external magnetic field and re-disperse when the magnetic field withdraws. Although MNPs have been widely used in targeted drug delivery [19-22], the amount of drug that MNPs can carry is little and their dispersion and stability against oxidation need to improve. A good way to solve these problems is coating with polymer. Polymer-coated MNPs will have advantages of good dispersion, high stability against oxidation and appropriate amount of drug can be loaded to the polymeric shell [23,24]. If a pH-responsive polymer uses for coating, the carrier can use for both delivering a drug to the target and control of release rate. Drug-polymer interactions are also well known in the literature [25,26] which may be physical through hydrogen bonding or chemical through the formation of insoluble complexes[27] between either anionic drug-cationic polymer [28] or cationic drug-anionic polymer [29].

Atorvastatin is the most efficacious of the HMG-CoA reductase inhibitors in terms of lowering plasma cholesterol levels by suppressing the hepatic production of very low-density lipoprotein (VLDL) and low-densitylipoprotein (LDL) cholesterol [30]. It is soluble in water and according to its structural formula, it contains tertiary amine nitrogen which favors interaction with a carboxylic acid of the polymer and a carboxyl group which favors interaction with amine groups of APTS coated MNPs (Fig. 1).

In this paper, APTS modified Fe_3O_4 nanoparticles was coated by plain polymer composed of poly (methacrylic acid-co-acrylic acid)-grafted polyvinyl-pyrrolidone and used as a nano-carrier for targeted

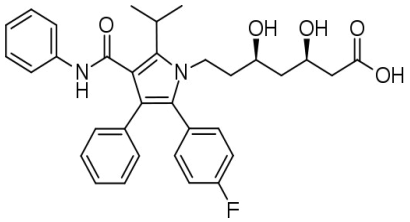

Fig. 1. Chemical structure of atorvastatin.

and controlled delivery of atorvastatin. TEM, XRD, and FT-IR techniques were used to characterize the synthesized nano-carrier and swelling behavior of the plain polymer along with the drug loading percent, drug release percent, and release kinetics and mechanism were studied. Effect of different parameters such as the amount of MNPs, cross-linker, initiator and MAA monomer on the release of atorvastatin was also investigated. The results show that the prepared nano-carrier can be successfully used as a drug carrier which can guide to a specific position by an applied magnetic field and then release the drug with respect to pH.

MATERIALS AND METHODS

All chemicals were of analytical grade and used without purification. Polyvinylpyrrolidone (PVP, Mw = 40000) was purchased from Rahavard Tamin Chemical Co. (Saveh Iran). 2 2'-azobis isobutyronitrile (AIBN, 98%) was purchased from ACROSS and atorvastatin standard was received as a gift from faculty of pharmacy, Tehran University. Ferrous chloride hexahydrate ($FeCl_3.6H_2O$), ferric chloride tetrahydrate ($FeCl_2.4H_2O$), aqueous ammonia (25% w/w), 3-aminopropyl triethoxysilane (APTS), methanol, acetic acid, sodium acetate trihydrate ($CH_3COONa.3H_2O$), sodium hydroxide, potassium hydrogen phosphate, glycerol (about 87%), hydrochloric acid, potassium chloride, AAc, MAA, and ethylene glycol dimethacrylate (EGDMA 98%), were purchased from Merck Company (Darmstadt Germany) and used without further purification. Deionized water was used throughout the experiment.

Instrumentation

Absorbance spectra of the released drug and other solutions were carried out using UV-240 Shimadzu UV-Vis spectrophotometer. A Metrohm 827 pH meter was used for measuring and adjusting the pH of solutions. Phase characterization of MNPs was performed using Phillips PW-1800

X-Ray diffractometer. Characterization of MNPs, nano-carrier and atorvastatin loaded nano-carrier were carried out by Spectrum one Bv5.3.0 Perkin Elmer FT-IR spectrometer. Phillips CM120 and a EM2085 transmission electron microscopes with an accelerating voltage of 100 kV were used to characterize the size and morphology of MNPs and the nano-carrier. A water bath Memmert WB10 was used to precise control of the temperature (37 ± 0.1 °C).

Synthesis of APTS coated MNPs

The MNPs were prepared via chemical co-precipitation method reported previously [22]. Briefly 11.68 g $FeCl_3.6H_2O$ and 4.3 g $FeCl_2.4H_2O$ were dissolved in 250 mL deionized water under N2 atmosphere with vigorous stirring at 85 °C. Then 40 mL of aqueous ammonia (25% w/w) was added to the solution. The color of the solution turned immediately to black and Tthe magnetic precipitates were stirred in these conditions for 15 min. Then, naked MNPs was washed three times with 100 mL deionized water and once with 100 mL of 0.02 M sodium chloride to neutralize. The suspension was placed in a 250 mL round bottom flask and allow participates to settle. The supernatant was removed and an aqueous solution of 80 mL APTS 10 % (v/v) was added followed by 60 mL glycerol. The mixture was stirred and heated at 90 °C for 2 h under N_2 atmosphere. After cooling to room temperature, the suspension was washed sequentially with 200 mL deionized water (three times), 100 mL methanol (twice) and 200 mL deionized water (three times). Finally the APTS coated MNPs dried to powders at 50 °C in oven.

Synthesis of plain polymer and the nano-carrier

An amount of 1.0 mL of 0.37% (w/v) of PVP solution in methanol was added to 12 mL methanol in 50 mL conical flask. 1.0 mL AAc (0.49 mM) and variable amount of 0.39 mM MAA (0.7-3 mL) were added simultaneously. Then, variable amount of APTS coated MNPs (0-100 mg), variable amount of 0.39 mM EGDMA (0.7-3 mL) as a cross-linker and variable amount of AIBN (0.3-1.2 mmol) as initiator were added to the mixture to prepare different polymer compositions. The solutions were bubbled with N_2 gas for 15 min. Then, the solution was placed in a water bath at 60 °C for 6 h with vigorous stirring. After that, the reaction solution allowed to cooling down to ambient temperature and the prepared polymer sequentially washed twice with 200 mL deionized water, twice with 100 mL methanol, and three times with 200 mL deionized water to remove un-reacted monomers and reagents. Finally the polymer powders dried at 50 °C in vacuum oven for 24 h. Plain polymer was prepared in the same manner without adding MNPs. Polymer with 20% (v/v) of MAA and EGDMA and 0.6 mmol of AIBN was used as plain and that with 20% (v/v) of MAA, 15% (v/v) of EGDMA, 0.6 mmol of AIBN and 10 mg of MNPs was used as the nano-carrier for further study of swelling and loading behaviors.

Characterization

MNPs phase characterization was performed using X-Ray diffraction (XRD) by Cu-Kα radiation wavelength 1.540598 A° and matching peak position to JCPDS card file No.79-0418. The size and morphological characteristics of APTS coated MNPs and the nano-carrier were analyzed using transmissions electron microscopy (TEM). The images were obtained by placing one drop of each sample on a carbon plate. The average size of nanoparticles based on more than 300 particles was measured from TEM images. Surface modification of MNPs and the carrier and loading of atorvastatin on the nano-carrier were analyzed using FT-IR spectroscopy. The spectra were measured in the 400–4000 cm^{-1} region for samples dispersed in KBr pellets.

Drug content and encapsulation efficiency

The amount of 0.5 g of plain polymer or nano-carrier was placed into a 100 mL beaker and various concentration of atorvastatin were added. Then, the solutions were left to equilibrate in room temperature for 24 h. Concentration of unloaded drug was measured by UV-Vis spectrophotometry at 255 nm. Appropriate dilution performed to ensure that the absorbance were in linearity range of Beer's law. The %drug content and encapsulation efficiency were calculated by following equations:

$$\text{Drug content}(\%)=(W_{\text{Drug loaded}})/(W_{\text{carrier}})*100$$
$$\text{Encapsulation efficiency}(\%)=(W_{\text{Drug loaded}})/(W_{\text{Total drug}})*100$$

Where, $W_{\text{Drug loaded}}$ is the weight of atorvastatin encapsulated in the carrier. W_{carrier} is the weight

Table 1. Mathematical representations of models used to describe the release profile of atorvastatin.

Model	Equation
Zero-order	$Q_t = Q_0 + K_0 t$
First-order	$LnQ_t = \ln Q_0 + K_1 t$
Higuchi	$Q_t = K_H t^{1/2}$
Korsmeyer-Peppas	$M_t / M_\infty = Kt^n$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$

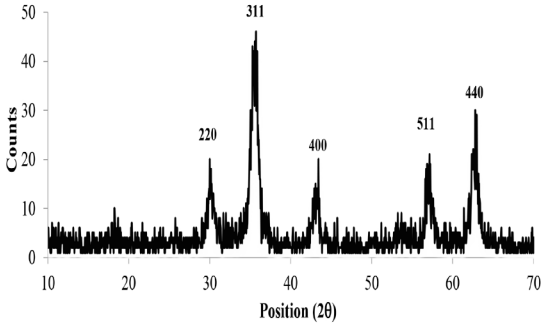

Fig. 2. The XRD pattern of prepared APTS coated Fe_3O_4 nanoparticles.

of each carrier and $W_{Total\ drug}$ is the total weight of atorvastatin. Then, the drug-loaded carriers were washed with deionized water to remove free drug for further release studies.

Release studies

In-vitro release studies were performed in simulated body conditions. Three buffered solutions with pH 1.2, 5.5 and 7.2 were selected for release medium and the temperature was precisely controlled at 37 ± 0.1 °C. The atorvastatin loaded plain polymer and the nano-carrier were immersed into 25 mL of each buffered solution. At certain time intervals, 6 mL of release medium was taken and the same volume of fresh buffer solution was replaced to compensate this volume. The removed solution was analyzed spectrophotometrically to determine the amount of drug released. Effect of the amount of MAA, the initiator, the cross-linker and MNPs content on the atorvastatin release was also investigated and the average of three replicate was taken.

Kinetic and mechanism of atorvastatin release

In order to determine the kinetics of atorvastatin release from the polymeric matrix various kinetic models were used to analyze release data. Mathematical equations used to describe each model were summarized in Table 1.

Mechanism of drug release was investigated by Korsmeyer equation shown in Table 1 where Mt represent 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 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 as described in Table 2 [22,31].

Swelling studies

Different buffer solutions with pH 1.2-9.0 were used for determination of swelling behavior of the plain polymer. A simple gravimetric method was used to study the polymer swelling. After soaking into each pH, the polymer allowed to swell for approximately 148 h. Then, the swollen polymer was removed and blotted with filter paper to remove excess water on the polymer surface and weighed. The average values of three measurements were taken for each sample and the degree of swelling for each sample was calculated by using the following equation:

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

Where Wt is the weight of swollen polymer at each time and Wd is the weight of the polymer before swelling experiments.

RESULTS AND DISCUSSION

Characterization

XRD pattern of prepared APTS coated MNPs was presented in Fig. 2. The results show a cubic

Table 2. Release exponent and mechanism for polymeric carriers.

Release exponent (n)			Drug release mechanism
cylindrical shape	spherical shape	film shape	
0.45	0.43	0.5	Fickian diffusion
0.45 < n < 0.89	0.43 < n < 0.85	0.5 < n < 1	Anomalous (non Fickian)
0.89	0.85	1	Case-II transport
n > 0.89	n > 0.85	n >1	Super case-II transport

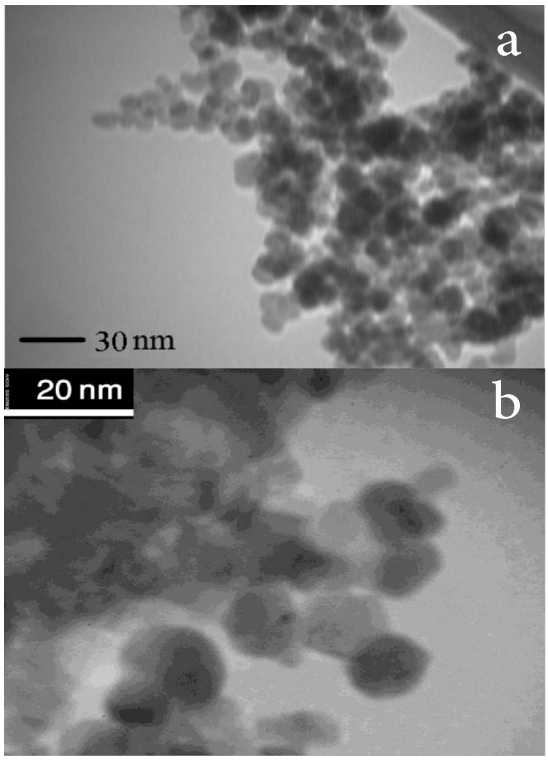

Fig. 3. TEM images of (a) APTS coated MNPs and (b) the nano-carrier.

structure and with the diffraction peaks at peak position (2) of 30.10, 35.53, 43.08, 53.48, 57.16, and 62.73 correspond to the crystal planes of 220, 311, 400, 422, 511, and 440 of pure nanoparticles according to the JCPDS card file No. of 79-0418. The results indicate that the modification with APTS did not change the MNPs crystal structure.

TEM images of the modified MNPs and the nano-carrier are shown in Fig. 3. The images identify that both particles have spherical shape and fairly smooth with average size of 8.6 ± 1.6 nm for MNPs. After grafting with the polymer, their average size increased to about 19.0 ± 2.1 nm.

Fig. 4 compares the FT-IR spectra of APTS coated MNPs (a) the nano-carrier (b) plain polymer (c) and atorvastatin loaded nano-carrier (d). From Fig. 4(a), the characteristic peak of MNPs mainly occurs at ~580 cm^{-1}, a strong sharp peak that is due to Fe-O stretch vibration. A peak at 1093 cm^{-1} is due to stretch vibration of Si-O band and the vibration Fe-O-Si band at 587 cm^{-1} overlaps with Fe-O peak of MNPs, and cannot be distinguishable. A strong broad absorption peak at ~3400 cm^{-1} may be due to residual moistness in KBr and also surface OH groups of magnetite. The ~1730 cm^{-1} peak is typical of the ester/acid asymmetric stretching vibration of carbonyl groups in plain polymer, the nano-carrier and atorvastatin loaded nano-carrier were seen in Fig. 4b, c and d. Furthermore vibrational peak at about 2987 cm^{-1} may correspond to asymmetric stretching of -CH_3 in the structure of the polymer. An intense characteristic band at 1390 cm^{-1} is attributed to bending of -CH_3 group in plain polymer deceased in Fig. 4b because of decrease in polymer content.

Swelling studies

Fig.5 displays the swelling behaviors of the plain polymer in different pHs. From the figure, the maximum swelling was occurred in pH 8.5. In fact, most carboxylic acid groups in the polymer were in the form of COOH in lower pH, as the pKa of PMAA and PAAc are about 7.0 and 6.6 respectively [32, 33]. When pH is lower than the pKa values, the H^+ concentration is high and effectively suppresses the ionization of the carboxylic acid groups. Thus, the polymer is neutral form and the hydrogen bonds between COOH groups in MAA and AAc monomers together and with C=O groups in PVP

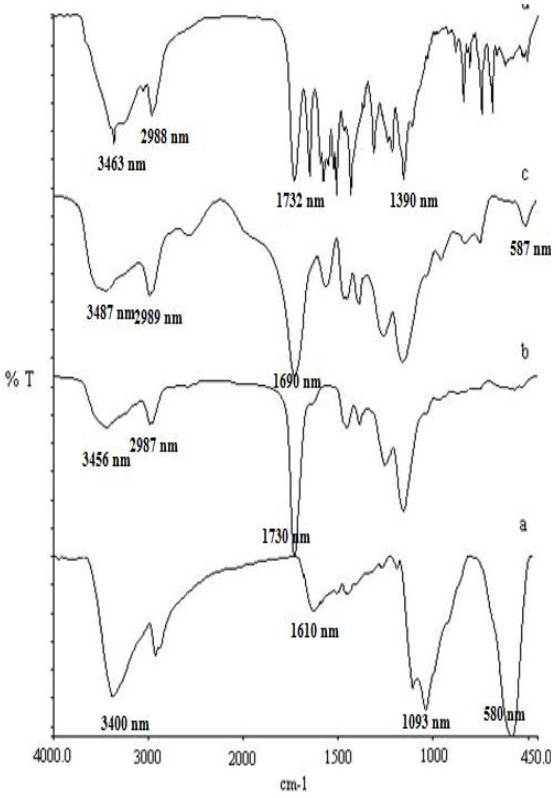

Fig. 4. FT-IR spectra of (a) APTS coated MNPs (b) nano-carrier (c) plain polymer and (d) atorvastatin loaded nano-carrier

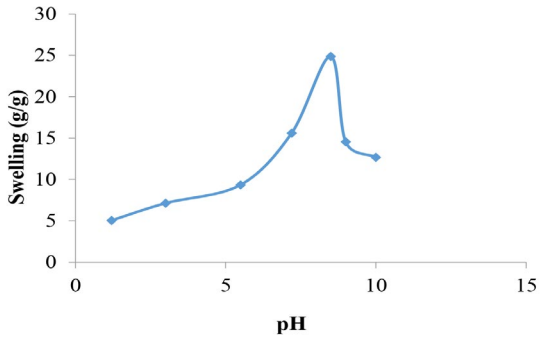

Fig. 5. The swelling behavior of poly (MAA-co-AAc)-grafted PVP in different pH.

led to polymer-polymer interactions. As a result, the polymer collapes and the swelling ratio of the polymer is relatively low. As the pH of raises above the pKa, the carboxyl groups ionize which effectively raises the concentration of free ions inside the polymer causing swelling increase. Additionally the polymer trends to expand and minimize the repulsion between the ionized carboxylic groups resulting in the increase of the swelling ratio.

Drug content and encapsulation efficiency

Drug content and encapsulation efficiency of atorvastatin were determined by varying weight ratio of carrier to drug. The loading characteristics of both plain polymer and the nano-carrier were summarized in Table 3. For plain polymer, when carrier to drug weight ratio was 2.5:1, the encapsulation efficiency was above 98% andwhen the carrier to drug ratio increases a decrease in encapsulation efficiency occurs. The same behavior was observed for the nano-carrier with slightly decrease in encapsulation efficiency to about 87% which occurs because of lower polymer content in the carrier with the same weight which may decreases the overall interactions of the drug with the carrier. To investigate the effect of loading on the atorvastatin release different concentration of atorvastatin ranging from 50 to 500 mgmL^{-1} were added to the 0.5 g of the nano-carrier and left 24 h to equilibrate, then isolated and washed. Thereafter, atorvastatin loaded nano-carrier was transferred to the buffered solution with pH 1.2 and allowed to release. Results were shown that the amount of atorvastatin release increases with decreasing the weight ratio of carrier to drug. Similar results were reported previously by other authors [34-36].

Drug release studies

The potential of plain polymer and the nano-carrier as drug carriers were evaluated by determination of their release behavior in different buffered solutions with pH 1.2 5.4 and 7.2 at 37 °C. In-vitro drug release of the carriers was shown in Fig. 6. It was observed from Fig. 6a that the atorvastatin was released above 60% at pH 1.2 in first 1 h and then sustainably release to about 85% in 12 h. For the nano-carrier these values were about 55 and 72% respectively. With increasing the pH to 5.5 the overall release of atorvastatin was about 7 and 6% for plain polymer and the nano-carrier respectively. However with further increase to pH 7.2, the final release was 28 and 31% for the plain polymer and the nano-carrier respectively. Thesebehavior can be explained based on the pKa's of the PMAA and PAAc monomers (7.0 and 6.6 respectively). The carboxylic acid groups in the polymer chains dissociated (ionized) as the pH increased from 1.2 to 7.2 which is above the pKa of the building blocks and repulsion between similar negative charges may causes swelling of the polymer which can form a gel that slows the drug release rate. In addition the negatively charged carboxylate groups can strongly interact with the drug which can decreased the drug release. On the other hand as mentioned before, the swelling of polymer increases with increasing pH value.

Table 3. Loading characteristics of the plain polymer and the nano-carrier.

Carrier	Sample	Weight ratio (carrier:drug)	Drug content (%)	Encapsulation efficiency (%)
Plain polymer	Sample I	2.5:1	36.8-39.2	92-98
	Sample II	10:1	8.9-9.4	89-94
	Sample III	25:1	3.2-3.6	81-90
The nano-carrier	Sample I	2.5:1	32.4-34.8	81-87
	Sample II	10:1	7.9-8.1	79-81
	Sample III	25:1	2.9-3.1	73-79

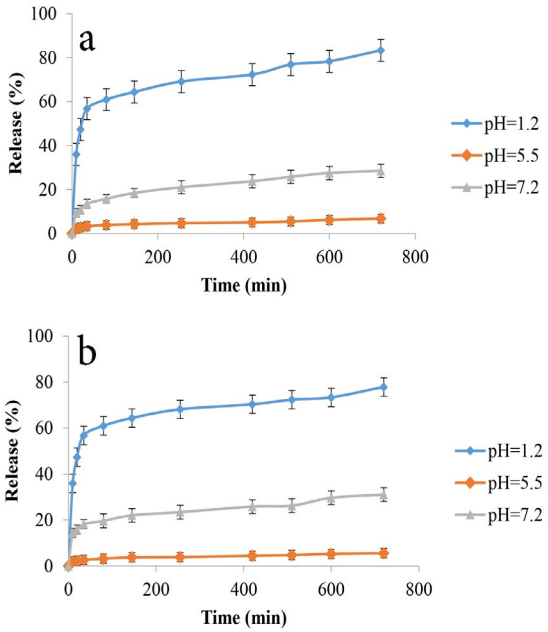

Fig. 6. Atorvastatin release profile from (a) plain polymer and (b) nano-carrier in different pH.

Therefore, a little increase in atorvastatin release was observed in pH 7.2 with respect to pH 5.5 which may explained by increasing in diffusional pass due to expanding the polymer.

Effect of the amount of MNPs on atorvastatin release

MNPs content effect on the atorvastatin release was investigated by using different amount of MNPs ranging from 0 to 100 mg in polymerization mixture. We observed that the amount of drug released from polymeric shell of the carrier was decreased with increasing in of MNPs amount. This can be explained by decreasing hydrodynamic volume sizes and the polymer. Furthermore, considering the amount of atorvastatin released from the nano-carrier showed that most of the loaded atorvastatin was released immediately at primary release time. This trend continues with increasing the MNPs amount which is due to the physical adsorption of the drug onto the surface of nano-carrier and confirms the low pore density of the nano-carrier carrier.

Effect of MAA amount on atorvastatin release

To investigate the effect of polymer chemical structure on the release of atorvastatin different amount of MAA ranging from 3-14 % (v/v) were used to the synthesis process. Addition of different

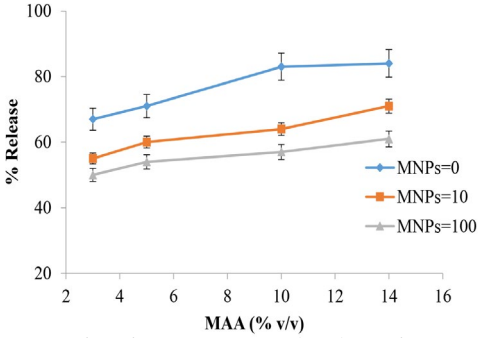

Fig. 7. Effect of MAA amount on the release of atorvastatin.

MAA amount can alter chemical structure of the polymer through variation of carboxylic groups amount. The reactions were down in the absence and presence of 10 and 100 mg MNPs to investigate the effect of amount of carboxylic groups on the release of atorvastatin from both plain polymer and the nano-carrier and the results were presented in Fig. 7. It is observed that polymer yield increases by increasing MAA amount in absence of MNPs which may be due to the decreasing in solution pH which occurs with increasing MAA amount. This can increase the solubility of PVP and accelerate decomposition of the initiator. In addition, increase in monomer concentration provides high reagent availability to react with other reagents. Thus, the polymer has had more chains. Similar results were observed by other authors previously [36,37]. From the figure, higher release was observed with increasing MAA concentration in plain polymer. Increasing in carboxylic groups of the polymer chains can produce greater hydrodynamic free volumes for atorvastatin encapsulation and more porosity which increase diffusional passes for atorvastatin release. In the case of nano-carrier, an increase in atorvastatin release was observed up to 10 % (v/v) MAA and then it was decreased which is probably due to the decrease in free volume accessible for drug molecules because of largely crowded polymeric chain layer onto the MNPs.

Effect of the amount of EGDMA on atorvastatin release

Effect of the EGDMA amount was investigated by varying it in the range of 3-14 % (v/v). The results are shown in Fig. 8. Amount of cross-linker significantly affects on the porosity of the polymer. As can be seen, the atorvastatin release increases with increasing the amount of EGDMA up to 10

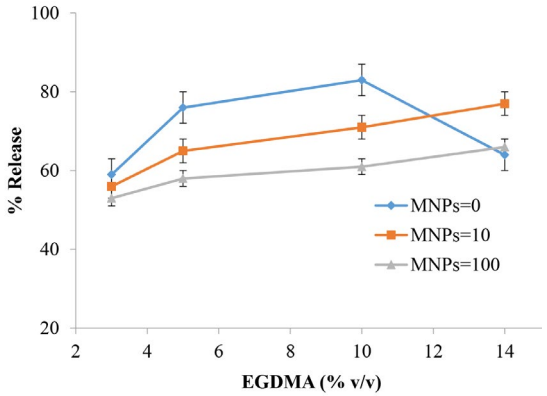

Fig. 8. Effect of EGDMA amount on the release of atorvastatin.

% and then it was deceased. Network loosening which occurs in lower cross-linked density may explain the increased releases. Thus, the hydrodynamic free volumes are large and allow the drug to penetrate. Hence, decrease in drug release for higher EGDMA amount could be explained by lower free volumes accessible due to more density cross-linked polymer. Another reason may be the hydrophobic nature of EGDMA which decreases the interaction of hydrophilic atorvastatin with the polymer. Similar results have been reported by other authors [38,39]. The same pattern was observed with addition of 10 and 100 mg MNPs to the polymerization reaction. However the lower release amount was obtained when the amount of MNPs was increased.

Effect of the amount of AIBN on atorvastatin release

Since, the initiator amount has an important effect on the molecular weight of prepared polymer, effect of AIBN concentration on the atorvastatin release was investigated by varying it in the range of 0.3-1.2 mmol. The release results are shown in Fig 9. As can be seen, an increase in drug release was observed by increasing AIBN amount up to 0.6 mmol. This can be explained by increasing the number of free radicals construct the polymer which produces a polymer with low molecular weight and therefore, low diffusional barrier for atorvastatin release. A decrease in drug release beyond the 0.6 mmol may be due to the smaller pores size which reduce loading efficiency and therefore release amount of atorvastatin. Similar pattern was observed with addition of modified MNPs (10 and 100 mg) to polymerization reactions.

Drug release kinetics and Mechanism

Various kinetic equations including zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell were used and release data fit to them the best model was choose based on the correlation coefficient of each model to evaluate their fitness. Table 4 shows the correlation coefficient and kinetic rate constant of each model for atorvastatin release from plain polymer and the nano-carrier. As can be seen, the data was best fitted to Korsmeyer-Peppas model except for the nano-carrier at pH 1.2. The release exponent was found to be <0.45 indicating Fickian release pattern and diffusion controlled release mechanism. Release data from the nano-carrier at pH 1.2 primarily follows first-order kinetics (R^2=0.944) and secondarily followes Korsmeyer model (R^2=0.912). These data reveal that drug release follows first-order kinetics with Fickian diffusion mechanism. In addition, kinetic rate constants were determined at different pH for both plain polymer and the nano-carrier and the results showed that the value of K was high at pH 1.2 and when the pH was increased to 5.5 the rate constants decreased to a minimum value. Then the release rate constant slightly increased in pH 7.2. Thus, there is a direct relationship between total percent drug released and K. However, decrease in kinetic rate constants which observed for the nano-carrier at pH 1.2 may be explained in part by the

Table 4. The correlation coefficient and kinetic rate constants of different kinetic models.

carrier	pH	Zero-order		First-order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
		K	R^2	K × 10^4	R^2	K	R^2	K	n	R^2	K	R^2
Plain polymer	1.2	0.018	0.81	4.34216	0.836	0.566	0.88	26.1216	0.08	0.919	0.0014	0.83
	5.5	0.005	0.93	0.04342	0.928	0.163	0.962	1.37404	0.23	0.974	0.0009	0.92
	7.2	0.025	0.93	4.34216	0.941	0.786	0.989	5.12861	0.26	0.995	0.0013	0.94
Nano-carrier	1.2	0.055	0.85	4.34216	0.944	1.747	0.92	21.1836	0.25	0.910	0.0019	0.92
	5.5	0.004	0.93	0.08681	0.931	0.141	0.979	1.14551	0.23	0.988	0.0007	0.93
	7.2	0.019	0.93	4.34216	0.943	0.636	0.975	9.61612	0.12	0.977	0.0016	0.94

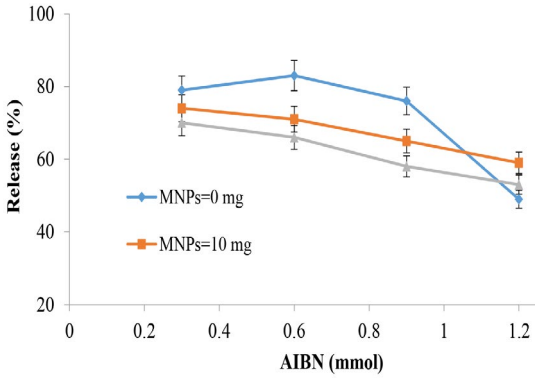

Fig. 9. Effect of AIBN amount on the release of atorvastatin.

increase in electrostatic interaction and hydrogen bonding between atorvastatin and additional NH_2 functional group of APTS coated MNPs.

CONCLUSIONS

A novel APTS modified Fe_3O_4 nanoparticles coated by poly (MAA-co-AAc)-grafted PVP was successfully synthesized as an efficient drug carrier. Atorvastatin was selected as a model drug to study the loading and release kinetics and mechanism. XRD, TEM, and FT-IR techniques were used to characterize the carriers. pH-sensitive properties of polymeric shell enable the carrier to control atorvastatin release through pH changes . Three different buffered solutions withpH 1.2, 5.5 and 7.2 in 37 °C were selected to simulate body conditions for in-vitro release studies. It was observed that about 78% of the drug released at pH 1.2 while at pH 5.5 virtually no drug was released and the final drug released at pH 7.2 was about 31%. The results indicate that the novel system has potential application for targeted drug-controlled release.

CONFLICT OF INTEREST

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

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