Article

Grafting Amino Drugs to Poly(styrene-*alt*-maleic Anhydride) as a Potential Method for Drug Release

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Sistemas de liberação de fármacos baseados em conjugados polímero-fármaco fornecem um tratamento melhorado com menor toxidade ou efeitos colaterais e são usados no tratamento de diferentes doenças. Conjugados de poli(estireno-*alt*-anidrido maleico) (PSMA) biodegradável, com agentes terapêuticos tais como cloridrato de amantadina, amlopidina, gabapentina, zonisamida e mesalamina, foram gerados pela formação de ligações de amidas dos fármacos amino que reagiram com os grupos anidridos do PSMA. As quantidades de fármacos covalentemente conjugados foram determinadas por ressonância magnética nuclear (NMR) de ^{1}H, e a taxa de liberação *in vitro* em solução tampão (pH 1.3) foi estudada à temperatura do corpo (37 ºC). Em estudos de cinética, modelos de dissolução diferentes foram examinados a fim de se obter dados de liberação do fármaco e os dados coletados se ajustaram bem a equação de Korsmeyer-Peppas, revelando um mecanismo de difusão Fickaniano dominante na liberação do fármaco em condições *in vitro*.

Drug delivery systems based on polymer-drug conjugates give an improved treatment with lower toxicity or side effects and be used for the treatment of different diseases. Conjugates of biodegradable poly(styrene-*alt*-maleic anhydride) (PSMA), with a therapeutic agents such as amantadine hydrochloride, amlodipine, gabapentin, zonisamide and mesalamine, were afforded by the formation of the amide bonds of the amino drugs that reacted with the PSMA anhydride groups. The amounts of covalently conjugated drugs were determined by a ^{1}H NMR spectroscopic method, and the *in vitro* release rate in buffer solution (pH 1.3) was studied at body temperature 37 °C. In kinetic studies, different dissolution models were examined to obtain drug release data and the collected data were well-fitted to the Korsmeyer-Peppas equation, revealing a dominant Fickian diffusion mechanism for drug release under the *in vitro* conditions.

Keywords: drug release, polymer-drug, poly(styrene-*alt*-maleic anhydride), PSMA, kinetic

Introduction

Nowadays, in order to improve the curative effect of drugs, drug delivery systems are studied and developed. Two general procedures are used to supply the polymers containing pendant bioactive substituents. One method consists of the polymerization of drug containing monomers.[1]

In this method, bioactive compounds, which have reactive functional groups, such as carboxyl,[2-6] hydroxyl,[7-11] sulfhydryl[12-14] and amino,[15-19] can be converted to their derivatives with the capability of polymerization, and then the drug containing monomers becomes polymerized by currently polymerization methods. Another one uses drugs attached to the prefabricated polymers.[20] In these systems, drugs or their derivatives are chemically linked to the synthesized[21,22] or natural[23,24] polymeric chains by chemical reaction.

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Poly(styrene-*alt*-maleic anhydride) (PSMA) is a commercially available copolymer, including reactive anhydride groups. Anhydride groups of PSMA can easily react with hydroxyl, sulfhydryl or amine groups.[25-27] PSMA copolymers were applied to clinically deliver neocarzinostatine,[28-31] which is an antitumor protein. Henry *et al.*[31] showed that showed that alkyl amine derivatives of PSMA are capable of destabilizing biological membranes at acidic pH values and showed how this activity can be modulated for use in intracellular drug delivery applications.

In this work, our group reported novel types of polymer-drug conjugates based on PSMA and amino medicinal compounds, such as amantadine (antiviral and anti-parkinson),[32-34] amlodipine (anti-hypertensive),[35,36] gabapentin (treatment of epilepsy),[37-39] zonisamide (anti-convulsant)[40,41] and mesalamine (anti-inflammatory).[42] Amino drugs containing –NH$_2$ were linked up with PSMA by amide bond formation, and then, hydrolysis reactions were carried out in buffer solution (pH 1.3) at 37 °C, as the human gastric simulated conditions. Drug release kinetics and release mechanisms are afforded by acquiring experimental data in different ranges of times.

Experimental

Materials and apparatus

Styrene, maleic anhydride, methanol, hydrogen chloride, benzoyl peroxide, potassium chloride and organic solvents were purchased from Merck Chemicals branch in Iran, and used without further purification. Dimethylformamide (DMF) was dried over MgSO$_4$ for 72 h, and then distilled once, and tetrahydrofuran (THF) was refluxed on Na/benzophenone for 8 h and distilled twice before use. Amantadine, gabapentin, amlodipine, zonisamide and mesalamine were received from Alborz-Daro Antibiotic Manufacturer, Iran. Buffer solution (pH 1.3) was prepared by addition of KCl aqueous solution (25 mL, 0.2 mol L^{-1}) to HCl (33.6 mL, 0.2 mol L^{-1}) in a volumetric flask.

All the UV-Vis spectrophotometric data were recorded by using a Shimadzu UV-265 spectrophotometer. A Shimadzu 435-U-04 FTIR spectrophotometer was used to obtain the FTIR (Fourier infrared spectroscopy) spectra of powder pressed KBr pellet samples. ^{1}H nuclear magnetic resonance (NMR) spectra were performed in DMSO-d_6 sample solutions by a Bruker 300 MHz spectrometer. Molecular weight of PSMA was determined by a Waters-150 GPC analysis instrument (mobile phase: THF, flow rate: 1.0 mL min^{-1}, and column temperature: 30 °C).

Preparation of poly(styrene-*alt*-maleic anhydride)

Poly(styrene-*alt*-maleic anhydride) (PSMA) was prepared through a thermally initiated free-radical polymerization of styrene and maleic anhydride[31] (Scheme 1a): a mixture of equimolar amounts (0.0432 mol) of styrene (4.99 mL) and maleic anhydride (4.236 g) was added to THF (25 mL) solution with benzoyl peroxide (0.0043 mol, 1.042 g) as polymerization initiator agent, and then, poured into a flask equipped with a
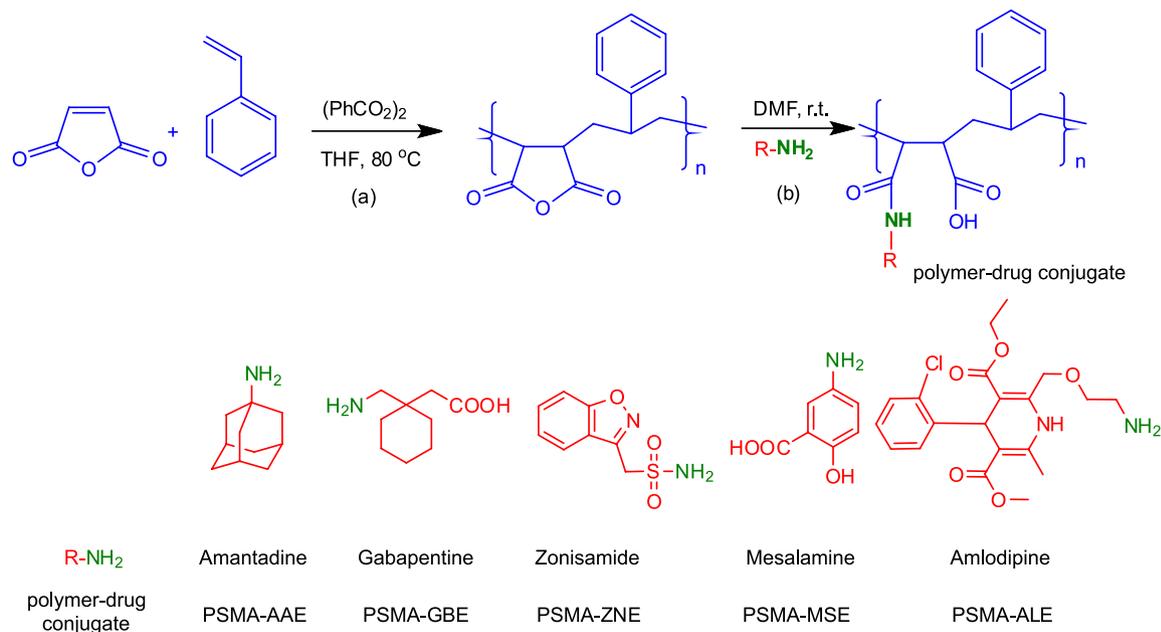
Scheme 1. General synthetic scheme: (a) copolymerization of PSMA and (b) grafting of amino drugs to PSMA.

reflux condenser and a magnetic stirrer under nitrogen atmosphere. Polymerization was carried out at 80 °C for 7 h. The viscous liquid, which resulted from the polymerization reaction, was washed in cold methanol to precipitate pure PSMA polymer. The purified PSMA was filtered off and dried under vacuum at room temperature.

General procedure for preparation of drug-loaded polymer

The grafting of selected drugs onto PSMA was carried out by reacting the drug amino group with the anhydride groups of PSMA to form amide bonds (Scheme 1b). Each drug was added with an equimolar ratio of monomers. For this purpose, PSMA (0.005 mol, 1.00 g) was dissolved in dry DMF (25 mL) by magnetic stirrer, and then, 0.005 mol of a selected drug, amantadine (0.939 g), gabapentin (0.856 g), zonisamide (1.061 g), mesalamine (0.766 g) and except for amlodipine (0.0025 mol, 1.202 g), due to its larger molecules and lower reactivity, were added to the solutions. The reaction was carried out at room temperature under nitrogen atmosphere for 12 h. Drug loaded polymer was purified by washing with distilled water and dried under vacuum at room temperature. The crude product of PSMA-MSE was gummy and sticky, so it was washed with cold diethyl ether to reach its powder form.

In vitro drug release study

In vitro drug release studies were performed by placing drug loaded polymer samples in a predefined volume of buffer (pH 1.3) at 37 °C. The quantity of released drugs was measured by UV-Vis spectrophotometer; the absorbance was recorded in the maximum wavelength value (λ_{max}) related to each drug (Table 1). Standard calibration curves (drug concentration *vs.* absorbance at appropriate λ_{max}) for suitable dilutions of drugs in buffer solution (pH 1.3) were first obtained. Sampling to determine the amount of released drugs (in ppm) was performed at different times (ranges as shown in Figure 1).

Results and Discussion

PSMA copolymerization

The free radical copolymerization of PSMA is facile and the copolymer readily affordable. As long as the polymerization was going on, the vinylic peaks disappeared in the ^{1}H NMR spectrum of PSMA, and aliphatic peaks such as methylene (CH_2) and methyne (CH) replaced them. Overlapped broad peaks between *d* 1.1-2.8 and 6-7.9 ppm are due to methylene/methane and aromatic ring protons of styrene, respectively. Methyne protons of maleic anhydride appear between *d* 3.3-3.5 ppm. Average molecular weight of PSMA was determined by gel permeation chromatography (GPC) (Table 2). In the FTIR spectrum for PSMA, anhydride group peaks appear at 1856, 1799 (cyclic anhydride C=O) and 1224 cm^{-1} (cyclic C–O–C).

Grafted drugs to PSMA

Spectroscopic characterizations of the functional groups proved that drugs were grafted with covalent bonds to PSMA. The FTIR spectra show that the carboxylic acid and amide groups are formed after the drug amine group attacked the anhydride groups of PSMA. It is noticeable that the corresponding peaks of anhydride groups of PSMA are not entirely removed due to the unreacted remaining parts of the polymeric chains. Table 3 summarizes the FTIR spectra of drug loaded PSMA samples.

Using ^{1}H NMR data, the molar ratio of attached drug *per* monomer unit was calculated separately for each PSMA-drug copolymer sample. The percentages of attached drugs *per* monomer unit were about 17.8, 23.0, 39.3, 33.6 and 25.7 for amantadine, amlodipine, gabapentin, zonisamide and mesalamine, respectively.

In vitro drug release investigations of drug-loaded PSMA

All the drugs used in this work are oral, hence, *in vitro* hydrolysis investigations of drug-loaded PSMAs were done according to the simulated gastric juice condition of human body[43] at acidic pH values (range of 1.1-1.5). In such acidic medium, drug-loaded PSMA hydrolyses were completed gradually as shown in Figure 1, in this way, the drug release is more controlled and permanent. In another study, which was done in simulated intestine media (at higher pHs such as 5, 6 and 7.4), the drug release was carried out by cleavage of the polymeric backbone and were more rapidly accomplished.

The drug release percentage and the cumulative release profiles of amantadine, amlodipine, gabapentin, zonisamide and mesalamine from their polymeric backbones,

Table 1. Maximum absorbance wavelength of pure drugs in buffer solutions (pH 1.3)

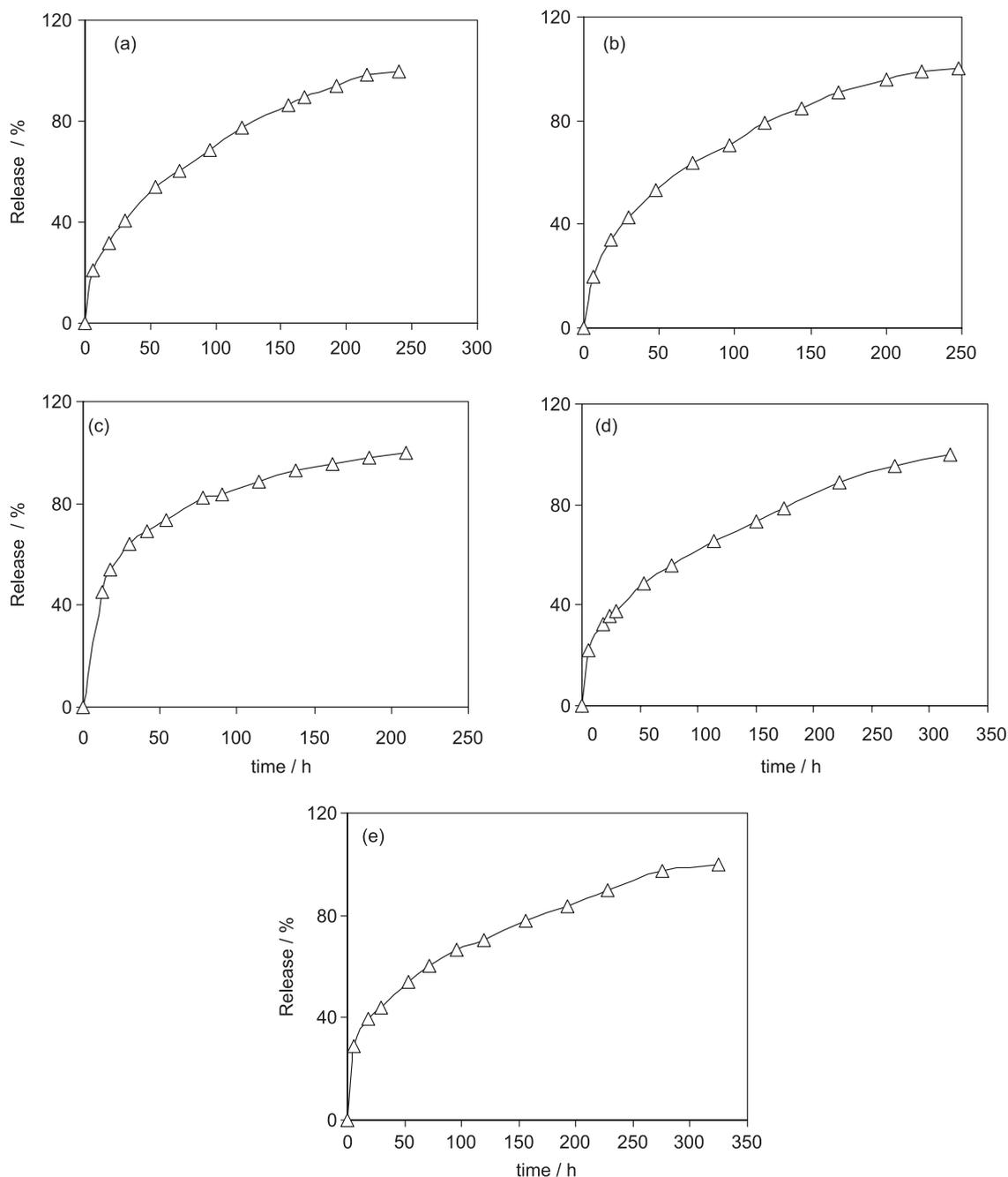| Drug	Amantadine	Zonisamide	Amlodipine	Gabapentin	Mesalamine
λ_{max} / nm	206	284	239	210	302

Figure 1. Drug release profiles (pH 1.3, T = 37 °C): (a) amantadine (PSMA-AAE), (b) amlodipine (PSMA-ALE), (c) gabapentin (PSMA-GBN), (d) zonisamide (PSMA-ZNE), and (e) mesalamine (PSMA-MSE).

Table 2. Average molecular weight (M_w) and polydispersity (PDI = $M_w M_n^{-1}$) of PSMA

Polymer	M_w / (g mol^{-1})	M_n / (g mol^{-1})	PDI
PSMA	3995	1973	2.024

PSMA-AAE, PSMA-ALE, PSMA-GBN, PSMA-ZNE and PSMA-MSE are presented in Figure 1. Drugs are released rather fast at the beginning of the process. However, a mild variation appeared as the process proceeds.

In order to analyze the kinetics of drug release from PSMA matrix, it was clear that, *in vitro* release results were fitted by first order equations, according to Higuchi[45] and Korsmeyer-Peppas. A first order model (equation 1) describes the systems in which the rate of drug release is linearly proportional to the drug concentration on the polymer matrix. Higuchi[45] described the release of drugs from porous and insoluble matrices as a square root of time dependent process based on Fickian diffusion, as presented in equation 2.[46-48] Korsmeyer *et al.*[49] derived a

Table 3. FTIR results of drug grafted PSMA samples

Compound	Region / cm^{-1}	Band assignment
PSMA-AAE, PSMA-ALE, PSMA-GBN, PSMA-ZNE	1799, 1780, 1777, 1780	anhydride C=O stretch vibration
PSMA-AAE, PSMA-ALE, PSMA-ZNE	1857, 1856, 1857	anhydride C=O stretch vibration
PSMA-AAE, PSMA-ALE, PSMA-GBN, PSMA-ZNE, PSMA-MSE	1646, 1648, 1665, 1647, 1660	amide C=O stretch vibration
PSMA-AAE, PSMA-ALE, PSMA-GBN, PSMA-ZNE, PSMA-MSE	1725, 1726, 1733, 1729, 1726	carboxylic acid O–H stretch vibration
PSMA-AAE, PSMA-ALE, PSMA-GBN, PSMA-ZNE, PSMA-MSE	3440, 3447, 3442, 3321, 3321	carboxylic acid O–H stretch vibration

simple relationship which described drug release from a polymeric system (equation 3).[49-51]

$$C_t = C_\infty (1 - e^{-k_1 t}) \tag{1}$$

$$C_t = k_H \sqrt{t} \tag{2}$$

$$\frac{C_t}{C_\infty} = k_{KP} \, t^n \tag{3}$$

where C_t is the amount of drug released at time t, C_∞ is the maximum amount of released drug experimentally measured after long times (more than 200 h), k_1 is the first order drug release constant, k_H is the Higuchi rate constant, k_{KP} is the Korsmeyer-Peppas rate constant and n is the kinetic order. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as $-\ln[1 - (C_t/C_\infty)]$ *vs.* time in the first order model, as amount of drug released *vs.* square root of time in the Higuchi model and as log (C_t/C_∞) *vs.* log t in Korsmeyer-Peppas equation.

The obtained kinetic data of drugs release from drug-loaded PSMA, together with the coefficient of determination (r^2), are listed in Table 4. Fitting data to the three kinetic models and investigation of the r^2 values show that the Kormeyer-Peppas model agrees with the release curves most accurately.

Water uptake

The water diffusion into PSMA-drug copolymers is based on Fickian diffusion that supposes proportionality between the flow and concentration gradient. The water uptake (S_w) of the conjugated polymer was determined gravimetrically in distilled water at room temperature overnight (W_s). Before each measurement, the dry weight of polymer (W_d) which was dried under vacuum overnight was also determined. The excess of water was gradually removed with filter paper. The water uptake was determined with the following equation:[52]

$$S_W(\%) = \frac{W_d - W_s}{W_d} \, 100 \tag{4}$$

Swelling percentages were obtained as 30, 75, 66, 55 and 70% for PSMA, PSMA-AAE, PSMA-ALE, PSMA-GBN and PSMA-ZNE, respectively. It is worth mentioning that PSMA-MSE is entirely soluble in water.

These results indicate that, drug-loaded PSMA systems have more water uptake potential in comparison with the original polymer. This is expected due to the possible hydrogen bonding of the carboxylic acid groups, in the backbone of the drug loaded polymeric chains, increasing its swelling.

Mechanism of drug release

To explain the nature of the drug release mechanism, Korsmeyer *et al.*[49] developed a simple empirical model, which described drug release from a polymeric system. Some processes may be classified as either purely diffusion or purely erosion controlled; many others can only be interpreted as being governed by both. The analysis of experimental data in the light of equation 3, as well as the interpretation of the corresponding release exponent values,

Table 4. Release kinetic parameters of the drugs

Model	Parameter	Drug				
		Amantadine	Amlodipine	Gabapentin	Zonisamide	Mesalamine
First-order	k_1 / h^{-1}	0.0151	0.016	0.021	0.010	0.011
	r^2	0.923	0.940	0.945	0.958	0.938
Higuchi	k_H / (ppm h$^{-1/2}$)	3.202	2.879	0.358	3.353	2.750
	r^2	0.992	0.981	0.761	0.978	0.919
Korsmeyer-Peppas	k_{KP} / h^{-n}	0.092	0.094	0.249	0.104	0.153
	n	0.441	0.441	0.267	0.392	0.321
	r^2	0.999	0.996	0.987	0.997	0.996

leads to a better understanding of the balance between these mechanisms.[53-55] The equation can be written as:

$$\log\left(\frac{C_t}{C_\infty}\right) = \log k_{KP} + n \log t \tag{5}$$

where (C_t/C_∞) in equation 5, is the mass fraction of drug released at time t and n is a characteristic of the drug-polymer system.

By determining the release exponent, it is possible to obtain information about the physical mechanism controlling the drug release from a particular device.[50,56] Based on the value of this exponent n, the drug transport was classified as given in Table 5.[57]

Table 5. Drug release mechanisms in agreement with Korsmeyer-Peppas model[57]

Exponent n	Drug release mechanism
$n \leq 0.45$	Fickian diffusion (case I diffusional)
$0.45 < n < 0.89$	anomalous (non-Fickian) diffusion
0.89	zero-order release (case II transport)
$n > 0.89$	super case II transport

The exponent n in this work varies from 0.256 to 0.441 for all the formulations (Table 4), i.e., less than 0.45; therefore, this suggests that Fickian diffusion is the main release mechanism under the conditions used. Drug mass transfer flow in this mechanism is related to the product of a molecular diffusivity and a concentration gradient. In order to further characterize the drug release process, the mean dissolution time (t_m) was calculated for each drug according to the following equation.[54]

$$t_m = \frac{\int_0^{C_\infty} t \, dC_t}{C_\infty} \tag{6}$$

This parameter reflects the level of drug release retarding by the polymer matrix and the *in vitro* media. The t_m obtained values are presented in Figure 2.

Mean dissolution times are within 40.4 to 99.9 h. Among the used drugs, zonisamide and gabapentin exhibit the highest and lowest dissolution times, respectively. This can be attributed to the resonance between S=O and NH bonds (between PSMA and zonisamide) which in turn causes the bond cleavage to occur in longer times.

Conclusions

The covalent grafting of five well-known drugs to PSMA was successfully done by the formation of amides from the reaction of amino group drugs with the anhydride groups of PSMA. *In vitro* release of amantadine, amlodipine,
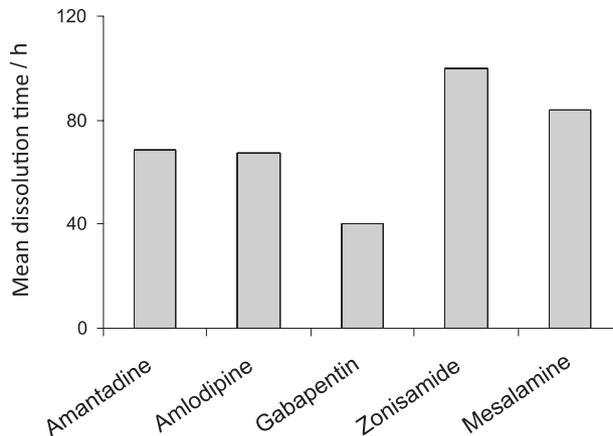
Figure 2. Mean dissolution time for drugs under study.

gabapentin, zonisamide and mesalamine from their corresponding drug-loaded PSMA was also studied, and indicated that the drug release can occur smoothly during long times, and this can be considered as an useful method for drug delivery. The kinetic analysis and the mean dissolution time indicate that Fickian diffusion controls the release of the drugs under study, and also zonisamide and gabapentin exhibit the slowest and the fastest release rates, respectively.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as a PDF file.

Acknowledgements

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Supplementary Information

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Figure S1. A gel permeation chromatography (GPC) chromatogram for PMSA.

*e-mail: Khazaei_1326@yahoo.com, ssaednia@gmail.com
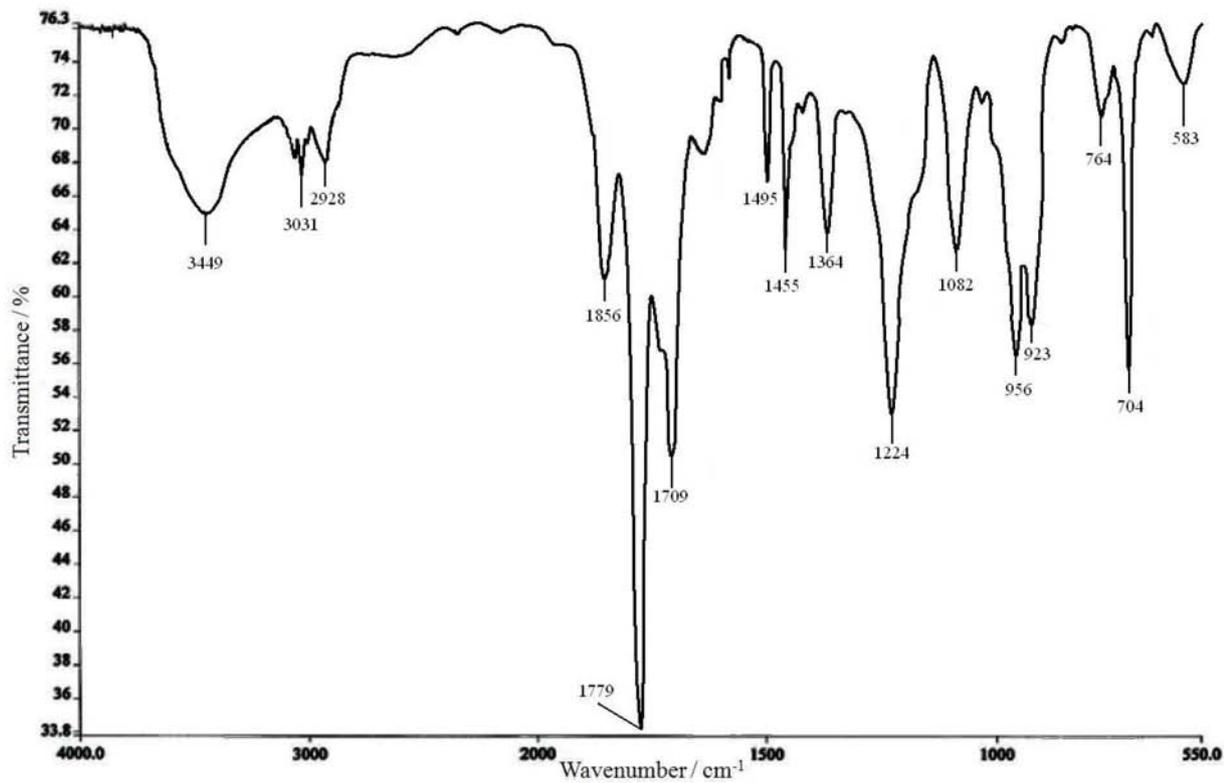
Figure S2. FTIR spectrum (KBr) of PSMA**.**
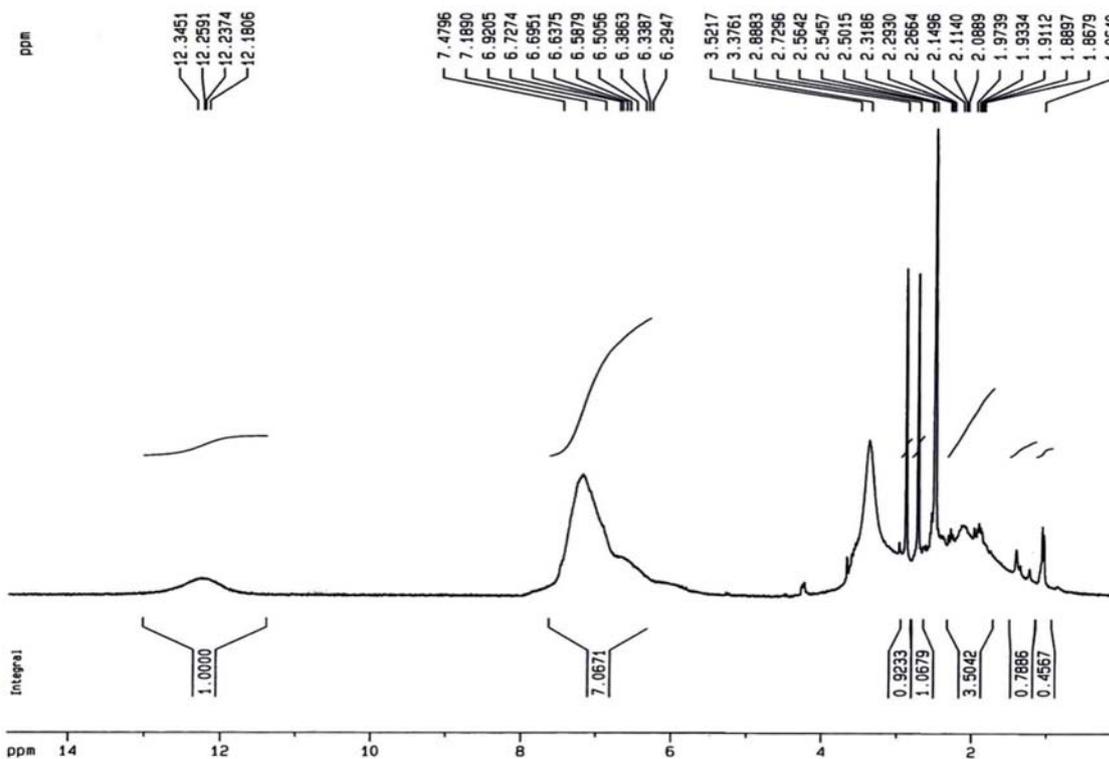
Figure S3. ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of PSMA.
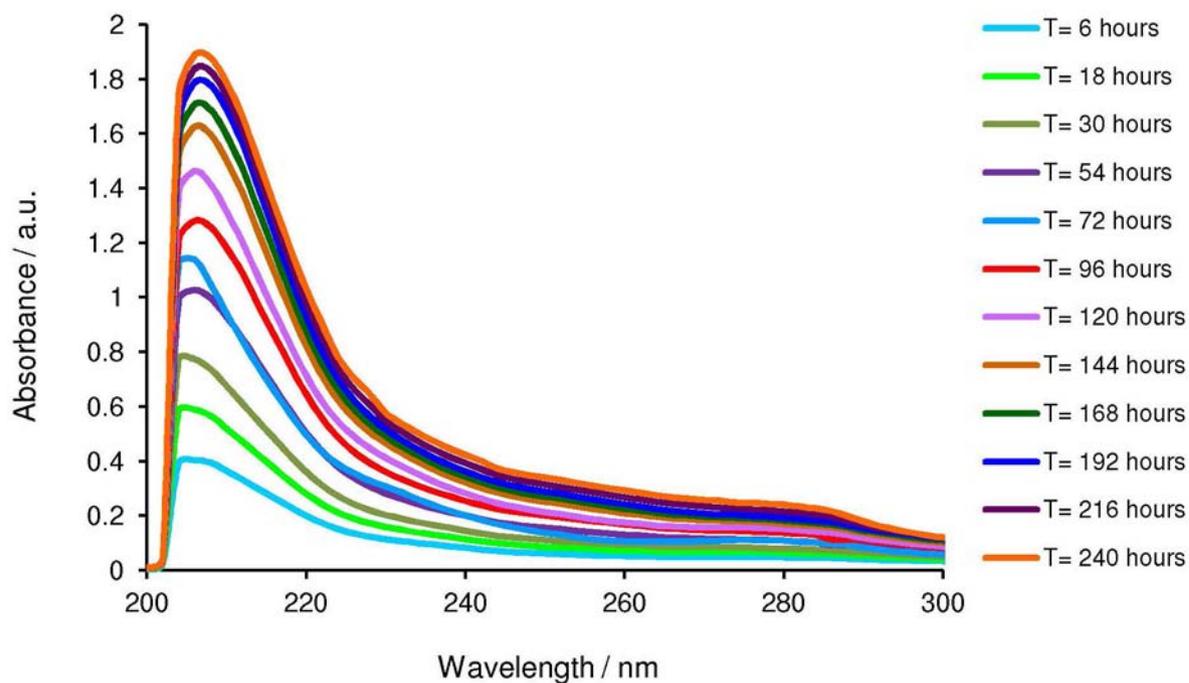
Figure S4. Release of amantadine from PSMA-AAE undertaken in buffer pH 1.3 at 37 °C.
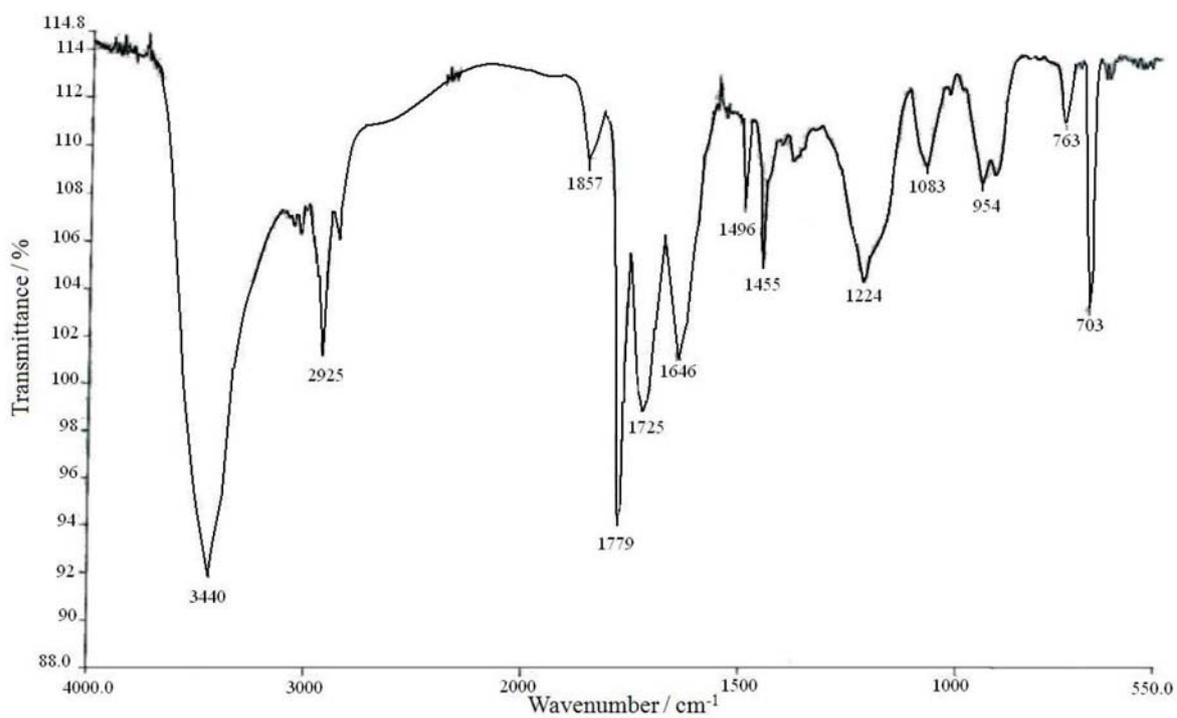
Figure S5. FTIR spectrum (KBr) of PSMA-AAE.
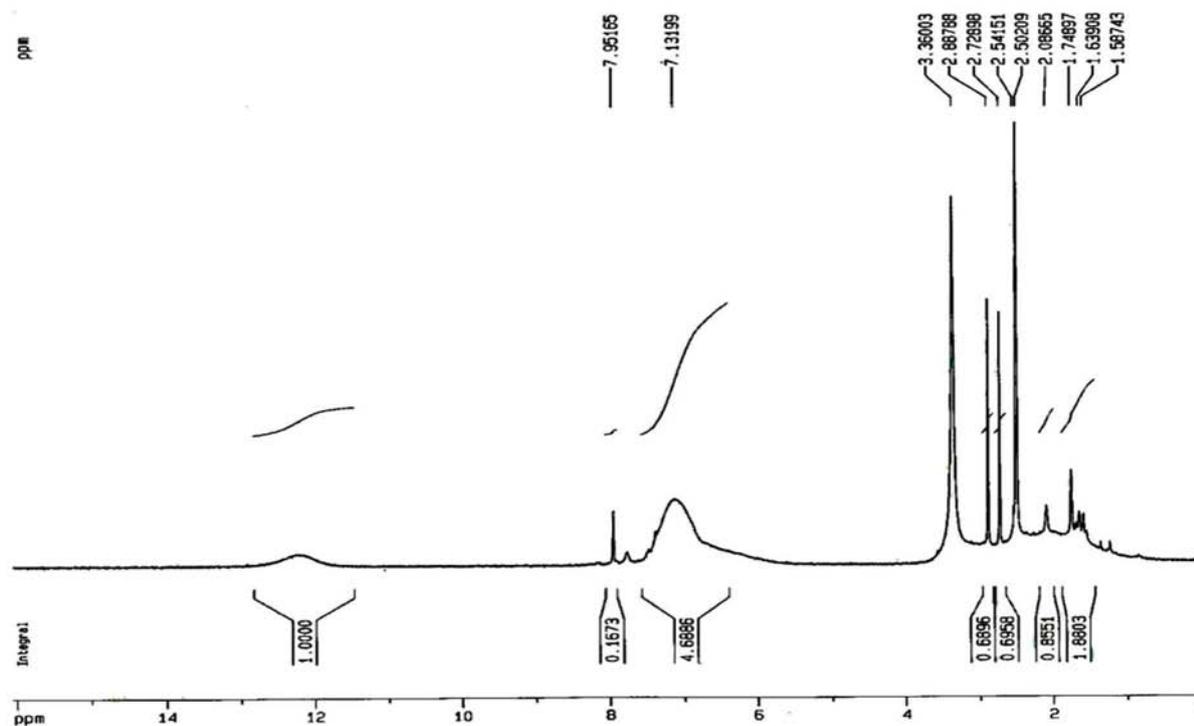
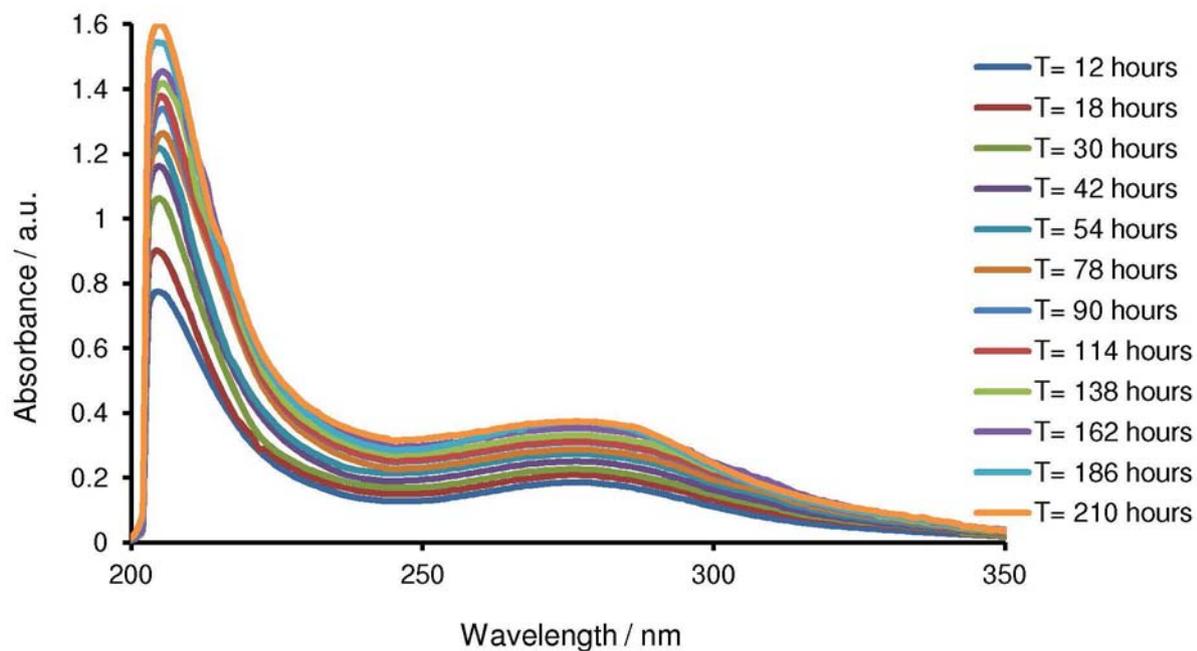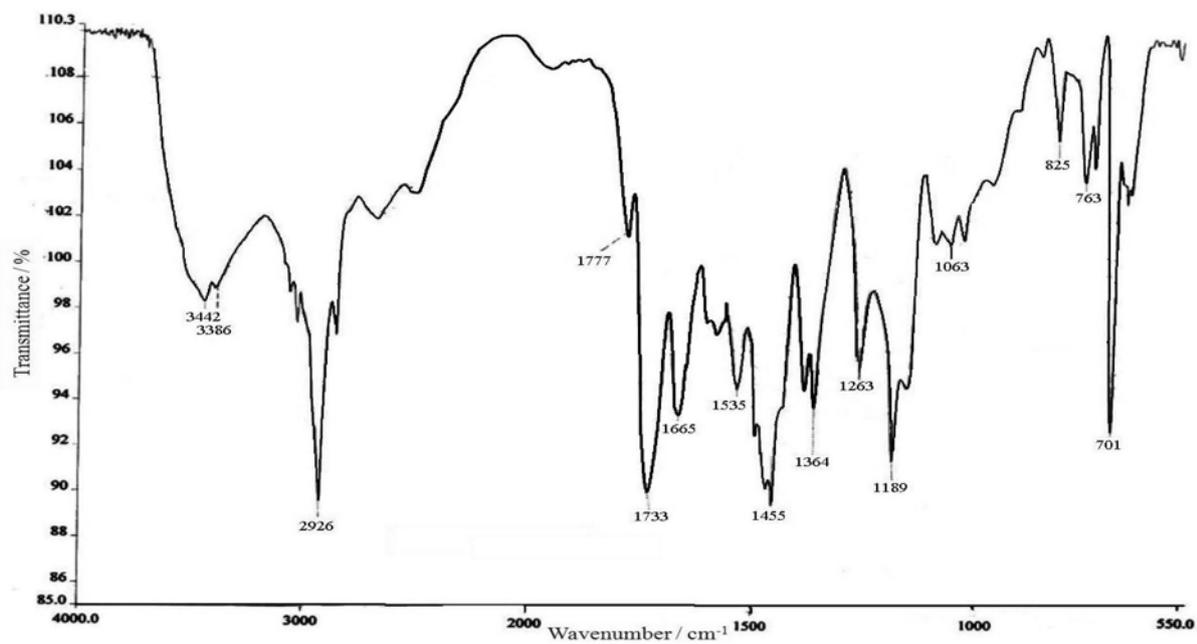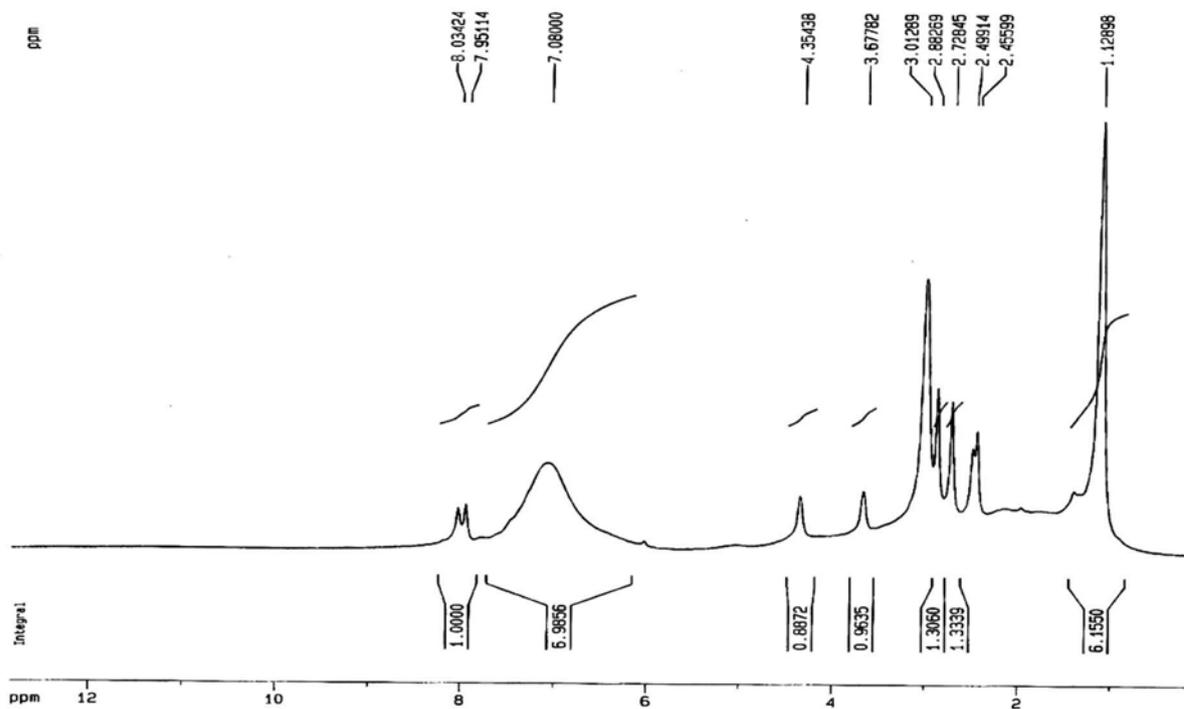**Figure S6.** ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of PSMA-AAE.
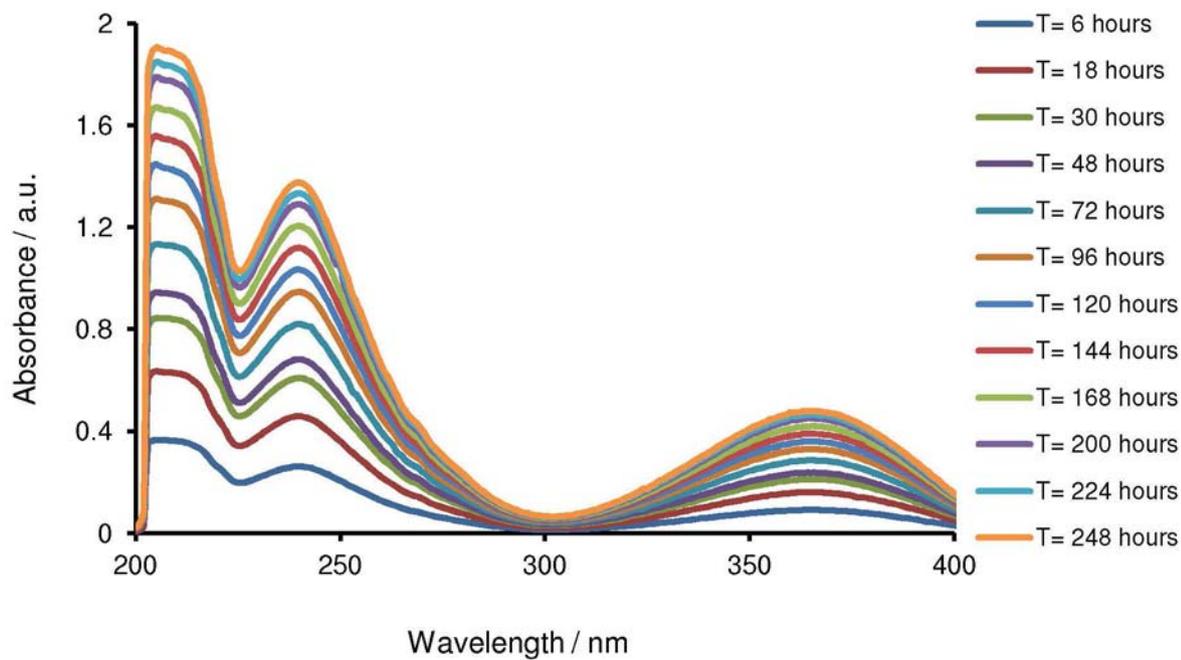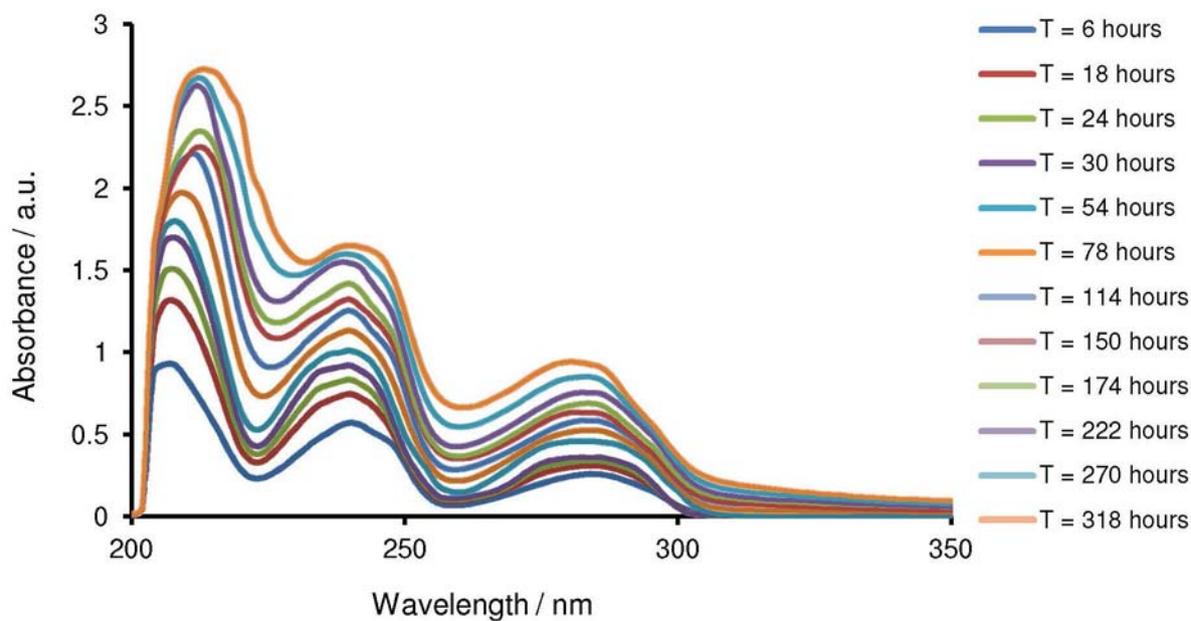

Figure S7. Release of amlodipine from PSMA-ALE undertaken in buffer pH 1.3 at 37 °C.
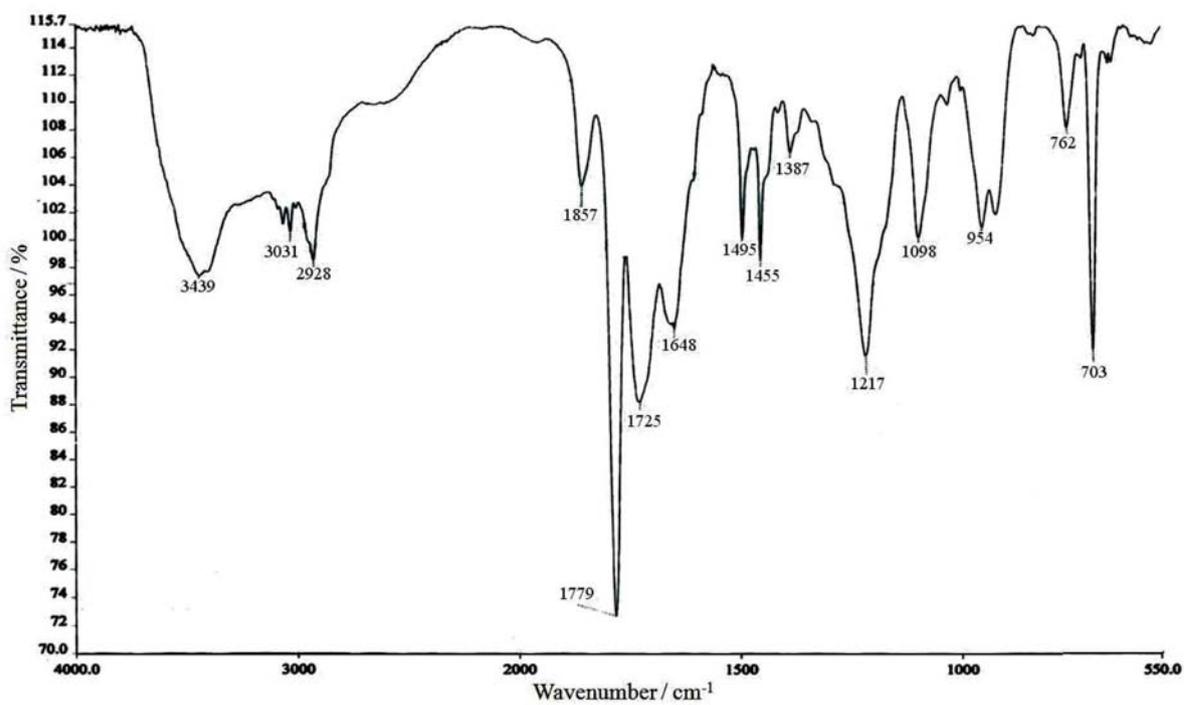
Figure S8. FTIR spectrum (KBr) of PSMA-ALE.
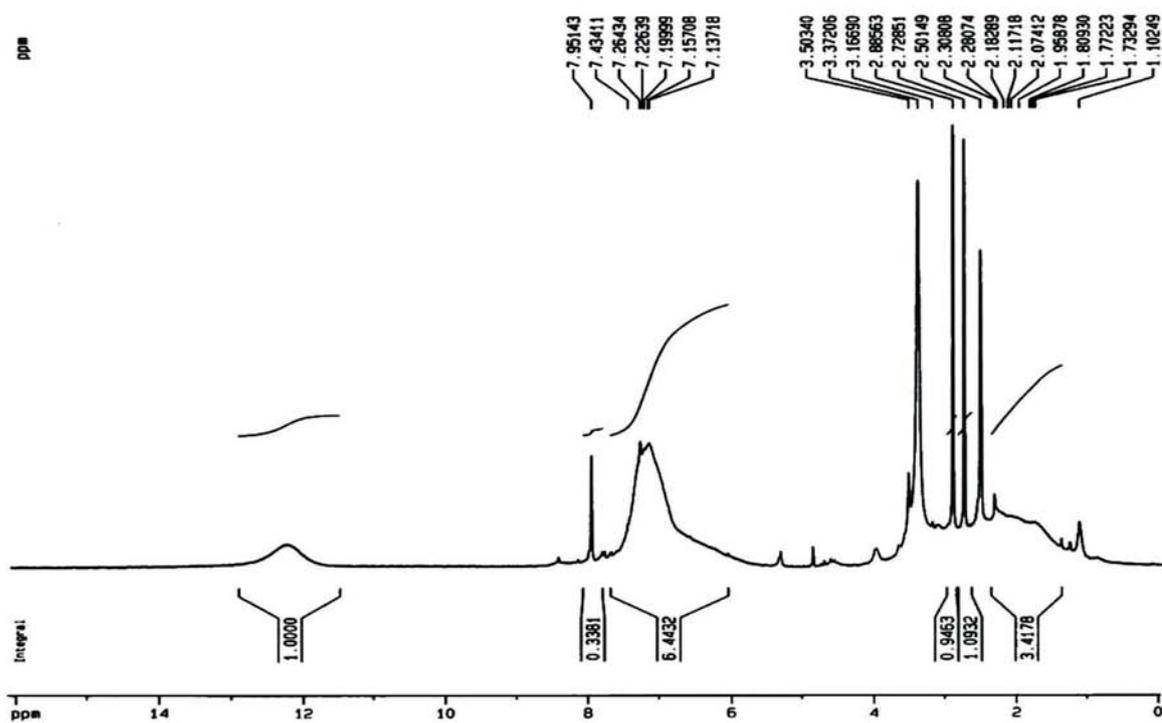
Figure S9. ¹H NMR (300 MHz, DMSO-*d₆*) spectrum of PSMA-ALE.

Figure S10. Release of gabapentin from PSMA-GBN undertaken in buffer pH 1.3 at 37 °C.

Figure S11. FTIR spectrum (KBr) of PSMA-GBN.

Figure S12. ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of PSMA-GBN.

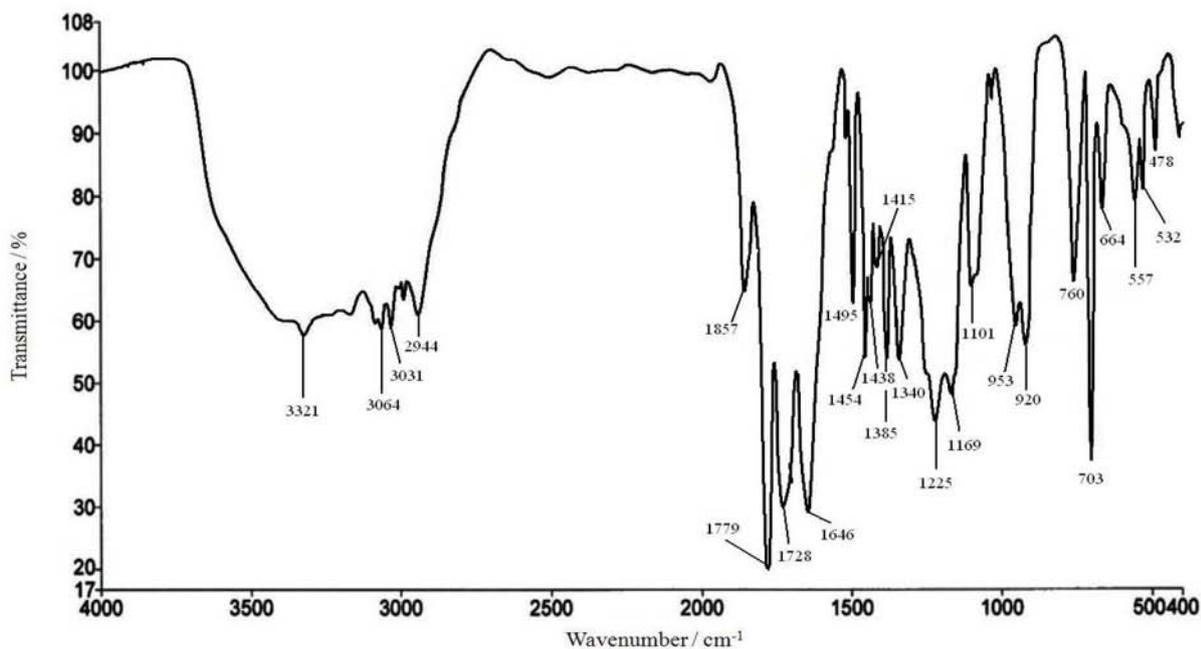**Figure S13.** Release of zonisamide from PSMA-ZNE undertaken in buffer pH 1.3 at 37 °C.
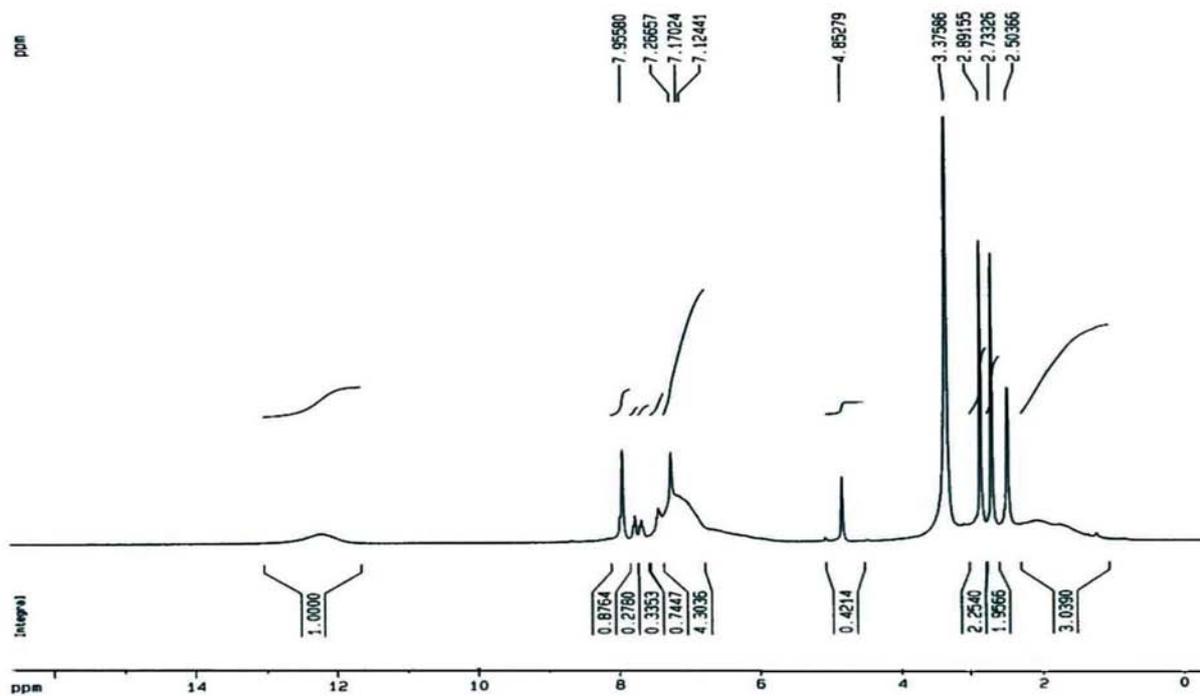
Figure S14. FTIR spectrum (KBr) of PSMA-ZNE.

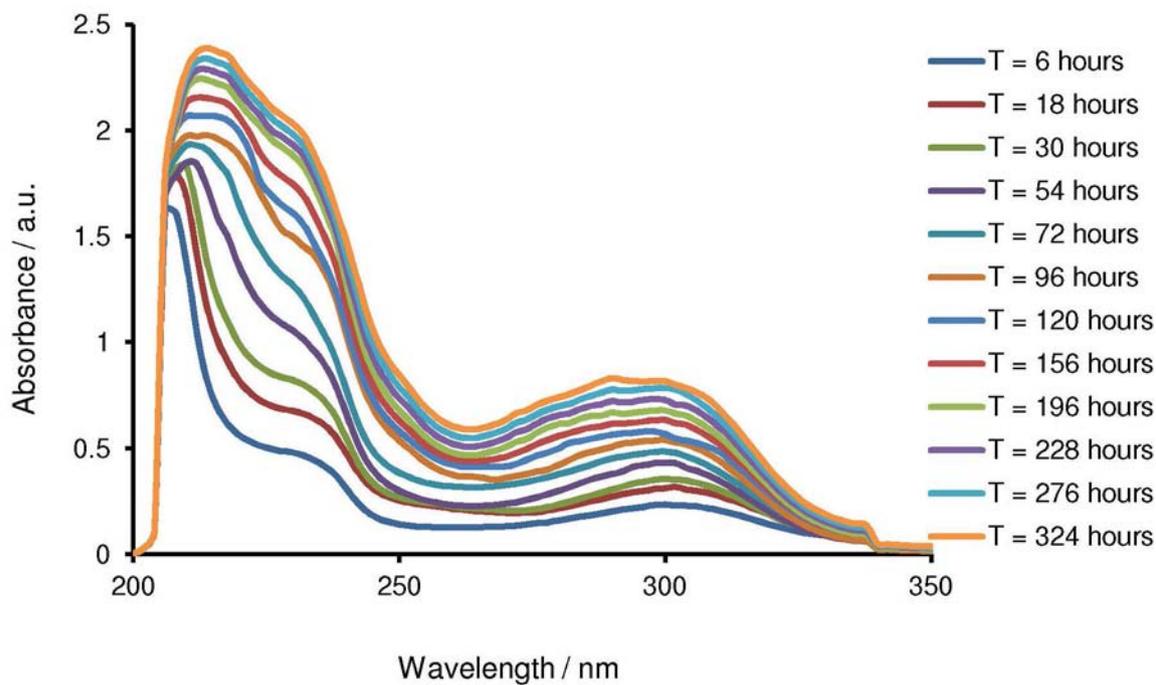**Figure S15.** ¹H NMR (300 MHz, DMSO-*d₆*) spectrum of PSMA-ZNE.

Figure S16. Release of mesalamine from PSMA-MSE undertaken in buffer pH 1.3 at 37 °C.
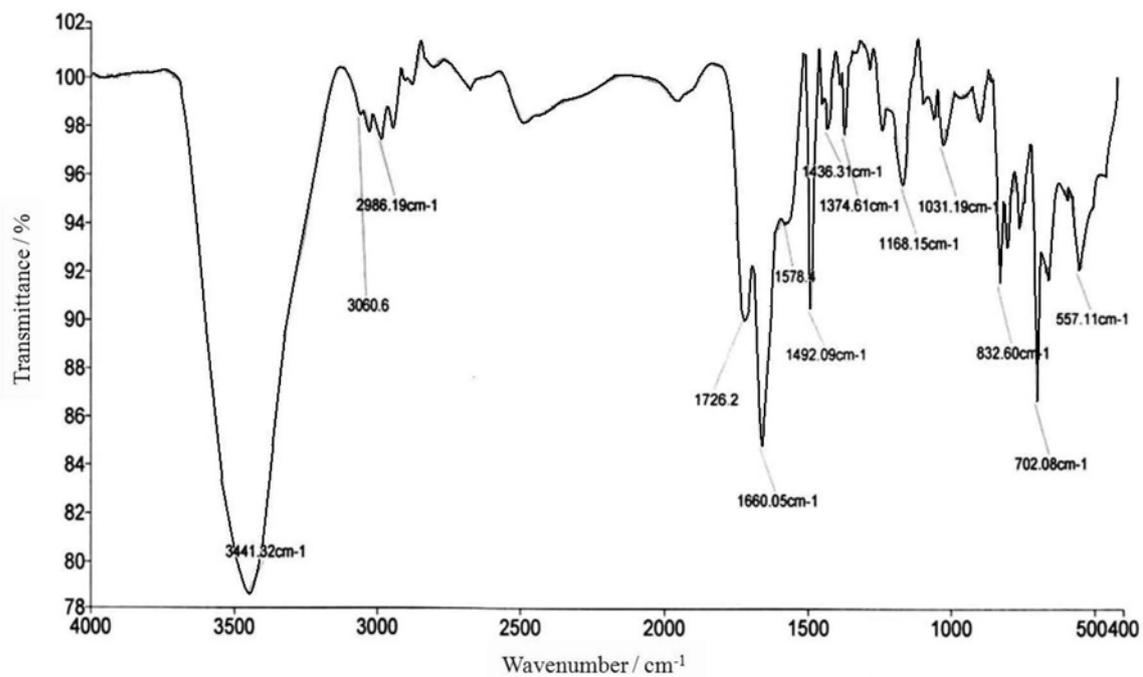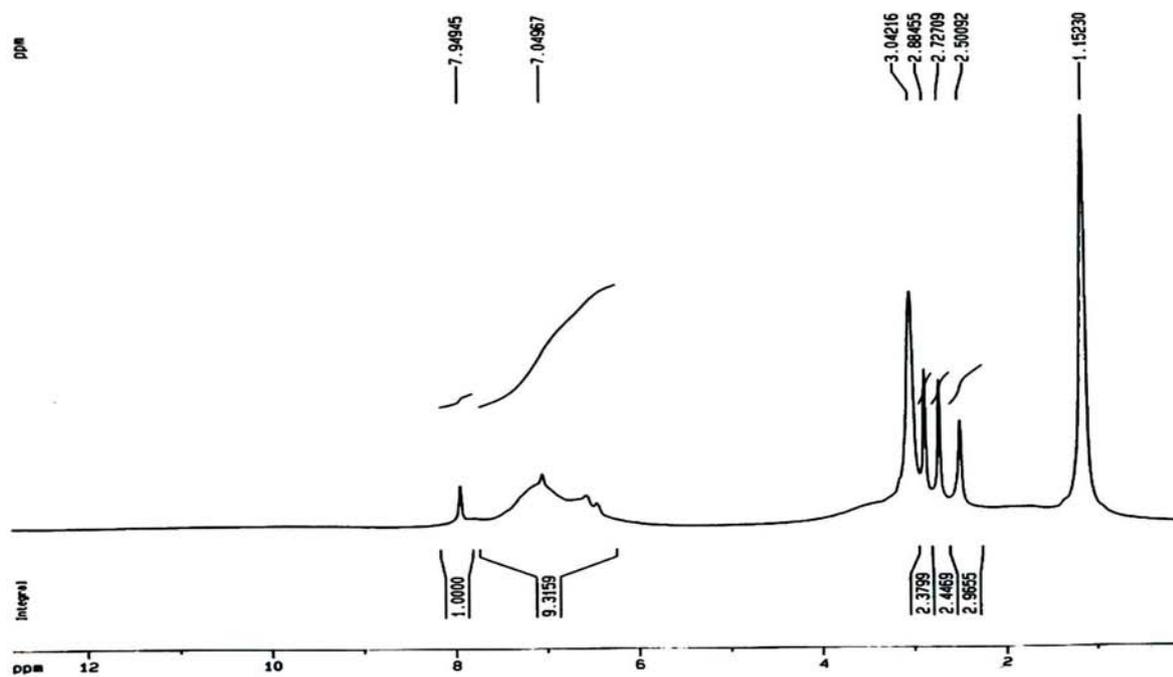

Figure S17. FTIR spectrum (KBr) of PSMA-MSE.

ppm

7.94945

7.04967

3.04216
2.88455
2.72709
2.50092

1.15230

Integral

1.0000

9.3159

2.3799
2.4469
2.9655

ppm   12   10   8   6   4   2

Figure S18. ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of PSMA-MSE.