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Contributed Paper

Kinetic Study of Ibuprofen Release from a pH- and Temperature-Sensitive Hydrogel, Based on Poly(styrene-alt-maleic anhydride) Copolymer

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ABSTRACT

The development of amphiphilic copolymers with pH- and temperature-responsive properties by grafting isopropyl amine and poly(ethylene glycol) monomethyl ether onto poly(styrene-alt-maleic anhydride) copolymer for drug delivery of ibuprofen as the model drug is reported. The modified hydrogel matrices were studied by FT-IR spectroscopy. The synthesized hydrogel behaves as a "smart" dual-responsive material showing transition at the temperature/pH values close to the physiological ones. Hence, swelling and release kinetic studies were performed at 37 °C in acid medium, at pH=3, for mimicking conditions of the gastric fluid in the stomach. The release of the drug was monitored by UV-Vis. spectrophotometer.

In order to study the release kinetics, experimental data obtained from *in vitro* drug release were approximated by several mathematical models including zero-order, first-order, Hixson-Crowell and Korsmeyer-Peppas to determine the kinetics of drug release from drug delivery systems. The quantitative analysis can ultimately help to yield information on the efficacy of various release models. The results obtained showed that the Korsemeyer–Pappas model fits well to data of ibuprofen release.

Keywords: pH- and temperature--sensitive hydrogel, Controlled release, Stomach-specific drug delivery, Ibuprofen, Mathematical model

1. INTRODUCTION

Hydrogels are hydrophilic polymeric networks that can swell in water and absorb large quantities of water while maintaining the structure due to chemical or physical cross-linking of individual polymer chains [1]. Hydrogels have gained considerable attention in recent years as an excipient for various dosage forms, owing to their unique biological and biocompatibility characteristics [1]. Modified release systems based on hydrogels possess many advantages over conventional polymeric systems, because their hydrophilic nature and porous structure networks allow solute diffusion through the swollen hydrogel [2]. Thus, a hydrogel is a versatile system that can be used in either loading or release of

solutes with specific therapeutic properties. In addition, hydrogels exhibit properties in common with soft biological materials, enabling them to be used in pharmaceutical formulations as release polymer systems [3,4]. In recent years, significant efforts have been devoted to use the potentials of hydrogels in controlled drug delivery systems [5-13].

In comparison to commonly used hydrophobic polymers, the conditions for fabricating hydrogels are relatively mild. Gel formation usually proceeds at ambient temperature and organic solvents are rarely required. In-situ gelation with cell and drug encapsulation capabilities further distinguishes hydrogels from the other hydrophobic polymers [3]. Hydrogels can be prepared from natural or synthetic polymers [7]. The hydrogels prepared from natural polymers may not provide sufficient mechanical properties and may contain pathogens or evoke immune/inflammatory responses. Synthetic polymers usually have well-defined structures that can be modified to yield tailorable degradability and functionality [14].

Poly (styrene-alt-maleic anhydride) (PSMA) as an alternating copolymer is a readily synthesized copolymer of styrene and maleic anhydride that incorporates two carboxylic groups and a phenyl group in each repeating unit (Figure 1). The molecular weight and polydispersity of the PSMA copolymers can be controlled by varying the molar ratio of free-radical initiator and volume of added solvent. In PSMA (120,000 average MW), the hydrophobic phenyl side group, contributed by the styrene unit, is directly attached to the hydrocarbon backbone. PSMA derives its anionic charge from two free carboxyl groups (pK_a 1.9 and 6.0) of maleic acid, which are also directly attached to the hydrocarbon backbone instead of the aromatic ring [15]. This compound is commercially available (Sigma-Aldrich, Product no. 662631, www.sigmaaldrich.com). The synthesized hydrogel was applied recently by our research group to develop several new preconcentration and microextraction methods [16,17]. Also this hydrogel was applied successfully for synthesis of gold nano particles [18].

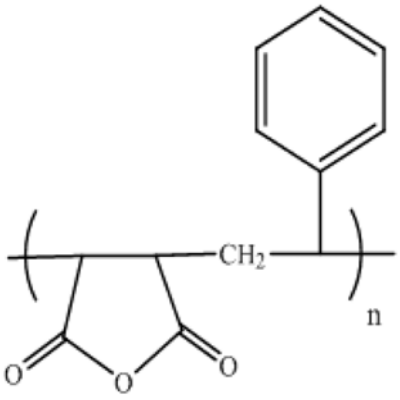

Figure 1. The structure of poly (styrene-alt-maleic acid).

Recently, polymer systems that undergo phase transition in response to pH and temperature have attracted tremendous attention because of their promising potential applications in fields such as drug delivery, gene delivery, sensors, separation, purification [19-22]. Hydrogels sensitive to pH comprise weak acidic or weak basic functional groups, which can be ionised. Approximately at the apparent pK_a of the hydrogel the ionisation begins and the electrostatic repulsions of the same charges present in the polymer network cuases a drastic swelling of the hydrogel. If the ionisation of the ionisable component is completed the swelling process stops and further pH increase only increases the ionic strength [23].

Most polymers increase their water-solubility as the temperature increases. However, in some cases water-solubility

decreases with an increase in temperature [1]. This unusual behavior produces a phenomenon of polymer phase transition as the temperature is raised to a critical value, called the "lower critical solution temperature" or LCST, which is an entropy-driven process. Right below this LCST, where water is a good solvent for the polymer, hydrogen-bonding interactions between the polymer and water molecules leading to enhanced dissolution in water. However, when the temperature exceeds the LCST, these interactions are broken, and the polymer chains collapse and then precipitate in the media [24,25]. The LCST of hydrogels can be modulated to increase by adding a hydrophilic component, or to decrease with a hydrophobic one. Due to this property, temperature-sensitive hydrogels swell below the LCST and collapse in an aqueous environment above this value of temperature, being thus suitable for controlled drug delivery.

Ibuprofen (IBU) is an extensively employed nonsteroidal anti-inflammatory drug (NSAID) used for the treatment of inflammation, pain, or rheumatism. This drug shows similar efficacy for reducing pain and inflammatory symptoms, but it has lower toxicity than other NSAIDs. IBU is a poor water soluble drug, which in the body environment absorbs more than 95% in the plasma and almost completely bounds to plasma proteins [26]. IBU has a short biological half-life (2 h) [27], which makes it a suitable candidate for controlled drug delivery.

Herein, we have developed the first example of pH- and temperature-sensitive poly(styrene-alt-maleic anhydride) copolymer grafted by isopropyl amine and poly(ethylene glycol) monomethyl ether for stomach-specific drug delivery of IBU. Several mathematical models were tested to fit and describe the solute release profiles from hydrogel network.

2. EXPERIMENTAL

2.1 Materials

Styrene was purchased from Merck (Darmstadt, Germany) and was purified by distillation under vacuum before use. Maleic anhydride, benzoyle peroxide (BPO), tetrahydrofuran (THF), N, N-dimethylformamid (DMF) and isopropyl amine (IPA) were purchased from Merck and used without further purification. The polyethylene glycol monomethyl ether (PEG) with molar masses of 500 and 2000 were purchased from Aldrich and used without further purification. IBU (>95%) was supplied by Tabriz Dana Pharmacies. Sodium phosphate dibasic (Na_2HPO_4) and potassium phosphate monobasic (KH_2PO_4) were purchased from Aldrich. Cellulose membrane dialysis bag (3500 molecular weight cut-off) was provided by Serva Electrophoresis GmbH. Poly(styrene-alt-maleic anhydride) (PSMA) was prepared according to literature method [28] and characterized by ^{1}H-NMR spectrum in DMSO-d_6 and (Figure 2) FT-IR spectrum (Figure 3(a)).

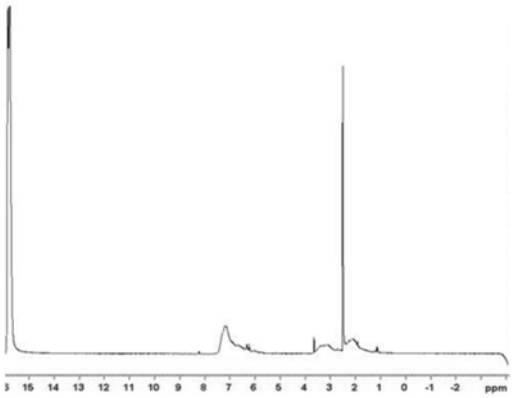

Figure 2. ^{1}H-NMR spectrum of the poly (styrene-alt-maleic anhydride) in DMSO d_6

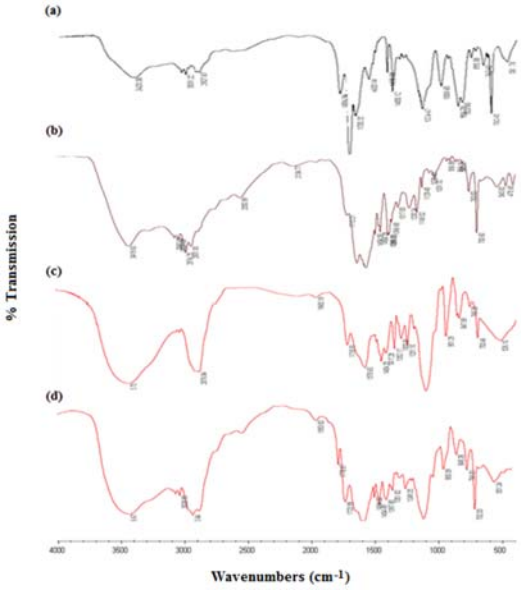

Figure 3. FT-IR spectrum of (a) PSMA, (b) IPA-g-PSMA, (c) PEG-g-PSMA, and (d) IPA-PEG-g-PSMA.

2.2 Instruments

UV-visible spectra were measured by using Shimadzu UV-2550 double-beam spectrophotometer with 1-cm quartz cells. Fourier transform infrared (FT-IR) spectra were recorded on a Thermonicolet (Nexus 670) spectrometer by forming thin transparent KBr pellets. ^{1}H-NMR spectra were recorded on a Bruker DMX-300 spectrometer using tetramethylsilane as an internal standard.

2.3. Preparation of Isopropyl Amine Modified PSMA (IPA-g-PSMA)

Alkylamine derivatives of PSMA can be synthesized by reacting primary alkylamines with the anhydride groups in the PSMA backbone. Amine modified PSMA was synthesized by a reaction of primary alkyl amine as isopropyl amine with the repeated anhydride groups in backbone of PSMA [29]. Firstly, the PSMA (1 g) was dissolved in anhydrous THF (40 mL) in a 100 mL round-bottomed flask. Then copolymer solution was deoxygenated with nitrogen, and 0.29 gr (0.005 mol) of isopropyl amine modifier was added. The reaction was stirred at room temperature for 5 h. The grafted copolymer was recovered by precipitation in cold diethyl ether followed by filtration and dried under vacuum at room temperature. The reaction was repeated for various molar ratios of amine to the PSMA copolymer. The reaction yield was 80%.

2.4 Preparation of Polyethylene Glycol Monomethyl Ether Modified PSMA (PEG-g-PSMA)

According to the literature method [30], a solution of lithium alcoholate was obtained by reacting 2.1 mL (0.0024 mol) polyethylene glycol monomethyl ether with 1.5 mL (0.0024 mol) butyllithium in 20 mL dried THF. The mixture was added dropwise to a solution of 0.5 g of the PSMA copolymer in 30 ml of dried THF. The reaction was carried out for 4 h at room temperature by stirring under nitrogen atmosphere. The grafted copolymer was precipitated into 500 mL of diethyl ether and dried in a vacuum oven at 40 °C for 48 h. The reaction was repeated for various molar ratios of PEG to the PSMA copolymer (Figure 4).

2.5 Preparation of Isopropyl Amine and Polyethylene Glycol Monomethyl Ether Modified PSMA (IPA-PEG-g-PSMA)

Modification of the PSMA copolymer with both PEG and IPA was carried out exactly by the same procedure described in the two previous sections, except with different molar ratios of PEG and IPA to the PSMA and initial addition of PEG followed by IPA after specified time. The grafted copolymer was precipitated into 500 mL of diethyl ether and dried in a vacuum oven at 40 °C for 48 h.

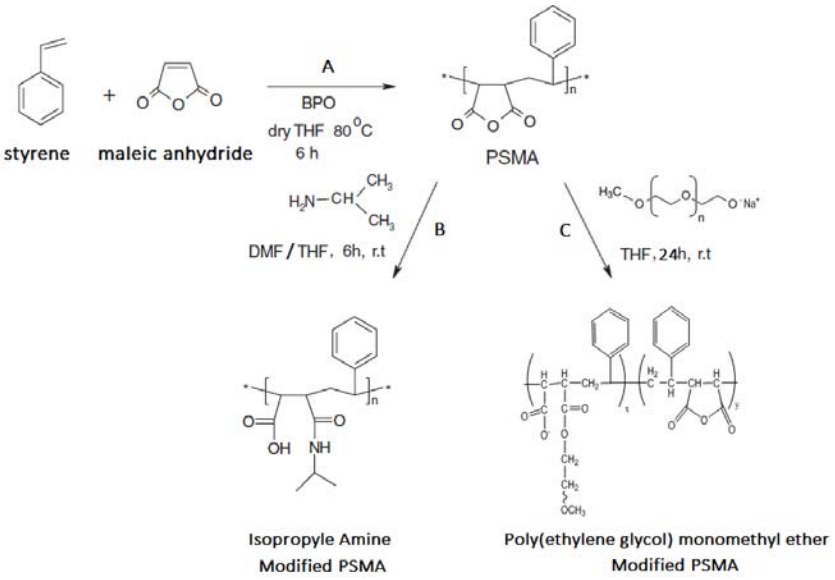

Figure 4. (A) Synthesis of PSMA alternating copolymer, (B) Modification by isopropyl amine to form PSMA-sopropyl amide and (C) Modification by poly(ethylene glycol) monomethyl ether to form PSMA-poly(ethylene glycol) monomethyl ether.

2.6 Swelling Properties

A dialysis bag was weighted and immersed in solution for a predetermined time, and then it was removed and kept for a few minutes until the water was completely dripped. 1 g of modified hydrogel was precisely weighted and put into the dialysis bag. The bag was immersed in solution and removed in the predetermined time intervals and weighted. When a constant weight was reached or a decrease was observed the procedure was ended. The percentage of mass swelling (S_M) was calculated by applying the following expression [31]:

$$\%S_M = \frac{M_t - M_0}{M_0} \times 100 \quad (1)$$

where M_0 and M_t are the initial mass and mass at different time intervals, respectively.

2.7 Calibration Curve Preparation

A stock solution of IBU (100 µg mL^{-1}) was prepared by dissolving appropriate amount of drug in distilled water. It was further diluted to obtain the known standard solutions. The absorbance was measured at 229 nm with the mean data (n = 5) used for the calibration curve. Linearity in the absorbance-concentration relation was verified in the concentration range 2-20 µg mL^{-1}. The concentrations of released drug were calculated from the regression equation obtained from the calibration curve.

2.8 Drug Loading and Release

The loading of the drug was carried out by dissolving 0.1 g IPA-PEG-g-PSMA in deionized water (10 mL) and by adding aliquots of NH_4OH solution; a clear and colorless solution was obtained. Then 1.5 g IBU was dissolved in 10 mL deionized water and added to the above obtained solution. The gentle mixing was carried out at room temperature for 5 h. The product was recovered by acid precipitation using hydrochloridric acid (0.1 N). The precipitate was filtered and washed with water and

dried under vacuum for 48 h.

0.01 g of the drug-loaded hydrogel was precisely weighted and was put into a dialysis bag, and placed into 100 mL buffer solution with various pH values and kept at 37 °C (normal body temperature). Then, the release of IBU was determined at 15 min intervals by UV-Vis spectrophotometer. Sampling intervals was chosen according to the preliminary release rate studies. The faster the drug release rates, the less sampling time intervals.

2.9 Measurement of Cloud Point

The IPA-PEG-g-PSMA hydrogel (33 mg mL^{-1}) were dissolved in deionized water and by adding aliquots of NH_4OH solution; a clear and colorless solution was obtained. The final volume of solution was 15 mL. The aqueous polymer solutions at pH 11.00 were titrated with 0.1 N HCl to reach cloud point pH by constant stirring. The titration was performed on a Metller MA235 pH/ion meter at room temperature.

2.10 Measurement of LCST

As it was assumed that the IPA-PEG-g-PSMA hydrogel is both thermo- and pH-sensitive, the LCST's of amphiphilic grafted copolymer solutions were measured in different molar ratios of IPA and PEG to PSMA (the LCST values are reported in Tables 2, 3 and 4). Determinations of the LCSTs were carried out by UV-Vis spectroscopy at 220 nm in which the heating rate was fixed at 1 °C/min to perform the measurements in a relatively short time. The phase transition temperature was considered as a temperatures at which the absorbance is dramatically increased, proving the starting point of the precipitation of the copolymers.

2.11 Release Mechanism Studies

To explain the nature of the drug release behaviors, various kinetic models were used to describe the release kinetics.

i) Zero-order release kinetics

The zero-order rate describes the systems where the drug release rate is independent of its concentration. As a result of this, blood levels of the drug would remain constant throughout the delivery period. This ideal delivery is particularly important in certain classes of medicines intended, for example, for antibiotic delivery, heart and blood pressure maintenance, pain control and antidepressants. In its simplest form, zero-order release can be represented as:

$$Q_t = Q_0 + K_0 t \quad (2)$$

where, Q_t is the amount of drug released or dissolved at time t, Q_0 is the initial amount of drug in solution (it is usually zero) and K_0 is zero-order rate constant expressed in units of concentration/time. Plotting a graph as cumulative percentage of drug release *versus* time would yield a straight line with a slope of K_0.

ii) First-order release kinetics

The first-order describes the release from system where release rate is concentration dependent. Thus, the rate of drug release depends directly on the initial concentration and increases linearly with increasing concentration of the drug. Drug delivery based on first-order kinetics is expressed by the following equation:

$$\log Q_t = \log Q_0 - Kt / 2.303 \quad (3)$$

where Q_t and Q_0 are defined the same as

the zero-order model, K is the first-order rate constant in units of concentration/time and t is the time in hours. Plotting a graph as log cumulative percentage of drug release *versus* time would give a straight line with a slope of -K/2.303.

iii) Hixson-Crowell model

The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets [32]. For a drug powder consisting of uniformly sized particles, it is possible to derive an equation that expresses the rate of dissolution based on the cube root of the particles.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t \qquad (4)$$

where, Q_t is the amount of drug released at time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation. Plotting a graph as the cube root of the initial concentration minus the cube root of percent remaining *versus* time would yield a straight line with a slope of K_{HC}.

iv) Korsmeyer-Peppas model

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer-Peppas model:

$$F = M_t / M_\infty = K_{KP}\, t^n \qquad (5)$$

where, F is a fraction of drug released at time t, M_t is the amount of drug released at time t, M_∞ is the total amount of drug in dosage form, K_{KP} is kinetic rate constant, n is the diffusional release exponent indicative of the drug release mechanism and t is time [33]. Different release mechanisms as given in the following table for cylindrical shaped matrices.

Table 1. Diffusion exponent and solute release mechanism for cylindrical shape.

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45< n<0.89	Anomalous (non-Fickian diffusion)
0.89	Case-II transport
n > 0.89	Super case-II transport

3. RESULTS AND DISCUSSION

3.1 Characteristics of Isopropyl Amine Modified PSMA (IPA-g-PSMA)

IPA derivative of the PSMA copolymers is used to control its pH-solubility response. Modification of the PSMA was carried out by isopropyl amine amidation of anhydride moieties in various ratio of amine to repeated anhydride groups of the PSMA. Each IPA reacts with one maleic anhydride group in the PSMA backbone to form an alkylamide linkage and one carboxylic acid group, which confers pH-sensitivity property to the modified copolymer. The pH of cloud point (swelling-shrinking transition) can be adjusted by degree of modification of PSMA by amine. Table 2 shows that when the ratio of amine to PSMA increases, the pH of cloud point is also increased. This can be ascribed to the fact that hydrophobicity is increased by increasing the degree of modification with IPA. As the hydrophobicity of the PSMA backbone is increased by modification with IPA groups, the pK_a of the copolymer is shifted upward, while the LCST is shifted downward.

In the FT-IR spectrum of the PSMA-IPA (Figure 3(B)), the anhydride peaks have disappeared, and instead, the spectrum shows the characteristic absorption peaks of

the amide carbonyl (1637 cm^{-1}) and the carboxylic acid (1781 cm^{-1}) at a lower frequency.

Table 2. Modification of PSMA with IPA.

Molar ratio IPA/PSMA	pH of cloud point	LCST (°C)
0.5	3.44	38
1	4.56	36
2	5.12	35

3.2 Characteristics of Polyethylene Glycol Monomethyl Ether Modified PSMA (PEG-g-PSMA)

Modification of PSMA with PEG was carried out in various ratio of PEG to repeated anhydride groups of PSMA. Each PEG reacts with one maleic anhydride group in the PSMA backbone to form an esteric linkage and one carboxylic acid group, which confers thermo-sensitivity to the modified copolymer. While the carboxylic acid groups are available in the backbone, PEG units form intra/intermolecular hydrogen bonds with the acid groups and any excess PEG is free to hydrogen bond with water. Thus, the copolymer undergoes hydrated and dehydrated stats in response to small changes in temperature [28].

Table 3 shows that when the ratio of PEG to PSMA increases, the pH of cloud point is decreased. These results clearly indicate that, incorporated PEG units in the copolymer make it more hydrophilic due to the poly(ethylene glycol) chains along the backbone. As the hydrophilicity of the PSMA backbone is increased, the pK_a of the copolymer is shifted downward, while the LCST is shifted upward because of the increasing number of hydrogen-bonding interactions between the water molecules and the copolymers. As it is shown in Table 3 (upper part), with the increasing PEG ratio to PSMA, the phase transition temperature increases while pH of the cloud point decreases due to the increasing hydrophilicity of the polymer. LCST of the grafted copolymer solutions are also dependent on the length of the grafted PEG chains. This fact is readily aparent in Table 3 (lower part). As it can be seen, the higher the PEG content in the copolymer is, the higher the LCST, due to the increasing hydrophilicity of the polymer.

Modification of PSMA with PEG is confirmed by the infrared spectrum in Figure 3(c). A broad band arises between 2400 and 3425 cm^{-1} is attributed to the acidic O-H, indicating that the ring-opening reaction of the maleic anhydride unit was completed. In the spectrum of PEG-g-PSMA, the anhydride peaks have disappeared, and instead the spectrum shows characteristic absorptions of ester carbonyl at 1781 cm^{-1}, which overlaps with the acidic C=O.

Table 3. Modification of PSMA with PEG with molar masses of 500 and 2000.

Molar ratio PEG/PSMA	pH of cloud point	LCST (°C)
M_n = 500		
0.5	4.05	35
1	3.65	37
1.5	3.45	40
2	3.31	45
M_n = 2000		
0.5	3.86	no[a]
1	3.56	65
2	3.43	72

[a] No phase transition observed.

3.3 Characteristics of Isopropyl Amine and Polyethylene Glycol Monomethyl Ether Modified PSMA (IPA-PEG-g-PSMA)

In order to the balance between hydrophilicity/hydrophobicity of the

copolymers, PSMA was modified with both IPA and PEG. In comparison with PEG-g-PSMA the copolymer is shifted toward hydrophobicity due to the decreasing number of hydrogen-bonding interactions between the water molecules and the copolymers.

Figure 3(d) shows infrared spectrum of the IPA-PEG-g-PSMA copolymer. It confirms the efficiency of the grafting reaction. Modification of PSMA with IPA and PEG (in molar ratios of 3:1) was carried out in various ratio of grafting agents to PSMA copolymer (Table 4). For the remainder of our study, the molar ratio of 0.5:1 of the grafting agents to the PSMA copolymer was selected as an appropriate ratio for controlled delivery of IBU.

Table 4. Modification of PSMA with IPA and PEG.

Molar ratio IPA and PEG (3:1)/PSMA	pH of cloud point	LCST (°C)
0.5	2.96	37
1	3.45	37
2	4.25	37

3.4 Influence of pH on Drug Loading

Due to changes in the physical state of hydrogel, pH is one of the most critical factors affecting the amount of loaded drug. According to the Figure 5 it can be inferred that with increasing of pH, the amount of loaded drug on hydrogel also increases. On the basis of experimental data analysis, one can conclude that the highest amount of loaded drug occurred at alkaline pH=9.5 and with the increase of media pH, the result is not much change. This can be explained by the fact that below the pH of the cloud point, as the hydrogel starts to shrink, the porosity decreases and diffusion becomes the dominant mechanism to describe the drug release from hydrogels. However, above the cloud point hydrogel has liquid-like properties and physical entrapping in the hydrogel matrix as well as hydrophobic-hydrophobic interaction between IBU and the hydrophobic moieties of IPA-PEG-g-PSMA copolymer become the dominant mechanisms. As it is shown, no significant change occurred at higher media pH, which implies that hydrogel starts to saturate.

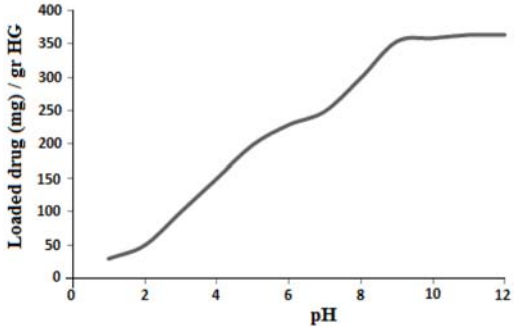

Figure 5. Variations of the loaded drug with pH.

1.1 In Vitro Drug Release

According to the UV spectra of modified hydrogel, IBU and drug-loaded hydrogel, λ=229 nm was selected as an appropriate wavelength to measure drug release (Figure 6). At this wavelength IBU has an acceptable absorption intensity and also in comparison with other wavelengths the amount of spectral overlap is minimum, therefore the measured absorbance is directly attributed to the released drug. Hence all of the measurements performed at λ=229 nm.

In vitro release of IBU was performed in dissolution media with pH=2, 3 and 3.5 at 37 °C, where IPA-PEG-g-PSMA become protonated. It should be noted that in neutral and alkaline pHs IPA-PEG-g-PSMA is in a water-swollen state, which prevents the drug release. Based on this fact we did not investigate drug release in neutral and

alkaline media. This property can be used to prevent release of the drug into the neutral pH environment of the intestine, while drug release can be occurred at acidic media of stomach.

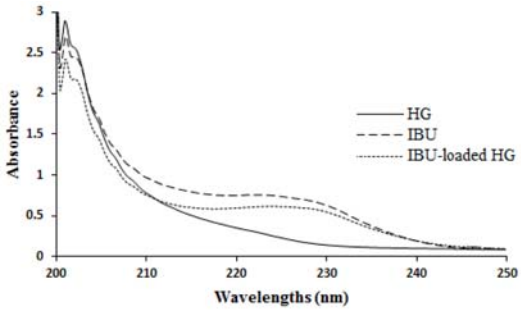

Figure 6. Absorption spectra of hydrogel (solid line), IBU (dashed line), and drug-loaded hydrogel (dotted line).

The percentage of the released drug was calculated using the following equation:

$$\% \text{ Released drug} = R_t/L \times 100$$

where R_t is the amount of drug released at time t and L is the initial amount of drug in solution. The pH of the medium significantly affected the release rate. It was found that the release rate of IBU was increased as the pH of medium increased. The release rate profiles in acidic media are depicted in Figure 7. As it is shown, at media pH=2 drug release rate is low, while a more rapid release was observed at pH=3.5. The reason being that, at low pH, carboxylic acid groups of IPA-PEG-g-PSMA are well-protonated and the hydrophobic interactions become strengthened, resulting in self-aggrigation of the hydrogel, as a consequence drug release rate is low and relatively long time required to release 100% of the loaded drug. Maximum drug concentration in release medium was achieved within 2-3 hours. This ideal delivery is particularly important in certain classes of medicines, which should cause a rapid increase of the drug concentration in the body. On the other hand, the rapid destruction of the copolymer prevents polymer accumulation in the body.

At temperatures below the LCST, IPA-PEG-g-PSMA was in a water-swollen and extended state, which prevented IBU to diffuse from the hydrogel matrix. While at temperatures above the LCST, hydrogel was in a collapsed, hydrophobic state because the intramolecular hydrogen bonds between CP%O and N-H groups in hydrogel chains along the backbone. The drug molecules could be released from the hydrogel.

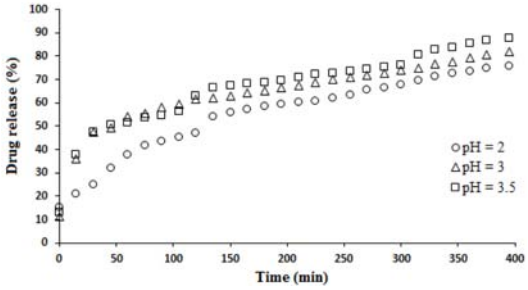

Figure 7. In vitro drug release profiles of IBU from the IPA-PEG-g-PSMA in various pH values at 37 °C.

3.4 Drug Release Kinetics

In order to study the release kinetics, experimental data obtained from *in vitro* drug release was fitted into the zero-order, first-order, Korsmeyer-Peppas and Hixson-Crowell kinetic models.

The criteria for selecting the most appropriate model were correlation coefficient (R^2) and sum of square of residuals (SSR). The Solver function, available in Microsoft® Excel, was applied to fit the experimental data with the predicted data obtained from kinetic models. Residual values between predicted and experimental data were used to calculate the sum of squares of residuals (SSR). The Solver function would

minimize the SSR by optimizing drug release kinetic parameters in Equations 2-5. Kinetic parameters, R^2 values and sum of squares residuals (SSR) in media pH 2, 3 and 3.5 are given in Table 5. The highest value of R^2 (0.988) and lowest sum of square residuals (0.0063) was found for the Korsmeyer-Peppas model. The correlation of zero-order, first-order, Korsmeyer-Peppas and Hixson-Crowell kinetic curves to data of IBU release at pH=3 and 37 °C are graphically presented in Figure 8. One can observe that for discussed pH values Korsmeyer-Peppas model approximates the experimental points very well. This suggests that, IBU release mechanism conforms Korsmeyer-Peppas kinetic model. However, zero-order, first-order and Hixson-Crowell curves do not fit sufficiently to the release data, therefore, these models do not determines release process. Furthermore, release exponent values (n) ranging from 0.2224 to 0.3959, indicating the tendency of drug release by Fickian mechanism.

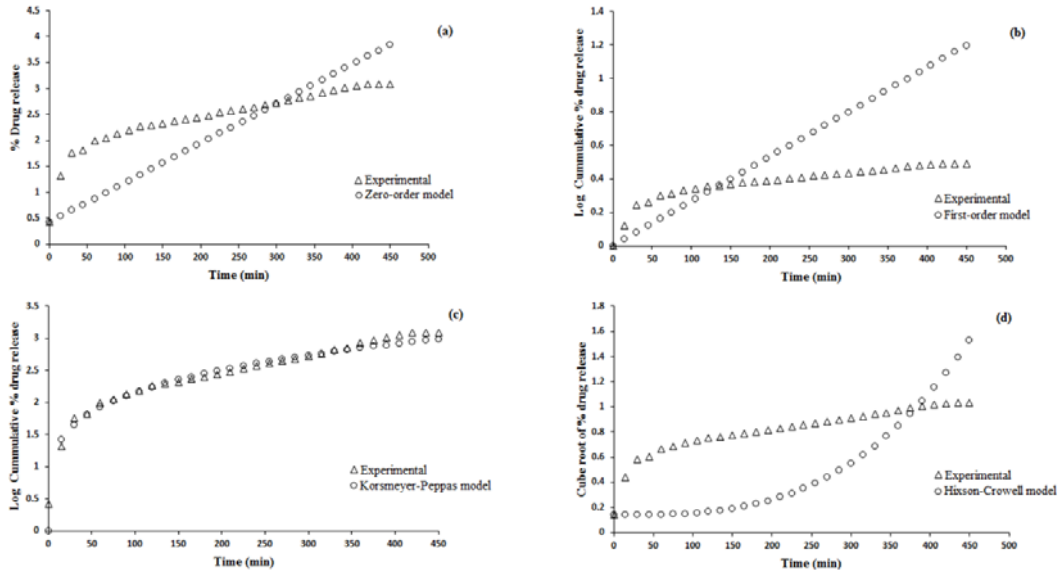

Figure 8. (a) Zero-order, (b) First-order, (c) Korsmeyer-Peppas, and (d) Hixson-Crowell kinetic models for IBU release at pH=3 and 37 °C.

Table 5. Kinetic studies on the IPA-PEG-g-PSMA.

pH	Zero-order			First-order			Hixson-Crowell			Korsmeyer-Peppas			
	R^2	K_0	SSR	R^2	K_t	SSR	R^2	K_{HC}	SSR	R^2	K_{KP}	n	SSR
2	0.910	0.0076	2.789	0.765	-0.0056	0.677	0.595	-0.0041	23.14	0.988	0.2912	0.3959	0.0063
2.96	0.808	0.0076	13.00	0.519	-0.0061	2.858	0.535	-0.0036	53.31	0.982	0.7532	0.2282	0.0038
3.5	0.902	0.0079	9.672	0.656	-0.0057	2.026	0.703	-0.0035	50.47	0.974	0.7711	0.2224	0.0149

CONCLUSION

PSMA was modified by isopropyle amine and poly(ethylene glycol) monomethyl ether in order to prepare IPA-PEG-g-PSMA pH- and temperature-sensitive hydrogel. The IPA-PEG-g-PSMA copolymer in the molar ratio of 0.5:1 of the grafting agents to the PSMA copolymer exhibited a cloud point and LCST at pH 2.96 and 37 °C, respectively, which makes in an appropriate for controlled delivery of IBU, as a model drug, at acidic media of stomach. *In vitro* release of the drug was determined at λ=229 nm as a function of time. The release was monitored in phosphate-buffered solutions of pH 2, 3, and 3.5 at 37 °C. To investigate the drug-release kinetics, data were fitted to various kinetic models such as zero-order, first-order, Hixson-Crowell and Korsemeyer-Pappas equations. The regression analysis was done for pH 2, 3 and 3.5 dissolution media. The Korsemeyer-Pappas model fits well to data of IBU release and showed the highest correlation (R^2=0.988) and lowest sum of square residuals (SSR=0.0063). The release exponent values are found that would indicate a diffusion controlled drug release mechanism. It is concluded that isopropyle amine and poly(ethylene glycol) monomethyl ether modified PSMA would be a promising system for delivery of water insoluble drugs such as IBU.

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