Polym. Bull. (2012) 68:197–207
DOI 10.1007/s00289-011-0549-1

ORIGINAL PAPER

pH- and temperature-sensitive semi-interpenetrating network hydrogels composed of poly(acrylamide) and poly(γ-glutamic acid) as amoxicillin controlled-release system

D. E. Rodríguez-Félix · C. J. Pérez-Martínez · M. M. Castillo-Ortega · M. Pérez-Tello · J. Romero-García · A. S. Ledezma-Pérez · T. Del Castillo-Castro · F. Rodríguez-Félix

Received: 10 January 2011 / Revised: 8 June 2011 / Accepted: 11 June 2011 /
Published online: 22 June 2011

Abstract Hydrogels of semi-interpenetrating networks composed of poly(acrylamide) (PAAm) and poly(γ-glutamic acid) (γ-PGA) with different proportions were studied as potential amoxicillin controlled-release devices. The effects of the hydrogels composition, pH, and temperature on the kinetics and final release of amoxicillin were determined in batch experiments. The release kinetic tests were conducted using a buffer solution as the release medium under pH conditions of 3 and 7.2, and temperature of 25, 37, and 45 °C. The final percentage of amoxicillin released from the hydrogels was found to increase with temperature, pH, and the amount of γ-PGA in the hydrogels formulation. Overall, equilibrium conditions in the kinetics experiments were achieved within 240 min of hydrogel–solution contact. The overall rate of amoxicillin release was represented with a two-parameter empirical model as a function of time.

Keywords Polymer gels · Semi-interpenetrating networks · Amoxicillin controlled release · Poly(acrylamide) · Poly(γ-glutamic acid)

D. E. Rodríguez-Félix (✉) · C. J. Pérez-Martínez · M. M. Castillo-Ortega · T. Del Castillo-Castro
Departamento de Investigación en Polímeros y Materiales, Universidad de Sonora,
Rosales y Luis Encinas s/n, Colonia centro, Hermosillo, Sonora 83000, México
e-mail: dora@polimeros.uson.mx

M. Pérez-Tello
Departamento de Ingeniería Química y Metalurgia, Universidad de Sonora,
Rosales y Luis Encinas s/n, Colonia centro, Hermosillo, Sonora 83000, México

J. Romero-García · A. S. Ledezma-Pérez
Centro de Investigación en Química Aplicada, Blvd. Enrique Reyna #140,
Saltillo, Coahuila 25100, México

F. Rodríguez-Félix
Departamento de Investigación y Posgrado en Alimentos, Universidad de Sonora,
Rosales y Luis Encinas s/n, Colonia centro, Hermosillo, Sonora 83000, México

Introduction

In recent years, the controlled drug release systems have been widely studied because they offer a number of advantages over classical methods of drug delivery. Some of such advantages include the possibility of delivering the drug to specific parts of the human body, the assurance of treatment continuity during night, drug stability, optimum drug absorption by the living tissues, and the decrease of secondary effects by patients [1]. As a result, a variety of controlled antibiotic release systems have been developed [2, 3]. Amoxicillin (α-amino-hydroxybenzyl-penicillin) is a broad-spectrum, semisynthetic antibiotic which is administered orally [2]. Amoxicillin is one of the β-lactam antibiotics most frequently used to treat bacterial infections in humans and animals [3].

Hydrogels are one of the most promising and versatile materials with many potential applications, especially, in the development of systems for the controlled release of drugs. In addition to exhibiting good swelling-controlled drug release capabilities, hydrogels are considered to be intelligent materials because their volume and physicochemical properties change as a response to environmental stimuli. Among the large number of intelligent materials currently under investigation by the research community, pH- and temperature-sensitive hydrogels are some of the most extensively studied because both factors are important inside the human body [4–6].

Hydrogels of interpenetrating polymer networks (IPNs) consist of an assembly of two crosslinked polymers in which at least one of them is synthesized and crosslinked in the presence of the other, but there are not covalent bonds between the polymers within the network. If only one component of the assembly is crosslinked leaving the other polymer in linear form, the system is called a semi-interpenetrating polymer network (semi-IPN). Because of their drastic change of properties in response to environmental stimuli, semi-IPNs may be used in controlled drug release devices [7].

PAAm has been widely studied because of its good swelling properties; however, its mechanical properties are not suitable for pharmaceutical applications. As a result, PAAm is usually blended with other components to yield a drug release material with improved characteristics. Taking this into consideration, the present authors reported on the synthesis and swelling properties of semi-IPNs made up of poly(acrylamide) (PAAm) and poly(γ-glutamic acid) (γ-PGA) [8]. The hydrogels thus obtained are materials that combine the swelling capability of the rigid PAAm and the flexibility of γ-PGA to improve the mechanical properties of the resulting composite. An additional benefit of this material stems from the fact that γ-PGA is a biopolymer produced by *Bacillus licheniformis*, a bacteria commonly found in soils and bird feathers. Therefore, γ-PGA is both biodegradable and biocompatible, which makes it suitable for potential applications in controlled drug release [9]. The hydrogels thus obtained were found to be sensitive to both pH and temperature variations [8].

The goal of this investigation was to test the potential of semi-IPNs made up of PAAm and γ-PGA as controlled-release devices for amoxicillin delivery. To achieve this major goal, the effects of pH and temperature on the release rate of

amoxicillin were determined for hydrogel devices prepared with different proportions of PAAm and γ-PGA.

Experimental

Materials

Amoxicillin, acrylamide (AAm), *N*′*N*′-methylene-bis(acrylamide) (MBAAm), and *N*,*N*,*N*′,*N*′-tetramethylenediamine (TEMED) were purchased from Sigma, and ammonium persulfate (APS) was obtained from J. T. Baker. All reagents were used as received, except amoxicillin, which was treated with a 1 M sodium hydroxide solution to produce the amoxicillin salt which was further freeze-dried. This procedure was carried out to increase the solubility of amoxicillin in water. Deionized water was used in all the experiments.

Synthesis of semi-IPNs of PAAm and γ-PGA

The γ-PGA was obtained by means of a liquid culture of *B. licheniformis* ATCC 9945a based on our method previously published [8]. The semi-IPNs of PAAm and γ-PGA were also obtained by the corresponding method reported in the original Ref. [8]. In this manner, the hydrogels were obtained upon addition of acrylamide solution (29 g AAm and 1 g MBAAm in 100 mL of aqueous solution) into a γ-PGA aqueous solution (10% w/v). Gelation process was initiated by free radical polymerization by adding PSA (2.5 mg/mL) and TEMED (3.75 μL/mL). Hydrogels of semi-IPNs composed of PAAm:γ-PGA (Mw 150000 g/mol) were prepared in molar ratios of 95:5, 90:10, 85:15, and 80:20 using 16-mm diameter cylindrical molds. The hydrogels were washed in deionized water for 48 h and were further freeze-dried during 48 h in a Labconco Freezone 4.5 unit under a vaccum atmosphere of 0.5 mBar and −46 °C in the collector.

Preparation of the calibration curve for amoxicillin concentration measurement

Amoxicillin concentration in the aqueous solution was determined with a Perkin-Elmer Lambda 20 UV–Vis spectrophotometer. The calibration curve for this unit was obtained by preparing a number of standard solutions containing from 0.2 to 1.2 mM of amoxicillin and measuring the corresponding absorbance in the UV–Vis unit at 274 nm. The calibration curve is shown in Fig. 1 and was constructed by plotting the concentrations of the standard solutions versus the absorbance readings and fitting the values to a linear relationship.

Loading of amoxicillin into the hydrogels

The loading of amoxicillin into the hydrogels was carried out by the swelling equilibrium method. Cylindrical hydrogels samples with 16-mm diameter and 3-mm thickness were immersed into a 5 mL solution containing 1000 mg of amoxicillin,

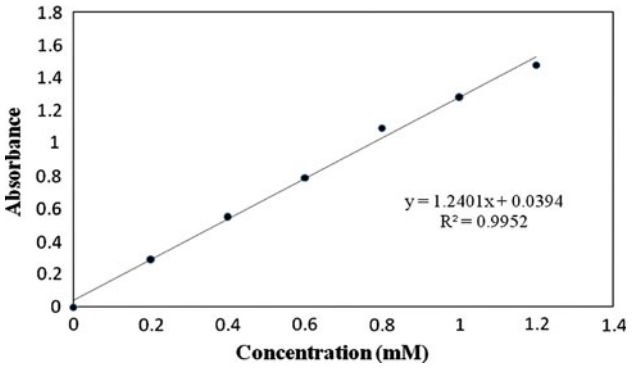

Fig. 1 Calibration curve of amoxicillin obtained by UV–Vis absorbance at 274 nm

which is equivalent to one daily dose of the medication. The hydrogel samples were kept for 3 days in the amoxicillin solution at 8 °C to reach maximum swelling and equilibrium loading of the medicament, after which the samples were frozen and dried by the freeze drying method. The remaining amoxicillin solution was carefully measured to determine the total amount of amoxicillin absorbed by the hydrogels matrix. In this manner, the hydrogels absorbed an average percentage of amoxicillin corresponding at 94.5 (945 mg).

Preparation of buffer solutions

Two buffer solutions with pH 3 and 7.2 were prepared for the kinetics experiments. The buffer solution of pH 3 was prepared by mixing 102 mL of Na_2HPO_4 0.2 M and 398 mL of $C_8H_8O_7$ 0.1 M (citric acid) into a volumetric flask and adding deionized water up to complete 1000 mL. The buffer solution of pH 7.2 was prepared similarly by mixing 436 mL of Na_2HPO_4 0.2 M and 65 mL of $C_8H_8O_7$ 0.1 M into a volumetric flask and adding deionized water up to complete 1000 mL.

Amoxicillin release kinetic experiments

For the release kinetic experiments, dried hydrogel samples loaded with amoxicillin were used. The cylindrical samples (16 mm of diameter, 3 mm of thickness) were immersed in 250 mL of buffer solution at the pH and temperature conditions pre-specified for the experiment. The system was continuously stirred at a constant speed by mechanical stirrer. At certain time intervals, 50 μL aliquots were collected from each release system, and buffer solution was added up to the aliquots complete 3 mL. The resulting solutions were then analyzed in the UV–Vis spectroscopic unit to obtain their corresponding absorbance readings at 274 nm. The amount of amoxicillin released up to the time of collection was determined by interpolation of the absorbance readings within the calibration curve previously developed.

Two sets of experiments were conducted according to the above procedure. First, the effect of temperature on the kinetics of amoxicillin release was tested by setting

pH = 7.2 and varying the system temperature at 25, 37, and 45 °C. Next, the effect of pH was tested at 25 °C by setting the pH to 3 and 7.2.

Results and discussion

The release behavior of solute molecules from hydrogels depends on a number of factors, such as the chemical nature of the gelling polymers and the solute, hydrogel composition and structure, and the experimental conditions of the release medium such as pH and temperature [4]. In this study, the effects of pH and temperature on the release rate of amoxicillin were determined for hydrogel devices prepared with different proportions of PAAm and γ-PGA.

Effect of pH on amoxicillin release from hydrogel matrix

Figures 2 and 3 show the amoxicillin release kinetics from hydrogels with different molar ratios of PAAm and γ-PGA in buffer solutions with pH 3 and 7.2 at 25 °C. The pH values were selected by considering an acid environment similar to stomach and a neutral environment similar to thin intestine in which amoxicillin is mostly absorbed. The hydrogels with molar proportions of PAAm: γ-PGA corresponding to 95:5, 90:10, 85:15, and 80:20 showed a final percentage of amoxicillin released at pH 3 of 39.5, 44.3, 49.0, and 54.9, respectively. Whereas, in the studies conducted at pH 7.2 the final values were 49.6, 61.8, 65.2, and 70.2. The final percentage of amoxicillin released is noted to increase as the content of γ-PGA in the hydrogel increases. As a result, the semi-IPNs of PAAm:γ-PGA with the molar ratio of 80:20

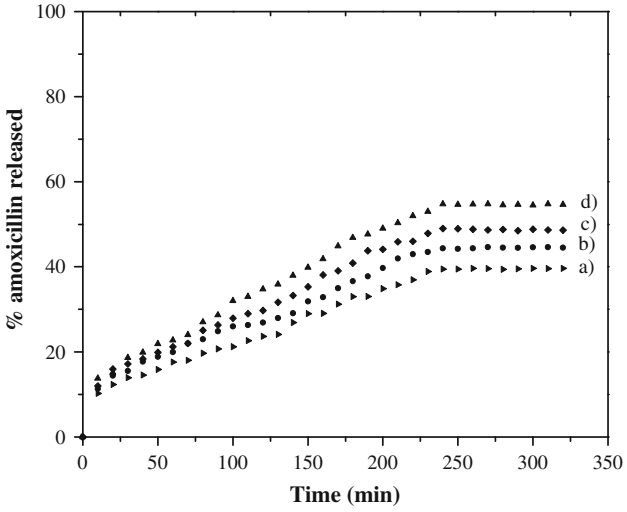

Fig. 2 Release kinetics of amoxicillin from semi-IPNs with different molar proportion of PAAm:γ-PGA, *a*) 95:5, *b*) 90:10, *c*) 85:15, *d*) 80:20, carried out in buffer solution with pH 3 at 25 °C

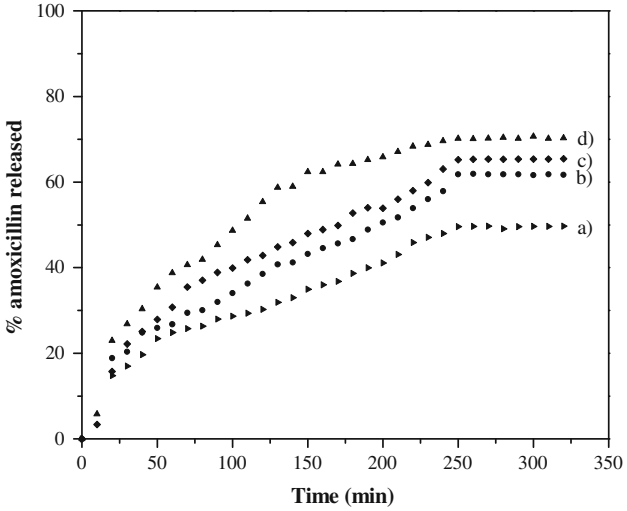

Fig. 3 Release kinetics of amoxicillin from semi-IPNs with different molar proportion of PAAm:γ-PGA, *a*) 95:5, *b*) 90:10, *c*) 85:15, *d*) 80:20, carried out in buffer solution with pH 7.2 at 25 °C

showed the highest value in the final percentage of amoxicillin released. All the experiments reached equilibrium in about 240 min.

Moreover, in all the experiments the amount of amoxicillin released from the samples increased when the pH of the buffer solution was increased from 3 to 7.2. This behavior may be explained in terms of the free carboxyl groups (FCGs) within the γ-PGA chains, as follows. At pH of 3, the FCGs are present as non-ionized form (–COOH) that are linked with PAAm chains through hydrogen bonds. This causes an increase in the crosslinking density and a decrease in the free space within the polymeric matrix which in turn hinders the release of amoxicillin.

On the other hand, when the pH of the buffer solution is set to 7.2 the FCG within the γ-PGA chains are expected to be present mostly in ionized form ($-COO^-$). Therefore, the number of hydrogen bonds between PAAm and γ-PGA is significantly small. This causes a decrease in the crosslinking density and an increase in the free space within the polymeric matrix which favors the release of amoxicillin.

Effect of temperature on amoxicillin release from hydrogel matrix

The results obtained in the release kinetics experiments carried out at 25, 37, and 45 °C in buffer solution at pH 7.2 are shown in Figs 3, 4, and 5, respectively. At 37 °C, the hydrogels with molar proportions of PAAm:γ-PGA corresponding to 95:5, 90:10, 85:15, and 80:20 showed percentages of drug released of 78.6, 83.7, 89.7, and 96.9, respectively. At 45 °C, the percentages of drug release obtained were 81.8, 87.0, 92.9, and 98.8, respectively. In general, the percentage of drug released increased when temperature was increased. This behavior can be attributed to the dissociation of hydrogen bonds between PAAm chains and between PAAm

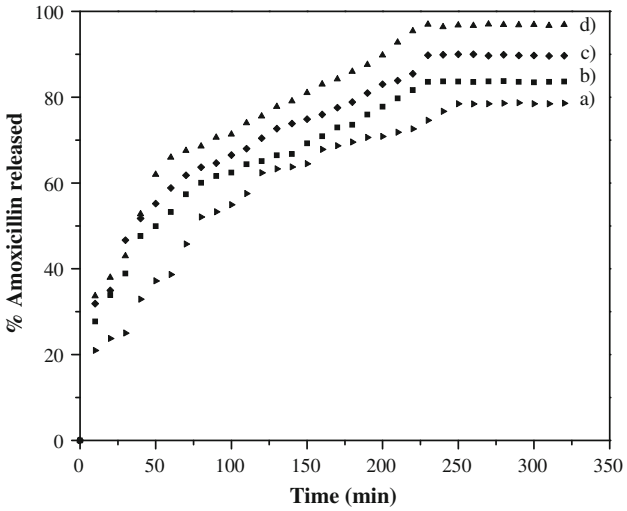

Fig. 4 Release kinetics of amoxicillin from semi-IPNs with different molar proportion of PAAm:γ-PGA, *a*) 95:5, *b*) 90:10, *c*) 85:15, *d*) 80:20, carried out in buffer solution with pH 7.2 at 37 °C

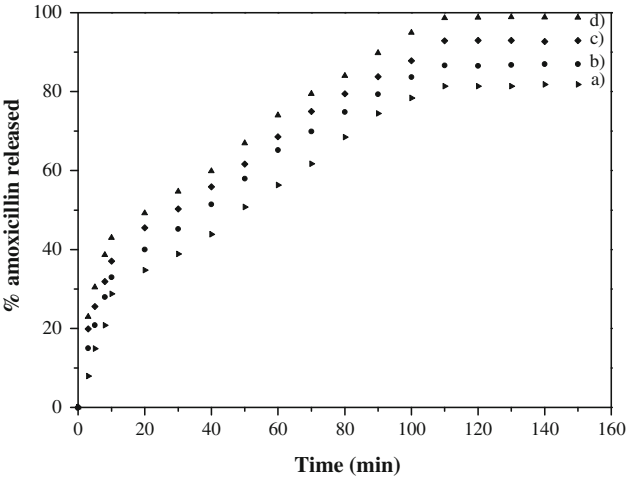

Fig. 5 Release kinetics of amoxicillin from semi-IPNs with different molar proportion of PAAm:γ-PGA, *a*) 95:5, *b*) 90:10, *c*) 85:15, *d*) 80:20, carried out in buffer solution with pH 7.2 at 45 °C

and γ-PGA chains, which causes a decrease in the crosslinking density in the hydrogel matrix, which in turn favors the solute release [10]. Also, the higher temperature makes the higher kinetic energy of amoxicillin molecules, which also favors its release from the hydrogel matrix. The release kinetics carried out at 25 and 37 °C reached equilibrium in a period of time of 240 min, whereas at 45 °C the equilibrium was reached in about 120 min. In practical terms, this behavior may be

convenient because the corporal temperature rapidly increases following a bacterial infection. In this case, a rapid release of the antibiotic is necessary.

Overall, the results discussed in this article are considered to be satisfactory because at 37 and 45 °C amoxicillin was released almost completely. The highest percentage of amoxicillin released (98.8) was obtained at pH 7.2. This pH is similar to typical pH values prevalent in the thin intestine, where most of the absorption of antibiotic is expected. Also, the hydrogel systems studied prolonged amoxicillin release during 4 h. Therefore, the systems of semi-IPNs hydrogels based on PAAm and γ-PGA have a high potential in applications as systems of controlled release of amoxicillin.

Effect of semi-IPNs composition on amoxicillin release rate

In general, the amoxicillin release showed a strong dependence on the hydrogel composition, as can be inferred from Figs 2, 3, 4, and 5 previously discussed. It is noted that the percentage of amoxicillin released at a given time increases as the content of γ-PGA in the hydrogel increases, these results can be widely analyzed in Table 1 which shows the values of percentage of amoxicillin released in equilibrium of all release experiments studied. This behavior can be attributed to a decrease in the polymeric density due to minor content of crosslinked PAAm which allows more free space in the polymeric network, thus allowing the release of amoxicillin. Because release of medicaments from hydrogel systems is favored by the swelling of the polymeric network, the increase of γ-PGA content favors the swelling of hydrogel in aqueous medium due to the existence of highly hydrophilic carboxyl groups in their structure, which may in turn favor the release of amoxicillin. It is also noted that the release of amoxicillin during the first minutes is very fast, i.e., a burst effect is observed. The release rate then decreases as time progresses until equilibrium is reached in about 240 min.

Empirical model for the amoxicillin release rate

Theoretical studies by other authors (Ritgers and Peppas [11, 12]; Siepmann and Peppas [13]) have identified a number of factors which may affect the rate at which a particular solute is released from a polymeric matrix into a liquid phase. Such

Table 1 Percentage amoxicillin released in equilibrium from hydrogels of semi-IPNs composed of PAAm and γ-PGA

Molar proportion PAAm:γ-PGA	Percentage amoxicillin released in equilibrium			
	pH 3	pH 7.2		
	25 °C	25 °C	37 °C	45 °C
95:5	39.5	49.6	78.6	81.8
90:10	44.3	61.8	83.7	87.0
85:15	49.0	65.2	89.7	92.9
80:20	54.9	70.2	96.9	98.8

factors include, but are not restricted to imbibitions of water followed by relaxation of the polymers making up the network, which causes the swelling of the releasing device; solute dissolution upon water imbibitions; internal diffusion of the solute within the polymer matrix to reach the surface, and interface mass transfer which transports the solute molecules from the matrix surface to the liquid phase. Interface mass transfer depends on other factors such as the temperature and pH of the release medium, which also affect the physicochemical interactions between the polymer matrix and the solution components.

In this study, an overall evaluation of the rate of amoxicillin release from the semi-IPN hydrogels was done according to the exponential model developed by Ritger and Peppas [12]:

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t and M_∞ are the mass of amoxicillin released at time t and ∞, respectively; k is a kinetic constant, and n is the diffusion exponent that can be related to the drug transport mechanism.

Whereas Eq. 1 has become a popular model to interpret release kinetic data, it should be pointed out that parameters k and n have physical significance only when a number of assumptions regarding the experimental system can be made; namely, (1) the geometry of the releasing device may be approximated at all times as a flat slab, long cylinder, or sphere; (2) the solute does not participate in any chemical reaction; (3) the diffusivity of the solute is constant within the device; (4) the liquid phase behaves as a perfect sink and thus there is no resistance to interface mass transfer, and (5) the volume of the device does not increase beyond 25% of its original volume upon swelling [12].

In this study, the dimensions of the hydrogel samples before the contact with the buffer solutions were about 16-mm diameter, 3-mm thickness, for an initial volume of 603 mm^3. Their dimensions upon swelling in the buffer solutions were about 17-mm diameter, 4-mm thickness, for a final volume of 908 mm^3. The corresponding aspect ratio values (diameter/thickness) before and after swelling were 5.3 and 4.2, respectively. This indicates that diffusion within the devices was mostly two-dimensional, and thus they cannot be represented as flat slabs, long cylinders, or spheres [11]. Also, the volume increase upon swelling represents about 50% of the original volume, which is larger than the 25% limit for the theoretical validity of Eq. 1.

The above results indicate that parameters k and n in Eq. 1 are empirical parameters. In this context, parameter k can be seen as an overall indicator of the rate of amoxicillin release under specific experimental conditions in the reactor, whereas parameter n indicates the dependency of the release rate with time. Both parameters are expected to be dependent upon the geometry of the hydrogel devices, the degree of swelling upon contact with the buffer solution, the hydrogel composition, and the pH and temperature conditions in the reactor.

Parameters k and n were obtained by plotting the experimental values of $\ln \frac{M_t}{M_\infty}$ versus $\ln t$ and fitting the data to a straight line. Parameter n was obtained from the

Table 2 Parameters of the empirical model at 25 °C

Molar proportion PAAm:γ-PGA	pH 3			pH 7.2		
	n	k (1/min^n)	r^2	n	k (1/min^n)	r^2
100:0	0.45	0.0765	0.96	0.41	0.0953	0.95
95:05	0.45	0.0714	0.95	0.41	0.0953	0.98
90:10	0.46	0.0742	0.96	0.41	0.0992	0.98
85:15	0.46	0.0713	0.95	0.41	0.1002	0.99
80:20	0.49	0.0626	0.96	0.42	0.1353	0.92

Table 3 Parameters for the empirical model at pH 7.2

Molar proportion PAAm:γ-PGA	25 °C			37 °C			45 °C		
	n	k (1/min^n)	r^2	n	k (1/min^n)	r^2	n	k (1/min^n)	r^2
100:0	0.41	0.0953	0.95	0.43	0.1165	0.98	0.44	0.1199	0.95
95:05	0.41	0.0953	0.98	0.43	0.1173	0.94	0.44	0.1544	0.99
90:10	0.41	0.0992	0.98	0.43	0.1286	0.95	0.43	0.1635	0.99
85:15	0.41	0.1002	0.99	0.44	0.1298	0.93	0.42	0.1636	0.99
80:20	0.42	0.1212	0.92	0.44	0.1326	0.93	0.42	0.1725	0.99

slope of this plot, whereas parameter k was obtained from the intersection at $\ln t = 0$. Tables 2 and 3 summarize the results thus obtained. In general, parameter k increased as the pH, temperature, and relative amount of γ-PGA in the hydrogel increased. This is consistent with the previous discussion of Figs 2, 3, 4, and 5. On the other hand, parameter "n" varied in the range of 0.41–0.49 and it decreased as the pH increased, whereas no apparent trend is observed with respect to temperature and the relative amount of γ-PGA in the hydrogels. The results shown in Tables 2 and 3 may be used to calculate the overall rate of amoxicillin release from the hydrogel devices under different experimental conditions. A detailed discussion on the mechanisms governing the motion of amoxicillin molecules in this type of system should await further development of a fundamental model. Such study is currently in progress and will be the subject of a future article.

Conclusion

The hydrogels of semi-IPNs composed by PAAm and γ-PGA showed potential in applications as controlled amoxicillin release systems. The percentage of amoxicillin released increased as the relative amount of γ-PGA in the hydrogel, temperature, and pH increased. The hydrogels with molar proportion PAAm:γ-PGA of 80:20 in a release medium with pH 7.2 at 37 °C showed the best results for amoxicillin release. All release kinetics experiments reached equilibrium conditions

within 240 min, with exception of the experiments conducted at 45 °C in which equilibrium was reached in 120 min. The overall rate of amoxicillin release was represented with a two-parameter empirical model. The elucidation of the mechanisms governing the motion of amoxicillin in this type of systems should await the further development of a fundamental model.

Acknowledgments C. J. Pérez-Martínez acknowledges CONACYT (Consejo Nacional de Ciencia y Tecnología, México) for the financial support provided for her graduate studies during this study.

References

1. Risbud MV, Hardikar AA, Bhat SV, Bhonde RR (2000) pH-sensitive freeze-dried chitosan-polyvinyl pyrrolidone hydrogels as controlled release system for antibiotic delivery. J Control Release 68: 23–30
2. Liu Z, Lu W, Qian L, Zhang X, Zeng P, Pan J (2005) In vitro and in vivo studies on mucoadhesive microspheres of amoxicillin. J Control Release 102:135–144
3. Santos DP, Bergamini MF, Zanoni MV (2008) Voltammetric sensor for amoxicillin determination in human urine using polyglutamic acid/glutaraldehyde film. Sens Actuators B Chem 133:398–403
4. Liu J, Lin S, Li L, Liu E (2005) Release of theophylline from polymer blend hydrogels. Int J Pharm 298: 117–125
5. Huang Y, Yu H, Xiao C (2007) pH-sensitive cationic guar gum/poly(acrylic acid) polyelectrolyte hydrogels: swelling and in vitro drug release. Carbohydr Polym 69:774–783
6. Zhao Y, Kang J, Tan T (2006) Salt-, pH- and temperature-responsive semi-interpenetrating polymer network hydrogel based on poly(aspartic acid) and poly(acrylic acid). Polymer 47:7702–7710
7. Caykara T, Sengül G, Birlik G (2006) Preparation and swelling properties of temperature-sensitive semi-interpenetrating polymer networks composed of poly[(*N*-tert-butylacrylamide)-co-acrylamide] and hydroxypropyl cellulose. Macromol Mater Eng 291:1044–1051
8. Rodríguez DE, Romero-García J, Ramirez-Vargas E, Ledezma-Pérez AS, Arias-Marín E (2006) Synthesis and swelling characteristics of semi-interpenetrating polymer network hydrogels composed of poly(acrylamide) and poly(γ-glutamic acid). Mater Lett 60:1390–1393
9. Gonzales D, Fan K, Sevoian M (1996) Synthesis and swelling characterizations of a poly(gamma-glutamic acid) hydrogel. J Polym Sci A Polym Chem 34:2019–2027
10. Rodríguez–Félix DE, Castillo-Ortega MM, Real-Félix D, Romero-García J, Ledezma-Pérez AS, Rodríguez-Félix F (2011) Synthesis and swelling properties of pH- and temperature sensitive interpenetrating polymer networks composed of poly(acrylamide) and poly(γ-glutamic acid). J Appl Polym Sci 119:3531–3537
11. Ritger PL, Peppas NA (1987) A simple equation for description of solute release I Fickian and Non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J Control Release 5:23–36
12. Ritger PL, Peppas NA (1987) A simple equation for description of solute release II Fickian and anomalous release from swellable devices. J Control Release 5:37–42
13. Siepmann J, Peppas NA (2001) Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev 48:139–157