Fluconazole Release Through Semi-Interpenetrating Polymer Network Hydrogels Based on Chitosan, Acrylic Acid, and Citraconic Acid

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ABSTRACT: Semi-interpenetrating polymer network hydrogels with different compositions of chitosan (Cs), acrylic acid, and citraconic acid were synthesized via free-radical polymerization with ethylene glycol dimethacrylate as a crosslinker. The variations of the swelling percentages of the hydrogels with time, temperature, and pH were determined, and Cs–poly(acrylic acid) (PAA) hydrogels were found to be most swollen at pH 7.4 and 37°C. Scanning electron micrographs of Cs–PAA and Cs–P(AA-*co*-CA)-1 (Cs-poly(acrylicacid-co-citraconir acid)$^{-1}$) were taken to observe the morphological differences in the hydrogels. Although the less swollen hydrogel, Cs–P(AA-*co*-CA)-1, had a sponge-type structure, the most swollen hydrogel, Cs–PAA, displayed a uniform porous appearance. Fluconazole was entrapped in Cs–P(AA-*co*-CA)-1 and Cs–PAA hydrogels, and the release was investigated at pH 4.0 and 37°C. The kinetic release parameters of the hydrogels (the gel characteristic constant and the swelling exponent) were calculated, and non-Fickian diffusion was established for Cs–PAA, which released fluconazole much more slowly than the Cs–P(AA-*co*-CA)-1 hydrogel. A therapeutic range was reached at close to 1 h for both hydrogels. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 113: 2613–2619, 2009

Key words: chitosan; drug delivery systems; hydrogels

INTRODUCTION

Hydrogels are hydrophilic three-dimensional networks held together by crosslinked chemical or physical bonds.[1] Hydrogels have been extensively studied and used for a large number of applications in medicine, such as controlled drug release matrices,[2,3] enzyme and yeast cell immobilization,[4] and blood-contact applications.[5]

Interpenetrating polymer networks (IPNs) are mixtures of two crosslinked polymers. If one polymer is crosslinked and the other is linear, the structure is called a semi-IPN.[6] IPNs are preferred in a number of biotechnological and biomedical applications because of certain unique biophysical properties, such as ease of fabrication into various geometrical forms, a soft and rubbery texture, minimal mechanical irritation to surrounding tissues, and unusual stability against biofluids.[7] IPN structures are also used to control overall hydrogel hydrophilicity and drug release kinetics.[8] A wide range of so-called semi-IPNs have been prepared through the dissolution of a preformed linear polymer in a hydrophilic monomer and crosslinking agent mixture, which is subsequently polymerized. In this way, a synthetic hydrogel network is formed around a primary polymer chain, which modifies the behavior of the hydrogel.[9] A wide variety of linear polymers (e.g., polymethacrylates, polyurethanes, and modified celluloses) have been used as interpenetrants in semi-IPN hydrogels. The use of semi-IPNs in pH-sensitive and temperature-sensitive drug delivery systems is well documented.[10,11]

Because of its easy polymerization and biocompatible properties, acrylic acid (AA) is widely used to prepare hydrogels designed for drug release. In an anionic polymeric network containing carboxylic acid groups, ionization takes place as the pH of the external swelling medium increases above the p*K* of the ionizable moiety. There are numerous studies about preparing anionic hydrogels with AA in the literature.[12] Besides many studies about poly(acrylic acid) (PAA) hydrogels, some investigations have focused on copolymeric hydrogels containing different vinyl monomers, such as hydroxyethyl methacrylate, *N*-isopropylacrylamide, crotonic acid, itaconic acid, and acrylonitrile.[13] Citraconic acid (CA) is known as a suitable monomer for radical copolymerization with vinyl monomers.[14] Because of its two carboxylate groups, CA-containing hydrogels are favorable for swelling at high pH values. However, at low pH values, carboxylate groups cannot be

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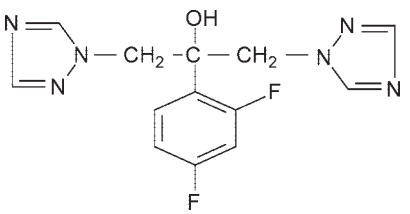
easily ionized, and the structure swells less than the expected values. Therefore, various copolymeric conformations can be used to arrange the swelling response of the hydrogels.

Chitosan (Cs) is a natural polymer obtained through the alkaline deacetylation of chitin; it exhibits its excellent biological properties such as biodegradation in the human body and immunological, antibacterial, and wound-healing activity. Cs has also been found to be a good candidate as a support material for gene delivery, cell culture, and tissue engineering.[15] Moreover, Cs has antacid and anti-ulcer activity and can prevent or weaken drug-induced irritation in the stomach. These interesting properties make Cs an ideal candidate for use in controlled drug release formulations. However, this naturally abundant material also exhibits limitations in its reactivity and processability. One strategy to overcome these shortcomings is to incorporate Cs into IPN hydrogels.[16]

Fluconazole is an orally effective azole-based antifungal drug with low toxicity and shows very significant efficacy against *Candida albicans*.[17] Because oral usage causes some side effects in the gastrointestinal system such as heartburn, many studies have been focused on local applications of fluconazole. Furthermore, local applications are more convenient then oral or invasive usage during pregnancy. It is chemically designed as 2,4-difluoro-α,α^{i}-bis(1*H*-1,2,4-triazol-1-ylmethyl)benzyl alcohol with an empirical formula of $C_{13}H_{12}F_2N_6O$ and a molecular weight of 306.3. The structural formula is



The aim of this study was to develop suitable semi-IPN hydrogels based on Cs, AA, and CA for the controlled release of fluconazole. We planned to investigate the effects of the monomer composition on the swelling behaviors and morphological structures of the hydrogels. Therefore, convenient hydrogels were chosen for drug delivery studies to be carried out a vaginal medium *in vitro* at 37°C and pH 4.0. The kinetic results for fluconazole release were explained on the basis of the swelling values and morphological structures of the hydrogels.

EXPERIMENTAL

Preparation of the hydrogels

An aqueous solution mixture (2.5 mL) of AA (Aldrich, Seelze, Germany) and CA (Aldrich) at a certain molar ratio (Table I) was placed into a glass tube. A 5.0-mL solution (1.0%) of Cs (Aldrich) and acetic acid (Aldrich), the crosslinking agent ethylene glycol dimethacrylate (EGDMA; Aldrich; 0.1 mL), and the initiator $(NH_4)_2S_2O_8/Na_2S_2O_5$ (redox pair; 0.05 g/0.05 g; Merck) were added to the monomer mixture solution. The reaction proceeded for 24 h at room temperature. The fresh hydrogel rods that were obtained were cut into pieces 0.5 cm long. The gel discs were washed several times with distilled water and dried first in air and then in a vacuum oven at 37°C, and they were stored for further use.[18] The dimensions of the dried hydrogels were measured with a micrometer. The average thicknesses were 0.35 ± 0.05 cm, with the radius differing between 0.40 and 0.50 cm according to the content of the gel matrix. The average amount of Cs per gel disc was calculated to be 0.005 g. As a result of the standard degradation tests performed in accordance with the literature, it was found that these hydrogels were stable in neutral media and acidic media of pH 4.0 at 37°C for 30 days.[19]

TABLE I
Amounts of AA and CA (mol/L) in the Monomer Mixture Solutions Used To Form the Hydrogels

Hydrogel	AA	CA
P(AA-*co*-CA)	3	3
Cs–PAA	5	—
Cs–P(AA-*co*-CA)-1	5	1
Cs–P(AA-*co*-CA)-2	5	2
Cs–P(AA-*co*-CA)-3	5	3
Cs–P(AA-*co*-CA)-4	5	4

According to the literature, the general mechanism shown in Figure 1 could be suggested for semi-IPN formation from Cs and poly(acrylic acid-*co*-citraconic acid) [P(AA-*co*-CA)] polymers.[20,21] This reaction mechanism has been promoted by other researchers too.[22] The persulfate initiator is reduced to the $(SO_4)^{-\bullet}$ anion radical. This radical abstracts hydrogen from the monomer to form vinyl radicals. Thus, the radically initiated copolymerization reaction between AA and CA is performed.[23,24] It can be thought that P(AA-*co*-CA) is the host polymer in this IPN system. Intermolecular forces between the polymer molecules in semi-IPN hydrogels are also shown in Figure 1.

Swelling

Swelling tests of hydrogel discs were gravimetrically carried out in three steps.[25] In the first step, dried discs were left to swell in a Britton–Robinson tampon (BRT; Riedel-de Haën) solution (pH = 7.4) at 37°C. Swollen gels, removed from the swelling medium at regular intervals, were dried superficially

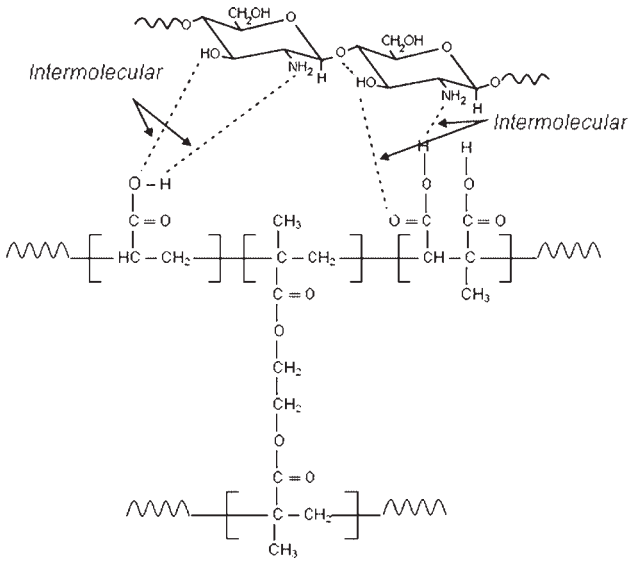


Figure 1 General mechanism for semi-IPN formation with Cs and P(AA-*co*-CA) polymers.

with filter paper, weighed, and placed into the same bath. The measurements were performed until a constant weight was reached for each sample. The swelling percentage (*S*%) values were calculated with the following equation:[18,26,27]

$$S\% = \frac{m_w - m_d}{m_d} \times 100 \quad (1)$$

where m_w is the wet weight of the sample and m_d is the dry weight of the sample before swelling. The incubation times for all gels were approximately 24 h.

In the second step, the dried hydrogel discs were swollen in BRT (pH = 7.4) solutions at different temperatures ranging from 10 to 60°C so that we could investigate the effect of temperature on swelling behaviors. At the end of 24 h, the swollen discs were removed from the swelling medium, dried superficially with filter paper, and weighed. *S*% values were calculated with eq. (1).

In the last step, the dried hydrogel discs were swollen in different BRT solutions at various pHs between 2 and 12 so that we could investigate the effect of pH on the swelling behaviors. The temperature and swelling time were kept constant (37°C and 24 h, respectively). The swollen discs were removed from the swelling medium, dried superficially with filter paper, and weighed. *S*% values were calculated with eq. (1).

Reproducible results for all swelling studies were obtained with triplicate measurements.

Scanning electron microscopy (SEM)

Cs–PAA and Cs–P(AA-*co*-CA)-1 semi-IPN hydrogel disc samples, swollen to equilibrium in water at room temperature, were removed and placed in a deep freezer at −20°C for 24 h and then transferred into a Christ-Alfa 2-4 freeze dryer (Martin Christ GmbH, Germany) at −85°C for 1 week. Besides fluconazole-entrapped discs, the dried and swollen discs were coated with 200 Å of Au. Surface micrographs of the samples were obtained with a JEOL Mark JSM 840A scanning electron microscope (Hitachi, Japan).

Release of fluconazole from the hydrogels

Because of their high swelling values in a vaginal pH medium and their different morphologies, Cs–PAA and Cs–P(AA-*co*-CA)-1 hydrogels were chosen for release studies. As the vaginal pH range is 3.5–4.5, controlled release studies were carried out at pH 4.0 and 37°C.[28]

The loading of model drugs in crosslinked polymer networks can be accomplished with two loading techniques: equilibrium partitioning and copolymerization/crosslinking in the presence of the drugs.[29] In this work, particular amounts of fluconazole (110 mg per disc) were added to Cs–PAA and Cs–P(AA-*co*-CA)-1 hydrogels during copolymerization/crosslinking reactions.[29–31]

Fluconazole-entrapped hydrogel discs were placed into a vessel containing 100 mL of BRT solution (pH 4.0). At different times, aliquots of 100 μL were drawn from the medium to follow the fluconazole release; a maximum of 30 aliquots were taken, so the vessel volume could be considered constant. The drug release always maintained sink conditions.[32,33] Fluconazole release was determined spectrophotometrically with a Unicam UV-2100 spectrophotometer (Haverhill, MA) at a wavelength of 261 nm for 30 h.[17] Reproducible results were obtained with triplicate measurements.

The cumulative release (%) of the drug was calculated with the following equation:

$$\text{Release}\,(\%) = \frac{W_t}{W_{\text{total}}} \times 100 \quad (2)$$

where W_t is the weight of the released drug in the releasing medium at any time and W_{total} is the initial total weight of the drug taken by the gel system.[34]

RESULTS AND DISCUSSION

Swelling behavior of the hydrogels

Figure 2 presents the variation of *S*% with time at pH 7.4 and 37°C. *S*% increased with time initially and then remained constant at close to 24 h. From this experiment, average *S*% values were determined to be 1510% for Cs–PAA, the most swollen hydrogel, and 900% for Cs–P(AA-*co*-CA)-4, the least swollen

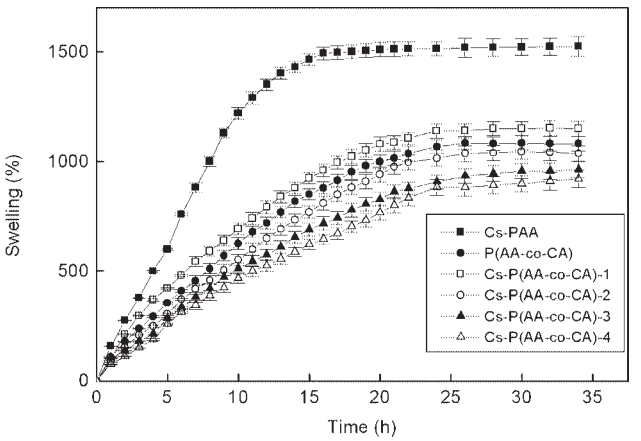


Figure 2 Variation of *S*% values with time at 37°C and pH 7.4.

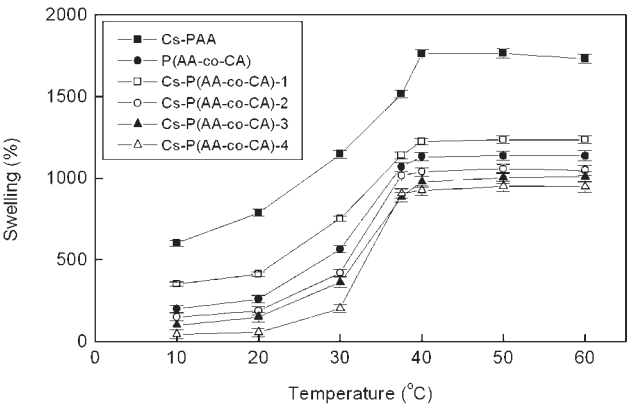


Figure 3 Variation of *S*% values with temperature at pH 7.4 for 24 h.

gel. With an increase in the molar ratio of CA in the monomer mixture, *S*% of the hydrogels decreased from 1150 to 900%. When the concentration of CA in the hydrogel was increased, the hydrophobicity imparted by un-ionized CA became much more pronounced than the hydrophilic tendency of ionized carboxylate groups in the polymer matrix, which finally caused a slight decrease in *S*% of the hydrogel samples.[35]

Different swelling values between 80 and 3000% have been reported in the literature for similar hydrogels, depending on the composition or monomer ratio, polymerization route, type of crosslinker, crosslinker density, and so forth.[16] The ionic charge content concept was emphasized in those studies. Instead of the swelling value of pure Cs IPN hydrogels (nearly 100%), Cs hydrogels containing ionic copolymers were reported to present much more swellable behavior.[36] AA and CA have —COOH units, and the high swelling values of semi-IPN hydrogels including Cs–PAA–poly(citraconic acid) (PCA) are due to these ionizable units. The results are in agreement with those in the literature.[37,38]

Figure 3 presents the variation of *S*% of hydrogels with the temperature at pH 7.4 and 24 h. All the hydrogels swelled much more at high temperatures than at low temperatures. The swelling of PAA and polyacrylamide hydrogels is known to be positively dependent on the temperature. As the temperature increases, the thermal mobility of the polymer chains also increases, hydrogen bonds are broken, and the hydrogels can easily swell.[37,39] As the swelling values of all hydrogels exhibit great differences between 20 and 40°C, it is thought that these hydrogels are sensitive to variations in temperature in this range.[40,41]

Figure 4 shows the variation of *S*% with pH at 37°C and 24 h. Low *S*% values were obtained for all hydrogels at pH 2.0 versus other pH values. In all compositions, the maximum extent of swelling was reached at about pH 7.4, this being due to the complete dissociation of acid groups of CA and AA at this pH value. The dissociation constants of AA and CA were $pK_a = 4.25$ and $pK_{a1} = 6.17$, respectively. The difference between these values affected the swelling behaviors of the hydrogels with respect to pH variations. Although the curve of the Cs–PAA hydrogel starts to rise at pH 4.0, the curves belonging to Cs–P(AA-*co*-CA) hydrogels present a sharp variation near pH 6.0. On the other hand, because the two dissociation constants are close, the consecutive swellings at these pH values overlap, and only single-step swelling versus pH curves can be observed for the hydrogel including PAA and PCA.[42] As the swelling values of all hydrogels exhibit great differences between pH 4.0 and pH 8.0, it is thought that these hydrogels are sensitive to variations in the pH in this range.[12,18,42]

SEM analysis

SEM micrographs of dry, swollen, and fluconazole-entrapped hydrogels are presented in Figure 5. The appearance of the dry and fluconazole-entrapped

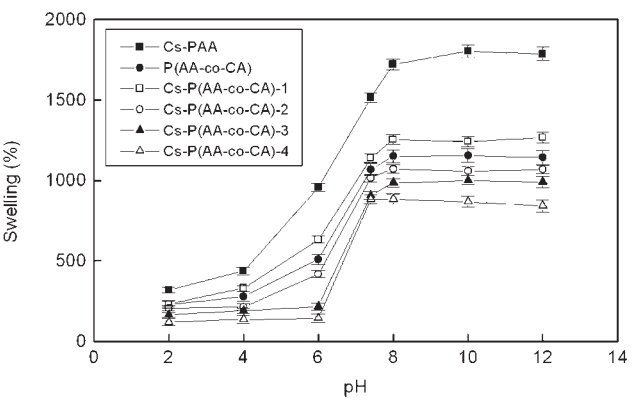


Figure 4 Variation of *S*% values with pH at 37°C for 24 h.

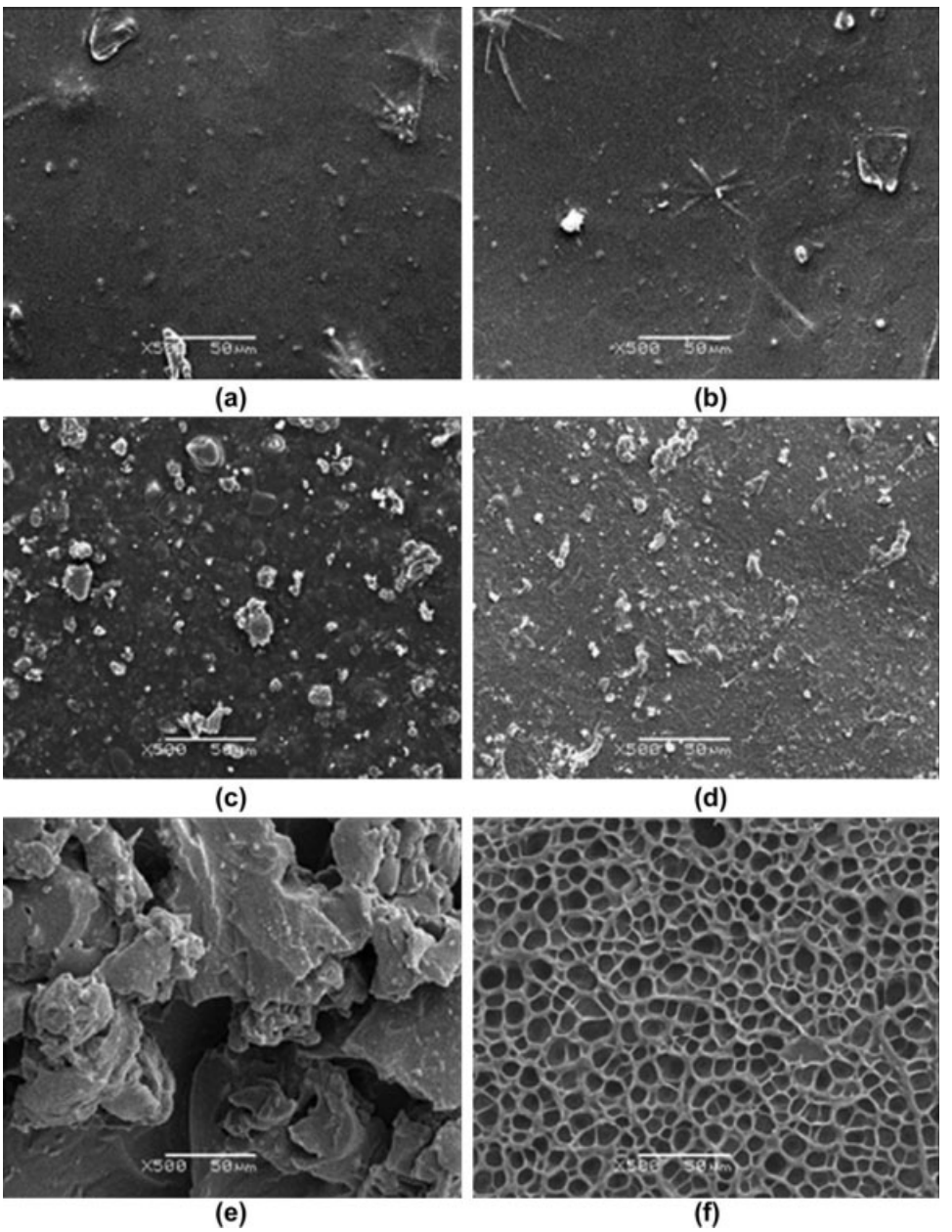


Figure 5 SEM micrographs of surfaces of (a) dry Cs–P(AA-*co*-CA)-1, (b) dry Cs–PAA, (c) fluconazole-entrapped and dried Cs–P(AA-*co*-CA)-1, (d) fluconazole-entrapped and dried Cs–PAA, (e) swollen Cs–P(AA-*co*-CA)-1, and (f) swollen Cs–PAA hydrogels.

hydrogels is similar. The morphological differences between the dry and wet states of the hydrogels can be clearly observed. The dry hydrogels showed a nonporous surface with a smooth structure. In contrast, the most swollen hydrogel, Cs–PAA, presented a regular homogeneous porous morphology. This uniform porosity enabled easy diffusion and absorption of water into the hydrogel structure. The Cs–P(AA-*co*-CA)-1 hydrogel had a sponge-type structure. Besides the differences in the chemistry of these two hydrogels, it could be concluded that the sponge-type structure of the Cs–P(AA-*co*-CA)-1 hydrogel also caused comparatively low swelling. The rugous structures of fluconazole-entrapped Cs–PAA and Cs–P(AA-*co*-CA)-1 hydrogels are also presented in the figure.

Fluconazole release

The cumulative release profiles of fluconazole from Cs–PAA and Cs–P(AA-*co*-CA)-1 hydrogels are presented in Figure 6. Fluconazole release from Cs–P(AA-*co*-CA)-1 increased rapidly at first and was complete at close to 5 h. Fluconazole was released rather slowly from the Cs–PAA hydrogel, and 100% release was reached at close to 25 h. Because the *S*%

values of the two hydrogels were close at pH 4.0, it can be concluded that the swelling behaviors did not cause the differences in the release profiles. The drug release could be explained with consideration of the SEM micrographs. The sponge-type morphology of the Cs–P(AA-*co*-CA)-1 hydrogel might be responsible for the rapid release. The homogeneous porous structure of the Cs–PAA hydrogel caused the steady drug release. It can be said that Cs–PAA is more convenient than the Cs–P(AA-*co*-CA)-1 hydrogel for long-term use. A therapeutic range ($\sim$ 20 μg/mL) was reached in the first hour for both hydrogels.[17] Because the overdose has been reported to be 1–2 g/kg, release of the entire amount of fluconazole trapped in the hydrogels does not pose a toxicity problem.[17]

A semiempirical equation is introduced to represent the drug release process of a swelling polymer:[35]

$$F = \frac{M_t}{M_\infty} = kt^n \tag{3}$$

where F is the fractional uptake, M_t and M_∞ are the amount of the drug released at time t and the maximum amount of the drug release, respectively; k is the gel characteristic constant; and swelling exponent n describes the type of diffusion. For cylindrical gels, $n = 0.45$–0.50 corresponds to Fickian diffusion, whereas $0.50 < n < 1.0$ indicates anomalous or non-Fickian diffusion. $n > 1.0$ implies super case II transport.[33]

The diffusion coefficient (D) is an important release parameter of some chemical species from polymeric systems. With n and k, D could be calculated with the following equation:[42–44]

$$k = (D/\pi r^2)^n \tag{4}$$

where r is the radius of the gel disc.

k and n values of Cs–PAA and Cs–P(AA-*co*-CA)-1 hydrogels were determined from graphs derived with eq. (3), and they are given in Table II. As the n value of Cs–PAA was calculated to be 0.52, non-Fickian diffusion could be concluded for this hydrogel, with both diffusion and polymer relaxation simultaneously controlling the overall rate of drug release. However, the n value of the Cs–P(AA-*co*-CA)-1 hydrogel was calculated to be 1.16, indicating the super case II diffusion mechanism: the osmotic pressure effectively rose, and the diffusion rate exponentially increased with time.[1,7]

D is a function of the polymer chain mobility, the average pore size, and the mobility of the solvent in the gel. The diffusion of fluconazole from Cs–PAA and Cs–P(AA-*co*-CA)-1 hydrogels mainly occurs through the pores of the polymer matrix according to the results of the swelling studies.

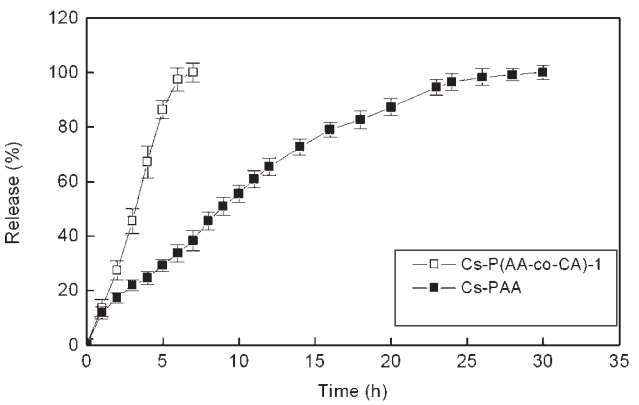


Figure 6 Cumulative release of fluconazole from Cs–PAA and Cs–P(AA-*co*-CA)-1 hydrogels at pH 4.0 and 37°C.

TABLE II
Release Parameters and D Values of the Cs–PAA and Cs–P(AA-*co*-CA)-1 Hydrogels

Hydrogel	n	k	R	$D \times 10^{11}$ (m^2/s)
Cs–PAA	0.52	1.40×10^{-2}	0.9978	1.99
Cs–P(AA-*co*-CA)-1	1.16	1.13×10^{-3}	0.9977	92.1

R (r^2) = deterministic coefficient.

CONCLUSIONS

Semi-IPN hydrogels based on Cs, AA, and CA for the controlled release of fluconazole were prepared via free-radical polymerization with EGDMA as the crosslinker. The variations of S% with time and pH were determined for these hydrogels at 37°C. Low S% values were obtained for all hydrogels at pH 2.0 with respect to other pH values. In all compositions, the maximum extent of swelling was reached at about pH 8.0. Fluconazole release from Cs–PAA and Cs–P(AA-*co*-CA)-1 hydrogels was investigated at pH 4.0 and 37°C. The kinetic release parameters of the hydrogels, n and k, were calculated, and non-Fickian diffusion was established for Cs–PAA, the most swollen hydrogel. A therapeutic range was reached at close to 1 h for both hydrogels.

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