Influence of Isomery in Drug Release from Poly(butyl monoitaconate-*co*-acrylamide) Hydrogels

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ABSTRACT: In this work, we report the synthesis and characterization of poly(butyl monoitaconate-*co*-acrylamide) hydrogels to be used as drug release agents. Four isomers of butanol were used to synthesize the hydrogels. The influence of butyl monoitaconate isomery on swelling behavior, Young's and compression moduli, cross-linking density and molar mass between cross-links are reported. It was found that by increasing butyl ramification, equilibrium degree of swelling, and the time for reaching swelling equilibrium decreases. Cross-linking density, Young's and compression moduli increases as butyl ramification increases. The release of theophylline and aminophylline drugs used in therapy for respiratory diseases were studied and it was found that theophylline was released faster than aminophylline © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 112: 1630–1635, 2009

Key words: hydrogel; theophylline; aminophylline; swelling; release

INTRODUCTION

Much of the recent literature on the preparation and properties of hydrogels is concerned to biomedical applications.[1–3] One of the applications of the hydrogels in medicine is as drug delivery system.[2–5] The rate of drug delivery depends on the structure and thermodynamic nature of the hydrogel as well as the drug and the medium where it is released. Theophylline and aminophylline are drugs used in therapy for respiratory diseases such as chronic obstructive pulmonary disease (COPD) or asthma under a variety of brand names. As members of the xanthenes family, they bear structural and pharmacological similarity to caffeine. Theophylline is naturally found in tea, although in trace quantities ($\sim$ 1 mg/L), which are significantly less than therapeutic doses and aminophylline, is obtained by combining theophylline and ethylendiamine. They are usually administrated in the form of tablets.[6] A further possible mode of application is from a suitable polymeric matrix placed in the buccal cavity.

Here, we report the synthesis and characterization of poly(butyl monoitaconate-*co*-acrylamide) hydrogels (swelling behavior, Young and compression moduli, cross-linking density, and molar mass between cross-links). Also, the release of the commercial drugs theophylline and aminophylline from the hydrogels is reported.

EXPERIMENTAL

Acrylamide (AM) and 2-Methylidenebutanedioic acid (itaconic acid, IA) were 99% pure from Aldrich, V-50 (2,2′-azobis(2-amidinopropane)) was from Wako Chemicals and all were used as received. Butyl monoitaconates were prepared in our laboratory by reacting itaconic acid with an excess of the corresponding alcohol (99% pure from Aldrich) in the presence of acetyl chloride (Merck) as described elsewhere.[7] The cross-linking agent, *N*,*N*′-methylenebisacrylamide (MBAAm; Fluka, purity >98%) was purified by recrystallization from methanol. The water was deionized and doubly distilled.

Theophylline ($C_7H_8N_4O_2$, MW = 180.2 g/mol, sol. water = 8.3 mg/mL at 25°C) and aminophylline monohydrate ($C_6H_{24}N_{10}O_4$; MW = 420.43 g/mol, sol. water = 200 mg/mL at 25.0°C) were supplied by Sigma. In Figure 1, we show the molecular structure of the several chemical employed in this article.

Polymerization

Hydrogels were prepared by dissolving 10 wt % of the monomer mixture (0.42 mol acrylamide and 0.22

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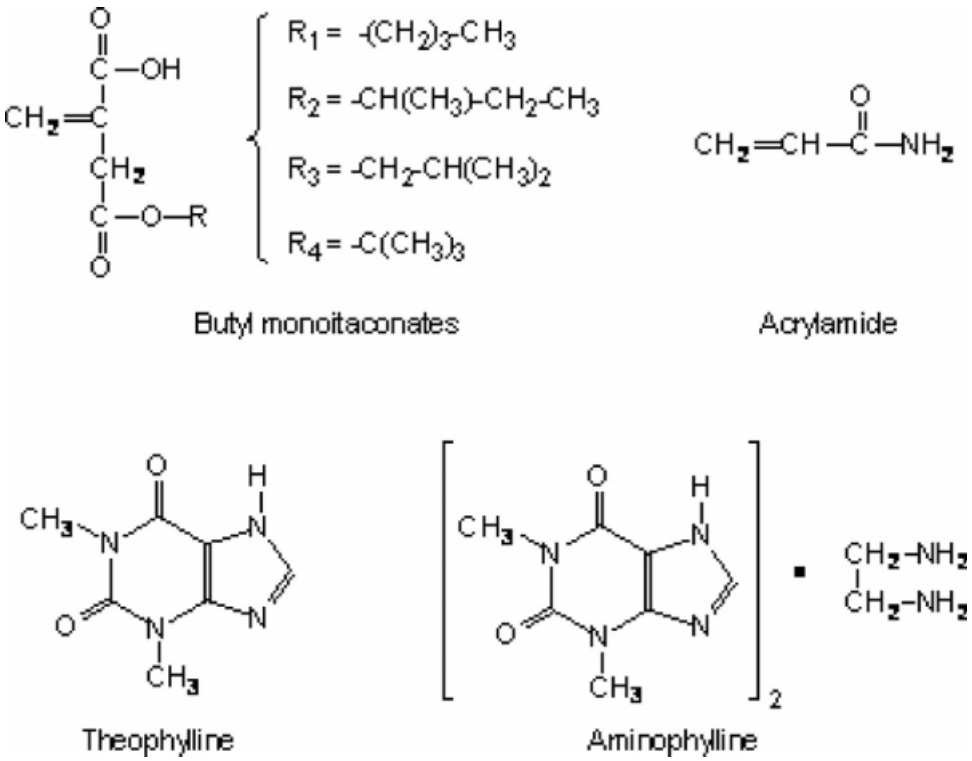

Figure 1 Molecular structures of butyl monoitaconates (R_1 = *n*-butyl, R_2 = sec-butyl, R_3 = iso-butyl, and R_4 = *tert*-butyl), acrylamide, theophylline, and aminophylline.

mol monoitaconate) and 0.1 wt % of MBAAm in 90 wt % of deionized water and then transferred to test tubes. The test tubes were silanized previously to facilitate subsequent removal of the copolymer solid roads.[8] Reactions were carried out at 60°C using as initiator the redox pair, potassium persulfate/sodium bisulphite (1% of monomers concentration). To guarantee complete conversion reactions were carried out for 3 h. After reaction, the hydrogels were thoroughly washed with distillate water and dried at 60°C.

Swelling experiments

Discs of 10 mm in diameter and 1 mm in thickness were cut from the hydrogels, and then were dried to constant weight in a vacuum oven at 330 K for 7 days. The xerogel discs were weighed, immersed in pure water, and their swelling kinetics was followed by removing the hydrogels from the water at given time, blotting them with a paper filter, and weighing. The degree of swelling of the hydrogels (W_t) was calculated as follows:

$$W_t = \frac{\text{weight of swollen disc} - \text{weight of dry disc}}{\text{weight of dry disc}} \quad (1)$$

Drug charge

Previously weighted hydrogels were loaded with the drug by immersing them in a saturated drug aqueous solution (5.0 mg/mL for the aminophylline and 2.5 mg/mL for the theophylline) until equilibrium was obtained. To determine the amount of drug charged, the loaded hydrogels were dried at room temperature under vacuum and weighted.

Drug release experiments

The drug release experiments were carried out at (37.0 ± 0.1)°C in a 100 mL vessel, using deionized and distilled water, under constant stirring and at "sink" conditions. To follow drug release, at different times, 100 μL aliquots of the solution were withdrawn and drug concentration was determined by HPLC (Waters) using a Spherisorb ODS 5 mm packed Teknokroma column. For the analysis of theophylline, the mobile phase was a mixture of methanol and 0.01*M* aqueous sodium acetate (10 : 90) and in the case of the aminophylline, a mixture of methanol/acetic acid (6/4) was used. In both cases, the solvent flow was 1 mL/min. The amount of drug liberated (M_t, μg) was determined by using calibration curves, which were obtained by using drug solutions of known concentrations (0.1–100 μg/mL). Each release experiment was performed twice.

Stress-strain tests

A Perkin–Elmer DMA7 Dynamic Mechanical Analyzer with parallel plate geometry was used for

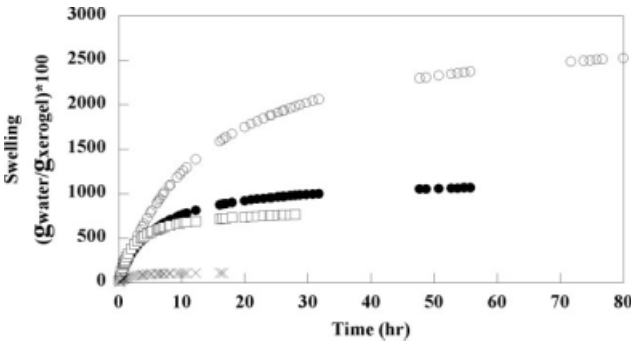

Figure 2 Degree of swelling as a function of butyl ramification: (○) *n*-butyl, (●) isobutyl, sec-butyl (□), *tert*-butyl (x).

compression stress-strain tests. The equilibrium swelled hydrogel discs were immersed in deionized water during measurements to minimize water loss. The Young modulus, E, of the hydrogels was estimated from the slope of stress-strain curves at low strains, where the stress, τ, depends linearly on strain deformation ($\lambda - 1$), λ is the ratio of the deformed to the initial length.[8] The shear modulus, G, of the hydrogels was determined from the slope in the linear portion of the compression tests at low deformations using the following equation[9]:

$$\tau = G(\lambda - \lambda^{-2}) \tag{2}$$

The effective cross-linking density, υe, and the molar mass between cross-links, M_c, were estimated according to Tobolsky et al.[10] using the G value obtained from eq. (2) and the following equations:

$$G = RT\upsilon_e{\phi_2}^{-1/3} \tag{3}$$

and

$$M_c = \rho_2/\upsilon_e \tag{4}$$

where R is the ideal gas constant and T the absolute temperature. The density of the xerogel, ρ_2, was determined by dividing the weight of the xerogel by its volume.

RESULTS AND DISCUSION

Swelling behavior

Figure 2 shows the degree of swelling, W_t, at 60°C as a function of time for the hydrogels studied. It can be observed that increasing butyl ramification the equilibrium degree of swelling and the time for reaching swelling equilibrium decreases. This behavior can be explained because the more compact the butyl itaconate molecule, there is less free space to accommodate the water molecules into the hydrogel. Also, because of the lower steric hindrance of the more compact butyl itaconate molecule a more cross-linked hydrogel is obtained.

Swelling kinetics was adjusted with a second-order kinetics proposed elsewhere[5] for the swelling kinetics of hydrogels as follows:

$$\frac{t}{W} = \frac{1}{(\pi^2 D_w/h^2)} + \frac{t}{W_\infty} \tag{5}$$

where W_∞ is the degree of swelling at equilibrium, D_w the apparent diffusion coefficient, and h the disk thickness.

Figure 3 shows that the swelling kinetics of the hydrogels regardless of its composition follows a second-order kinetics.

Because diffusion can be considered one-dimensional when the disk thickness is much smaller than its diameter, the following equation applies[11]:

$$F_t = \frac{W_t}{W_\infty} = k' t^n \tag{6}$$

where W_t and W_∞ are the degree of swelling at time t and at equilibrium, respectively, k' is a characteristic constant of the system and n describes the diffusion type (Type I, II, or anomalous).[11] By taking logarithm from both sides, the following equation is obtained.

$$\ln F_t = \ln\left(\frac{W_f}{W_\infty}\right) = \ln k' + n \ln t \tag{7}$$

In Figure 4(a,b), it can be observed that by plotting the logarithm of F_t against the logarithm of t^n, the swelling behavior of the poly(*n*-butyl monitaconate-*co*-acrylamide) and the poly(*tert*-butyl monoitaconate-*co*-acrylamide) hydrogels follows a straight line, from which the slope (n) and the intercept (k') can be obtained. Straight lines were also obtained for the other two copolymers when plotting the logarithm of F_t against the logarithm of t^n. Table I show the n and k' values for the different copolymers. In

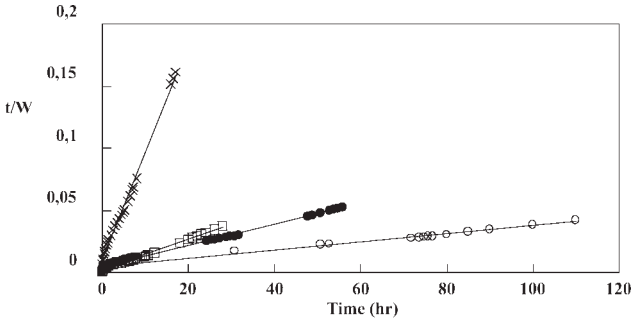

Figure 3 Plot of t/W as a function of time for the poly (monoitaconate-*co*-acrylamide) hydrogels: (○) *n*-butyl, (●) isobutyl, sec-butyl (□), *tert*-butyl (x).

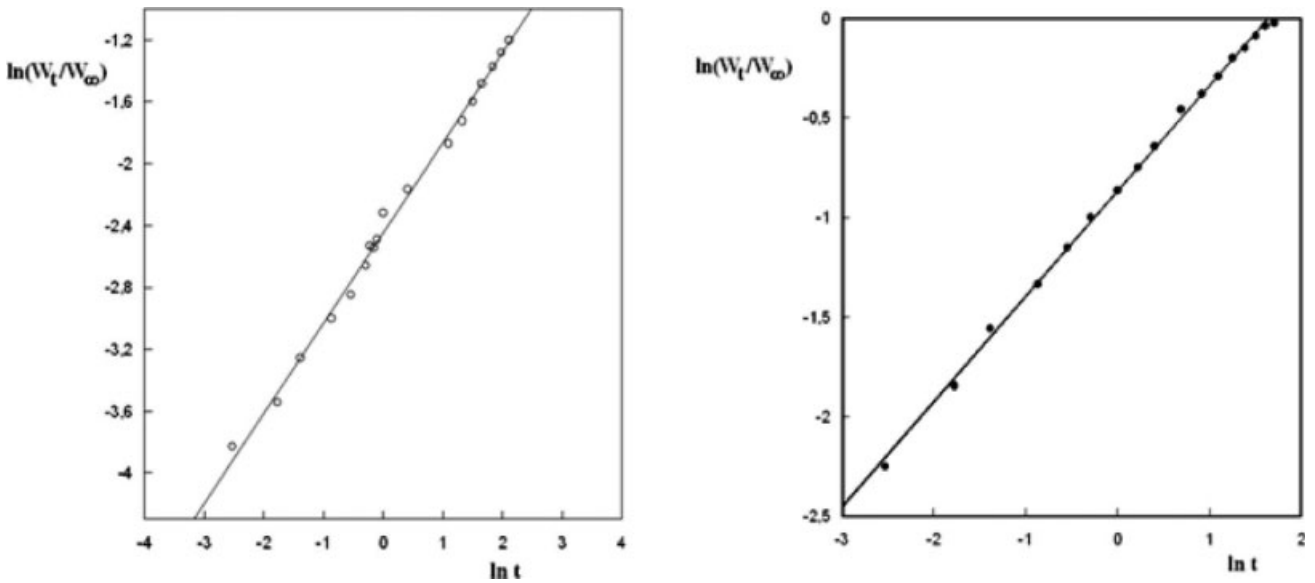

Figure 4 Plot of ln (W_t/W_∞), as a function of ln t: (a) poly(*n*-butyl monitaconate-*co*-acrylamide) and (b) poly(*tert*-butyl monoitaconate-*co*-acrylamide).

this Table, it can be observed that the n values are slightly higher than 0.5 (anomalous diffusion) and as ramification increases k' increases.

Because the n values are close to 0.5, the following equation, which can be derived from Fick's law of diffusion,[11] was used to estimate the apparent diffusion coefficients as follows:

$$\frac{W_t}{W_\infty} = 4\left(\frac{D_w t}{\pi h^2}\right)^{1/2} \tag{8}$$

where D_W is the apparent diffusion coefficient, t is the time, and h the hydrogel disk thickness. By plotting W_t/W_∞ versus the square root of time a straight line is obtained (Fig. 4) and from the slope, the D_w value was obtained. Table I shows that as the ramification increases D_w decreases in the following order

$$D_W(n-\text{butyl}) > D_W(\text{iso}-\text{butyl}) > D_W(\text{sec}-\text{butyl}) > D_W(tert-\text{butyl})$$

As butyl itaconate ramification increases, there is less free space for the water molecules to diffuse into the regions occupied by the monoitaconate.

Net parameters

Table II shows the variation of Young's and compression moduli as a function of butyl ramification. When butyl itaconate ramification increases, the water content at equilibrium of the hydrogels decreases, given as a result larger values of Young's and compression moduli. Compression modulus of the hydrogels studied here varies from 0.34 to 2.45 MPa, values which are in the same order of magnitude that some of the values reported in the literature. Perera and Shanks[12] reported for the compression modulus of a poly(*N*-vinyl-pyrrolidone-*co*-methyl methacrylate) hydrogel, cross-linked with 0.78% of EDMA a value of 0.83 Mpa. Davis and Huglin[13] reported a value of 2.27 MPa for the compression modulus of poly(*N*-vinyl-pyrrolidone-*co*-methyl methacrylate), hydrogel cross-linked with 1% of EDMA. Cross-linking density, ν_e, increases with butyl ramification as a result of lower steric hindrance. Since the same amounts of monomers and cross-linker were used in all cases, there is a decrease in molar mass between cross-links when cross-linking density increases.

TABLE I
The n and k' Values for the Different Copolymers

Hydrogel	n	k' (h^{-1})	$D_w \times 10^7 cm^2\ s^{-1}$
Poly(*n*-butyl monoitaconate-*co*-acrylamide)	0.58	0.11	0.91
Poly(iso-butyl monoitaconate-*co*-acrylamide)	0.59	0.18	0.87
Poly(sec-butyl monoitaconate-*co*-acrylamide)	0.64	0.28	0.71
Poly(*tert*-butyl monoitaconate-*co*-acrylamide)	0.54	0.42	0.63

TABLE II
The Variation of Young's and Compression Moduli as a Function of Butyl Ramification

Hydrogel	E (Mpa)	G (Mpa)	ν_e (10^3 mol dm^{-3})	M_c (g/mol)
Poly(*n*-butyl monoitaconate-*co*-acrylamide)	0.11	0.34	0.045	37.410
Poly(iso-butyl monoitaconate-*co*-acrylamide)	0.28	0.87	0.155	12.900
Poly(sec-butyl monoitaconate-*co*-acrylamide)	0.44	1.36	0.270	12.220
Poly(*tert*-butyl monoitaconate-*co*-acrylamide)	0.79	2.45	0.777	3.080

Drug liberation

For the drug release studies, hydrogel disks charged with the drug in thermodynamic equilibrium were used. The inclusion of the drug did not affect appreciable the degree of swelling at equilibrium of the hydrogels. Figures 5 and 6 show the fraction of theophylline and aminophylline released from the swelled hydrogels as a function of the square root of time (Fick's law). In this figures, it can be observed that the fraction of released drug versus $t^{1/2}$ follows a straight line and by using eq. (8), the apparent diffusion rate can be obtained from the slope and the values are shown in Table III.

Lower apparent drug liberation diffusion coefficients (D_a) when increasing ramification can be explained by the lower swelling degree of the hydrogels. Reported values in the literature for the apparent diffusion coefficient release of theophylline from different hydrogels vary. Vyavahare et al.[14] reported for theophylline release from poly(2-hydroxyethyl methacrylate) with 4% of cross-linker and a equilibrium swelling of 41%, an apparent diffusion value of 0.79×10^{-7} cm^2 s^{-1}. For copolymers of bovine serum and ethylenglycol with a swelling degree of 97%, Gayet and Fortier[15] reported a value of 15.2 cm^2 s^{-1}. Novoa and Apodaca[16] reported for theophylline release from poly(acrylic acid-*co*-methyl methacrylate) hydrogels values for D_a from 24.8×10^{-7} to 2.04×10^{-7} cm^2 s^{-1}. Korsmeyer and Peppas[17] reported a value of 2.8×10^{-7} cm^2 s^{-1} in the liberation of theophylline from copolymers of PHEMA and *N*-vinylpirrolidone (25/75 vol %) with a swelling degree of 557% Peppas and Franson[18] found a value of 2.0×10^{-7} cm^2 s^{-1} in the theophylline release from a poli(HEMA-*co*-MMA) hydrogel. Katime et al.[19] studied the liberation of theophylline from poly(acrylic acid-*co*-*n*-alkyl methacrylate) hydrogels and they found that by increasing the length of the alkyl group faster liberation were achieved, They reported values for D_a from 2.92×10^{-7} cm^2 s^{-1} (methyl) to $3.70 \times 10^{-}$ cm^2 s^{-1} (hexyl). As it can be observed theophylline release diffusion coefficients obtained in this work are in the same range that the values reported in other studies.

Table III shows that aminophylline has a lower diffusion coefficient than theophylline. Because molecular mobility is related to molar mass the lower diffusion coefficient of aminophylline can be attributed to its higher molar mass (420.44 g/mol)

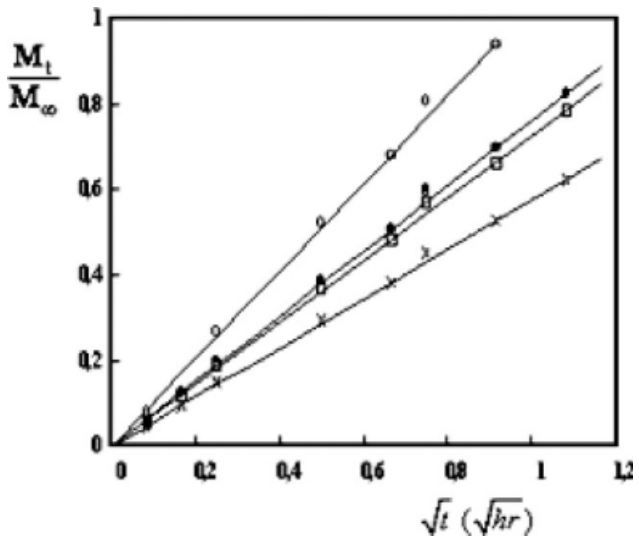

Figure 5 Released theophylline fraction, M_t/M_∞, as a function of $t^{1/2}$, from poly(*n*-butyl-monoitaconate-*co*-acrylamide): (○) *n*-butyl; (●) iso-butyl; (□) sec-butyl; (x) *tert*-butyl.

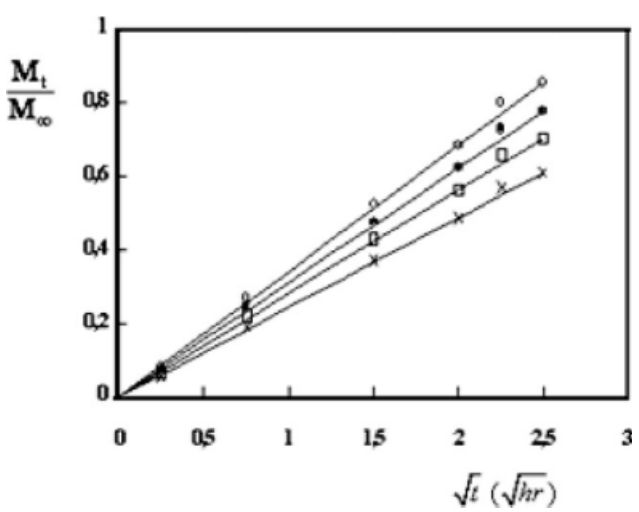

Figure 6 Released aminophylline fraction, M_t/M_∞, as a function of $t^{1/2}$, from poly(*n*-butyl-monoitaconate-*co*-acrylamide): (○) *n*-butyl; (●) iso-butyl; (□) sec-butyl; (x) *tert*-butyl.

TABLE III
Aminophylline Has a Lower Diffusion Coefficient Than Theophylline

Hydrogel	Theophylline D_a ($\times 10^7$ cm^2 s^{-1})	Aminophylline D_a ($\times 10^7$ cm^2 s^{-1})	ΔD_a ($\times 10^{-7}$ cm^2 s^{-1})
Poly(n-butyl monoitaconate-*co*-acrylamide)	2.75	0.302	2.448
Poly(iso-butyl monoitaconate-*co*-acrylamide)	1.66	0.281	1.379
Poly(sec-butyl monoitaconate-*co*-acrylamide)	1.39	0.211	1.179
Poly(tert-butyl monoitaconate-*co*-acrylamide)	1.00	0.181	0.819

compared with theophylline (180.17 g/mol) and to its higher capacity of hydrogen bonding because of the ethylamine group.

CONCLUSIONS

Hydrogel equilibrium water content and swelling rate depends on butyl degree of ramification. Increasing butyl ramification decreases equilibrium degree of swelling and the time for reaching swelling equilibrium because of the higher cross-linking density. Hydrogel apparent water diffusion constant decrease as butyl ramification increases.

Cross-linking density, Young's and compression moduli augments as butyl ramification increases.

Lower apparent drug liberation diffusion coefficients (D_a) are obtained when increasing butyl ramification. Because the theophylline molecule is smaller than the aminophylline molecule and has lower hydrogen bonding capacity it is released faster.

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