Kinetics and Equilibrium Swelling Properties of Hydrophilic Polymethacrylate Networks

Fatima Zohra Elouali,[1,2] *Ulrich Maschke*[*1]

Summary: Hydrogels were synthesized by polymerization of 2-Hydroxy ethylmethacrylate (HEMA) in the presence of ethyleneglycoldimethacrylate (EGDMA) as a crosslinking agent. Structural information and thermophysical properties of the hydrogels were analyzed using Fourier-Transform Infrared spectroscopy, thermogravimetrical analysis, and differential scanning calorimetry. The swelling behaviour of the obtained chemically crosslinked P(HEMA-EGDMA) networks in aqueous solution was investigated as a function of the pH value and concentration of crosslinking agent. Plateau values were found at equilibrium swelling for a low pH value after one day swelling, whereas increasing water uptake was obtained for pH = 6.32 even at swelling times of more than five days. For short swelling times, a linear relationship between swelling ratio and time was found. Experimental data were rationalized using Fick's second law of diffusion. For early and moderate times of diffusion, threshold values were found in all cases considered here, indicating a Fickian behaviour below and a non-Fickian diffusion mechanism above the threshold.

Keywords: biomaterials; copolymerization; crosslinking; DSC; FT-IR; hydrogels; photopolymerization; thermogravimetric analysis

Introduction

Hydrogels are cross-linked hydrophilic macromolecular networks swollen in water or biological fluids. Due to their hydrophilic character and potential to be biocompatible, hydrogels have been of great interest to biomaterial scientists for many years[1–6] because they offer interesting properties: high water content, a good permeability toward oxygen and metabolites. Hydrogels are sensitive to environmental parameters such as pH,[7,8] temperature,[7] ionic concentration,[9] electric fields,[10] solvent composition etc., these properties make hydrogels an ideal class of materials for medical and pharmaceutical applications such as drug delivery.[8–12] For applications in the medical field, hydrogels prepared from natural polymers are preferred as these are known to be biodegradable and biocompatible. For biomedical applications of hydrogels, the polymer network has to be composed of polymers with low toxicity and antigenicity such as poly ethylene oxide (PEO),[13] chitosan,[14–16] or poly 2-hydroxyethylmethacrylate (PHEMA). The success of PHEMA as a biomaterial has led to the investigation of novel copolymers to enhance particular properties, i.e., mechanical strength, imbibed water content, and stimuli-sensitivity, while retaining biocompatibility and low biological response.[17–21]

PHEMA has been shown to produce better response functions when small amounts of crosslinking agents are used.[22–25] Hydrogels are called ''permanent'' or ''chemical'' gels when they

[1] Unité Matériaux et Transformations (UMET), UMR 8207–CNRS, Bâtiment C6, Université Lille 1 - Sciences et Technologies, 59655 Villeneuve d'Ascq Cedex, France
Fax: (+33) (0) 3 20 43 43 45;
E-mail: ulrich.maschke@univ-lille1.fr
[2] Laboratoire de Recherche sur les Systèmes Biologiques et la Géomatique, Université de Mascara, Route de Mamounia, 29000 Mascara, Algeria

represent covalently crosslinked networks. Generally synthetic hydrogels were based on copolymerization of HEMA with the difunctional EGDMA.[12,26–28]

The aim of the present work is to study the swelling behaviour of PHEMA gel prepared by UV-irradiation since this technique allows to obtain easily chemically crosslinked polymer networks exhibiting strong interactions between chains through covalent bands. Polymeric (HEMA-EGDMA) samples were synthesized from HEMA monomer in presence of 0.1-0.5 wt-%. EGDMA as crosslinking agent. The obtained pure polymer networks were characterized by Fourier Transform Infrared spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and ThermoGravimetric Analysis (TGA).

The kinetic swelling behavior of poly-(HEMA/EGDMA) was studied as a function of time, pH of the swelling medium and concentration of EGDMA in the hydrogels. The experimental data were analyzed theoretically using Fick's second law.

Theoretical Background

The water transport mechanism into the polymer network is particularly important for assessing the suitability of these materials as drug delivery systems, as the amount of drug released is dependent on the rate and transport mechanism of water diffusing into the polymer network. In general, two types of mechanisms can be distinguished for the release of drugs from swollen hydrogels: diffusion-controlled and degradation-controlled release.

When a glassy polymer is exposed to a penetrant solvent, which can be gaseous or liquid, the latter diffuses into the former and a glassy-rubbery interface forms and moves through the polymer: 1.) Fickian diffusion (case *I* diffusion) occurs when the diffusion is significantly slower than the rate of relaxation of the polymer chains. 2.) case *II* diffusion occurs when the rate of penetrant diffusion is greater than the rate of relaxation of the polymer chains. 3.) anomalous diffusion (case *III* diffusion) accounts for behaviour that lies between the extreme case 1 and 2 models. Hence, the rate of penetrant diffusion is comparable to the polymer relaxation.

Since most complex models do not yield a convenient formula and require numerical solution techniques, generalized empirical equations have been widely used to describe both the water uptake through the swellable glassy polymers and the drug release from these devices. In the case of water uptake, the weight gain, M_s, is described by the following empirical equation:

$$M_s = kt^n \quad (1)$$

where k is a constant characteristic of the drug-polymer (or solvent-polymer) system, and n is the ''diffusion exponent'' characteristic of the release mechanism. Normal Fickian diffusion is characterized by $n = 0.5$, while case *II* diffusion gives $n = 1.0$. A value of n between 0.5 and 1.0 indicates Fickian behavior and case *II* diffusion, which is usually called non-Fickian or anomalous diffusion.[29] Ritger and Peppas showed that the above power law expression could be used for the evaluation of drug release from swellable systems.[30,31] In this case, M_t/M_∞ replace M_s in the above equation to give equation (2).

$$M_t/M_\infty = kt^n \quad (2)$$

where M_t/M_∞ is the fractional release of drug (or solvent) in time, t.

Experimental Part

Materials

The monofunctional monomer HEMA and the difunctional crosslinking agent EGDMA were purchased from Sigma-Aldrich. The chemical structures are displayed in Figure 1a and 1b.

To initiate the reaction of free radical photopolymerization, 2-hydroxy-2-methyl-1-phenyl-propane-1 (Darocur1173, from Ciba-Geigy) was employed (see Figure 1c). All products were used as received without further purification. Water used in all experiments was distilled.

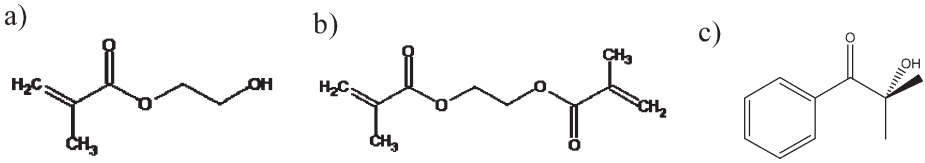

Figure 1.
Chemical structures of (a) the monomer 2-hydroxyethyl methacrylate (HEMA), (b) the difunctional crosslinking agent ethyleneglycoldimethacrylate (EGDMA), and (c) the photoinitiator 2-hydroxy-2-methyl-1-phenyl-propane-1 (Darocur 1173).

Gel Preparation

Blends of HEMA/EGDMA/Darocur1173 were prepared in different weight fractions by varying the quantity of EGDMA keeping the amount of the photoinitiator constant (HEMA/EGDMA/Darocur1173: 99/0.5/0.5 wt-% and 99.4/0.1/0.5 wt-%). These initial mixtures were stirred mechanically at room temperature during several hours before they were cast in small flat sample holders, exhibiting a single homogeneous phase. The samples were exposed to UV radiation under nitrogen atmosphere, using Philips TL08 UV lamps exhibiting a wavelength $\lambda = 365\,\text{nm}$ and intensity $I_0 = 1.5\,\text{mW/cm}^2$. The exposure time was fixed at 10 min which was sufficient to achieve maximum conversion of the two monomers in the precursor system. The obtained optically completely transparent crosslinked polymer networks were immersed in an excess of water at different pH-values. Swelling of the disk-like samples in distilled water was investigated at room temperature. In these studies, polymer gels represent roughly $1 \pm 0.3\,\text{g}$ in mass and $2.7 \pm 0.1\,\text{cm}$ in diameter.

Water Sorption Experiments

After the UV-curing process, the disk-like polymer networks were placed in distilled water which was maintained at room temperature. Periodically, samples were taken out of the water bath, excess water was removed from the surfaces with a lint free tissue and the disks were weighted. The amount of water absorbed was monitored gravimetrically for a period of 1 week.

FTIR Spectroscopy

Infrared spectra of thin films (less than 10 μm) were recorded in the transmission mode with a Perkin Elmer 2000 model. The spectra have been taken before and after the curing process and the chosen irradiation dose was applied only once and at room temperature. The number of accumulated scans was 16 with a spectral resolution of $4\,\text{cm}^{-1}$.

Thermo-Gravimetric Analysis

TGA thermograms were carried out on a Shimadzu-50 instrument using a heating rate of 10 °C/min under nitrogen flow (20 mL/min) from room temperature to 500 °C.

Differential Scanning Calorimetry

DSC measurements were performed on a Perkin Elmer Pyris Diamond calorimeter equipped with an Intracooler 2P system allowing cooling experiments. Samples for calorimetric measurements were prepared by introducing approximately 8 mg of the polymer network into aluminium DSC pans, which have been sealed to avoid evaporation effects during the temperature treatment. A rate of 10 °C/min (heating and cooling) was used in the temperature range -70 to + 100 °C. The program consists first in cooling the sample followed by three heating and cooling cycles to take into account eventual thermal events related to the sample preparation history. The thermograms presented in this work were obtained from the first heating ramps. In each case, at least five duplicate samples having the same composition and prepared

independently were used to check the reproducibility of results. The polymer glass transition temperature was determined from the midpoint of the transition range of the thermograms.

Results and Discussion

The FTIR spectra of the pure monomer HEMA and a UV cured HEMA/0.5 wt-% EGDMA blend are presented in Figure 2. Since one of the monomers in the initial mixtures was difunctional, radiation curing leads to chemically crosslinked polymer networks. In the present case of UV radiation, the molecules of the photoinitiator (Darocur 1173) were first broken into two radicals prior to react with the monomer. Then chain propagation occurs until all reactive groups are exhausted according to a process regulated by diffusion mechanism. HEMA and PHEMA exhibit characteristic peaks at 3431 cm^{-1} (–OH group), at 1723 cm^{-1} (–C=O group), at 1200 cm^{-1} (–C–O group), and at 1050 cm^{-1} (–C–O–C stretching). Characteristic peaks were observed around 1276 cm^{-1} which can be attributed to the methyl group of HEMA. The spectrum of the polymer has some absorption bands which are different from that of HEMA monomer. For example, at 2951 cm^{-1}, one observes a characteristic stretching vibration band (CH_2), arising from the comonomer EGDMA.

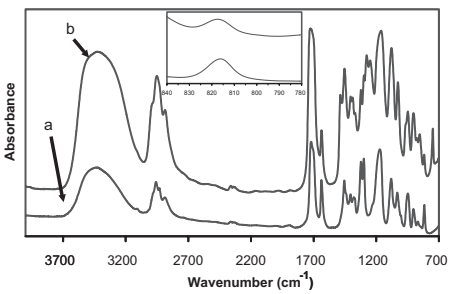

Figure 2.
FTIR spectra of: (a) HEMA monomer, and (b) Poly-(HEMA/0.5 wt-% EGDMA). The inset shows an enlarged view of the FTIR spectra between 840 and 780 cm^{-1}. (upper part of the inset: Poly(HEMA/0.5 wt-% EGDMA, lower part: HEMA).

Several absorption bands are available to monitor the polymerization/crosslinking processes and the conversion of double bonds in the acrylic functions of the monomers HEMA and EGDMA.

The monomers exhibit a strong absorption band near 817 cm^{-1} corresponding to the –CH=CH– deformation vibration of the acrylate groups. The calculation of the monomer conversion was made by considering the peak heights of the absorption band before and after UV-curing at 817 cm^{-1}. The conversion ratio C was calculated without an internal standard using:

$$C(\%) = \frac{(A_{817})_{(D=0)} - (A_{817})_{(D)}}{(A_{817})_{(D=0)}} \quad (3)$$

where $(A_{817})_{D=0}$ is the height of the absorption band of the monomeric system at 817 cm^{-1} (i.e., radiation dose D is zero) and $(A_{817})_D$ is the corresponding result for the system exposed to a dose D. From the inset of Figure 2, a conversion value of roughly 85% for an UV-exposure time of 10 min was obtained. This result shows clearly that a high conversion of acrylic double bonds was achieved and that, therefore, one of the conditions necessary for good performance of the crosslinked PHEMA-samples was fulfilled.

The TGA method was used to investigate experimentally the thermal stability of the crosslinked P(HEMA-EDGMA) and HEMA monomer. Figure 3 shows the results of the thermogravimetric analysis indicating that the polymer is thermally more stable than the monomer. The monomer shows significant degradation effects starting from 75 °C whereas P(HEMA/0.5 wt-% EGDMA) remains stable roughly up to 250 °C showing clearly the impact of the UV-crosslinking polymerization reactions.

The results of measurements by DSC are presented in Figure 4. This figure shows two thermograms corresponding to the first heating up cycle of a) pure monomer

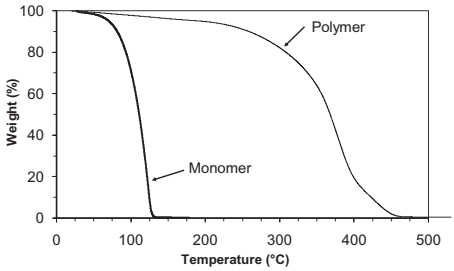

Figure 3.
TGA measurements of monomer HEMA and poly-(HEMA/0.5 wt-% EGDMA).

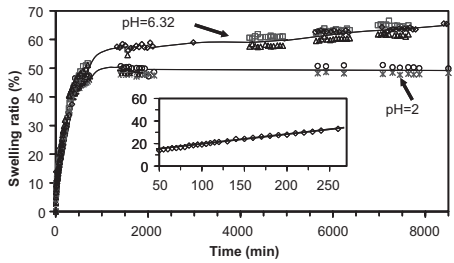

Figure 5.
Swelling dependency on pH of Poly (HEMA/0.1 wt-% EGDMA) hydrogels as a function of time at room temperature. The inset corresponds to the system with pH =2.

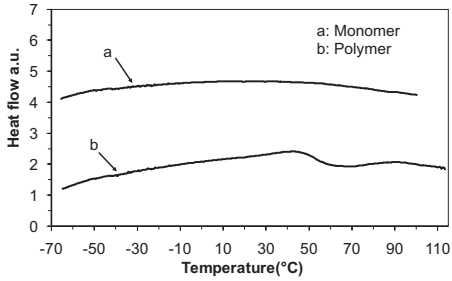

Figure 4.
DSC measurements of (a) monomer HEMA; (b) poly-(HEMA/0.5 wt-% EGDMA).

HEMA (upper part), and b) a cured mixture composed of 99.5 wt-% HEMA and 0.5 wt-% EGDMA (lower part). The monomer exhibits no transition in the temperature range explored by the experiments from -70 to 110 °C. A glass transition is expected at temperatures lower than -70 °C due to the high mobility of this low molecular weight molecule. The UV-cured crosslinked system shows a single glass transition between 45 and 60 °C, thus attesting the glassy state together with a certain mechanical rigidity of the sample at room temperature.

Figure 5 displays swelling curves in terms of the swelling ratio as function of time, obtained from poly(HEMA/0.1 wt-% EGDMA). The following equation was used to determine the swelling ratio of the hydrogels:

$$\text{Swelling ratio}(\%) = [(W_s - W_d)/W_d] * 100 \quad (4)$$

where W_s and W_d are the swollen and dry weights of the hydrogels, respectively. The degree of swelling W_t was determined at different times using equation (4) until swollen gels reached constant weights.

The influence of the pH value on the water-sorption kinetics of a poly (HEMA/0.1 wt-% EGDMA) gel at room temperature is shown in Figure 5. The swelling study shows that there is no dependence of pH for $t < 6$ h, for $t > 6$ h a dependence of the swelling ratio on the pH value was observed. It was shown that, as expected, the total swelling ratio increases with increasing pH from 2 to 6.32. Hydrogels loaded at pH 2 and 6.32 show similar swelling profiles with non linear swelling kinetics during the first 30 minutes, then linear kinetics were observed during 3 h, and finally plateau values were obtained up to 20 h. The values of the equilibrium degree of swelling W_∞ were found between 50% and 65% depending on the degree of crosslinking of the hydrogels and on the pH of the medium.

The diffusion mechanism can be determined by a variety of techniques; the easiest and most utilized method is by gravimetric water sorption studies as discussed before, where the mass of the water absorbed by

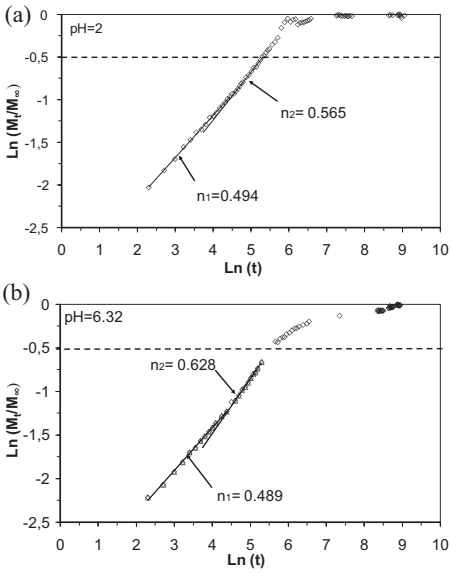

Figure 6.
Plot of $Ln(M_t/M_\infty)$ vs. Ln(t) of Poly(HEMA/EGDMA 0.1 wt-%) at (a) pH = 2 and (b) pH = 6.32.

the polymer, M_t, is monitored as a function of time, t. When M_t is normalized to the mass of water absorbed by the polymer at its equilibrium hydration level, M_∞, the transport mechanism can be determined according to equation (2). Alfrey et al.[29] distinguished three classes of diffusion: (1) case *I*, or Fickian diffusion, in which the degree of absorption is proportional to the square root of time; (2) case *II*, in which the amount of absorption is observed to be directly proportional of time; and (3) non-Fickian, or anomalous diffusion, which occurs when the absorption is proportional to time ($0.5 < n < 1$). Sorption data from Figure 5 were analyzed in terms of an empirical relation to establish the diffusion mechanism:

$$\mathrm{Ln}(M_t/M_\infty) = \mathrm{Ln}\ k + n{*}\mathrm{Ln}\ t \qquad (5)$$

By plotting $Ln(M_t/M_\infty)$ vs Ln(t) shown in Figure 6, the values of n can be deduced from the slopes of the regression lines. The resulting values of the "kinetic exponent" n are gathered in Table 1 as function of the pH value and concentration of the crosslinking agent, 0.1 and 0.5 wt-%.

Table 1.
"Diffusion exponent" n in crosslinked samples of P(HEMA/EGDMA).

wt -% of crosslinker EGDMA	0,1	0,5	0,1	0,5
pH	6,32	6,32	2	2
n_1	0,488	0,475	0,463	0,480
n_2	0,591	0,639	0,562	0,561

Figure 6 shows clearly the existence of two slopes in both cases pH = 6.32 and pH = 2 yielding two values of n (n_1 for shorter and n_2 for longer times), when $M_t/M_\infty \leq 0.6$. n_1 values were found in the range 0.444-0.505, close to the value 0.5, so that a Fickian diffusion behavior (case 1) can be considered. The values of n_2 were in the range 0.524-0.777, so that non-Fickian diffusion behavior (case 3) can be assumed.

The time corresponding to the first slope for pH = 2, in the range $0 < t < 90$ min, reveal a rapid diffusion phenomenon, followed by relaxation of polymer chains until the system reaches its thermodynamic equilibrium. The second slope which corresponds to the non-Fickian phenomenon $0.5 < n < 1$ is located in a time interval between 100 and 200 min; in this time interval diffusion is comparable to the relaxation phenomena of polymer chains. Generally values of n_1 and n_2 are higher in the case of pH 6.32 than for pH 2.

Conclusion

A sample preparation route based on UV curing was used to induce polymerization of methacrylates in order to obtain well-defined hydrogels. The conversion ratio of double bands of the methacrylate monomers was monitored by FTIR spectroscopy.

The dynamic swelling behavior of the elaborated crosslinked P(HEMA-EGDMA) networks were investigated. The kinetics of swelling depend not only on the degree of crosslinking of the polymer, but also on the pH of the solution. Swelling data were analyzed using a theoretical model of Fick, yielding a good

correlation between experimental and calculated data.

[1] M. E. Byrne, K. Parka, N. A. Peppas, *Adv. Drug Deliv. Rev.* **2002**, *54*, 149.
[2] Y. Tanaka, J. P. Gong, Y. Osada, *Prog. Polym. Sci.* **2005**, *30*, 1.
[3] L. Klouda, A. G. Mikos, *Europ. J. Pharm. Biopharm.* **2008**, *68*, 34.
[4] T. G. Van Thienen, F. Horkay, K. Braeckmans, B. G. Stubbe, J. Demeester, S. C. De Smedt, *Inter. J. Pharm.* **2007**, *337*, 31.
[5] A. S. Hoffman, *Adv. Drug Deliv. Rev.* **2002**, *43*, 3.
[6] L. Serra, J. Doménech, N. A. Peppas, *Europ. J. Pharm. Biopharm.* **2009**, *71*, 519.
[7] S. Lj Tomic, M. M. Micic, S. N. Dobic, J. M. Filipovic, E. H. Suljovrujic, *Radiat. Phys. Chem.* **2010**, *79*, 643.
[8] C. Zhao, X. Zhuang, P. He, C. Xiao, C. He, J. Sun, X. Chen, X. Jing, *Polymer* **2009**, *50*, 4308.
[9] M. S. Lorda, M. H. Stenzelb, A. Simmonsa, B. K. Milthorpe, *Biomaterials* **2006**, *27*, 567.
[10] A. Guiseppi-Elie, *Biomaterials* **2010**, *31*, 2701.
[11] F. Fornasiero, F. Krull, C. J. Radke, J. M. Prausnitz, *Fluid Phas. Equilib.* **2005**, *228-229*, 269.
[12] D. Gulsen, A. Chauhan, *Inter. J. Pharm.* **2005**, *292*, 95.
[13] J. Kang, K. J. Beers, *Europ. Polym. J.* **2009**, *45*, 3004.
[14] Y. Zhou, D. Yang, X. Gao, X. Chen, Q. Xu, F. Lu, J. Nie, *Carbohydr. Polym.* **2009**, *75*, 293.
[15] C. J. Muvdi Nova, D. Paolucci-Jeanjean, M. P. Belleville, M. Barboiu, M. Rivallin, G. Rios, *J. Membr. Sci.* **2008**, *321*, 81.
[16] Y. Liu, X. Cao, R. Hua, Y. Wang, Y. Liu, C. Pang, Y. Wang, *Hydrometallurgy* **2010**, *104*, 150.
[17] Y. Li, T. Tanaka, *J. Chem. Phys.* **1990**, *92*, 1365.
[18] J. Durner, U. I. Walther, J. Zaspel, R. Hickel, F. X. Reichl, *Biomaterials* **2010**, *31*, 818.
[19] M. Ansari, M. Kazemipour, M. Aklamli, *Inter. J. Pharm.* **2006**, *327*, 6.
[20] T. Yamaue, M. Doi, *J. Chem. Phys.* **2005**, *122*, 084703.
[21] M. Doi, T. Yamaue, *Phys. Rev. E* **2005**, *71*, 041404.
[22] T. Tanaka, *Phys. Rev. Lett.* **1978**, *40*, 820.
[23] H. Omidian, K. Park, U. Kandalam, J. G. Rocca, *J. Bio. Compat. Polym.* **2010**, *25*, 483.
[24] I. M. El-Sherbiny, H. D. C. Smyth, *Carbohyd. Polym.* **2010**, *81*, 652.
[25] M. Guvendiren, J. A. Burdick, S. Yang, *Soft Matter* **2010**, *6*, 2044.
[26] R. Yina, K. Wanga, J. Hana, J. Nie, *Carbohydr. Polym.* **2010**, *82*, 412.
[27] G. Bayramoglu, M. Y. Arıca, *React. & Funct. Polym.* **2009**, *69*, 189.
[28] Y. Kapoor, A. Chauhan, *J. Coll. Interf. Sci.* **2008**, *322*, 624.
[29] T. Alfrey, E. F. Gurnee, W. G. Lloyd, *J. Polym. Sci. Part C* **1966**, *12*, 249.
[30] P. L. Ritger, N. A. Peppas, (a). *J. Contr. Release* **1987**, *5*, 23.
[31] P. L. Ritger, N. A. Peppas, (b). *J. Contr. Release* **1987**, *5*, 37.

