Polymer Bulletin 38, 55–62 (1997)

Polymer Bulletin

Effect of the crosslinking with 1,1,1-trimethylolpropane trimethacrylate on 5-fluorouracil release from poly(2-hydroxyethyl methacrylate) hydrogels

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Received: 12 July 1996/Revised version: 8 October 1996/Accepted: 15 October 1996

ABSTRACT

The aim of this study is to examine the influence of crosslinking density on 5-Fluorouracil release from poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels crosslinked with 1,1,1-trimethylolpropane trimethacrylate (TPT).

PHEMA hydrogels were synthesized by bulk polymerization with different proportions of TPT (1-10 wt%) as crosslinker agent and ammonium persulphate as initiator, enabling polymerization in the feed mixture in the presence of water. As a result, 5-FU could be trapped by including it as a sodium salt in the feed mixture of polymerization. Discs with 5-FU loads between 1-16mg/disc were obtained.

Swelling and 5-FU release kinetics studies were carried out in saline solution at 310K. The diffusion studies were in accordance with Fick's second law during the initial stages, enabling the diffusion coefficients of the process to be determined. The time required for discs to reach total 5-FU release was between 35h and 160h and was a function of crosslinking density of the gels and 5-FU load of the discs.

KEYWORDS :Poly(2-hydroxyethyl methacrylate) (PHEMA), 5-fluorouracil (5-FU), 1,1,1-trimethylolpropane trimethacrylate (TPT), hydrogel, controlled release, diffusion coefficient.

INTRODUCTION

Polymers have been considered as vehicles for the immobilization, encapsulation and controlled release of many physiologically active substances (1).

The great versatility of synthetic polymers makes them very useful in the biomedical field in numerous different forms. The matrix may consist of bioerodible supports to facilitate the drug release or as a support for trapping drugs; in this last group the hydrogels are included. A hydrogel is a water swollen polymer network used for drug release. It is a highly biocompatible material, due to its soft, rubbery consistency, low interfacial tension and water content that make it extremely useful as a biomaterial because of its resemblance to living tissues (1,2).

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The release of drugs from hydrogels takes place by drug diffusion through the polymeric matrix, firstly in a glassy state, under water or biological fluid flow (3).

The drug can be incorporated in a hydrogel by one of two methods: one involves the formation of links between the drug and one of the hydrogel components and the other is by physical mechanisms. Of the latter, one possibility is the immersion of the gel into aqueous solutions of the drug followed by solvent evaporation when equilibrium of swelling has been reached (4,5); another possibility is to include the drug in the feed mixture of polymerization, when the drug is stable enough under synthesis conditions to directly obtain xerogel discs with the drug trapped inside (6,7).

This type of formulation of the active substance can be very useful to achieve drug release in an organism over a prolonged period of time, improving dosage control and reducing side effects. The diffusion rate of the drug from the hydrogel is probably the most important criterion by which a polymer matrix is chosen or developed, together with the biocompatibility of the matrix. Hydrogels are excellent materials for this application because their physical characteristics (degree of hydration, crosslinking density, porosity, mechanical strength, etc.) can be changed and controlled in order to modify the diffusion rate of a drug (8,9).

Crosslinker polymers exhibit different properties depending on their crosslinking degree and the polymerization method. In general, crosslinking degree affects swelling degree, pore size, total surface area and the mechanical strength of the network (10).

In this study, the influence of crosslinking degree on 5-FU release from PHEMA hydrogels has been assessed using TPT as a crosslinker agent. 5-FU is an antimetabolic drug commonly used in cancer chemotherapy (11). It has been the object of release studies from several hydrogels because of its high toxicity and large number of side effects resulting from the large doses required for the treatment of several malignancies. These doses can be minimized with this mode of administration (5,7).

The utility of hydrogels as a matrix for controlled release lies in their biocompatibility based on their water content. One of the monomers able to form biocompatible hydrogels is 2-hydroxyethyl methacrylate (HEMA) which has an increasing number of biomedical applications (12). It can be used as a matrix with a wide range of swelling degrees and mechanical properties that make it a versatile implement for controlled release studies (4-6).

MATERIALS AND METHODS

Materials: Hydroxyethyl methacrylate (HEMA) [Merck] was previously purified by distillation under vacuum at 315-318K and 3.7 mm Hg (vacuum pump Eduar 8) [Eduar]. 1,1,1-trimethylolpropane trimethacrylate (TPT) [Merk]; ammonium peroxodisulphate [$(NH_4)_2S_2O_8$] [Merck], dimethyldichlorosilane solution [BDH Limited Poole England], sodium chloride [Panreac] and sodium hidroxide (NaOH) [Probus] were used as received.

The antineoplastic drug, 5-fluorouracil (5-FU), with a molecular weight of 130, was kindly supplied by ROCHE LABORATORIES, as a crystalline powder.

Synthesis of PHEMA hydrogels: PHEMA hydrogels were synthesized by bulk polymerization. Eight PHEMA hydrogels were prepared as a function of crosslinker degree, from 1 wt% to 10 wt% (0.39-3.9 mol%, respectively) of TPT related to the total amount of the monomer.

The initiator solution used for polymerization was aqueous ammonium peroxodisulphate (concentration 0.05 g/cm^3) as described by Davis and Huglin (13,14), to obtain a high conversion. This initiator is employed when water is required in the feed mixture.

A total volume of 0.75ml of the feed mixture, that was formed by HEMA and TPT (66 vol%) and the aqueous initiator solution (34 vol%), was selected to obtain xerogels with adequate disc thickness and an appropiate amount of 5-FU. The feed mixture was poured into small glass vials, previously siliconised with a dimethyldichlorosilane solution to facilitate subsequent removal of the polymer. After outgassing with gaseous nitrogen for 5min, the vials were sealed and placed in an oven at 323K for 3 hours, in the dark (14). The vials were then broken and the polymer discs were removed and dried to constant weight for one week; disc dimensions were determined with a micrometer and discs were then placed in dark and dry environmental conditions.

Trapping of 5-FU in PHEMA hydrogels: 5-FU was trapped in the hydrogels by including it in the feed mixture and was dissolved in this before polymerization. In order to trap a maximun amount of 5-FU in the xerogel disc, an aqueous solution of 5-FU neutralized with NaOH was used instead of water in the feed mixture; in this way disc loads between 1 mg/disc and 16 mg/disc of 5-FU were obtained.

After polymerization, the samples were optically transparent, showing the complete solubility of 5-FU in the polymeric matrix. The sodium salt of 5-FU is active pharmacologically (15).

Swelling of the polymers in water: In order to determine the swelling behaviour of the PHEMA polymers, the xerogel discs (without drug) were placed into a saline solution (0.9 wt% NaCl) bath at a constant temperature (310K). The degree of swelling (W_t) was obtained at different times by withdrawing the discs, lightly drying them with filter paper and quickly weighing them in a tared sample bottle using an electronic balance [Sartorious $\pm$ 1x10^{-4} g]. The following expression was used (13,14):

$$W_t = \frac{\text{(weight of swollen discs - weight of dry disc)}}{\text{(weight of swollen disc)}} \; 100 \qquad \text{(I)}$$

5-Fluorouracil release experiments: 5-FU release from PHEMA hydrogels was determined by placing each xerogel disc with drug on a holder in a vessel containing 100 ml of saline solution, at a constant temperature (310K) and stirring rate. At intervals, 50 μl samples were drawn from the solution to determine the change in 5-FU concentration. The concentration of 5-FU in the release medium was always $< 10\%$ of the solubility of 5-FU (sink conditions) (16). These experiments were carried out in darkness.

The 5-FU concentrations were measured by UV/Vis spectroscopy (Unicam 8700 series spectrophotometer) using a 1cm path lengh microcuvette (50 μl volume) at 270nm. 5-FU standards of 0.1-50μg/ml were used to obtain a calibration curve (17,18).

No degradation of 5-FU was observed either during the loading of the gels or throughout the drug release process. All the xerogel discs with 5-FU were transparent and all the samples showed an absorption spectrum which belonged to 5-FU.

RESULTS AND DISCUSSION

The swelling experiments with xerogel discs (without 5-FU) were conducted at 310K in saline solution (0.9 wt% NaCl) in order to study the hydrogel behaviour in conditions similar to *in vivo*. Discs with 4.1 $\pm$ 0.3mm thick and 12.3 $\pm$ 0.4mm diameter were employed.

The degree of swelling (W_t) was determined at different times using equation I until swollen gels attained a constant weight. The time taken to obtain the equilibrium degree of swelling, W_∞, was

between 23h and 48h depending on the degree of crosslinking of the hydrogels. The values of W_∞ are given in Figure 1, they indicate that as the TPT concentration in the gel increases, W_∞ decreases. These results are consistent with those reported when the influence of crosslinker concentration on W_∞ in PHEMA hydrogels is observed. The influence of the initiator on swelling and elastic modulus may simply stem from the kinetic implications of initiator half-life and/or its concentration on the network structure. W_∞ values of 39 wt% (16) and 37.5 wt% (19) in water for uncrosslinked PHEMA have been reported; this discrepancy may be a result of the initiation mechanism. Equilibrium swelling degrees between 36-29 wt% have been reported for PHEMA hydrogels crosslinked with different proportions of EGDMA (0.33-3.3 mol%, respectively) (5).

Allen and coworkers studied the sorption of water in PHEMA hydrogels crosslinked with different ethylenglycol dimethacrylates, EGDMA (ethylenglycol dimethacrylate), DEGDMA (Diethylenglycol dimethacrylate) and TEGDMA (Triethylenglycol dimethacrylate). They reported that the influence of crosslinking density on the degree of swelling is due to two main effects: As the amount of crosslinker increases, the water content of the polymer matrix decreases as it becomes denser and less flexible. The hydrophobic character of the crosslinker molecule was found to significantly affect the equilibrium swelling degree of the gel in water. Therefore, less hydrophobic crosslinkers such as TEGDMA originate higher swelling values, independently of the crosslinking degree of the gel (20). The extreme case occurs in the presence of EGDMA, since this crosslinker, due to its chemical structure, originates a more strongly crosslinked polymer matrix (21).Thus, when the EGDMA concentration in the polymerization feed mixture is 14 mol%, the swelling of the hydrogel in water is 18 wt%, whereas the swelling of the hydrogels with DEGDMA, in the same synthesis conditions is 21 wt%, and with TEGDMA the value increases up to 22 wt% (22).

Davis and Huglin have reported that the equilibrium water content (W_∞) of PHEMA hydrogels crosslinked with EGDMA and TPT decreases as the concentration of the crosslinker agent increases in the feed mixture (19). Thus, hydrogels crosslinked with EGDMA showed an equilibrium swelling degree between 37-30 wt% when the crosslinking density was between 0.03-0.64 moldm^{-3}, whereas when PHEMA was crosslinked with TPT the values of W_∞ decreases, with values of 36.5-28.2 wt% for TPT concentrations between 0.064-0.64 moldm^{-3}. Therefore, comparison of the two crosslinker agents reveal smaller values of W_∞ for gels crosslinked with TPT with a functionality of f=6 whereas the EGDMA functionality is f=4 (19).

Therefore, taking into consideration the TPT percentges employed, the W_∞ values obtained in this study are in accordance with the results reported in the literature in spite of the different synthesis conditions used in each case.

For a controlled diffusion process, the uptake of water or saline solution into a polymer matrix may be expressed as: (3,6,23):

$$F_s = 4(D_s\, t/\pi\, h^2)^{1/2} \qquad \text{(II)}$$

where F_s is the fractional swelling due to saline solution ($F_s = W_t/W_\infty$), D_s the apparent diffusion coefficient for the transport of saline solution into the hydrogel, t the time and h the dry thickness of the xerogel disc. Equation II is a solution of the Fick's second law under simple boundery conditions such as swelling in water or biological fluids and simple geometrical forms (discs, cylinders and spheres) (24,25).

When F_s values are plotted against $t^{1/2}$, linearity is found for F_s values less than 0.5, thus D_s can be obtained from the slope of this linear stretch of the plot. Values of D_s are shown in Figure 2a. One can be observe that a higher degree of crosslinking leads to a reduction in D_s, indicating that swelling is less favourable when TPT concentration increases in the gel. Therefore, the kinetics of swelling are clearly determined by the network structure.

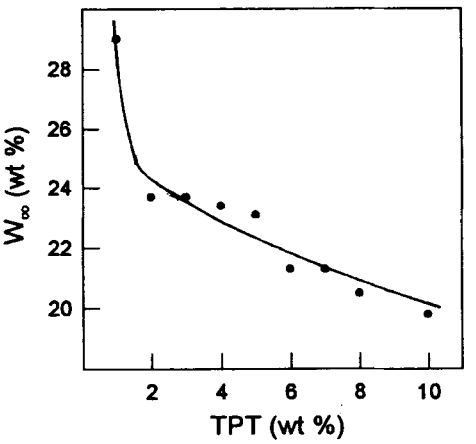

Figure 1.- Equilibrium swelling degree (W_∞) in saline solution (NaCl 0.9 wt%) of PHEMA hydrogels as a function of their percentage of crosslinker agent (TPT) at 310K.

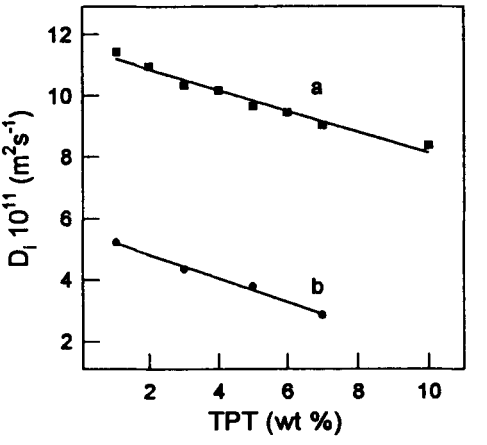

Figure 2.- Variation of the apparent diffusion coefficient (D_i) for a) saline solution uptake (D_s) and b) 5-FU release independent of disc load ($D_{5\text{-}FU}$) as a function of TPT percentage of PHEMA hydrogels at 310K.

Three different diffusion mechanisms for water absorption into PHEMA hydrogels crosslinked with EGDMA have been reported (26,27): a pore flow mechanism for low crosslinker content (approximately 0-2.5 mol%), an interaction water-matrix mechanism for higher crosslinking content (above 4 mol%) and an intermediate mechanism at intermediate crosslinker concentration.

These diffusion mechanism can be related to the hydration degree of the polymer matrix, since this depends on the crosslinking of the gel, through the following expresion (28):

$$\log D_s = \log D_o - K(1/W_\infty - 1) \qquad \text{(III)}$$

where D_o is the diffusion coefficient of water in pure water, D_s is the apparent diffusion coefficient for saline solution uptake and K is a proportionality constant.

The log D_s *versus* $1/W_\infty$ polt (Figure 3) shows three linear stretches. In the 29-23.7 wt% hydration range ($1/W_\infty$ = 0.034-0.042), corresponding to the gels with the lowest degree of crosslinking (1-2 wt% = 0.4-0.8 mol% TPT), the diffusion mechanism is through the pores. In the gels with the highest crosslinking degree (5-10 wt% = 2-4 mol% TPT), with hydration values less than 21 wt% ($1/W_\infty$ > 0.076), diffusion takes place through an interaction mechanism of saline solution-matrix. The gels with a TPT concentration between 2-5 wt% (0.8-2 mol%), with a hydration degree range of 23.7-21.3 wt% ($1/W_\infty$ = 0.0421-0.0476), show an intermediate diffusion behaviour between pore flow transport and flow by interaction of the saline solution with the polymer matrix. Thus, in our study three diffusion mechanisms had also been observed for saline solution uptake into PHEMA hydrogels crosslinked with TPT, as shown with gels crosslinked with EGDMA by *Chem and Wisniewky and coworkers* (26,27).

Diffusion coefficient values for water or saline solution uptake in PHEMA hydrogels are highly variable in the literature, but in all cases depend on the crosslinking degree of the gels. Thus Allen and coworkers have reported diffusion coefficient values between 2.1 10^{-12} - 0.08 10^{-12} m^2s^{-1} at 298K for water uptake into PHEMA hydrogels crosslinked with a large amount of EGDMA (14-33

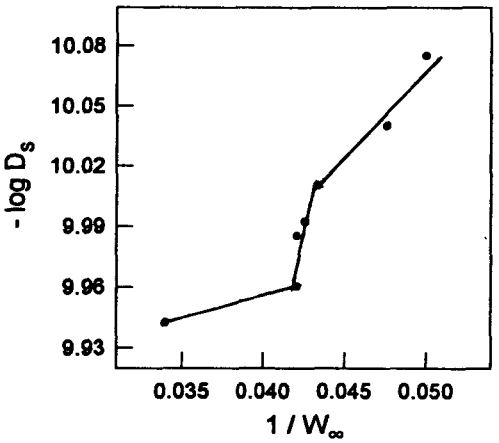

Figure 3.- Representation of the diffusion coefficient logarithm (-log D_s) for saline solution uptake *versus* the inverse of equilibrium swelling degree ($1/W_\infty$) for PHEMA hydrogels crosslinked with TPT at 310K.

mol%) (22). Similarly, in previous studies with PHEMA hydrogels crosslinked with EGDMA (0.33-3.3 mol%) (5,29), diffusion coefficient values for water uptake at 310K between 4.98 10^{-11}-3.77 10^{-11} m^2s^{-1} were obtained. These are very similar to those reported in this study revealing a similar diffusion behaviour in spite of the different crosslinker agent used.

On the other hand, the diffusion of saline solution through the matrix is influenced by both the type of salt and its concentration. Thus, a D_s value of 10.4 10^{-11} m^2s^{-1} was obtained for a PHEMA hydrogel crosslinked with 1 wt% of EGDMA at 310K in 0.25 M NaCl saline solution (30).

Therefore, both crosslinking density and the solvent medium that enters the polymer affect macromolecular relaxations and directly influence the diffusion mechanism through the matrix.

In the 5-FU xerogels, the maximun amount of crosslinker was 7 wt%. A higher concentration of TPT hydrogel was not possible since an incompatibility occurs in the system and the phases in the gel separate. This results in precipitation of the drug and its ejection from the polymer. This is one of the problems observed when a substance is included in the feed mixture of polymerization (31).

The 5-FU release studies from PHEMA hydrogels crosslinked with TPT were carried out in saline solution at 310K. The drug release, which was trapped in gel by including it in the feed mixture, depends on matrix swelling, 5-FU solubility in the solvent medium and possible matrix-drug interactions.

Drug release rate is directly related with drug solubility in the solvent medium because the solution medium (saline solution) has to penetrate the drug-loaded polymer matrix which starts to swell permitting drug release (32).

Release of 5-FU from the PHEMA hydrogels shows that the fractional release of 5-FU, $F_{5\text{-FU}}$, is linear with the square root of time, $t^{1/2}$, for values of $F_{5\text{-FU}}$ less than 0.5, thus the release experiments are in accordance with Fick's second law, and an equation very similar to the one used in the swelling studies can be employed (equation II):

$$F_{5\text{-FU}} = M_t/M_\infty = 4(D_{5\text{-FU}}\, t/\pi\, h^2)^{1/2} \qquad \text{(IV)}$$

where M_t and M_∞ correspond to the amount of 5-FU released at time t and the maximum amount of 5-FU released, respectively. $D_{5\text{-FU}}$ is the apparent diffusion coefficient for 5-FU release from the hydrogel and h is the thickness of the drug-loaded xerogel. This linear dependence yields $D_{5\text{-FU}}$ from the slope.

In order to determine the influence of the discs´ 5-FU load on its release from the hydrogels, at 310K, discs of similar thickness and six different drug loads from 1mg/disc to 16mg/disc were used.

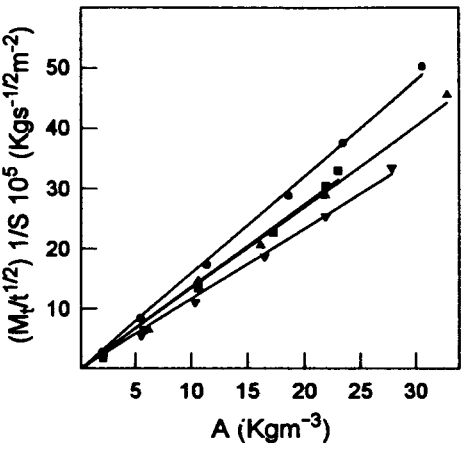

Figure 4.- Representation of 5-FU release rate per unit disc area ($M_t t^{-1/2} S^{-1}$) as a function of disc load (A) for PHEMA 1%TPT (●), PHEMA 3%TPT (■), PHEMA 5%TPT (▲) and PHEMA 7%TPT (▼) at 310K.

Taking into account that $M_\infty = AV = ASh$, where V is the xerogel disc-loaded volume, S its surface and A the drug load, another expression can be obtained from equation IV (4,33):

$$\frac{F_{5\text{-}FU}}{t^{1/2}} A h = \frac{M_t}{t^{1/2}} \frac{1}{S} = 4(D_{5\text{-}FU}/\pi)^{1/2} A \qquad (V)$$

where $M_t t^{-1/2} S^{-1}$ is the release rate per unit disc area. Plotting this parameter *versus* drug load (A) yields a straight line for each hydrogel composition (Figure 4), from the slope a diffusion coefficient that is independent of the disc load is obtained. These diffusion coefficient *versus* TPT percentage in the gel are plotted in Figure 2b, where it can be seen that the $D_{5\text{-}FU}$ value changes significantly with crosslinker concentration in the gel. This behaviour is the same as that observed in the swelling process. Thus, increasing crosslinking density reduces the $D_{5\text{-}FU}$, which results in slower 5-FU release. The time necessary to obtain the total release of 5-FU was between 35h (1.5 days) from PHEMA 1%TPT to 160h (6 days) from PHEMA 7%TPT.

The crosslinker effect on the drug diffusion is a function of polymer chain mobility, average pore size and the mobility of the solvent in the gel. The reduction in polymer chain mobility caused by crosslinking, reduces the range of pore sizes and may reduce the average pore size (34). Reduction of average pore size with an increase in crosslinking degree results in a decrease in $D_{5\text{-}FU}$ and a decrease in its water-sorption ability. Another phenomenon that explains the decrease in $D_{5\text{-}FU}$ with the increase in crosslinking density is the reduction of solvent mobility inside the polymer. When a hydrogel is polymerized and water is included in the feed mixture, this can be included as freezing or non-freezing water; crosslinking degree decreases the percentage of freezing water and increases the percentage of bound or non-freezing water (35,36). In addition, 5-FU, like all hydrophillic solutes, mainly diffuses through the freezing water (37). Therefore, increasing the crosslinker content reduces the effective free volume of the polymer matrix.

The $D_{5\text{-}FU}$ values, which are independent of 5-FU load, are smaller than the corresponding D_s values for PHEMA hydrogels with the same TPT percentage in the gel. As a result, the swelling process in saline solution is faster than release of 5-FU from the gel in all cases, in accordance with a thermodynamically easier process.

Release of 5-FU has been studied from different polymer matrices. Thus, hydrogels of PHEMA crosslink with EGDMA in which 5-FU was included by absortion (5) were used. Total drug release was reached between 7h and 27h for gels with 1 wt% and 5 wt% of EGDMA, respectively. 5-FU has also been delivered from poly(acrylamide-co-monoalkyl itaconates) hydrogels (7). The drug was included in the feed mixture of polymerization and total release took place between 70h and 100h.

The incorporation of 5-FU by including it into the feed mixture of polymerization has several advantages. Firstly, the release time of 5-FU increases, the distribution of the drug in the polymer

matrix is better than when 5-FU is included by immersion. Secondly, the amount of drug included in the gel discs can be accurately determined. With the PHEMA hydrogels crosslinked with TPT, 5-FU is trapped in the feed mixture of polymerization with a wide dosage interval of drug that is released appropriately (up to 160h). This is useful to keep 5-FU blood concentrations down to levels acceptable for *in vivo* studies.

AGWNOLEGSMENTS: The authors wish to thank ROCHE LABORATORIES for the gift of 5-fluorouracil. This work was funded by grant ref. MAT95-1661-E from Comision Interministerial de Ciencia y Tecnología (CICYT).

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