International Journal of Pharmaceutics, 94 (1993) 103–113

IJP 03137

A study of controlled-release systems for progesterone based on crosslinked poly(ethylene oxides)

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(Received 8 October 1992)
(Accepted 18 November 1992)

Key words: Controlled release; Crosslinked poly(ethylene oxide); Progesterone; Polymer matrix; Release model; Hydrogel

Summary

The characteristics of suspension-type matrices for the controlled release of hydrophobic drugs, based on crosslinked poly(ethylene oxides) (cr-PEO) have been investigated using progesterone (PGT) as a model drug. The drug amounts that can be reproducibly loaded in polymer by an impregnation technique are limited by crystalline drug expulsion from the matrix during solvent evaporation, depending on the degree of crosslinking of the polymer. cr-PEO of crosslinking degrees adequate to confer the required mechanical stability on the swollen matrix can be loaded with no more than 8–10% drug. A polymer with low crosslinking degree was loaded with up to 39% drug, but showed poor mechanical properties in its fully swollen state. The thermal behavior of the PGT-cr-PEO systems, as assessed by DSC, indicates drug-polymer interactions typical of monotectic dispersions. PGT release from cylindrical cr-PEO matrices is not influenced by the matrix swelling kinetics and is consistent with a model assuming that drug diffusion in the polymer phase of the fully swollen hydrogel is the rate-controlling factor. A cr-PEO of comparatively low degree of crosslinking was shown to match uncrosslinked polyethylene glycols with respect to the ability to enhance the dissolution rate of high PGT loads.

Introduction

Urethane-crosslinked poly(ethylene oxides)(cr-PEO) have been deemed suitable for the preparation of controlled-release matrices, on account of their excellent biocompatibility, outstanding chemical and physical stability and tailorable mechanical properties (Embrey et al., 1980; Brauman et al., 1981; Graham and McNeill, 1984; McNeill and Graham, 1984; Speckhard et al., 1984; Gander et al., 1988). Such materials are usually obtained by reacting poly(ethylene glycols)(PEG) with diisocyanates in the presence of branching agents carrying several hydroxyl functions. A three-dimensional network results from the formation of urethane groups.

The dispersion of drugs in these networks is usually accomplished by equilibrating the crosslinked polymer with a solution of the drug in a solvent able to swell the polymer network, then drying the drug-impregnated system. In fact, the impregnation method has been applied successfully to load cr-PEO with drugs having different

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solubility properties and molecular sizes, due to the ability of these polymers to swell considerably in water and such organic solvents as chloroform and benzyl alcohol (Embrey et al., 1980; Graham and McNeill, 1984; Gander et al., 1988). It has recently been shown, however, that problems may arise with the impregnation method when the desired load substantially exceeds the drug solubility in polymer. Indeed, when silicone elastomer was swollen in chloroform or xylene solutions of progesterone (PGT) to prepare suspension-type matrices, drug migration and crystallization off the polymer occurred during matrix drying. The solid drug remaining inside the matrix after completion of drying consisted of a mixture of polymorphs, which caused a high instability of the system (Carelli et al., 1989).

Considering that little information on the release of highly hydrophobic drugs from cr-PEO is available as yet, we have synthesized polymers of different crosslinking degrees and investigated their potential to be reproducibily loaded with PGT fractions exceeding the drug solubility in polymer, and to release the drug at controlled rates.

Materials and Methods

Materials

The following commercially available materials were used as received: progesterone (PGT) (Merck, Darmstadt, Germany), polyethylene glycols (PEG) 4000, 6000 and 8000 (Fluka Chemie AG, Buchs, Switzerland), 2-ethyl-2-hydroxymethylpropane-1,3-diol and hexamethylene diisocyanate (HMDIC) (Janssen, Beerse, Belgium).

Tolylene-2,4-diisocyanate (TDIC) (Janssen, Beerse, Belgium) was purified by distillation under reduced pressure before use.

Determination of average molecular weight of PEG

The hydroxyl numbers of PEG 4000 and PEG 8000 were determined according to the Italian Pharmacopoeia (FUI IX Edn). The number molecular weights of PEG 4000 and PEG 8000, as calculated from the corresponding hydroxyl numbers, were 4230 and 9400, respectively.

Synthesis of crosslinked poly(ethylene oxides) (cr-PEO)

A reported crosslinking reaction for PEG was used (Heiss, 1960; Axelrood et al., 1961). A mixture of polymer and branching agent in the proportion wanted was melted and agitated under vacuum at 100°C for 2 h, after which the temperature was lowered to 75°C and the desired proportion of crosslinker (either HMDIC or TDIC) was added while mixing. With PEG 4000 as the polymer and TDIC as the crosslinker the reaction was too rapid, so in this case TDIC was poisoned by adding one drop of benzoyl chloride to every 10 g of diisocyanate. The reaction mixture was stirred under vacuum for as long as allowed by its

TABLE 1

Data on crosslinking of PEG

Code of cr-PEO	Initial PEG	I [a]	EC (%) [b]	Yield of reaction (%)	N_{anal} (%) [c]	$N_{calc(A)}$ (%) [d]	$N_{calc(B)}$ (%) [e]	γ_0 (SD) [f]	SD/γ_0
P4000-C	PEG 4000	0.50	0	50.2	1.43	1.06	1.48	6.87 (0.63)	0.09
P4000-CC	PEG 4000	0.50	65	90.0	1.84	1.06	1.11	3.34 (0.04)	0.01
P8000-C	PEG 8000	0.68	0	50.0	0.85	0.57	0.85	18.1 (1.15)	0.06
P8000-CC	PEG 8000	0.68	65	87.7	1.05	0.57	0.60	5.18 (0.20)	0.04

[a] Molar ratio of branching agent to PEG.

[b] Excess of crosslinker (TDIC) with respect to the stoichiometric ratio to the hydroxyl functions of PEG and branching agent.

[c] Nitrogen content in the network resulting from the elemental analysis.

[d] Nitrogen content in the network as calculated according to hypothesis A (see text).

[e] Nitrogen content in the network as calculated according to hypothesis B (see text).

[f] Swelling degree in water at 30°C and standard deviation (γ_0 = ratio of fully swollen to dry weights) ($n \geqq 5$).

TABLE 2

Enthalphy of fusion, H_f, peak temperature, T_p, and degree of crystallinity, X, for cr-PEO and parent PEG

Polymer	H_f (J/g)	T_p (°C)	X
P4000-CC	82.37	47.3	0.35
P4000-C	104.8	50.6	0.45
P8000-CC	115.7	54.3	0.50
P8000-C	122.4	58.3	0.53
PEG 4000	200.1	60.0	0.86
PEG 8000	204.1	64.0	0.88

increasing viscosity, then the temperature was raised again and kept at 100°C for 24 h to complete the reaction. The crosslinked mass was removed from the reaction vessel with the aid of ethanol or chloroform-methanol (1:9), with PEG 4000 or PEG 8000, respectively, as the initial polymer, then it was washed repeatedly with the solvent to remove soluble materials, and finally dried and stored in a dessiccator. The more interesting products were obtained with TDIC as the crosslinker. Their relevant characteristics are listed in Table 1, where the codes of products are also reported, and in Table 2.

Swelling degree of cr-PEO

The swelling degree, γ, of cr-PEO in water was expressed as the ratio of swollen to dry weights. The swollen weight was measured in a weighing bottle after drying the sample surface by gentle blotting. The equilibrium swelling degree, γ_0, was the mean of at least five determinations carried out with samples cut at random from the polymer mass and equilibrated in water at 30°C.

Drug incorporation into cr-PEO

Parallelepiped-shaped pieces of P4000-CC, P8000-CC and P8000-C of known weights (30–40 mg) were used for these experiments. P4000-C was omitted as it showed a γ_0 value close to and more variable than that for P8000-CC.

The P4000-CC and P8000-CC samples were each equilibrated with 5 ml of drug solutions in chloroform or ethanol of various concentrations, at 30°C. The P8000-C samples were allowed to completely absorb 0.5 ml of drug solutions in chloroform. The solvent was evaporated from the swollen gels in a controlled air circulation drier at 37°C, then the drying was completed under vacuum at 40°C. The drug content in matrices was determined by extracting the matrices with a known volume of an appropriate solvent and analyzing the solutions spectrophotometrically. The matrices based on P4000-CC or P8000-CC were extracted with ethanol and the solutions analyzed at 240 nm. The matrices based on P8000-C were extracted with chloroform-methanol (1:9), the extracts evaporated to dryness, the residues dissolved in a known volume of ethanol, and the solutions analyzed for the drug. With some systems drug crystallization outside the polymer was observed during drying. In these cases the crystals were completely removed from the matrix surface before further processing.

Determination of drug solubility in dry and water-swollen cr-PEO

Dry polymers The property of petroleum ether of satisfactorily dissolving PGT while not interacting with the cr-PEO was exploited for these determinations. Polymer samples were immersed in a saturated solution of PGT in petroleum ether containing an excess of drug, at ambient temperature. Weekly, a sample was withdrawn, rinsed with clear saturated solution, blotted dry, vacuum dried, weighed and analyzed for its drug content by the procedure described above. Each solubility value reported in Table 4 is the mean of three samples at thermodynamic equilibrium.

Swollen polymers The procedure was the same as that described above for the dry polymers, except that water was used as the solvent, 37°C was the equilibrium temperature, and the withdrawn samples were weighed in the swollen state, with the aid of a weighing bottle.

Determination of the kinetics of PGT release from matrices based on cr-PEO

The polymers P4000-CC and P8000-CC were used for these experiments. Cylinder matrices of controlled size were prepared by the following procedure. Cylinders were cut from a fully water-swollen polymer layer by means of a cork-

borer of 0.5 cm diameter. The cylinders were rapidly trimmed to a length of 0.6 cm with a sharp blade. The mean dry weights of cylinders were 40.0 and 22.7 mg for P4000-CC and P8000-CC, respectively. The fully water-swollen P8000-C was jelly-like, therefore this hydrogel could not be used for preparing matrices of a rigidly controlled geometry. The cylinders were loaded with PGT by the soaking technique described before, using ethanol as the solvent.

For the measurement of the release kinetics the matrix under study was immersed, at time $t = 0$, in 1 l of distilled water contained in a conical flask thermostated at 37°C, whilst stirring with a blade propeller. This was mounted in an eccentric position, in order to prevent vortex formation, and operated by a synchronous motor at 300 rpm or, in one case to be specified, at 120 rpm. At appropriate time intervals samples of elution medium were withdrawn and analyzed spectrophotometrically for PGT at 249 nm. The drug concentration in the elution medium was never allowed to exceed 10% of solubility. No interference with the determinations was shown by runs with the drug-free cylinders. At the end of the release experiment the swollen matrix weight, diameter and height were measured, then the matrix was extracted with ethanol to determine the residual drug still present in the matrix.

Preparation of medicated granules of P8000-C

Fully water-swollen P8000-C was subdivided into particles by thrusting twice through a 425 μm wire mesh. The swollen hydrogel particles showed increasing adhesive properties on drying, and could not be cleared of water by the usual drying techniques without their sticking together. This difficulty was overcome by shifting the water from the granules using absolute ethanol, then adding the granules to an excess of petroleum ether, and finally drying under a stream of warm air. The granules were sieve-sized to 105–250 μm, then they were loaded with 35% of PGT by impregnating with a drug solution in chloroform of appropriate volume and concentration. The granules were then spread on a glass plate and partially dried in an air circulation drier, after which they were collected from the plate and vacuum dried. Finally, they were sieve-sized again to 105–250 μm.

Preparation of medicated granules of PEG

A dispersion of 35% PGT in PEG 6000 or PEG 8000 was prepared by the known fusion method. The drug-PEG mixture was brought to 135°C and stirred until a clear liquid resulted. Then the temperature was lowered at a rate of 1°C/min under continuous stirring, until the mixture finally solidified. The solid dispersion was ground in a mortar and sieve-sized to 105–250 μm.

Measurement of the kinetics of PGT dissolution from granules based on PEG 6000, PEG 8000, or P8000-C

The apparatus was the same as that used for the release experiments with the cylinder matrices. At time $t = 0$, a known weight of granules (around 5 mg) was added to 1 l of distilled water thermostated at 37°C and stirred at 300 rpm. At 1 h intervals, five samples of 10 ml each were taken from different zones of the stirred suspension, collected, filtered through a polytetrafluoroethylene filter (mean pore size, 0.45 μm), and the clear solution was analyzed for PGT at 249 nm. The polymers did not interfere with the determinations.

Differential scanning calorimetry (DSC) measurements

A Mettler TA 3000 Thermal Analysis System, consisting of a TC-10 TA processor, DSC 20 measuring cell and printer-plotter, was used. Polymer samples of 5–10 mg were scanned in sealed aluminum pans at a heating rate of 10 K/min. The measuring cell worked in a freezer.

Results and Discussion

Synthesis and characterization of cr-PEO

The conditions of the crosslinking reaction, such as the type of crosslinking agent (HMDIC or TDIC) and its molar fraction in the reaction mixture, and the molar ratio, I, between branching agent and PEG, were adjusted to yield at

least 50% w/w, based on the total weight of reactants, of crosslinked polymer having values of swelling degree in water, γ_0, greater than 3. The characteristics of the more interesting cr-PEO are listed in Table 1. They were all obtained using the more reactive TDIC as the crosslinking agent.

As can be observed, in those cases where the isocyanate functions of the crosslinker were in a stoichiometric ratio to the hydroxyl functions of the PEG and branching agent, lower yields of the reaction, lower crosslinking degrees of the network, indicated by higher γ_0 values, and greater variabilities of γ_0 through the polymer bulk, expressed by the SD/γ_0 ratio, resulted as compared to the corresponding cases where a substantial excess of TDIC was used in the reaction. In Table 1 the analytical values for the nitrogen content in the networks are compared with values calculated according to the hypothesis A, which assumes a stoichiometric addition of PEG, branching agent and TDIC to form urethane groups, and those calculated according to hypothesis B, based on the following assumptions:

(1) Only a portion of the initial PEG takes part in the insoluble polymer network;

(2) The branching agent is completely linked to the insoluble polymer network;

(3) The fraction of crosslinking agent that links the insoluble polymer network has reacted stoichiometrically with the hydroxyl functions to form urethane groups.

According to hypothesis B, the soluble material still present after completion of the reaction (weight = W_s) must be composed of the excess crosslinker (weight = C_{ex}), the uncrosslinked PEG (weight = P_{nc}) and an equimolar amount of crosslinker which has failed to crosslink such a PEG (weight = C_{nc}). Then:

$$W_s = P_{nc} + C_{nc} + C_{ex} \quad (1)$$

$$C_{nc} = M_c P_{nc}/M_p \quad (2)$$

where M_c and M_p represent the molecular weight of the crosslinker and the mean number molecular weight of the PEG, respectively. Once C_{ex} has been established and W_s has been calculated from the yield of the reaction, C_{nc} and P_{nc} can be calculated from Eqns 1 and 2, which in turn allows the calculation of the network composition and its nitrogen content according to hypothesis B.

As can be seen in Table 1, in those cases where an excess of crosslinker was used in the reaction the nitrogen level resulting from the analysis is substantially higher than either value calculated following hypothesis A or B. Since the latter calculated value is the maximum possible, if a stoichiometric addition to the hydroxyl functions is assumed to be the only reaction for the isocyanate groups, then it is inferred that the excess of crosslinker increases the nitrogen content in the network, and therefore, the crosslinking degree, possibly by forming allophanate groups, and/or by trimerization of terminal isocyanate functions (Heiss et al., 1959). The nitrogen content determined experimentally for the networks obtained with the stoichiometric amounts of crosslinker is seen in Table 1 to exceed the value calculated according to hypothesis A, and to correspond to the value calculated under hypothesis B. Compliance with the latter hypothesis implies that in these networks the actual molar ratio, I, is higher than its nominal value, and that the crosslinking has involved the formation of only urethane groups.

The crystallinity degree of cr-PEO and the parent PEG was calculated from the ratio of the enthalpy of fusion, as determined by DSC, to the reference value of 10 224 J/mol (232 J/g) (100% crystallinity) (Gander et al., 1988). In accord with previous knowledge, the crystallinity values for the present polymers, listed in Table 2, are directly dependent on the molecular weight of the initial PEG and inversely dependent on the crosslinking degree of polymer.

Loading of PGT in cr-PEO

Chloroform and ethanol were tested as solvents for the soaking solutions. The values of drug concentration in the external solution, C_e, and corresponding drug load in dry matrix, L, showed upper limits beyond which erratic expulsion of substantial fractions of crystalline drug from the matrix occurred on matrix drying,

whereby loading was non-reproducible. Such limits are shown in Table 3. The L values for the two solvents are seen to be rather similar, despite a much higher swelling of the polymers in chloroform than in ethanol. This is indicative of a higher gel-solution distribution coefficient for the drug, with ethanol as the solvent. From a practical standpoint ethanol is a better choice for P4000-CC and P8000-CC, since the matrices loaded by chloroform solutions showed some polymer cracking, due to sharp swelling gradients developing in the matrix during drying. On the other hand, no polymer cracking resulted from the drying of P8000-C matrices swollen by chloroform solutions, probably because of the greater flexibility of the PEO chains with this less densely crosslinked polymer. Such chain flexibility also limited drug expulsion from the matrix and allowed advantage to be taken of the exceedingly high swelling of this polymer in chloroform to load it with comparatively high drug fractions.

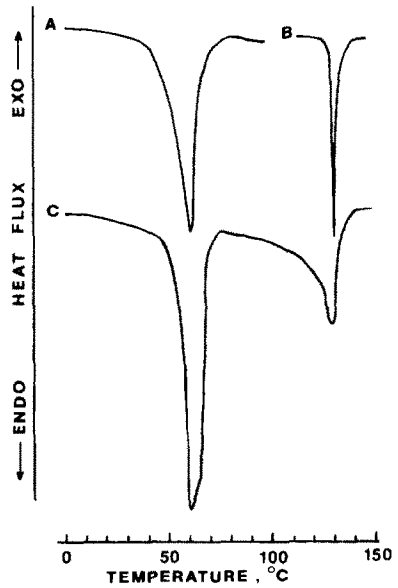

Fig. 1. DSC traces for P8000-C (A), PGT (B), and a matrix containing 39.5% PGT in P8000-C (C).

Information on the physical state of PGT in the matrices was sought by DSC. In Fig. 1, comparison between a representative DSC trace for a P8000-C matrix containing 39.5% PGT and those for the neat P8000-C and PGT indicates the presence in the matrix of the stable morph of PGT. The peak for the fusion of the neat polymer crystallites appears unaltered in the matrix. Also virtually unaltered is the enthalpy of fusion of crystallites per unit polymer mass (122.4 J/g for the neat polymer vs 121.6 J/g for the matrix). On the other hand, the peak for the fusion of PGT in the matrix is considerably broader than that for the pure drug. These observations point to the absence of significant interactions in the matrix between PGT and the polymer crystallites, and indicate the existence of interactions between the amorphous polymer chains and the drug, such as with monotectic binary systems (Craig and Newton, 1991). The DSC traces for P4000-CC and P8000-CC matrices containing drug loads close to the upper limits of reproducible loading (seen in Table 3) and the respective enthalpies of fusion of polymer crystallites were virtually identical to those for the respective neat polymers (not reported). No transitions attributable to fusion of solid PGT appeared, although the drug loads were far higher than the solubility of the stable morph of PGT in the respective polymers, found in Table 4. The analysis again indicates a monotectic nature of systems, yet it is unable to assess the actual physical state of PGT in matrix. Indeed, the lack of signals

TABLE 3

Uppermost values of drug concentration in external solution, C_e, and corresponding drug load in dry matrix, L, for reproducible loading of PGT in cr-PEO

Solvent	P4000-CC		P8000-CC		P8000-C	
	C_e (mg/ml)	L (SD) (%) [a]	C_e (mg/ml)	L (SD) (%) [a]	C_e (mg/ml)	L (SD) (%) [a]
Chloroform	50	10.0 (0.5)	20	10.5 (0.6)	–	39.1 (1.5)
Ethanol	50	9.0 (0.0)	25	8.3 (0.4)	–	–

[a] Mean and standard deviation of five samples.

TABLE 4

Solubility of PGT in dry and water-swollen cr-PEO

Polymer	Temperature (°C)	Solubility (%)
P4000-CC (dry)	22	0.612
P8000-CC (dry)	22	0.954
P4000-CC (swollen)	37	0.088
P8000-CC (swollen)	37	0.058

for the fusion of PGT may be due either to an amorphous state of the drug or to a progressive, complete dissolution of drug crystals in the polymer over the heating time.

Release of PGT from cr-PEO matrices

The polymers P4000-CC and P8000-CC were taken as representative of cr-PEO for studies of PGT release from monolithic matrices based on these materials. Fig. 2 shows data on PGT release from cylinder matrices. These systems appear from the swelling data of Fig. 3 to attain equilibrium swelling in 5 h, a time seen in the diagrams of Fig. 2 to correspond to the release of only around 10% of the initial drug dose. Moreover, it is reasonable to consider that such a dose fraction was released from the outer matrix layers, which were fully swollen in much less than 5 h. Then it can be assumed that the release kinetics are not influenced by the swelling kinetics, and that the release occurs at all times from the fully swollen hydrogel. In this respect, the present systems employing the poorly water-soluble PGT are diametrically opposed to cr-PEO systems employing water-soluble drugs. Indeed, with the latter systems the time scales of drug release and matrix swelling are comparable and, therefore, the release kinetics are profoundly influenced by phenomena related to progressive polymer hydration (Graham et al., 1985).

The uptake of water from the elution medium briefly turned the opaque matrices into clear hydrogels, which allowed the precipitation of PGT inside the matrix, caused by the non-solvent ef-

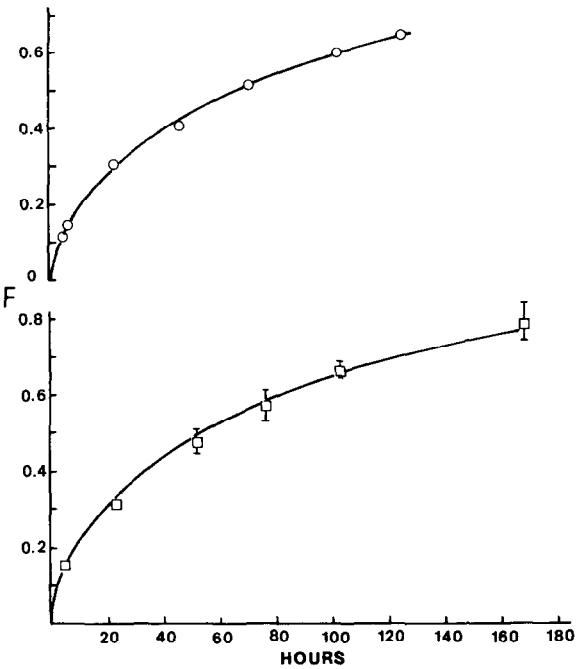

Fig. 2. Kinetics of PGT release from cylinder matrices based on P4000-CC (○) or P8000-CC (□). F: fractional amount of drug released. Each data point represents the mean of three values. Vertical bars represent the variation range. Where not reported, they fall within the drawn symbol. The full lines were calculated by fitting Eqn 3 to the experimental points using the values of R, H, C_S and C_0 found in Table 5.

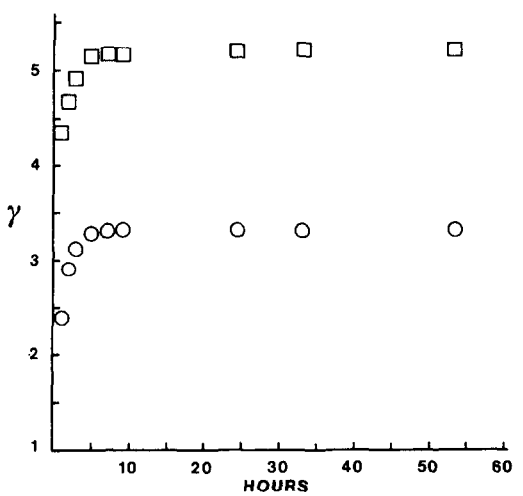

Fig. 3. Swelling kinetics in water at 37°C for P4000-CC (○) and P8000-CC (□) cylinders. γ: ratio of swollen to dry weights. Each point is the mean of two samples.

fect of water, to be seen. In principle, such a solid could be composed of several PGT morphs, which might lead to poor reproducibility of release. The physical nature of the suspended solids could not be assessed but, in fact, the release data appear from Fig. 2 to be fairly reproducible. Since the effect of diffusion layers of the elution medium adjacent to the matrix surface was of minor importance, as indicated by the release data being virtually unaffected by a change in rotational speed of the stirrer from 300 to 120 rpm, the release model analyzed by Cardinal (1984) is likely to apply to the present systems. The model implies that release is controlled by drug diffusion in the fully swollen hydrogel. This in turn involves the formation of a receding front separating an inner matrix region which is not yet influenced by release from an outer zone fully devoid of solid drug. Thanks to the clarity of the hydrogel, such a situation could in fact be verified visually during the course of the release experiments. The model is described by the following equations:

$$\frac{1-F}{1-b\sqrt{2KT}}\ln\frac{1-F}{1-b\sqrt{2Kt}}-\frac{1-F}{1-b\sqrt{2Kt}}+1=Kt \tag{3}$$

$$K=\frac{4DC_s}{C_0R^2} \tag{4}$$

$$b=\frac{R}{H}$$

where F is the dose fraction released at time t, R represents the radius of the cylinder matrix, H is the height of the cylinder matrix, D denotes the diffusion coefficient of the drug in the hydrogel, C_s is the solubility of the drug in the hydrogel and C_0 represents the initial concentration of the drug in the fully swollen hydrogel.

The release profiles calculated by fitting Eqn 3 to the experimental data are represented in Fig. 2 by full lines, whereas the experimental values of R, H, C_s and C_0 used for the computation and the values calculated for D are collected in Table 5. It should be noted that such D values were calculated using the C_s value determined for the stable morph of PGT, which is the minimum, not the only possible value of PGT solubility in the present hydrogels. The geometric parameters, R and H, were virtually constant throughout release since the gel is supposed to be fully swollen from the start and the matrix shrinking consequent to drug release is expected to be negligible, given the comparatively low C_0 values. As can be seen, the fitting is satisfactory, which supports the adherence of the experimental system to the theoretical model.

TABLE 5

Fitting of Eqn. 3 to data in Fig. 2 on PGT release from cylinder matrices based on P4000-CC or P8000-CC [a]

	P4000-CC	P8000-CC
Values used for the fitting		
R (cm)	0.251 ± 0.000	0.250 ± 0.001
H (cm)	0.612 ± 0.003	0.592 ± 0.014
C_s (%)	0.088	0.058
C_0 (%)	2.92 ± 0.01	1.56 ± 0.04
Values calculated via the fitting		
K ($\times 10^7$) (s^{-1})	3.90 ± 0.10	5.11 ± 0.97
D ($\times 10^7$) ($cm^2\ s^{-1}$)	2.01 ± 0.06	2.14 ± 0.33

[a] Three experiments were run with each matrix type. The values in the table are the means and standard deviations of values used for or calculated via fitting procedures applied to each run.

The polymer weight fractions in the fully swollen hydrogels P4000-CC and P8000-CC were 0.30 and 0.21, respectively. According to the available literature information about drug diffusion in hydrogels, when diffusion occurs in the aqueous phase and is hampered by the polymer, such a difference in polymer fraction would result in a significantly higher apparent diffusion coefficient for the less concentrated hydrogel (see, e.g., Davis, 1974; Flynn et al., 1974; Zentner et al., 1978). For instance, the D values calculated for the fully swollen P4000-CC and P8000-CC according to the equation of Davis (1974), taking 7×10^{-6} $cm^2\ s^{-1}$ as the value for the diffusivity of PGT in water (Ho et al., 1976), are 1.55×10^{-6} $cm^2\ s^{-1}$ and 2.43×10^{-6} $cm^2\ s^{-1}$, respectively. Instead, the D values for the two hydrogels re-

sulting from the present data are seen in Table 5 to be around one order of magnitude smaller than those above and statistically not different from each other. Such discrepancies may mean that drug release from the present systems occurs through dissolution and diffusion in the polymer rather than in the aqueous pores of the gel, and that the diffusivity in the polymer phase is greater for P8000-CC than for P4000-CC, perhaps due to more chain mobility for the former.

An evaluation of the possibility of the release rate being modulated through the crosslinking degree of the cr-PEO may be anticipated on the basis of the expected effects of the crosslinking-dependent factors on the ratio K in Eqn 3, as calculated for matrices having same dry load, L, and dry radius, R_d. The expression of K as given by Eqn 4 can be modified into the following:

$$K = \frac{4DC_s\gamma_w}{LR_d^2\gamma_v^{2/3}} \qquad (5)$$

where γ_w and γ_v represent the ratios of fully swollen to dry matrix weights and volumes, respectively.

Since L and R_d are fixed, the percent difference in K value between matrices based on P4000-CC and P8000-CC can be computed on the basis of Eqn 5, using the values of D and C_s found in Table 5 and taking the relevant γ_0 values in Table 1 as sufficiently approximate estimates of both γ_w and γ_v. Thus, the K value for the more densely crosslinked P4000-CC is found to exceed that for the less densely crosslinked P8000-CC by just around 24%. This result shows little promise of a suitable means of modulating the rate of release of PGT by the crosslinking degree of the cr-PEO.

Evaluation of P8000-C as a dissolution promoter for PGT

As pointed out in Materials and Methods, P8000-C could not be used to prepare matrices of controlled geometry. Although the present work was focused on controlled release, the ability shown by this material to be loaded reproducibly

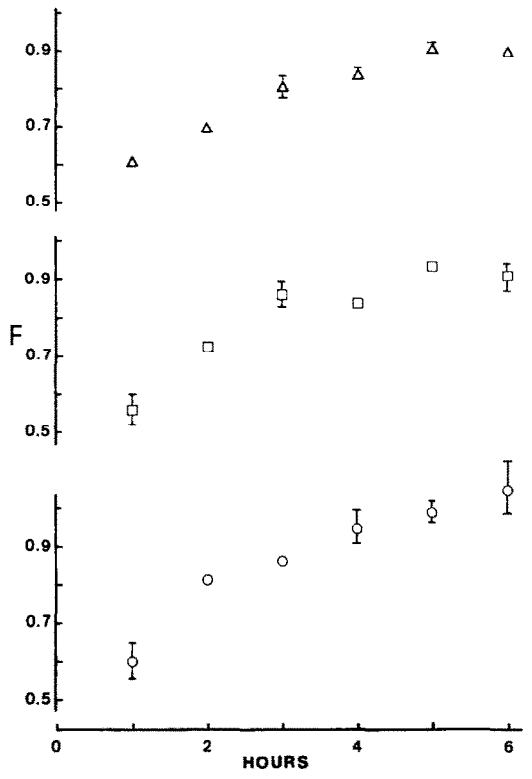

Fig. 4. Comparison of data on PGT dissolution (F: fractional amount dissolved) from granules in the 106–250 μm range based on P8000-C (○), PEO 8000 (□) and PEO 6000 (△) containing initial drug loads of 35, 36 and 37%, respectively. Each data point is the mean of three values. Vertical bars represent the range.

with high percentages of PGT has prompted us to test its potential as a drug dissolution promoter, as compared to uncrosslinked PEG. The mechanism of PGT dissolution from P8000-C-based granules is believed to be similar to that discussed earlier for the cr-PEO-based macromatrices, whereas with the uncrosslinked PEG the co-dissolution of drug and carrier is known to be an important process. It is also known that the co-dissolution mechanism is less effective at high drug fractions in the dispersion, due to the dissolving surface rapidly being depleted of hydrophilic carrier. In fact, despite the differences in dissolution mechanism, there appear to be no appreciable differences among the data on PGT

dissolution from granules based on P8000-C, PEG 6000 or PEG 8000 shown in Fig. 4. Therefore, P8000-C is expected to offer no particular advantages over uncrosslinked PEG in terms of increased dissolution rate, although the far higher resistance to fracture of the former in the dry state and its insolubility in physiological fluids are worth consideration.

Conclusions

The drug amounts that can be loaded reproducibly in cr-PEO by the impregnation technique have been shown to be limited by the expulsion of crystalline drug from the polymer during drying, depending on the degree of polymer crosslinking. Thus, P4000-CC and P8000-CC, whose crosslinking degrees were adequate to confer the required mechanical stability on the fully swollen matrix, could be loaded with no more than 8–10% drug, whereas the substantially less densely crosslinked P8000-C could be loaded with up to 39% drug, although it showed poor mechanical properties in the fully swollen state.

The PGT loaded in P8000-C has been shown by DSC to be in its stable crystalline form, whereas the drug loads in P4000-CC and P8000-CC were too low for the thermal analysis to yield clear indications of their physical state. The thermal behavior of all of the present PGT-cr-PEO systems was indicative of drug-polymer interactions typical of monotectic dispersions.

The release of PGT from cylindrical matrices based on P4000-CC or P8000-CC is not influenced by the matrix swelling kinetics, and is consistent with a model assuming that drug diffusion in the polymer phase of the fully swollen hydrogel is the rate-controlling factor. The analysis of the model has indicated a limited possibility of the release rate being modulated by the polymer crosslinking degree. Such a rate is nevertheless expected to be readily modulated by varying the matrix surface-volume ratio.

Finally, P8000-C has been shown to match uncrosslinked PEG as to the ability to enhance the dissolution rate of high PGT loads.

Acknowledgement

This research was funded by Ministero dell'Università e della Ricerca Scientifica e Tecnologica.

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