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CROSSLINKED POLOXAMERS AS A VERSATILE MONOLITHIC DRUG DELIVERY SYSTEM

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INTRODUCTION

There is growing interest in the development of homogeneous monolithic drug release systems for various routes of administration. One very attractive type of such dosage forms is based on hydrophilic water-swellable polymers which generally exhibit high biocompatibility. On contact with an aqueous liquid (dissolution medium or gastrointestinal fluid) the polymer swells. Liquid penetrates into the system and drug is released by counter-current diffusion. Depending on the physical characteristics of the polymer, different thermodynamic transitions such as glass-to-rubber transition of the amorphous zones or melting out of crystallites may occur during liquid penetration. These thermodynamic reactions might be responsible for the drug release kinetics not showing square-root-of-time dependance[1-5].

Other interesting aspects for the development of such matrix systems are that their preparation requires no special

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equipment and that any sample size and shape, in particular special geometries with pseudo-zero order release, can easily be obtained. In recent years, considerable efforts have been made in studying swelling-controlled drug release from crosslinked PHEMA and other related polymers.

In this work, we studied the feasibility of crosslinked copolymers of ethylene oxide and propylene oxide (Poloxamers NF) from which the drug release mechanism is not yet well understood. We were particularly interested in microshaped matrices as drug delivery system.

MATERIALS AND METHODS

Copolymers with variable proportions of ethylene oxide and propylene oxide (Pluronic^{R}, BASF Wyandotte) and poly-(ethylene oxide) (Fluka), were used as polyetherdiols. Some characteristics of these materials are presented in table 1.

Crosslinking was achieved in the presence of the trifunctional branching agent 2-ethyl-2-hydroxymethylpropane-1,3-diol (Fluka) and the crosslinking agents hexamethylene diisocyanate (Merck) and toluene diisocyanate (Desmodur T 80, Bayer) by the so called "one-shot technique". Polymer disks of about 3 mm thickness were obtained by pouring the warm liquid reaction mixture into aluminium molds 10 cm in diameter. Reaction and curing generally took place at 80-90° C for 24 hours.

Two drugs of different water solubilities, namely the purine base proxyphylline (PROXY) and the flavonoid derivative methylcatechine (METCAT), were used for the release experi-

Table 1

MOLECULAR WEIGHT AND COMPOSITION OF THE POLYETHERDIOLS USED

Polyetherdiol	$\bar{M}_n$	Ethylene oxide : Propylene oxide %(W/W)	Abreviation
Poly(ethylene oxide)	6300[a]	100 : 0	PEO 6000
Pluronic F 38	4500[a]	80 : 20	PEO-PO 82
Pluronic F 77	6600[b]	70 : 30	PEO-PO 73
Pluronic P 85	5800[a]	50 : 50	PEO-PO 55
Pluronic L 122	6300[a]	20 : 80	PEO-PO 28

a) Number average molecular weight determined from hydroxyl number

b) Value given by the manufacturer

ments. The polymer disks were loaded with about 9% of drug by soaking in benzylalcohol solutions at 37° C. Micromatrices in the range of 400 to 630 µm were obtained by grinding and sieving of the loaded polymer samples.

The appropriate drug concentration for impregnation was calculated according to equation (1):

$$c_{sol} = \frac{c_m}{(q_m - 1)\ (1 - c_m)} \qquad (1)$$

where c_{sol} is the weight fraction of the drug in the solution, c_m is the drug fraction in the dried polymer and q_m is the equilibrium weight swelling degree. Values of q_m were determined on slabs in water and benzylalcohol at 37° C and were calculated from:

$$q_m = W_{sw}/W_d \qquad (2)$$

W_{sw} and W_d being the weights of the sample in the swollen and in the dry state, respectively.

Drug release experiments were performed in a pH 6.8 phosphate buffer (Ph.Eur.) at 37° C under sink conditions. A flow cell dissolution apparatus (Dissotest, Sotax) with a laminar flow rate of 20 ml/min was used. Cumulative release curves were obtained using an automatic flow-through UV spectrophotometer (Beckman, model 35-7).

RESULTS AND DISCUSSION

Preparation of the micromatrices

The extent of crosslinking was defined by an interlinking degree, I, which is the molar ratio of branching agent to polymer. The crosslinking agent is added at the stoichiometric amount necessary to react with the hydroxyl groups of the polymer and the branching agent. In the case where only the two end-groups of the polymer chains react, the interlinking degree seems to be more appropriate than the ordinarily used crosslinking degree since tridimensional network formation can only be achieved by means of a multifunctional end-group branching of the polymer chains. In this study an I value of 4 was adopted.

In the case of the poloxamers containing 50% or more of propylene oxide groups the addition of an aromatic diisocyanate is required to get a solid product. Aromatic diisocyanates form more rigid "polyurethane" networks due to their higher cohesive energy in comparison with that of the aliphatic compounds.

The crosslinked colourless samples were either opaque, plastic and hard or transparent and highly elastic, depending on the presence of crystallites in the polymer.

Equilibrium weight swelling degree

The equilibrium sorption values of the crosslinked gels in water and benzyl alcohol are presented in figure 1.

The histogram clearly shows that swelling in the organic solvent is about 1.4 to 4 times higher than in water. These results are in agreement with those of Graham et al.[6] who found that swelling of a similar crosslinked PEO 6000 ($\bar{M}_n$ = 4200) in benzyl alcohol was about 2.2 higher than in water at 37° C.

The introduction of propylene oxide groups within the polymer diminishes the cohesive energy of the polyether chains, resulting in higher swelling degrees. However, with increasing propylene oxide content, this phenomenon is partially counter-balanced by the reduced lyophilic character of the poloxamer towards benzyl alcohol, which is even more pronounced towards water. The PEO-PO 28 sample was entirely crosslinked by the aromatic diisocyanate derivative which may be responsible for its slightly higher benzyl alcohol sorption in comparison with the PEO-PO 55 sample.

The polymer molecular weight can also influence the swelling degree as was shown in an earlier study[7]. Nevertheless, the molecular weights of the polymers used lie in a relatively small range and thus shouldn't greatly affect the sorption equilibrium.

It is interesting to note that solvent uptake varying from 16.7 to 89.4% can be achieved with these polymers. This

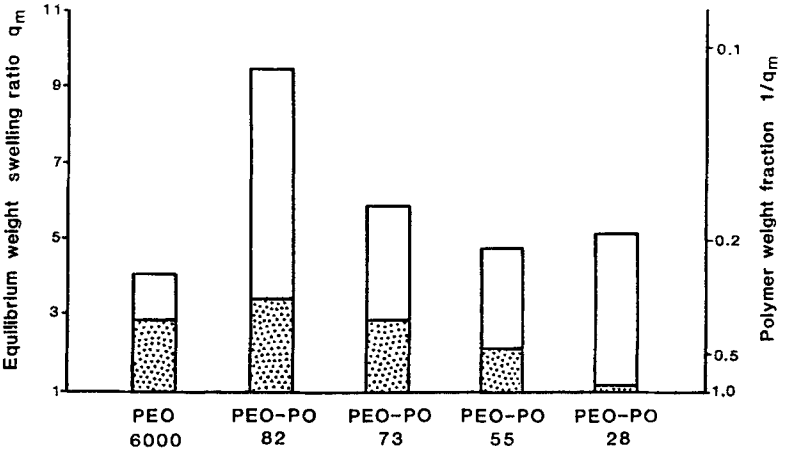


FIGURE 1

EFFECT OF THE ETHYLENE OXIDE: PROPYLENE OXIDE RATIO IN THE POLYMERS ON THEIR EQUILIBRIUM WEIGHT SWELLING DEGREE IN WATER (shaded part) AND IN BENZYL ALCOHOL (whole bar)

wide sorption range is of great importance for drug incorporation. Thus, large amounts of drugs with different solubility characteristics may be loaded into these polymers. Impregnation also could be performed at lower temperatures where swelling in water is even enhanced due to the negative entropy change of the polyethylene oxide groups in water.

Drug loading

Loading of the micromatrices was theoretically calculated by means of equation (1) and the intended value was 10%. Actually, the drug content of the systems varied from 6.6 to 10.8 (table 2).

Table 2

DRUG LOADINGS OF THE MICROMATRICES

Polymer	Drug	Loading %
PEO 6000	Proxyphylline	10.8
PEO-PO 55	"	9.3
PEO-PO 28	"	9.1
PEO 6000	Methylcatechine	10.1
PEO-PO 82	"	6.6
PEO-PO 55	"	9.3
PEO-PO 28	"	9.1

Although swelling behaviour of the polymers may be slightly modified by the drug dissolved in the impregnation solution as compared to pure solvent especially if higher concentrations should be used, equation (1) provides a meaningful tool for calculating drug loading in the dry polymeric samples.

Drug release

The highly water-soluble drug *proxyphylline* (59% at 37° C) is very rapidly released from these micromatrix systems (generally more than 93% in 10 min). Only the polymer with the highest propylene oxyde content, PEO-PO 28, retains this drug a little longer (76% in 10 min). In view of a prolonged drug delivery however, these release profiles lack any real interest and are therefore not more fully analyzed.

On the other hand, the release of the sparingly water soluble drug *methylcatechine* (1,25% at 37° C) is markedly pro-

longed. The effect of the polymer composition on the release of this drug is shown in figure 2.

An increasing fraction of propylene oxide makes the polymer less hydrophilic, producing slower hydration of the sample. Moreover, the slight branching of the polymer may also reduce the apparent diffusion coefficient of the drug in the swollen material.

For analyzing the release kinetics we used a generalized expression of the following diffusion equation for spherical matrices with dissolved drug:

$$M_t/M_\infty = k_1 t^{1/2} - k_2 \cdot t \qquad (3)$$

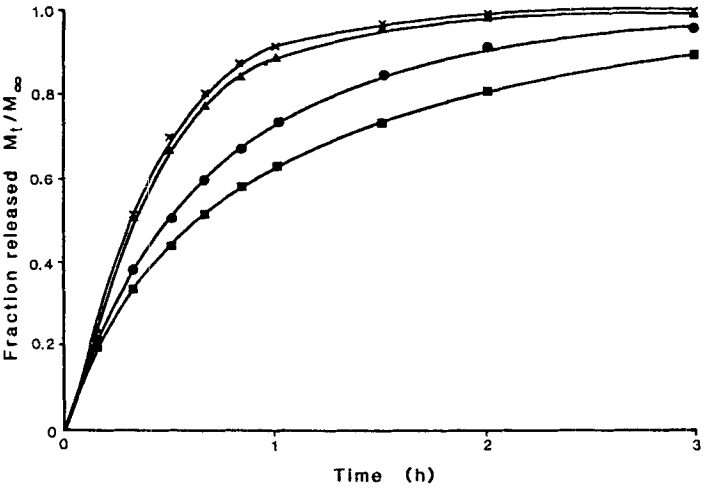
The rate constants k_1 and k_2 were determined for the profiles up to a fractional release, M_t/M_∞, of 0.95.

Moreover, in order to calculate an apparent diffusion coefficient, D_i, the final portion of the profiles ($0.60 \leq M_t/M_\infty < 1.0$) was analysed by means of the appropriate approximative diffusion equation[8] (4):

$$1 - \frac{M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \exp - \frac{\pi^2 \cdot D_i \cdot t}{r^2} \qquad (4)$$

with r being the mean radius of the swollen particles. A constant r value of 250 μm was adopted here.

The kinetic values show that the release of methylcatechine from these crosslinked poloxamer micromatrices follows almost a Fickian process since the terms $k_1 t^{1/2}$ are predominent in equation 3 (table 3).



Key: × PEO 6000 ● PEO-PO 55
▲ PEO-PO 82 ■ PEO-PO 28

FIGURE 2

EFFECT OF THE POLYMER COMPOSITION ON THE RELEASE OF METHYLCATECHINE

TABLE 3

KINETIC PARAMETERS OF METHYLCATECHINE DELIVERY

	RATE CONSTANTS (equation 3)		$D_i \cdot 10^8$ (equation 4)
	$k_1 \cdot 10^3$ ($min^{-1/2}$)	$k_2 \cdot 10^3$ (min^{-1})	($cm^2 \cdot s^{-1}$)
PEO 6000	383.6(±5.9)[a]	21.1(±0.5)[a]	2.99(±0.34)[a]
PEO-PO 82	339.4(±2.7)	18.1(±0.2)	3.78(±0.09)
PEO-PO 55	201.8(±0.6)	7.9(±0.04)	1.68(±0.13)
PEO-PO 28	142.8(±0.8)	4.6(±0.05)	1.06(±0.03)

a) confidence interval with a probability of 0.95.

Crosslinked PEO 6000 and PEO-PO 82 differ only slightly in release kinetics but it is interesting to note that the diffusion coefficient in PEO-PO 82 is significantly higher than in PEO 6000. The lower equilibrium swelling of the latter may explain this phenomenon.

CONCLUSIONS

Crosslinked poloxamers were shown to be an interesting versatile material for monolithic drug delivery systems. Depending on its composition, the polymer is elastic or thermoplastic, which offers multiple possibilities of moulding during or after crosslinking.

Furthermore, these polymers have outstanding swelling properties in aqueous and organic solvents which allow impregnation of drugs with different hydrophilic characters in considerable amounts.

Finally, the release characteristics of two drugs of different water-solubility was found to be highly dependent on the nature of the solute. In general, a higher propylene oxide content in the poloxamer reduced the release rate by means of a smaller apparent diffusion coefficient of the drug in the swollen polymer network. Drug release appeared to be a Fickian process.

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