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Some chemically modified poloxamer hydrogels: controlled release of prostaglandin-E_2 and testosterone

T.K. Law, A.T. Florence and T.L. Whateley

Department of Pharmacy, University of Strathclyde, Glasgow G1 1XW (U.K.)

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Summary

Cross-linked, swelling hydrogels derived from the acryloyl derivatives of poloxamer co-polymeric surfactants have been prepared and their morphology and swelling properties described previously. Using modified pure poloxamer 188 (Pluronic F68) to prepare the hydrogels (the system which gives release rates closest to the desirable time-independent, zero-order kinetics) the release of prostaglandin-E_2 (PGE_2) and testosterone has been studied. PGE_2 release was very closely described by the swelling controlled release model with a value of $n = 0.71$ and a time for 60% release of 670 min (at 37°C). Testosterone release, however, more closely followed Higuchi (or diffusion-controlled) release kinetics with a $t_{60\%}$ value of 56 h, probably reflecting the much lower solubility of testosterone in both water and the swollen, hydrated outer gel matrix.

Introduction

Polymeric hydrogels have attracted much interest as devices for the sustained release of drugs and other bioactive compounds. In non-swelling monolithic devices, release rates of solutes suspended in the matrix decline throughout the dissolution process, as described for example by the Higuchi model. In addition to the pure monolithic systems, devices of other structural features have been suggested and prepared, such as the laminated-matrix system (Paul, 1985), and the multiphase cross-linked poloxamer * systems developed in our laboratory and reported earlier (Law et al., 1984). The heterogeneous phase structure of these hydrogels, revealed in an aqueous environment, was attributed to the colloidal properties of the polymeric surfactants. The varying release profiles of some model compounds are reflected in the morphology of these hydrogels (Law et al., 1986). The increasing release rates from matrices of higher hydrophilicity was interpreted as being due to a higher degree of swelling and hydration within the polymeric matrices. The swelling-controlled release of drugs from hydrophilic polymeric systems and hydrogels have been considered by a number of groups as an approach to achieving a zero-order (time-independent) release rate (Hopfenberg and Hsu, 1978; Korsmeyer and Peppas, 1981; Korsmeyer et al., 1983; Lee, 1985). In such systems, there is a flow of water into the matrix resulting in a swollen outerlayer, and a countercurrent flow of solute through the swollen, hy-

* Poloxamer is the generic name for poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) block co-polymers sold under the trade name 'Pluronic' (BASF, Wyandotte Corporation).

Correspondence: T.L. Whateley, Department of Pharmacy, University of Strathclyde, Glasgow G1 1XW, U.K.

drated layer. If the diffusion of the drug molecule in the hydrated layer is very fast compared to the diffusion from the unswollen region into the swollen region, the rate determining step will be the advancing rate of the swollen region interface, i.e. the rate of water uptake. Release rate data from swelling polymeric hydrogels can generally be treated using Eqn. 1:

$$\frac{M_t}{M_\infty} = kt^n \qquad (1)$$

where M_t/M_∞ is the fraction of drug released at time, t, and k and n are constants and characteristic of the polymeric system. The situation of $n = 1$ corresponds to zero-order release kinetics whilst $n = 0.5$ corresponds to diffusion-controlled (Higuchi) release kinetics.

In this paper the release of prostaglandin-E_2 and testosterone, two drugs of diverse aqueous solubility, from matrices of cross-linked poloxamer swelling hydrogels is described.

Materials and Methods

Prostaglandin-E_2 (PGE_2), mol. wt. 352, was obtained from Vale of Leven Hospital and was marketed by Upjohn Company. [^{3}H]Prostaglandin-E_2 was obtained from Amersham International (U.K.), at a spec. act. of 160 Ci/mmol, and testosterone, mol. wt. 288 from Sigma Chemical Company.

The preparation of the chemically modified polymerisable poloxamer 188 (Pluronic F68), (designated as VF68) and the formation of the cross-linked poloxamer gel, has been described (Law et al., 1984). The conditions for the cross-linking reaction were modified slightly in this study. The modified poloxamer, VF68 (1.0 g), with the initiator for polymerization, azobisisobutyronitrile (AIBN) (0.01 g), were dissolved in ethanol (1.0 ml) in a 2 ml ampoule which was then purged with nitrogen prior to sealing. The cross-linking reaction and gel formation took place at 60°C for 3 h. The gel was then removed from the ampoule, and was treated in a Soxhlet extractor with ethanol for 3 h, and dried in vacuo at room temperature for 24 h. The dry weight of the gel was between 0.90 and 0.95 g.

Incorporation of solutes into the gels

For prostaglandin-E_2 loading the dry gel was shaken at −3.5°C for 72 h in an ethanol–chloroform mixture, 1 : 1 by vol., 20 ml, containing PGE_2 (5 μCi of ^{3}H-labelled material or 5 μCi of the labelled material plus 10 mg of unlabelled PGE_2). The drug loaded gel was dried in vacuo at room temperature for 24 h and was stored at 4°C before use. The absorption of the labelled PGE_2 was up to 90–95% of the available compound in the ethanol-chloroform mixture.

For testosterone loading into the gel, a dry gel was rotated in ethanol (20 ml) containing the drug (0.10 g) at 37°C for 96 h. The drug loaded gel was then dried in vacuo at room temperature for 24 h. The drug loading was calculated at about 2.7% based on the dried weight of the specimen, and 25% based on the available drug in solution. When a same amount of ethanol containing a lower amount of testosterone (0.01 g) was used for a similar drug loading procedure, the drug loading became 0.5% based on the dry specimen weight and 38% of the available drug absorbed into the gel.

Drug release experiments

All in vitro release tests were conducted at 37°C with a phosphate buffer (250 ml) at pH 7.2, containing 3.1 g/l $NaH_2PO_4 \cdot 2H_2O$ and 16.6 g/l $Na_2HPO_4 \cdot 12H_2O$.

Samples 0.5 ml each, were taken at appropriate time intervals for analysis by liquid scintillation counting for the labelled [^{3}H]PGE_2, and each was replaced by equal amounts of the same buffer solution. For testosterone release, the amount released was monitored by the absorbance at λ_{max} = 254 nm in a 10 mm silica cell.

The swelling of the gel was monitored throughout the release test and the gel swelling index used was defined as in the earlier report (Law et al., 1984).

Results and Discussion

As shown previously (Law et al., 1984), the greater the content of the modified hydrophilic poloxamer 188 (Pluronic F68) in mixtures with the

more hydrophobic poloxamer 181 (Pluronic L61), the greater the extent of water uptake and swelling. A non-swelling system, e.g. pure VL61 gel, showed diffusion-controlled (or Higuchi) type kinetics for benzoic acid release i.e. $M_t/M = kt^{0.5}$ (Law et al., 1986). As swelling systems have been shown to give release rate kinetics approaching zero-order (Hopfenberg and Hsu, 1978), a system showing a maximum value of n was desirable. The previously described (Law et al., 1984) range of multiphase hydrogels was extended to the preparation of a gel from pure modified poloxamer 188 (VF 68). This hydrogel showed release kinetics closer to zero-order than any admixtures, with a value of $n = 0.73$, for *p*-hydroxybenzoic acid.

The release profile of [^{3}H]PGE_2 from the initially dry VF68 gel is shown in Fig. 1: essentially identical release rates were observed when using ^{3}H-labelled drug alone and in the presence of unlabelled PGE_2 (10 mg).

Fig. 2 gives the rate of water uptake of the gel throughout a period of time beyond that necessary for the total release of the [^{3}H]PGE_2, which was close to 100% recovery. There were essentially similar swelling rates in the cases of the gels containing [^{3}H]PGE_2 and testosterone. Apparently, the diffusion of the PGE_2 molecules is not at the same rate as that of the inbibition of water into the initially dry gel. There was an initially fast release of the drug molecule from the dry gel, and the swollen network then imposed a slow-down on the diffusion of the drug. The cross-linking density of a 3-dimensional structure has been related to the hindering effect on the release of solute molecule (Al-Saden et al., 1980; Korsmeyer and Pappas, 1981).

Fig. 3 shows the Higuchi plot for the release

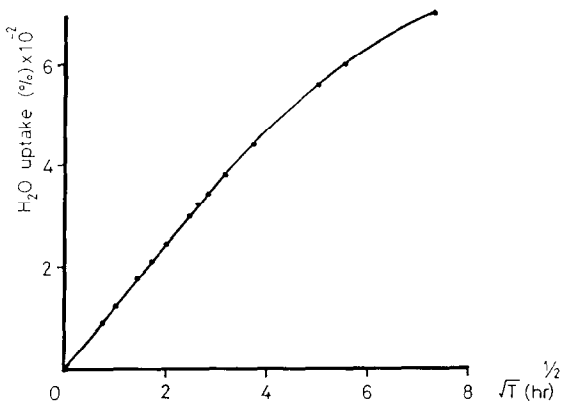

Fig. 2. Water (based on weight of the dry specimen) in VF68 hydrogel containing [^{3}H]PGE_2 or testosterone, in phosphate buffer, pH 7.2.

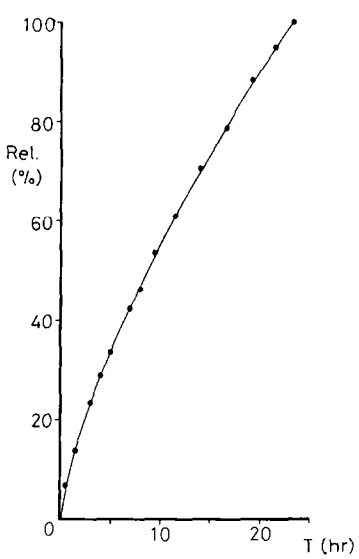

Fig. 1. Release profile of [^{3}H]PGE_2 from pure VF68 hydrogel.

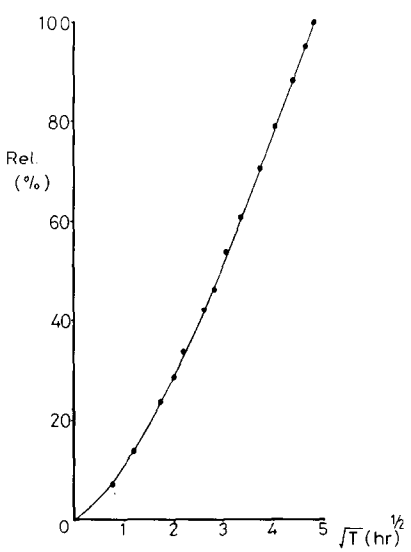

Fig. 3. Higuchi plot for the release of [^{3}H]PGE_2 from pure VF68 hydrogel.

process; this is non-linear with upwards curvature. The calculated value of n for the release of [^{3}H]PGE$_2$ from this gel was 0.71, as shown from the linear plot in Fig. 4. The time for 60% release was 670 min. The degree of swelling was well beyond that of the cross-linked VF 68 network formed as described previously (Law et al., 1984). This can be explained by a reduced average cross-linking density in the network in the present cases, brought about by the dilution effect in the ethanol solution during cross-linking gelation. Thus, this type of pure VF 68 structure could provide a release pattern approaching zero-order, based on these non-toxic, cross-linked poloxamer systems.

Testosterone is only sparingly soluble in water and has a molecular weight (288) lower than that of the PGE$_2$ (352). As shown in Fig. 5, it was released at a much slower rate from the VF68 hydrogels as compared with the [^{3}H]PGE$_2$. The release profile was very close to the Higuchi model as shown by a value of n = 0.5. The time for 60% release was 56 h.

While the VF68 gels could swell to a similar extent and with a similar rate (Fig. 2), irrespective of the drug present, the slow release of testosterone is attributed to its lack of solubility in both water and in the swollen network alike. In a continuously swelling domain, the concentration gradient of the drug within the hydrogel would be reduced rapidly. The initial step for the release process is for the dispersed drug to dissolve into the swollen region: the PGE$_2$ molecule would dissolve more rapidly into the swollen region than the testosterone, which would lead to the faster release of that drug. Fig. 6 shows the white, opaque, central part of a highly swollen VF68 gel containing testosterone. This was a phenomenon not observed in the [^{3}H]PGE$_2$ (with or without unlabelled drug) loaded gels.

Good (1976) derived equations for the diffusion

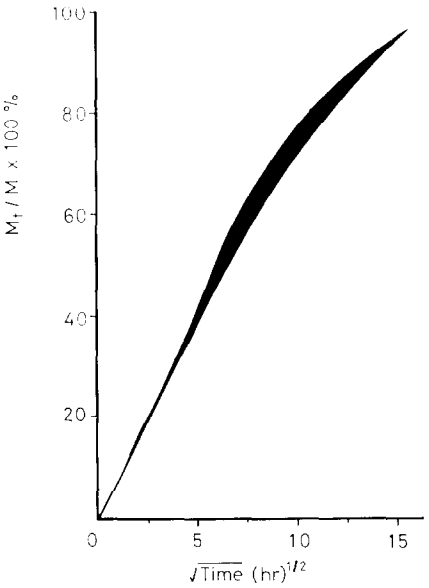

Fig. 5. Higuchi plot (including variance) of the release of testosterone from pure VF68 hydrogel with loading between 0.5 and 2.7% based on weight of dry specimen.

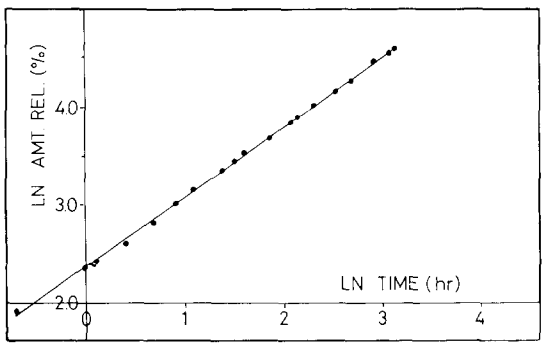

Fig. 4. Release of [^{3}H]PGE$_2$ from pure VF68 hydrogel, based on a swelling-controlled release model.

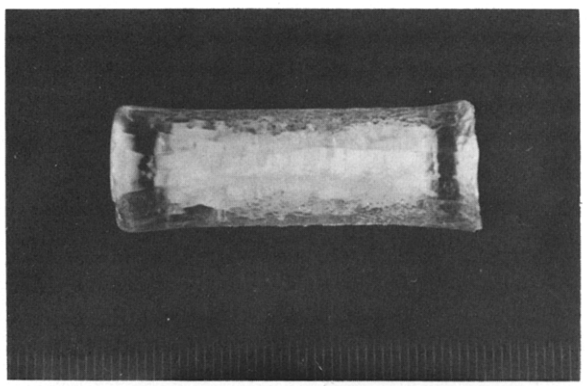

Fig. 6. Appearance of a VF68 hydrogel containing testosterone during the release study. Initial drug content, 2.7%, 48 h from the start of the release, with 58% of drug released.

of drugs from initially dry hydrogels; water solubility and fast diffusion are prerequisites in this model. In a study on constant-rate delivery based on swelling-controlled systems (Hopfenberg and Hsu, 1978), the solute was found to be completely denuded from the swollen layer which results from liquid penetration: the solutes in these cases were highly soluble in the penetration liquid.

Many medicinal and pharmaceutical substances are not highly soluble in water, nor small in size: in these cases, the diffusion of the drug molecule through the swollen region of a hydrogel device, could become a significant rate determining step, as shown in this study. However, a swollen layer rapidly reaching the equilibrium state and creating a constant domain between the drug reservoir and the external media could be designed as a rate regulating component, i.e. through its thickness and diffusion properties.

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