The Release of 5-Fluorouracil from a Swellable Matrix of a Triblock Copolymer of ϵ-Caprolactone and Ethylene Oxide

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Purpose. The purpose of this study was to investigate the influence of hydration characteristics on the *in vitro* release of 5-fluorouracil from a swellable matrix prepared using a novel triblock copolymer of poly(ϵ-caprolactone) and poly(oxyethylene).

Methods. Matrices were prepared by dry compression of mixtures of the drug and copolymer using low compressional forces. Release studies were performed using a custom made rotating basket dissolution apparatus. The positions of the eroding and swelling fronts within the matrices during hydration were monitored using freeze fracture scanning electron microscopy.

Results. Analysis of the release data revealed a predominantly diffusion controlled mechanism. Observations of the swelling characteristics of the copolymer matrices on immersion in Sørensen's buffer at pH 7.4 revealed gel formation and preferential swelling in the radial direction with visible erosion of the matrix after 4h. During hydration, a gradual increase in gel layer thickness was noted prior to the erosion and eventual dissolution of the matrix.

Conclusions. This study demonstrates a means of differentiating the relative importance of the swelling characteristics in determining the release mechanism and subsequent release rate from swellable matrices.

KEY WORDS: swellable matrices; controlled release; hydrophilic matrix; release mechanism.

INTRODUCTION

Drug release from swellable hydrophilic matrices involves the absorption of water, the swelling of the matrix and the diffusion of drug through the swollen gel layer (1). The mechanism of release from such systems has been accounted for in terms of contributions arising from Fickian diffusional release and from Case II relaxational release (2). Fickian release occurs by molecular diffusion of the drug along a chemical potential gradient; Case-II relaxational release is associated with stresses and state-transition in hydrophilic glassy polymers during their swelling. The relative importance of each of these contributions in the overall release behaviour can be estimated by an analysis of the drug release profile from a delivery system using an approach proposed by Peppas and Sahlin (3).

In this paper we have analysed the release behaviour of a swellable matrix prepared by dry compression of a novel triblock copoly(ϵ-caprolactone/oxyethylene/ϵ-caprolactone) with a molecular formula $CL_6\ E_{90}\ CL_6$ (where CL represents a ϵ-caprolactone unit and E an oxyethylene unit). The oxyethylene imparts water solubility to the poly(ϵ-caprolactone) and ensures swelling of the copolymer matrix in an aqueous medium. Poly(ϵ-caprolactone), which is known to be subject to degradation in vivo by hydrolytic chain scission involving the ester linkages, imparts biodegradability and also mechanical strength to the matrix. 5-Fluorouracil was selected as a suitable candidate for release studies in view of recent reports (4) which have shown that a constant infusion of this drug not only produces a higher response rate in the treatment of bowel cancer than repeated bolus dose injection but also can induce responses with cancers normally resistant to the drug. The objective of the study was to investigate the influence of hydration characteristics on the in vitro release of 5-fluorouracil from the swellable copolymer matrices.

MATERIALS AND METHODS

Materials. The triblock copolymer $CL_6\ E_{90}\ CL_6$ was prepared by using polyethylene glycol 4000 [α-hydro-ω-hydroxy poly(oxyethylene), E_{90}] to initiate the polymerisation of ϵ-caprolactone at 180°C in the absence of added catalyst: full details of the synthesis, purification and characterization by ^1H and ^{13}C NMR and by GPC have been described previously (5). The mole percentage of triblock in the sample, as determined by NMR analysis was 94%.

Matrix Preparation. Matrices (mean weight 145 ± 1.5 mg) were prepared by manually mixing the copolymer with 5-fluorouracil and then subjecting the mixture to dry compression at ambient temperature. The compressional characteristics of the copolymer were such that matrices could be produced without granulation or the addition of excipients, using relatively low compressional forces. A modified direct shear apparatus (ELE, Hemel Hempstead) designed to deliver compressional forces of approximately 750 N was used to produce matrices of 0.63 cm diameter and 0.40 cm thickness (aspect ratio of 1.58).

In Vitro *Drug Release.* Release studies were performed using a custom made rotating basket dissolution apparatus. The amount of drug released into 400 ml of de-aerated Sørensen's phosphate buffer pH 7.4 was determined spectrophotometrically at a wavelength of 266 nm, using a Cecil 202 flow-through spectrophotometer. Experiments were performed in triplicate and the data were analysed using a curve fitting programme (SigmaPlot) which uses the Marquardt-Levenberg algorithm to find the coefficients of the independent variables that gave the best fit between the equation and the data.

Swelling Measurements. Drug-free matrices were fixed to the base of a glass vessel using a thin spike, as described by Papadimitriou *et al* (6). 200 ml of de-aerated Sørensen's phosphate buffer pH 7.4 was used as the hydrating medium. Changes in the dimensions of the matrix were measured at ambient temperature by photographing the matrix against a graticule scale.

Freeze-Fracture Electron Microscopy. Drug-free matrices were permitted to hydrate in 200 ml of de-aerated Sørensen's buffer pH 7.4. At predetermined intervals, ma-

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trices were removed from the buffer and immediately frozen at −198°C (liquid nitrogen) in glass vials which provided protection against fragmentation from the vigorous freezing procedure. Once frozen, the matrices were fractured in the vertical plane and the resulting segments were freeze dried over a 24 hour period. The segments were viewed using a Cambridge 360 scanning electron microscope (SEM).

RESULTS AND DISCUSSION

Matrix Swelling

The changes in the dimensions of the copolymer matrices as determined from the swelling studies are plotted as a function of period of contact with Sørensen's buffer in Figure 1. It is apparent that the swelling proceeded in both the axial and radial directions. After approximately 240 minutes exposure to buffer solution, erosion of the matrix was visibly apparent and it is this erosion process which is responsible for the increase in error associated with measurements at this time interval. A preferential swelling in the radial direction was noted from changes in the aspect ratio (diameter/height) from the initial value of 1.58 to 2.11 over a time interval of 240 minutes. The swelling process was quantified in terms of the swelling dimensionality index (d), which is a measure of the degree of inhibition of the swelling in each direction (7). For example, complete unhindered swelling of the matrix in three dimensions is characterized by a value of d = 3, while complete inhibition of swelling in one direction gives d = 2.

Peppas *et al* (7) related d to the volume swelling ratio, Q, as given by the ratio of the volume of the gel (V_{gel}) to that of the dry matrix (V_{dry}),

$$Q^{d/3} = V_{gel}/V_{dry} \quad (1)$$

and to the swelling area as given by the ratio of the surface areas of the gel (A_{gel}) and dry matrix (A_{dry}),

$$Q^{(d-1)/3} = A_{gel}/A_{dry} \quad (2)$$

In our work, a value of d = 2.80 was calculated from the gradient [(d-1)/3] of a plot of ln (A_{gel}/A_{dry}) as a function of ln

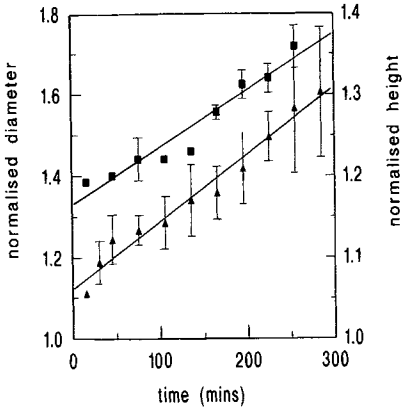


Fig. 1. Variation of (■) normalized diameter (ratio of the diameters of the gels and dry matrices) and (▲) normalized height (ratio of the heights of the gels and dry matrices) as a function of time for hydrating copolymer matrices.

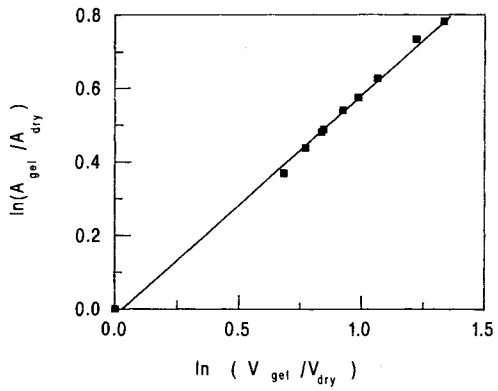
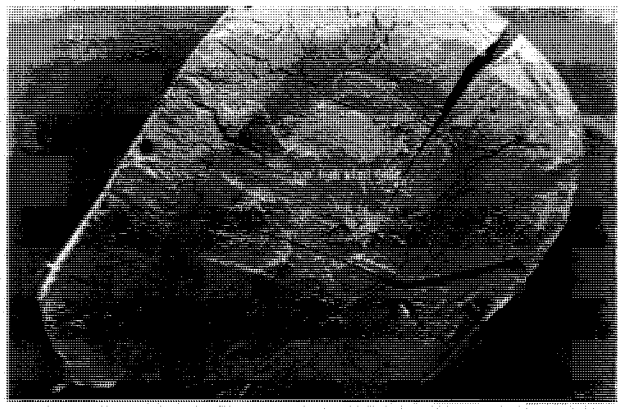


Fig. 2. Variation of ln normalized area (ratio of the surface areas, A, of the gels and dry matrices) as a function of ln normalized volume (ratio of the volumes, V, of the gels and dry matrices) for hydrated copolymer matrices.

(V_{gel}/V_{dry}) (Figure 2). In a study of coated and uncoated tablets of hydroxypropylmethylcellulose (HPMC), Peppas *et al* (7) obtained values of d = 2.91 for the uncoated tablets; d = 2.77 for face film coated tablets and d = 2.89 for edge coated tablets, indicating hindrance of swelling due to the presence of film coats and/or excipients. The deviation from the d value for unhindered swelling noted in our study for the drug-free copolymer compacts containing no added excipients is unlikely to be a consequence of the forces used for compression, since these were low, but may be due to the effects of a nonhydrated glassy core as suggested by other workers (7,8).

Hydrated copolymer matrices removed from the buffer solution at set intervals were examined by scanning electron microscopy using the freeze fracture technique. Figure 3 shows the electron micrographs obtained for one such study after hydration intervals of 15, 60, 120 and 240 minutes. A distinct gel layer, morphologically different from the dry core, was apparent even after 15 minutes of hydration, indicating that initial copolymer hydration and subsequent solvent penetration were relatively rapid processes. Freeze fracture electron micrographs obtained after 60 minutes of hydration showed two distinct regions within the gel layer, an outer region which was evenly hydrated and an inner region which showed a lesser and more uneven degree of hydration. Closer inspection of the outer region of the gel layer revealed a regular 'honeycomb' texture, indicating that extensive 'ice-crystal' formation had occurred upon freezing, supporting the view that this layer was extensively hydrated. The hydration of the inner gel layer became progressively more uneven with increasing distance from the surface, showing distinctive domains of poorly hydrated copolymer. These observations suggest that the rate of ingress of the solvent front is dependent on water transport through the reticular network of poorly hydrated copolymer adjacent to the 'core'. The uneven distribution of poorly hydrated domains around the core may be responsible for the non-uniformity of swelling (d = 2.80) which occurs with these matrices. Other workers have reported hydration and erosion fronts coupled with a glassy core, using scanning electron microscopy and nuclear magnetic resonance techniques (9,10).



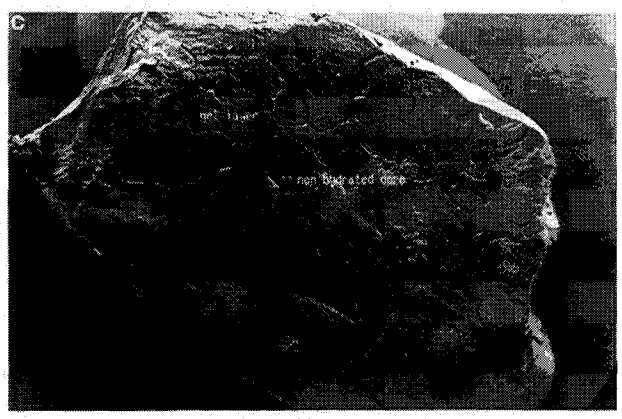


Fig. 3. Freeze-fracture electron micrographs of copolymer matrices after hydration for a) 15 min; b) 60 min; and c) 120 min.

Drug Release

Figure 4 shows a typical plot of the fraction of the initial matrix loading of 5-fluorouracil released *versus* time for copolymer matrices with several specified initial drug loadings (1.33 - 5.32% w/w). It is apparent from the shape of these curves, that zero order delivery has not been achieved. The release profile was not affected significantly by the initial drug loading concentration.

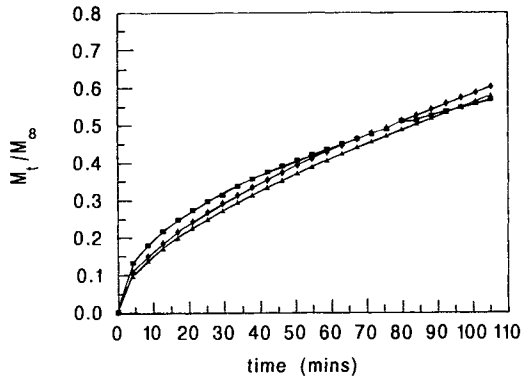


Fig. 4. Fraction of 5-fluorouracil released as a function of time from copolymer matrices loaded with (■) 1.33; (▲) 2.66; and (◆) 5.32% w/w of drug.

A lack of synchronisation of the hydration and erosion processes leading to a gradual increase in gel layer thickness may be deduced from the changes in the relative positions of the hydration and erosion fronts (as measured from the electron micrographs) as matrix contact time with the hydration medium was increased (Figure 5). The relationship between the hydration characteristics of hydrophilic matrices and the mechanism of drug release from them has been discussed by Conte *et al* (11). These workers have reported that release of sodium diclofenac from polyvinylalcohol matrices (Mowiol 40-88 mix) followed zero-order kinetics when there was a constant gel layer thickness resulting from synchronisation of the hydration and erosion fronts. However, when sodium diclofenac was released from HPMC (Methocel K4M) a lack of synchronisation between the two fronts was noted which resulted in a gradual increase in the gel layer thickness during release. As a consequence, the diffusional pathway for drug release increased with time resulting in non zero-order kinetics. The results of our study are in agreement with the conclusions of these workers, showing non zero-order release kinetics from a matrix system in which the gel layer did not remain constant during the period of drug release.

Ritger and Peppas (2) introduced a simple exponential equation to describe general solute release from polymeric matrices,

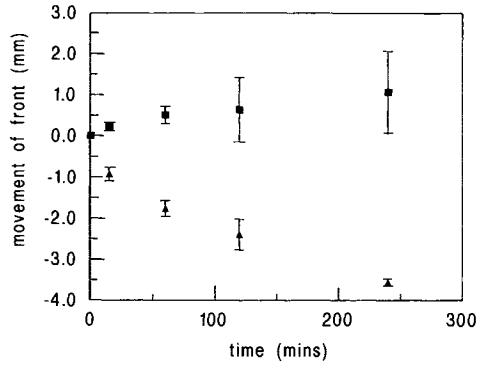


Fig. 5. Plots showing the movement of the (▲) hydration and (■) erosion fronts relative to the dry matrix surface following hydration for different periods of time.

$$M_t/M_\infty = kt^n \quad (3)$$

where M_t/M_∞ is the fraction of drug loading released, k is a constant incorporating characteristics of the macromolecular network system, t is the release period and n is the diffusional exponent. The dependence of the value of n on matrix geometry was discussed for matrices of varying shape and for swelling and non-swelling systems. Of particular relevance are the values of n quoted for Case 1 (Fickian) and Cases II release from moderately swelling (equilibrium swelling ratio not exceeding 1.33) cylinders (n = 0.45 and 0.89 respectively). The relationship between Fickian diffusional release, and Case II transport was explored by Peppas and Sahlin (3). The two release mechanisms were considered to be additive and the fractional release was described by an expression of the form,

$$M_t/M_\infty = K_a t^m + K_b t^{2m} \quad (4)$$

The first term of the right-hand side of the equation is the Fickian contribution, the second term is the Case-II relaxational contribution. K_a and K_b are the Fickian and the relaxational kinetic constants respectively. The coefficient, m, is the purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release, and can be determined from a plot of the exponent (m) *versus* aspect ratio (3).

Values of K_a and K_b for the release from the copolymer matrix were evaluated from the release data plotted according to eqn (4) for the first 60% of release (see Table I). The fraction F of drug load released from the matrix by Fickian diffusion was calculated from (3),

$$F = 1/(1 + K_b t^m/K_a) \quad (5)$$

Figure 6 shows the variation of F with time for a range of drug loadings. At the highest initial drug loading (5.32%) the percentage of drug released by Fickian diffusion exceeded 80% over the time period of measurement. Decrease of the initial drug loading resulted in a corresponding decrease of F at any given time, but even at the lowest drug loading (1.33%) the Fickian contribution exceeded that of Case II release. A similar reinforcement of the Fickian component of the release with increase of drug loading has been noted by other workers (12) and attributed to the effect of the presence of the water-soluble drug on both the swelling osmotic pressure and the associated time-dependent relaxation of the hydrogel network during the simultaneous absorption of water and desorption of drug.

Table I. Fickian and Relaxational Kinetic Constants for the Release of 5-Fluorouracil From Swellable Matrices of the Triblock Copolymer CL_6 E_{90} CL_6

Drug loading % w/w	Fickian kinetic constant K_a ($min^{-0.43}$)	Relaxational kinetic constant K_b ($min^{-0.86}$)
1.33	0.0689	0.0001
2.66	0.0449	0.0030
5.32	0.0443	0.0033

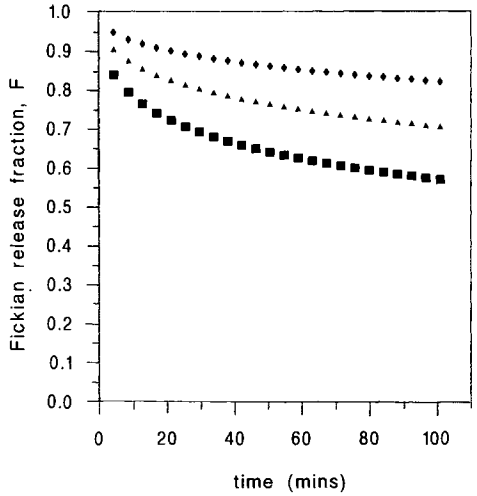


Fig. 6. Fraction of 5-fluorouracil released by Fickian diffusion from copolymer matrices loaded with (■) 1.33; (▲) 2.66; and (♦) 5.32% w/w of drug.

CONCLUSIONS

Our studies have shown a relationship between the in vitro release of 5-fluorouracil from a swellable matrix prepared from a triblock copoly(ϵ-caprolactone/oxyethylene/ϵ-caprolactone) and the hydration characteristics of the matrix. Analysis of the release data has shown non zero-order release kinetics which, it is suggested, are a consequence of a gradual increase in the gel layer thickness during release. The percentage of the initial drug load released by Fickian diffusion decreased with decrease of the initial drug loading over the range 5.32%-1.33% but exceeded that of Case II release for all systems examined.

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