Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release

A. Apicella, B. Cappello*, M.A. Del Nobile, M.I. La Rotonda*, G. Mensitieri and L. Nicolais

*Department of Materials and Production Engineering, *Department of Pharmaceutical and Toxicological Chemistry, University of Naples Federico II, 80131 Naples, Italy*

An interpretation of the drug release from monolithic water-swellable and soluble polymer tablets is presented. A convenient parameter, α, which compares the drug-diffusive conductance in the gel layer with the swelling and dissolving characteristics of the unpenetrated polymer was used to describe the release behaviour of β-hydroxyethyl-theophylline (etofylline) from compression-moulded tablets of hydrophilic pure semicrystalline poly(ethylene oxides) of mol wt 600 000 and 4 000 000 and of two blends of the two molecular weights of poly(ethylene oxides). The water swelling and dissolution characteristics of two polymers and two blends were analysed, monitoring the thickness increase of the surface-dissolving layer and the rates of water swelling and penetration in the tablets. The drug diffusivities in the water-penetrated polymer gels were measured by carrying out permeation tests. Finally, drug release tests were performed to investigate the release kinetics of the different systems in an aqueous environment at 37°C. The drug release from the high molecular weight poly(ethylene oxide) is principally related to the material swelling rather than polymer dissolution, leading to a progressive decrease of the drug's diffusive conductance in the growing swollen layer, and hence to a non-constant release induced by the prevailing diffusive control. Conversely, drug release from the low molecular weight poly(ethylene oxide) is strictly related to the polymer dissolution mechanism. The achievement of stationary conditions, in which the rate of swelling equals the rate of dissolution, ensures a constant release rate, even in the case of very low drug-diffusive conductance in the external gel layer. Intermediate behaviours were detected in the case of the two blends.

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Diffusion-controlled release technology, based on polymer barrier characteristics, is a good alternative to conventional delivery systems. Complex reservoir systems and monolithic matrix systems are two important applications. For the former, a zero-order kinetic release may be maintained until the drug activity in the reservoir can be kept constant. However, environmentally passive monolithic matrix systems, containing dispersed or dissolved active ingredients, are not able to give a constant delivery rate, at least for simple device geometries. In such cases, the diffusion control generally leads to a square root of time dependency of the drug delivery.

Alternatively, the use of environmentally interactive monolithic devices made with hydrophilic polymers was first proposed by Hopfenberg *et al.*[1,2], and extensively investigated[3–5]. As the penetrant enters the drug-entrapping matrix, the polymer swells and the active ingredient diffuses from the swollen part. This relaxation-controlled sorption is governed by the solvent concentration at the interface separating the swollen from the unpenetrated polymer. The polymer at the interface relaxes and swells at a constant rate as long as the penetrant concentration at the moving boundary remains constant. Zero-order release from this type of device requires a constant surface area and a constant swelling rate of the polymer matrix (limiting Case II sorption) as well as a high diffusivity of the entrapped species. These conditions, generally, cannot be protracted for long release times[2], since they are strongly dependent on the time evolution of the interactions involving polymer, penetrant and solute. It is only in the early stages of polymer swelling that, due to the small thickness of the swollen layer, the diffusive conductances of both the solvent toward the unpenetrated core and the drug moving outside are much higher than the swelling rate, and the constant delivery is brought about by the constant rate polymer relaxation. However, as the swollen thickness increases, lower values of the diffusive conductance are attained and both

Correspondence to Dr A. Apicella.

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swelling and release rates are progressively reduced. Hopfenberg *et al.*[2] and Peppas and Franson[3] proposed similar dimensionless parameters to identify zero-order release conditions in terms of initial solvent penetration rate, swelling thickness, and diffusivity of the active ingredient in the swollen polymer. To guarantee zero-order releases from swelling systems of increasing thicknesses, the drug should present the proper high diffusivity in the swollen polymer. The addition of water-soluble components in the polymer has been proposed[4] to enhance the diffusivity of the drug in the more porous swollen layers created.

Poly(ethylene oxide) (PEO)-based systems have been proposed as drug delivery devices. In particular, Graham *et al.* reported the constant release of prostaglandin E_2 from cross-linked crystalline–rubbery hydrogel matrices based on PEO which were undergoing solvent sorption and from crystallites melting in aqueous environments[5–11]. In the case of uncross-linked PEO matrices, the solubility of the polymer can alter the characteristics of the penetrated layer, leading to different behaviours in systems presenting different dissolution features. To control the release of the active agent, there should be a balance between diffusion of the active agent and solubilization of the polymer matrix. The diffusivity of the drug through the matrix, the swelling of the polymer, and its solubilization rate can be biased by changing the molecular weight of the polymer or blending polymer fractions with different molecular weights.

Mucoadhesive capability is another important property of a polymer to be used as matrix for monolithic drug delivery devices. In fact, in the development of oral-controlled release devices, considerable benefit may result from the use of bioadhesive polymers providing relatively short-term adhesion between the drug delivery system and the epithelial surface of the gastrointestinal tract. Due to the linear flexible structure of the PEO macromolecule, this polymer shows a particular ability to form entangled physical bonds by interpenetrating deeply and rapidly into mucous substratum networks. The mucoadhesive properties of PEO reported in the literature are strongly dependent on the polymer molecular weight and are more pronounced in the case of the high molecular weight materials[12–14]. In particular PEO shows a behaviour[14] ranging from no bioadhesion at mol wt 20 000 to very good bioadhesion at mol wt 4 000 000. Consequently, both the release and the mucoadhesive properties of PEO-based systems are expected to be finely tuned by blending PEO fractions with different molecular weights.

We were therefore interested in the analysis of the capability of PEO to be used as mucoadhesive control release devices. In the present investigation, we relate the sorption, melting and dissolution characteristics of two PEOs of different molecular weight to the diffusivities in the swollen polymer of an active ingredient (etofylline) and the release behaviour observed.

RELEASE MECHANISMS FROM MONOLITHIC DEVICES

The release rate of a dissolved or dispersed drug from a polymeric film or tablet introduced in a specific environment, strongly depends on the nature of the diffusion and sorption processes involving the polymer/environment system and the polymer/drug system.

Diffusion-controlled devices

The dissolved species will diffuse from a matrix which does not actively interact with the external environment according to an ordinary diffusion law (*Figure 1a*). In such a case, the concentration profile in the slab decreases with time leading to the progressive reduction of the release rate (i.e. the slope of the fractional release *versus* time curve).

Swelling-controlled devices

Completely different release behaviour is observed for hydrophilic polymers when water sorption is followed by significant polymer swelling. Limiting Case II sorption occurs when constant rate water absorption is associated with a front advancing at a constant rate into the confines of the glassy polymer. A sharp boundary separates the essentially unpenetrated core from an uniformly swollen shell (*Figure 1b*). The polymer relaxation and swelling is driven by the osmotic stresses generated at the moving boundary by the presence of the penetrant[15–17] and remains constant as long as a constant local concentration persists. Drug release is controlled quantitatively by the invasion of the swelling solvent and by the solute counter diffusion in the swollen polymer. Zero-order release kinetics may be achieved from a polymer which swells at a constant rate and with a constant penetration surface area, but only if the counter diffusion of the solute molecules is rapid compared with the swelling rate.

Intermediate cases

There are intermediate cases in which both the swelling and the diffusive control can be important during drug release. The swelling front advancing rate (v) and the diffusive conductance (the ratio between the solute diffusivity and the shell thickness at a given time $D/\delta(t)$) have been used[2] to define a convenient dimensionless parameter:

$$\alpha = D/[\delta(t) \times v]$$

which accounts for the relative contribution of the solute counter diffusion and of the penetrant uptake rate to the overall rate of release.

In the early stages of swelling, the diffusive conductance is high, due to the small value of the swollen shell thickness ($\delta(t)$). Release is controlled by the polymer swelling rate (*Figure 1*) and values of $\alpha > 1$ are measured. Conversely, the diffusion of the solute molecules through the outer shell will increasingly control the release kinetic observed as the swollen layer progressively thickens. In this case, values of α smaller than unity are observed. Diffusive control is reflected by the fractional release *versus* time curve as a progressive reduction of the release rate (*Figure 1b*). For low values of α, the polymer rapidly swells, after which the drug is depleted by an exclusively diffusive mechanism[2]. As a consequence, a zero-order release rate is expected when $\alpha(t) > 1$ and the penetration rate of the swelling agent is constant.

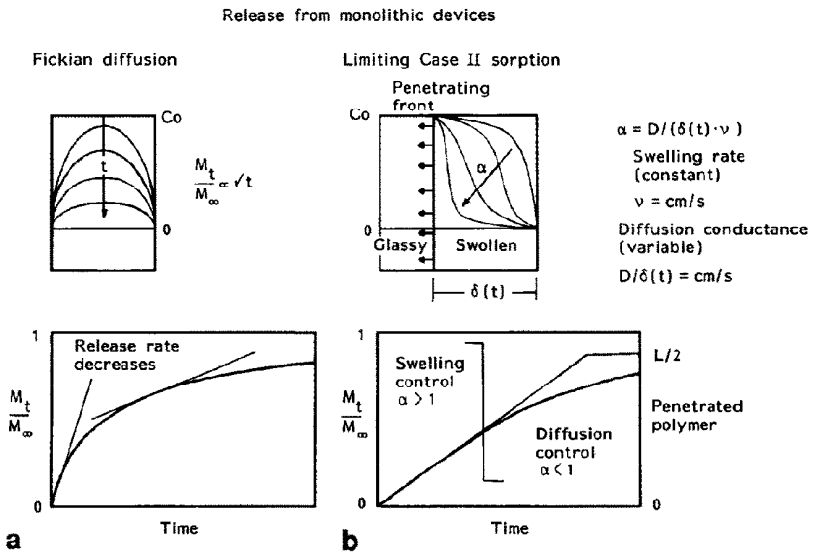

Figure 1 Release mechanisms from monolithic devices. **a**, Fickian diffusion; **b**, limiting Case II sorption.

A theoretical framework of penetrant uptake and solute release was developed by Peppas *et al*[3,18] and by Davidson and Peppas[19,20] to characterize monolithic swellable systems for controlled drug release. It has been shown that two dimensionless parameters should be used to predict the release behaviour of these systems. The swelling interface number, Sw ($1/\alpha$ in the present context), and the diffusional Deborah number, De, have been introduced. The former represents the ratio of the penetrant uptake rate to the rate of solute diffusion. The latter represents the ratio of the characteristic swelling time of polymer chains, related to the presence of the swelling penetrant, to the characteristic diffusion time of the penetrant into the polymer. Zero-order release rates should be expected if both the solute diffusion through the swollen polymer layer is rapid compared to the penetrant uptake rate ($Sw \ll 1$) and the penetrant uptake is controlled by polymer relaxation ($De = 1$). As consequence the solute release kinetics cannot be uniquely related to α (or $1/Sw$) and also the value of De has to be taken into account.

Polymer swelling and dissolution-controlled devices

Thermoplastic polymers which are sufficiently hydrophilic are also water soluble. A sharp advancing front divides the unpenetrated core from a swollen and dissolving shell. Under stationary conditions, a constant thickness surface layer (δ) is formed by the swollen polymer and by a high concentration polymer solution[21].

In fact, once the hydrodynamic external conditions are defined, a stationary state is reached where the rate of penetration of the moving boundary (v) equals the rate of removal of the polymer at the external surface. The time lapse until the quasi stationary state is reached is swelling time[21].

Figure 2 reports the typical polymer concentration in

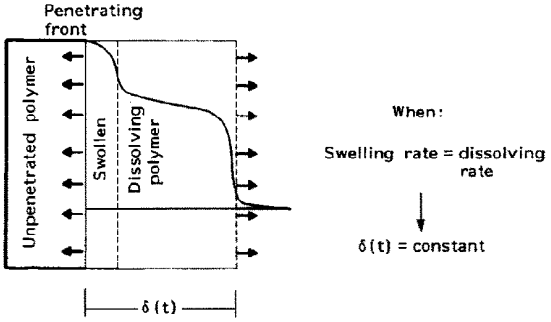

Figure 2 Polymer concentration profile for swelling and dissolving materials.

the surface layer of a dissolving polymer. If the dissolution occurs normally, the steady-state surface layer consists of four different sublayers[21]: liquid sublayer (adjacent to the pure solvent), gel sublayer, solid swollen sublayer and infiltration sublayer (adjacent to the polymer base into which the solvent has not yet migrated). If the test temperature is higher than the glass transition temperature of the polymer, the surface layer consists of only liquid and gel sublayers.

At steady state, the dissolution rate is constant and can be defined equally by either the velocity of the retracting front of the polymer or the velocity of the front separating the pure penetrant and the liquid dissolving sublayer. Thus both fronts are synchronized.

The dissolution rate strongly depends on hydrodynamic conditions, temperature, polymer molecular weight and crystallinity level. Close analogies have been found between crystallization and dissolution behaviours for semicrystalline polymers[21]. In fact, dissolution and crystallization rates are maximal when plotted as

function of temperature and are both expected to decrease with increasing polymer molecular weight.

In the case of a dissolving polymer, a dimensionless parameter $\alpha(t)$ can still be defined as the ratio of the diffusive conductance $D/\delta(t)$ and dissolution (or penetration) rate v. Consistent with the previous discussion concerning swellable polymers, a zero-order release rate is to be expected only if $\alpha > 1$ and the dissolution rate is constant with time. Two different dissolution stages can be identified: the initial time lapse (swelling time) and the steady-state conditions. During the initial transient, neither the thickness of the dissolving surface layer or the dissolution rate are yet constant. A time-dependent diffusive conductance $(D/\delta(t))$ and a time dependent dissolution rate $(v(t))$ should be considered for the evaluation of the parameter $\alpha(t)$. Conversely, under steady-state conditions, a constant diffusive conductance (constant gel layer thickness) and a constant dissolution rate are attained. As a consequence, in the first stage α changes during the dissolution; release process and release rate can be a function of time. During the second stage, however, a time-independent concentration profile develops into the external surface layer. A constant release rate is obtained, determined by the penetrating front rate or equally by the rate of advancement of the liquid sublayer–pure solvent boundary, synchronized to the penetrating front. A similar example of zero order release kinetics resulting from the synchronization of front velocities of the identical velocities of diffusing and eroding fronts in erodible polymer matrix delivery systems[22].

MATERIALS AND METHODS

Materials

PEO of average mol wt of 600 000 (Aldrich Chimica S.r.l., Catalogue No. 18,202-8) and 4 000 000 (Aldrich Chimica S.r.l., Catalogue No. 18,946-4) were used. Analytical grade (purity 99.8%) β-hydroxyethyl-theophylline (etofylline) was supplied by Sigma Chemical. The materials were used as received.

Methods

Tablet preparation

The polymer and the etofylline powders were first desiccated under vacuum, next mixed in the desired proportions, then dissolved in chloroform. The solution was stirred well to assure a homogeneous mixing of the components. Polymer films containing the drug were obtained by casting. After desiccation, several film layers were then compression moulded at 75°C to form sheets from which were cut circular tablets (25 mm diameter) with thicknesses of 2.0 or 3.3 mm. Four different kinds of tablets were produced, all containing 10% etofylline. The four different polymer matrices used were: pure PEO (mol wt = 600 000), pure PEO (mol wt = 4 000 000), 50% b.w. blend of the two PEOs and 87% b.w. mol wt of 4 000 000 and 13% b.w. mol wt of 600 000 blend of the two PEOs (50% mol blend).

Calorimetric analysis

In order to characterize PEOs and PEOs/etofylline mixtures, a Du Pont differential scanning calorimeter (DSC instrument 910) operating under nitrogen flux and at a heating rate of 10°C/min was used.

Gel layer thickness measurement

Water swelling and penetration depths, and gel layer evolution were optically measured during the water conditioning at fixed times. The samples were cleaved on glass plates and placed in thermostated distilled water held at 37°C. The water was continuously stirred and measurements were taken using a cathetometer.

Etofylline permeation tests through the swollen polymers

An apparatus equipped with a cell for liquid permeation measurements in membranes was used for the permeability measurements (absorption simulator made by Sartorius AG). The polymers, free of drug, were confined in the cell between two semipermeable cellulose acetate membranes and equilibrated with distilled water at 37°C before the start of the permeability measurements. The equilibrium water swelling thicknesses of the four different polymeric materials confined in the cell were measured and used in the calculation of the permeability values. The concentration increase of the etofylline in the downstream chamber of the permeability cell was monitored. The amount of drug passing through the polymer was then evaluated as function of time.

Reference permeation tests were performed to determine the influence of the supporting cellulose acetate membranes on the drug permeation kinetics. The resistance to the drug transport due to the supporting membranes was found to be negligible compared to the values detected during the permeation tests performed on swollen polymers. The drug concentration into the swollen polymer on the upstream side was evaluated from the permeation tests by means of the calculated water-swollen polymer etofylline partition coefficient. The resulting concentration was approximately ten times lower than the tablet drug loading. Accordingly, a different drug diffusion rate could occur in the tablet dissolving layer. Nevertheless, a drug concentration lower than the drug loading is to be expected in the dissolving layer of the tablet, due to the swelling. For this reason, the diffusion constant evaluated by means of the permeation tests was used in the evaluation of the dimensionless numbers introduced in the previous sections. Eventual composition dependence of etofylline diffusivity through the surface tablet layer not measured.

Drug release kinetics analysis

A dissolution apparatus (Erweka D.T.) operating at 50 rev min^{-1} and at a constant temperature was used for the evaluation of the etofylline release kinetics from the polymer tablets. Each tablet was placed in a container filled with a known amount of distilled water and the increasing concentration of etofylline in the aqueous conditioning environment was measured as function of time.

The etofylline concentrations in the aqueous solutions during the permeability and the release tests were determined by means of UV spectroscopy using a

Beckman DU-40 spectrometer operating at 262 nm. All tests were carried out at 37°C.

RESULTS AND DISCUSSION

Drug release system characterization

To characterize properly the drug release from the present swelling and dissolving systems, the solvent penetration, polymer swelling and dissolution behaviour, drug solubility in the host polymer and diffusion in the swollen and gelled layer were examined.

Differential scanning calorimetry (DSC)
The DSC thermograms of etofylline, PEO and of tablets made of the four different PEO matrices containing 10% etofylline were taken. The thermogram relative to the etofylline shows a well-defined melting peak around 170°C while that of the semicrystalline pure PEOs and blends present a melting peak in the range 63–65°C. Only the melting peak of the polymer matrix is evident in the thermogram of tablets made of PEOs blended with etofylline. The absence of the melting peak of the etofylline indicates complete dissolution of the drug in the amorphous regions of the polymer. The crystalline fraction of the tablet matrices was about 0.65. This value was evaluated[23] assuming an enthalpy of crystallization of PEO equal to −210 J/g.

Polymer swelling and dissolution properties
The photo reproduced in *Figure 3* shows the initial swelling conditions observed for the two homopolymer tablets of different molecular weights. *Figures 4* and *5* report the penetration depth evolution kinetics in the case of the tablets made of pure PEOs with average mol wt of 600 000 and 4 000 000 containing 10% etofylline. The PEO of mol wt of 600 000 (*Figure 4*) shows an almost linear shape of the penetration depth curve as a function of time which indicates that, after a very short initial transient, the penetration front moves into the polymer at a constant rate. The higher molecular weight PEO tablet (*Figure 5*) is characterized by an initial rapid water penetration rate. A sharp front moves at a constant rate through the unpenetrated tablet core after a swelling time significantly larger than the time lapse detected for lower

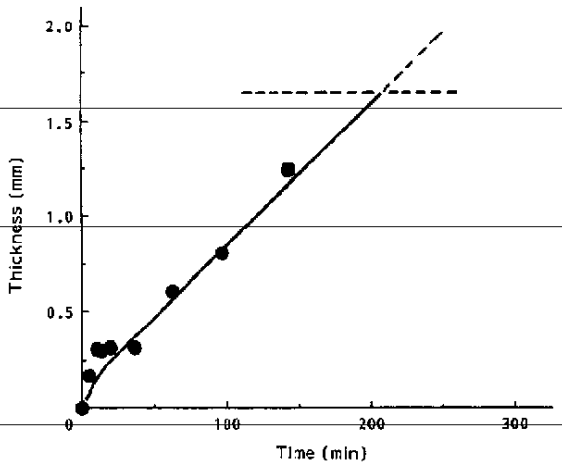

Figure 4 Penetration depth kinetics of water at 37°C in mol wt of 600 000 PEO: the horizontal dotted line represents the time corresponding to the total penetration in the case of a 3.3 mm thick tablet. $v = 1.3 \times 10^{-4}$ mm/s.

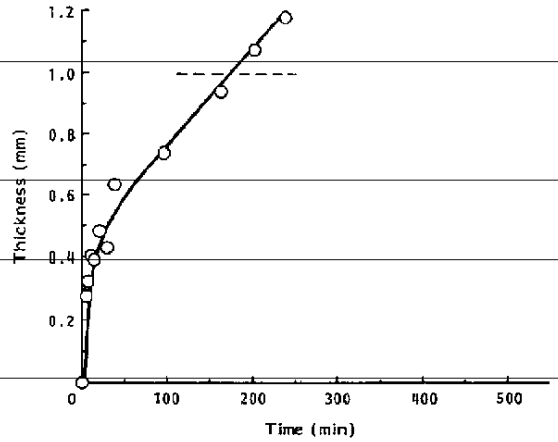

Figure 5 Penetration depth kinetics of water at 37°C in mol wt of 4 000 000 PEO: the horizontal dotted line represents the time corresponding to the total penetration in the case of a 2 mm thick tablet. $v = 5.0 \times 10^{-5}$ mm/s.

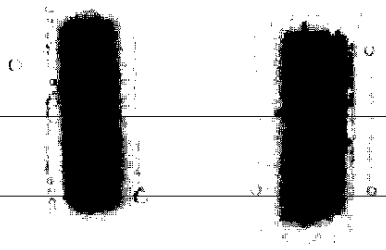

Figure 3 Water swelling of PEO tabs of mol wt of 600 000 (left) and 4 000 000 (right).

molecular weight PEO. The behaviour of PEO blends is similar to that of pure PEO with a mol wt of 4 000 000. The corresponding values of the steady-state penetration rates for the four kinds of polymer matrices, *vs*, are reported in *Table 1*. As expected v decreases with increasing molecular weight. The PEO crystallization rate is reported[24] to decrease with increasing molecular weight for mol wt values exceeding about $2\text{–}6 \times 10^5$. Hence, as previously discussed, similar behaviour was observed in the case of dissolution rate.

When the dissolution rate equals the penetration rate, a constant thickness surface layer should be observed. The dissolving layer evolution during water conditioning should reflect the different dissolution characteristics of the materials. The surface layer thicknesses as a function of time are compared in *Figure 6*. It is evident that a

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