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Research paper

A study of release mechanisms of different ophthalmic drugs from erodible ocular inserts based on poly(ethylene oxide)

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Abstract

When topical controlled delivery of ophthalmic drugs is realised via erodible inserts, drug bioavailability is maximised, if release is controlled exclusively by insert erosion, since parallel mechanisms which increase the release rate, also increases the dose fraction cleared from the precorneal area by tear fluid draining. The respective contributions of diffusion and erosion to the release mechanism of different drugs, namely, prednisolone (PDS), oxytetracycline hydrochloride (OTH) and gentamicin sulfate (GTS), from erodible ocular inserts based on poly(ethylene oxide) (PEO) of molecular weight 400 or 900 kDa was determined by an in vitro technique adequate to predict the release mechanism in vivo. PDS and OTH were released with erosion-controlled kinetics. With therapeutic doses of these drugs in the inserts (0.3 mg, 1.5%), the possibility of a purely erosive mechanism was shown to rely upon drug–PEO molecular interactions, which limit drug diffusion in the swollen matrix. This was the case with OTH, for which strong interactions with PEO were measured, whereas some contribution from the parallel diffusive mechanism was evidenced for PDS, which showed weaker interactions with polymer. Such a contribution disappeared when the PDS concentration in the insert was increased to 6%, which suggested that the erosive mechanism is favoured by a drug concentration in the hydrated insert substantially higher than solubility. On the other hand, the release of about 50% GTS dose was controlled by diffusion, due to the high water solubility of this drug, accompanied by weak drug–PEO interactions. In this case the residence time of drug in the precorneal area is expected to be significantly shorter than that of the PEO carrier.

Keywords: Release mechanism; Ocular insert; Poly(ethylene oxide); Prednisolone; Oxytetracycline; Gentamicin; Ofloxacin

1. Introduction

It is now common knowledge that topical controlled delivery of ophthalmic drugs improves their ocular bioavailability with respect to traditional eyedrops, by decreasing the rate of drug elimination from the precorneal area. When the controlled delivery is realised via an erodible insert, the drug residence time in the precorneal area, and thereby, the bioavailability will be maximised if drug release is controlled exclusively by insert erosion, since any parallel release mechanism increases the release rate, and thereby, the dose fraction cleared from the precorneal area by tear fluid draining. In a previous study, the release of ofloxacin from erodible inserts based on poly(ethylene oxide) (PEO) of molecular weight 400 kDa (PEO 400) or 900 kDa (PEO 900) was found to be essentially erosion-controlled, both in vitro and in the rabbit eye, and the drug availability in the aqueous humour was increased by one order of magnitude with respect to the commercial eyedrops [1]. For given insert swelling and erosion rates, dependent on polymer molecular weight, the mechanism of drug release from PEO inserts may depend on several factors relevant to the drug, such as, e.g. diffusivity, solubility and loading dose [1–6]. Therefore, it is felt that an investigation of the ability of ocular inserts based on PEO 400 or PEO 900, to release therapeutic doses of different drugs by an erosive mechanism would contribute to a fuller evaluation of the potential usefulness of these delivery systems. The results of the previous study [1] have demonstrated the suitability of the relevant in vitro technique to predict the in vivo erosive mechanism. In the present work such a technique has been used to assess the relative relevance of diffusion and erosion to the release mechanism of drugs of interest in ophthalmology, such as oxytetracycline, prednisolone (PDS) and gentamicin, from PEO-based inserts, and a correlation between drug properties and release mechanism has been sought.

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2. Materials and methods

2.1. Materials

Ofloxacin (OFX), PDS, oxytetracycline hydrochloride (OTH), gentamicin sulfate (GTS) and benzocaine (BZC) (Sigma-Aldrich S.r.l., Milano, Italy), PEO of different molecular weights, namely, 400 kDa (PEO 400) (Polyox® WSR N-3000) and 900 kDa (PEO 900) (Polyox® WSR-1105) (gifts from Union Carbide Italia S.r.l., Milano, Italy) were used as received. Buffer substances and all other chemicals or solvents were of reagent grade.

2.2. Preparation of matrices

PEO was medicated by the following procedures. OTH or PDS was adsorbed onto the surface of PEO powder, sieve-sized to the 180–250 μm range, by wetting the powder, portionwise, with a 4.0 mg/ml drug solution in absolute ethanol, while mixing with a spatula and letting the solvent evaporate. Following the addition of a solution volume corresponding to 1.5 or 6% w/w drug on a medicated PEO basis, the powder was vacuum dried to a constant weight. Since GTS is insoluble in absolute ethanol, this drug was mixed with PEO by freeze-drying an aqueous solution containing 5% PEO and 0.25% GTS, corresponding to 4.8% w/w drug in the lyophilised product. Substantially higher GTS concentrations in the solution yielded a non-homogeneous product. The actual load of OTH or PDS was determined spectrophotometrically at 273 or 247 nm, following dissolution of medicated PEO samples in phosphate buffer 0.0026 M, pH 7.4, made isotonic with sodium chloride (PB). The actual percentage of GTS in the freeze-dried product was determined spectrophotometrically at 334 nm, following dissolution in PB and derivatisation with the phthalaldehyde reagent, according to the British Pharmacopoeia, 1998. Three aliquots of each formulation were analysed and the results were averaged. None of the determined mean values were substantially different from the nominal load. The variation ranges were always less than 1.5% of the respective means, indicating a satisfactory homogeneity of drug–PEO mixtures. In order to prepare matrices suitable to be used as ocular inserts, the medicated PEO powders or freeze-dried products were compressed by a hydraulic press into flat faced tablets of 6 mm diameter, 0.8–0.9 mm thickness and 20 mg weight, by applying a force of 9800 N.

2.3. Measurement of drug release and matrix erosion kinetics

Each matrix, after accurate weighing (10^{-5} g), was tightly inserted into a 3-mm deep cylindrical cavity, of exactly the same diameter as the matrix, bored at the centre of a 4-mm thick Teflon disk. At time $t = 0$, one or two disks, each containing a matrix, were immersed, with the exposed matrix surface in upward position, into a known volume of PB, thermostated at 37°C and stirred under controlled hydrodynamics. With PDS or OTH as the drug, two disks were immersed in 50 ml PB, and the hydrodynamics were controlled by a previously described apparatus [7]. With GTS, a reduced volume of dissolution medium was needed, due to a limited sensitivity of the analytical method used for determination of this drug in such a medium. Then, one disk was immersed in 10 ml PB, contained in a stoppered bottle of 25 ml capacity, immersed in a thermostated shaking water bath (130 min^{-1}). To determine the drug fraction released and the matrix weight fraction eroded, after a pre-established elution time, each disk was withdrawn and the dissolution medium analysed for the drug as described in Section 2.2. Each disk was dried and weighed (10^{-5} g) and the undissolved matrix weight was computed, knowing the disk weight. To assess the drug release and matrix erosion kinetics, the above procedure was repeated for different elution times. Sink conditions in dissolution medium were always ensured.

2.4. Determination of diffusion coefficient of drugs in PB

The diffusion coefficient at 37°C of OFX, PDS, OTH or GTS in PB, i.e. the dissolution medium of the release experiments, was determined by measuring drug flux through a porous cellulose membrane (Spectra/Por®, molecular weight cut-off, 3500 Da, Spectrum Laboratories Inc., Rancho Dominguez, CA, USA) under quasi-steady state conditions. For this purpose, a diffusion cell, apparatus and procedure similar to those described by Bottari et al. [8], were used. The initial concentration of the stirred drug solution in PB at the donor side of membrane was in all cases lower than solubility and ranged between 0.22 mg/ml (for OFX) and 0.38 mg/ml (for GTS). Sink conditions were ensured in the stirred PB at the receptor side of membrane. The receiving phase was analysed for OTH, PDS or GTS as described in Section 2.2. OFX was determined at 286 nm. The dialysis data were analysed by the following equation [9]

$$\ln A = \ln A_0 - kt \tag{1}$$

where A_0 and A are the drug concentrations in the donor at time zero and t, respectively, and the dialysis rate constant, k, is expressed as follows:

$$k = \frac{k_m}{V} PD \tag{2}$$

where k_m is a coefficient depending on the physical characteristics of the membrane, such as surface area, thickness, porosity and pore tortuosity; V, the donor volume; P, the drug partition coefficient for the aqueous medium in the membrane pores and the donor; D, the drug diffusion coefficient in such a medium. For the present experiments, where PB was both in the donor compartment and in the membrane pores, $P = 1$. Considering the very low drug concentration in the pore medium, where diffusion occurred, drug–drug

association phenomena were unlikely, so D was assumed as concentration-independent. With all drugs, a very good fit of Eq. (1) to the dialysis data was obtained ($r^2 \geq 0.999$, with at least ten degrees of freedom of each linear regression). The diffusion coefficient of each drug could be calculated from the following equation, derived from Eq. (2):

$$D = D_{ref} \frac{k}{k_{ref}} \quad (3)$$

where D_{ref} is the known diffusion coefficient of a reference drug, while k and k_{ref} are the dialysis rate constants determined with the drug under study and the reference, respectively. BZC was chosen as the reference, since its diffusion coefficient in water at 35°C (8.6×10^{-6} cm^2/s) was found in the literature [8]. The dialysis run with the drug and that with the reference were carried out in sequence, using the same membrane specimen. The run with BZC was performed at 35°C using water as the donor and receptor medium, i.e. the conditions in which the diffusion coefficient of this molecule was determined [8]. BZC was analysed spectrophotometrically at 286 nm.

2.5. Determination of drug–PEO interactions

Since drug–PEO molecular interactions depress the drug thermodynamic activity coefficient in the medium, they can be measured by the relative activity coefficient, γ_r, defined as the ratio of the activity coefficients in the presence and absence of PEO. If, following the Hildebrand convention, activity = 1, is taken for the pure drug, γ_r is equal to the drug partition coefficient for the PEO-free and the PEO-containing medium [10]. On this basis, such a partition coefficient was determined for OFX, PDS, OTH or GTS in a fluid solution containing 1.5% PEO 900, and for OFX or PDS in a semisolid solution containing 10% PEO 900.

2.5.1. Case of fluid solution

The dynamic dialysis technique described in Section 2.4 was used to determine the drug–PEO interactions in fluid solution. The donor medium was PB containing 1.5% PEO 900. For each drug the initial concentration in such a medium was the same as in the experiments described in Section 2.4. The linear regression for the fitting of Eq. (1) to the dialysis data was always highly significant ($r^2 \geq 0.999$; $n \geq 10$). The membrane pore size was such as to allow the drug and PB salts to enter the aqueous pores while excluding the PEO macromolecules. Under these conditions, P in Eq. (2) is the required PEO-free-PB/PEO-containing-PB partition coefficient ($P_{PB/PEO}$). Since $P = 1$ in the absence of PEO from the donor, the ratio of the dialysis rate constant obtained in the presence of PEO in the donor to that obtained in the absence of PEO yields the required $P_{PB/PEO}$, which can be easily verified by expressing the rate constants through Eq. (2). For each drug the run with the PEO-containing PB was followed by one with the PEO-free PB, using the same membrane specimen.

2.5.2. Case of semisolid solution

The PEO-containing medium was a semisolid solution obtained by dispersing 10% PEO 900 into a drug solution in PB, with the aid of an Ika Ultra-Turrax T25 mixer. In this case, $P_{PB/PEO}$ was obtained from the ratio of the partition coefficient for the PEO-free PB and an appropriate immiscible organic solvent ($P_{PB/S}$), to the PEO-containing-PB/organic-solvent partition coefficient ($P_{PEO/S}$):

$$P_{PB/PEO} = \frac{P_{PB/S}}{P_{PEO/S}} \quad (4)$$

$P_{PB/S}$ was determined by equilibrating the phases in a separating funnel, while $P_{PEO/S}$ was determined by the following procedure [11]. Six cells, each containing a 0.2-cm thick layer (2 ml) of a semisolid PEO-containing solution in PB of known drug concentration (0.9 mg/ml, for OFX; 0.2 mg/ml, for PDS) separated by a porous cellulose membrane (surface area, 10.2 cm^2) from 2 ml of drug solution in the organic solvent, were simultaneously shaken in a water bath thermostated at 37°C. The initial drug concentration in the organic solution was different for the different cells and spanned a range to encompass the unknown equilibrium concentration with the semisolid solution. In each cell, the drug tended to equilibrate between phases, therefore, in the cells where the initial concentration in the organic solution was below the equilibrium concentration, the drug would transfer from aqueous to organic phase, whereas the opposite occurred where the initial concentration in the organic phase exceeded the equilibrium value. After an appropriate time interval, sufficient for a positive or negative concentration change in each organic solution to be detectable, such a change was determined and plotted vs. the corresponding initial concentration. As expected [11], a straight line with negative slope was obtained in all cases ($r^2 \geq 0.993$; $n = 6$), the abscissa intersection of which gave the equilibrium concentration with the semisolid solution, needed to compute $P_{PEO/S}$ and thereby, the required $P_{PB/PEO}$ in Eq. (4). The organic solvent for OFX was *n*-octanol, for PDS it was *n*-octanol/petroleum ether (1:4). OFX and PDS were determined spectrophotometrically in the organic solvent at 298 and 247 nm, respectively. The before described method could not be used for GTS, since this molecule is insoluble in organic solvents.

3. Results and discussion

3.1. Drug release mechanism

Drug release from PEO matrices is elicited by water absorption into matrix, which converts the semi-crystalline polymer into a gel. The drug dissolves either completely or partly in the gel and diffuses to the exterior with a rate depending on its diffusivity and concentration gradients in gel. Concurrently, the gel is eroded at its surface with a rate depending on polymer molecular weight and hydrody-

namics of dissolution medium. The release pattern depends on the relative rates of these processes. A great deal of research has dealt with the mechanism of drug release from PEO matrices (see, for example, Refs. [2–6]). A complete elucidation of release mechanism for the different drugs under study is beyond our scope. In fact, for each drug we aimed at verifying whether or not release was controlled by gel erosion, evidencing and quantifying deviations from the purely erosive mechanism and correlating deviations with factors relevant to the drug. As described under Section 2.3, two different techniques were used to obtain kinetic data. Preliminary runs carried out with the two techniques yielded similar matrix erosion data, indicating similar hydrodynamics of dissolution medium in the two cases. A direct comparison between drug release and matrix erosion kinetics can give information on the relative importance of the erosion mechanism. Kinetic data on PDS release and matrix erosion for matrices based on PEO 400 or PEO 900 are compared in Fig. 1. It is seen in Fig. 1a that, with PEO 400 as the matrix material, after an initial phase where release is faster than erosion, the release and erosion data virtually coincide, indicating that the release process soon became completely erosion-controlled. In the early stages of the process, PEO dissolution is indeed expected to lag behind drug release, since the former must be preceded by polymer hydration and swelling to an extent sufficient to allow disentanglement of polymer chains, whereas the latter occurs meanwhile, via drug diffusion through the swollen

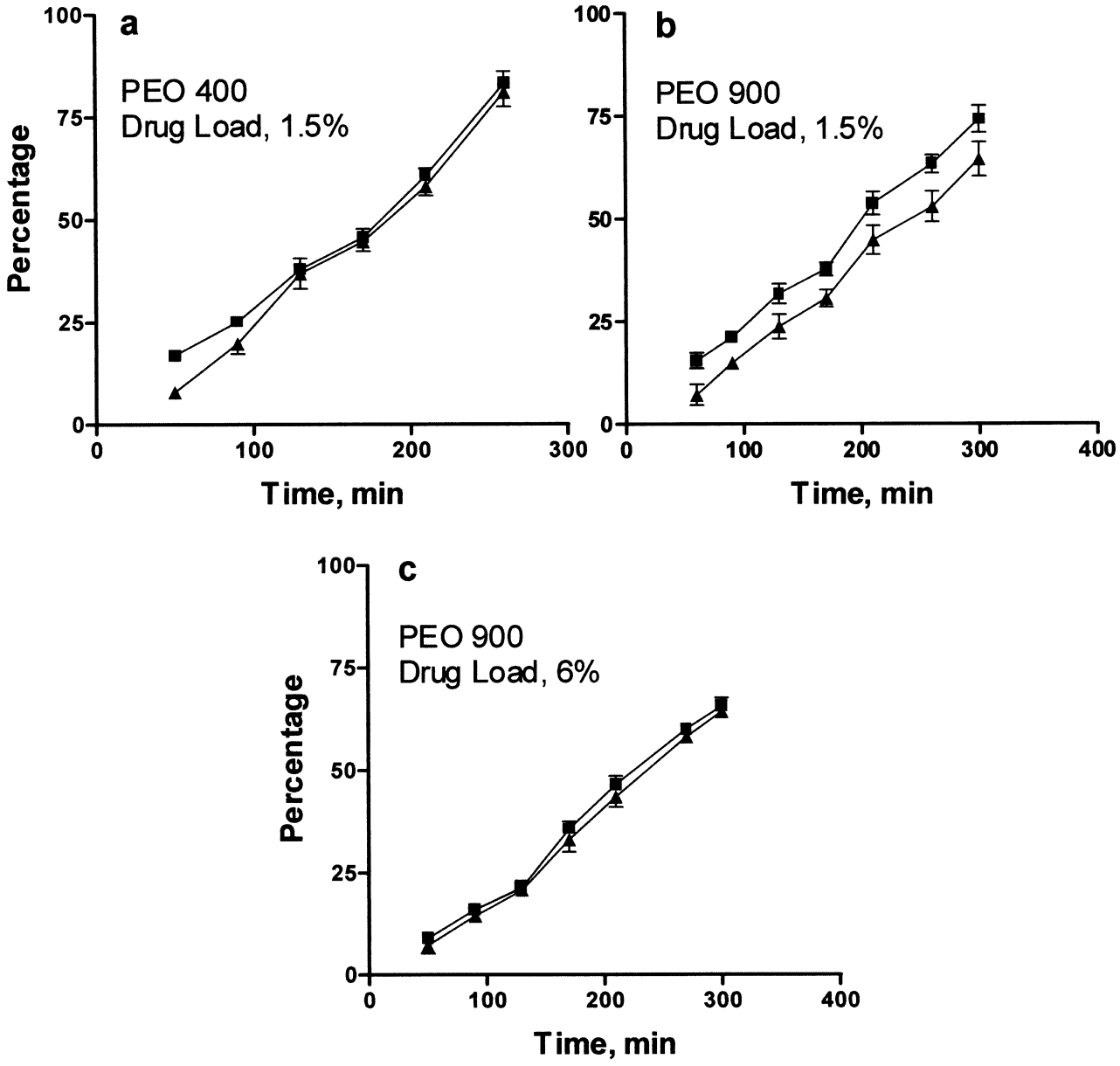

Fig. 1. Comparison of drug release and insert erosion kinetics for inserts based on PEO of different molecular weight, medicated with PDS. Key: ■, percent of released dose; ▲, percent of eroded insert. Each data point is the mean ± SD of at least three values.

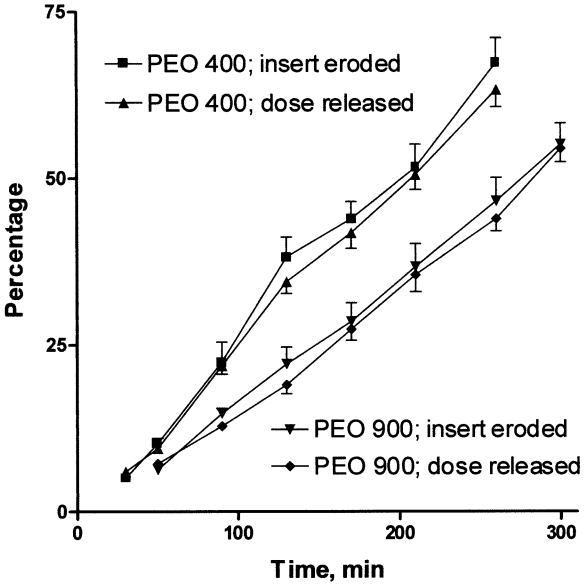

Fig. 2. Comparison of drug release and insert erosion kinetics for inserts based on PEO of different molecular weight, medicated with 1.5% OTH. Each data point is the mean ± SD of at least three values.

polymer. The tendency of drug release and matrix erosion data points to coincide later in the process indicates that with PEO 400, erosion soon became faster than diffusion and the diffusion layer within the matrix was eliminated in around 2 h. With PEO 900 as the matrix material, the released fraction exceeded the corresponding erosion level by substantially the same magnitude throughout the process, as can be seen in Fig. 1b. Again this indicates an erosion-controlled release mechanism preceded by a short-term swelling-diffusive phase. In this case, however, due to the lower erosion rate of PEO 900 compared to PEO 400, the erosion front did not catch up with the diffusion front, but rather, a constant distance between moving fronts was maintained during the time of experiment, as shown by the virtually constant difference between percent dose released and percent insert eroded. The data in Fig. 1a, b are similar to those obtained in the previous study with PEO 400 and PEO 900 ocular inserts loaded with 1.5% OFX [1]. When the PDS concentration in the PEO 900 matrix was substantially increased, as in Fig. 1c, the process was completely erosion-controlled since the start, indicating that higher concentrations of this drug reduced the diffusive contribution to the release mechanism. Fig. 2 shows a non-significant difference between corresponding release and erosion data points for PEO 400 and PEO 900 matrices loaded with 1.5% OTH. Such a coincidence of release and erosion was still observed when the drug load was raised to 6% (data not shown). A perfectly erosive mechanism with OTH, apparent from the data, points to a slower diffusion of this molecule in the PEO gels as compared to OFX or PDS, the reasons for which will be discussed below. With GTS, on the other hand, the release of large drug fractions was not governed by matrix erosion. Indeed, as shown in Fig. 3a, with PEO 400 as the matrix material, 45% of drug dose was released in the first hour, while only 20% matrix was eroded. Up to such a time the release rate was higher than the erosion rate, clearly indicating that the parallel swelling–diffusive mechanism prevailed over erosion in controlling release. Later, the release and erosion rates apparently became equal, meaning that erosion had taken control of the process. According to an analogous interpretation of the data in Fig. 3b, with the matrix based on PEO 900, which showed a slower erosion, release became erosion-controlled after about 80 min, when 53% of the drug dose had been released and 16% matrix had been eroded. These findings suggest a comparatively fast GTS diffusion in the hydrated PEO. In the previous study, in vivo data confirmed the erosive mechanism for OFX release from PEO inserts that had been expected by the same in vitro experimental procedure as that used in the present work for PDS and OTH [1]. Then, a similar in vivo mechanism can be expected for these drugs on the basis of the present in vitro data. For GTS, on the other hand, the in vitro results suggest that swelling–diffusion should be an important contributing mechanism of in vivo release.

3.2. Correlation between release mechanism and drug physicochemical properties

The foregoing discussion has suggested that the deviation of release mechanism from pure erosion is directly correlated, for a given erosion rate of the PEO gel, with the drug diffusion rate in gel. In principle, then, such a deviation should depend directly on an intrinsic property of the drug molecule, such as the diffusivity in the PEO gel. In order to verify this correlation, the rank order of diffusivities for the drugs under study was compared with that of the respective deviations from a purely erosive mechanism. For each drug, such a deviation was quantified by the averaged difference between drug fraction released and matrix fraction eroded at corresponding times. The mean value of the difference, Δ (Table 1), was computed for data points relative to PEO 900 inserts, over a period where such a difference was virtually constant because the process had become erosion-controlled. For PDS, OFX and GTS, such a period was 60–300 min (Fig. 1b), 30–300 min (see Fig. 3 of the paper of Di Colo et al. [1], graph relative to PEO 900) and 80–175 min (Fig. 3b), respectively. In fact, for each drug, linear regression analysis of release and erosion data points over the respective, above indicated period yielded slopes are not significantly different (according to 95% confidence intervals), thus, testifying to a constancy of Δ in the stated time interval. For OTH the mean Δ value was not significantly different from 0, as apparent from the relevant data in Fig. 2. To test the hypothesis that drug diffusion occurred in the aqueous phase of the PEO gel, the diffusion coefficient in PB was determined for the different drugs under study and the rank order of the obtained values was compared with that of the Δ values. No direct correlation between the two

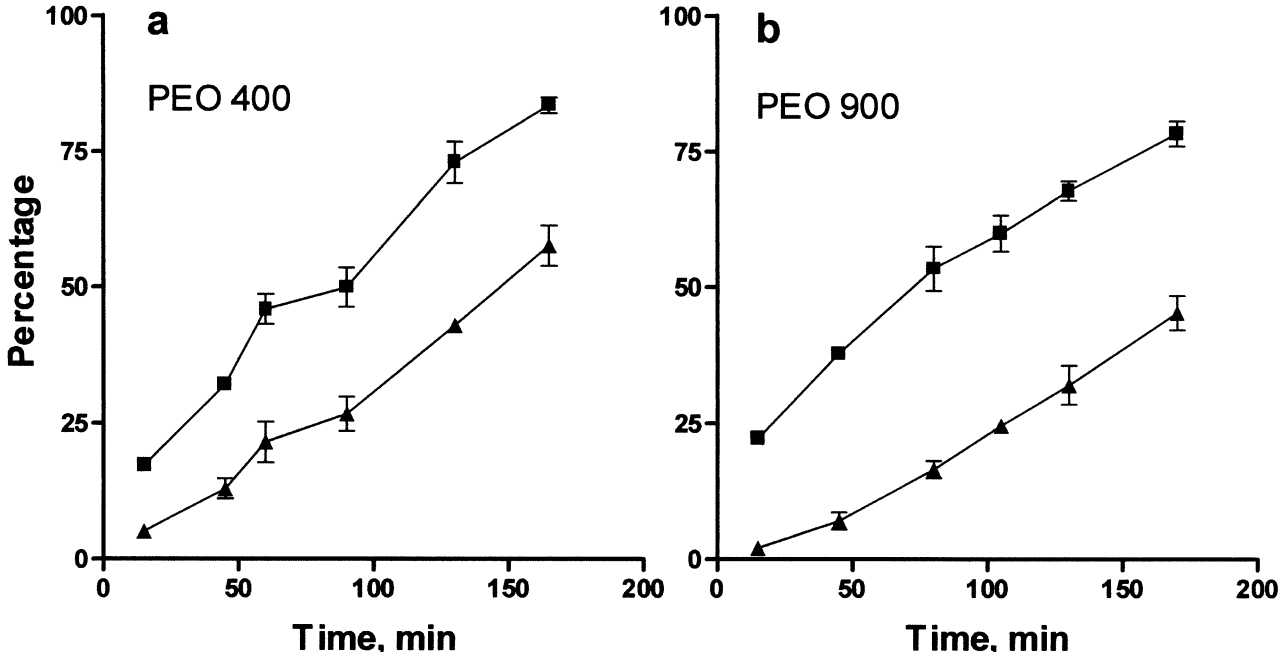

Fig. 3. Comparison of drug release and insert erosion kinetics for inserts based on PEO of different molecular weight, medicated with 4.8% GTS. Key: ■, percent of released dose; ▲, percent of eroded insert. Each data point is the mean ± SD of at least three values.

data sets is apparent (Table 1), in fact, the maximum Δ value corresponds to the minimum D value. Probably, then, the rank order of the real diffusivities of drugs in gel should rather be assessed on the basis of drug–PEO molecular interactions, assuming that stronger interactions correspond to lower diffusivity. Since stronger interactions also correspond to lower relative activity coefficient, γ_r, a direct correlation between γ_r and diffusivity is inferred. As described under Section 2.5, γ_r values were determined for the drugs in PB solutions containing PEO 900. If the same rank order of the γ_r values reported in Table 1 for the 1.5% PEO concentration is assumed to hold for the PEO gel resulting from matrix hydration, then the actual diffusivities in such a gel should rank in the order OTH $\ll$ OFX $\cong$ PDS $<$ GTS, which is the same order as that of the Δ values. The foregoing discussion leads to the conclusion that strong drug–PEO molecular interactions will result in a purely erosive release mechanism. This was indeed the case with OTH, as indicated by the very low γ_r and Δ values seen in Table 1 for this drug. It should be stressed that, at the pH 7.4 of PB, i.e. the medium used for both the determination of γ_r and the release/erosion experiments, the hydrochloride form of OTH was converted into the free base, hence the latter form was involved in the interactions. On the other hand, the high γ_r value seen in Table 1 for GTS suggests weak GTS–PEO interactions, and hence, a comparatively high diffusivity of this molecule in the PEO gel. This is consistent with the high deviation of release mechanism from pure erosion that appears in Table 1 for this drug. The γ_r values for PDS and OFX in 1.5% PEO are not so low as to justify, per se, the almost entirely erosion-controlled release of these drugs, indicated by the relevant Δ values. It should be recognised, however, that the PEO concentration in the swollen matrix, where drug diffusion actually occurred, was much greater than 1.5%, hence the real γ_r values could be lower than those reported in Table 1 for the 1.5% PEO concentration, although their rank order should be maintained. Indeed, data in Table 1 show that when the PEO concentration was raised to 10% the γ_r values for PDS and OFX decreased considerably, indicating stronger drug–PEO interactions, and hence, lower diffusivities at higher polymer concentrations. This would justify the low Δ values for these drugs. As explained under Section 2.5.2, the γ_r value for GTS in 10% PEO could not be determined. Nevertheless, strong interactions of GTS with PEO in aqueous solution are unlikely, even at high polymer concentrations, considering the salt nature of this drug. On the other hand, the ability of PEO to interact with different unionised molecules, such as PDS, OFX and the

Table 1
Comparison of aqueous diffusion coefficient, D, and relative activity coefficient, γ_r, with deviation from purely erosive release mechanism, Δ, for different drugs (see text)

Drug	D ($cm^2\ s^{-1}$)	γ_r		Δ,% (SD; n)
		PEO 1.5%[a]	PEO 10%[a]	
OTH	3.36×10^{-6}	0.09	–	n.s.[b]
PDS	3.68×10^{-6}	0.82	0.49	8.4 (0.9; 7)
OFX	3.36×10^{-6}	0.79	0.52	10.9 (2.8; 5)
GTS	2.18×10^{-6}	0.93	–	35.3 (1.6; 4)

[a] PEO 900.
[b] Not significantly different from zero.

free base form of OTH, is consistent with the chemical nature of this polymer, which allows it to interact by either hydrogen or hydrophobic bonding. In addition to diffusivity, drug solubility in the swollen insert can determine the diffusive contribution to the release mechanism, in so far, as it determines the concentration gradients in cases where the drug is not completely dissolved in the matrix zone where diffusion occurs. Then, in these cases a difference in solubility should result in a significant difference in Δ value. A marked difference between the solubility of PDS and that of OFX in the PEO gel is suggested by the very different aqueous solubilities (0.32 mg/ml [12] vs. 2.57 mg/ml [7]) and the similar degree of drug–PEO interactions testified by the similar γ_r values, seen in Table 1. Yet, the corresponding Δ values are not significantly different. Then it is inferred that in neither case, was the drug concentration in the swollen matrix much higher than solubility. Indeed, it must be noted, that the Δ values listed in Table 1 refer to inserts loaded with therapeutic drug doses, corresponding to low concentrations in the swollen matrix. At these concentrations also OTH and GTS should be completely dissolved in the PEO gel, the former, due to strong molecular interactions with PEO, the latter, due to high water solubility. With PDS a substantial dose increase has been found to decrease the diffusive contribution to the release mechanism, as seen from a comparison of data in Fig. 1b, c, probably because the increased drug concentration in the PEO gel substantially exceeded solubility and the initial diffusion-controlled fractional release rate was decreased.

4. Conclusions

Erodible ocular inserts based on PEO 400 or PEO 900 have shown an ability to release different drugs of interest in ophthalmology, such as PDS and OTH, with the same erosion-controlled kinetics that had previously been evidenced with OFX [1]. The absence of any substantial contribution from the parallel diffusive mechanism is thought to maximise the residence time of drugs in the precorneal area, and thereby, the ocular bioavailability. With doses of these drugs in the inserts equal to those applied by the commercial dosage forms, corresponding to low concentrations in the hydrated matrices, the possibility of a purely erosive mechanism relies on drug–PEO molecular interactions, which limit drug diffusion in the swollen matrix. This has been shown to be the case with OTH, for which strong interactions with PEO have been measured, whereas some contribution from diffusion was evidenced for PDS and OFX, which showed weaker interactions with the polymer. Such a diffusive contribution disappeared when the PDS concentration in the insert was substantially increased, which has suggested that the erosive mechanism is favoured by a drug concentration in the swollen insert substantially higher than solubility. Then, with drugs having a limited solubility in the PEO gel or undergoing strong interactions with PEO, the amount released per unit time can be increased to the extent necessary to achieve the wanted therapeutic effect, simply by increasing the dose, without any decrease of the bioavailable dose fraction. On the other hand, a high water solubility accompanied by weak drug–PEO interactions should favour the parallel diffusive mechanism, as was the case with GTS, substantial dose fractions of which were released by diffusion. In this case the residence time of drug in the precorneal area is expected to be significantly shorter than that of the PEO carrier. Sterility of inserts was unnecessary for the present in vitro study. Sterility, however, is a prerequisite for insert application in the eye. Therefore, further work is needed to establish an adequate sterilisation method or an aseptic insert preparation technique.

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