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Concomitant and controlled release of dexamethasone and 5-fluorouracil from poly(ortho ester)

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Abstract

A viscous bioerodible and hydrophobic poly(ortho ester) has been developed as a biocompatible, sustained drug release system for an ophthalmic application in intraocular proliferative disorders. The combination of wound healing modulators such as 5-fluorouracil and dexamethasone is a major advantage since these drugs act at different stages of these diseases. Since 5-fluorouracil is an acidic, water-soluble compound and dexamethasone exists in three chemical forms, i.e. the water-insoluble base, the highly hydrophobic acetate ester or the basic phosphate salt, it was of interest to investigate whether the physicochemical properties of the drugs have an influence on their release rates, and whether a concomitant and sustained release of both 5-fluorouracil and dexamethasone could be achieved. It has been found that lipophilicity and acidobasicity play a major role in controlling drug release rates and polymer degradation. The combination of 5-fluorouracil and dexamethasone phosphate allows a sustained and concomitant release of both drugs, due to the basic characteristics of the corticosteroid which stabilize the polymer. This system appears to be promising for concomitant and controlled drug delivery aimed at the pharmacological treatment of intraocular proliferative disorders.

Keywords: Poly(ortho esters); Bioerodible polymer; Drug delivery; Ocular delivery; Release kinetics; Sustained release; 5-Fluorouracil; Dexamethasone

1. Introduction

Bioerodible polymers such as poly(ortho esters) (POE) have gained increasing interest in the field of controlled drug delivery. A viscous biocompatible POE carrier has been developed for an ophthalmic application in intraocular proliferative

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disorders such as glaucoma filtration surgery failure and proliferative vitreoretinopathy (PVR; Zignani et al., 1999).

Fibroblast proliferation plays an important role in the pathogenesis of these diseases; various wound healing modulators, such as antimetabolites or corticosteroids, have been shown to inhibit this proliferation (Blumenkranz et al., 1984). 5-Fluorouracil is an antimetabolite which is used to prevent subsequent scarring following trabeculectomy (The Fluorouracil Filtering Surgery Study Group, 1996), and to improve the prognosis for long-term retinal reattachment following PVR (Rubsamen et al., 1994). This postoperative administration requires frequent intraocular injections, with subsequent patient discomfort and risks of complications. Dexamethasone is a corticosteroid, which has proven to be effective in the treatment of intraocular inflammation (Hainsworth et al., 1996). Multiple intraocular injections are necessary to provide an efficient treatment. The combination of antimetabolites and corticosteroids is a major advantage since these drugs inhibit progression of the disease at various stages, i.e. the inflammatory and proliferative phases. A controlled-release system will allow a sustained delivery of drugs and thus prolong the duration of drug action, avoiding the need for frequent intraocular injections and decreasing the risks of complications.

POE are bioerodible hydrophobic polymers containing labile ortho ester linkages which are subject to acid-catalyzed hydrolysis. As a result, the incorporation of an acidic species can accelerate the hydrolysis of the polymeric matrix while a basic compound stabilizes the ortho ester linkages and thus prolongs the life time of the polymer (Merkli et al., 1995). A second important property of POE is their hydrophobicity. Water hardly penetrates the bulk of the polymeric matrix, leading to a preferential hydrolysis of the labile bonds at the surface (Heller, 1993). Another erosion process has been described for more hydrophilic polymers such as poly(lactic-co-glycolic acid), the so-called bulk erosion (Göpferich, 1996). Drug release from biodegradable matrices occurs by one or, more frequently, a combination of these processes: matrix degradation by surface- and/or bulk-erosion, solubilization of the dispersed drug and diffusion through the polymer continuum via connected channels (Vert et al., 1991).

If POE undergo surface erosion, the release rates should not be influenced by the nature of the incorporated compounds. The therapeutic agents investigated in the present study are characterized by different physicochemical properties. 5-Fluorouracil (5-FU) is an acidic and hydrophilic substance. Dexamethasone is available as a poorly soluble free base (DEX-B), a highly hydrophobic acetate ester (DEX-A), and a basic sodium phosphate salt (DEX-P).

The aim of this study was to prepare POE matrices containing 5-FU and/or different DEX. The release characteristics of each drug, alone or combined, was established, as well as the polymer degradation. Since the physicochemical properties of the drugs, such as aqueous solubility, lipophilicity and acidobasicity are very different, the effects of these physicochemical properties on drug release and polymer degradation were investigated.

2. Materials and methods

2.1. Materials

Trimethyl orthoacetate and 1,2,6-hexanetriol were purchased from Aldrich® Chemie (Steinheim, Germany). 5-fluorouracil, dexamethasone, dexamethasone sodium phosphate and dexamethasone acetate were purchased from Sigma® Chemie AG (Buchs, Switzerland). All other chemicals used were reagent grade.

2.2. Polymer synthesis

As previously described by Merkli et al. (1993), semi-solid POE is synthesized by a transesterification reaction between 1,2,6-hexanetriol and trimethyl orthoacetate under anhydrous conditions. The polymer is purified by a precipitation procedure to remove impurities such as residual monomers and oligomers. Eventually, it is dried under high vacuum in order to eliminate all residual solvents (Merkli et al., 1996).

2.3. Molecular weight determination

The average molecular weight of the POE was determined by size exclusion chromatography (SEC) using a Waters® 150 CV instrument with four Ultrastyragel® columns of 500, 10^3, 10^4 and 10^5 Å pore size in series (Waters®, Volketswil, Switzerland) and tetrahydrofuran as eluent. Monodisperse polystyrene standards were used for the calibration (Merkli et al., 1993).

The semi-solid POE used in this study had a weight-average molecular weight of 8 kDa.

2.4. Drug release studies

In vitro drug release studies were carried out in specially designed thermostated cells (37°C; Merkli et al., 1993). POE was loaded with each drug alone (5-FU, DEX-B, DEX-A, DEX-P) or with a combination of 5-FU with each DEX form. For each batch, the drug loading was 1% w/w. The drugs were incorporated by simple mixing at room temperature and about 200 mg of this mixture were placed into each cell. Phosphate buffer solution pH 7.4 was circulated through the cells at the rate of 6 ml/h, and collected every 4 h. Release kinetics were monitored over 96 h. Aliquots of 450 μl of the released medium of each cell were sampled and 50 μl of an indoprofen solution were added as an internal standard.

2.5. Quantification of the amount of drug released

The amount of 5-FU and DEX released was determined by a capillary electrophoresis assay. A micellar electrokinetic chromatographic (MEKC) method was developed. Experiments were carried out using a $HP^{3D}CE$ system (Hewlett Packard®, Wilmington, DE, USA) and fused-silica capillaries with an internal diameter of 50 μm equipped with an extended path-length detection window, 64.5 cm total length. The separation buffer was 20 mM tetraborate-phosphate pH 9.0 solution containing 50 mM of sodium dodecyl sulfate. Electrophoresis was performed at a constant voltage of 30 kV and the capillary was thermostated at 30°C. Detection was performed using a diode array detector. Electropherograms were monitored at 242 nm for DEX, at 265 nm for 5-FU and at 300 nm for the internal standard.

2.6. Erosion studies

Erosion studies were performed on 200 mg samples immersed in 5 ml phosphate buffer solution pH 7.4, and agitated at 50 rpm at 37°C. Buffer solutions were changed at appropriate intervals of time to maintain sink conditions throughout. At predetermined intervals, matrices were removed from the media and lyophilized.

Polymer weight loss was evaluated by a gravimetric analysis. The percentage weight loss WL (%) of each semi-solid POE was obtained from the following equation:

$$\mathrm{WL}\ (\%) = 100 \cdot \frac{W_0 - W_r}{W_0}$$

where W_0 and W_r are the initial weight and the residual weight of the same dried and partially eroded matrices (Merkli et al., 1994).

To investigate molecular weight changes during degradation of the matrices, the lyophilized samples were dissolved in tetrahydrofuran and their molecular weight determined by the SEC method described above.

3. Results and discussion

3.1. Physicochemical characteristics of the drugs

The drugs used in this study have very different characteristics. 5-Fluorouracil is a fluorinated pyrimidine analog with a low molecular weight ($MW = 130$) whereas the three dexamethasones possess a fluorinated steroidal backbone with a higher molecular weight ($MW \geq 393$). Dexamethasone sodium phosphate (DEX-P) is freely water soluble due to the ionic sodium salt, followed by sparing water solubility of 5-fluorouracil (5-FU) and very low aqueous solubility of dexamethasone (DEX-B) and dexamethasone acetate (DEX-A). While DEX-B and DEX-A are neutral compounds, 5-FU is acidic, whereas DEX-P is basic. According to partition coefficients experimentally determined by a partition between oc-

tanol and phosphate buffer solution pH 7.4, DEX-B and DEX-A are hydrophobic, particularly DEX-A, while 5-FU is hydrophilic. Despite its steroidal structure, DEX-P, because it is a sodium salt, is also hydrophilic. Therefore, these four compounds have very different physicochemical characteristics, and cover a wide range of water solubility, hydrophilic/hydrophobic balance and acidobasicity (Table 1).

3.2. In vitro release studies

Fig. 1 shows cumulative and individual release profiles of 1% w/w 5-FU, DEX-B, DEX-A and DEX-P from a 8-kDa POE. 5-FU is released much faster than the three forms of DEX. The release follows a nearly linear pattern, and is completed in 36 h. Among the dexamethasones, DEX-B shows the fastest release, with a sigmoidal release profile. All the drug is released in 96 h. Compared to DEX-B, DEX-P exhibits a linear and much slower release. About 20% of the drug is released in 96 h, and complete release occurs over 10 days approximately (data not shown). DEX-A is not released from the polymeric matrix.

These different release profiles can be attributed to the different physicochemical characteristics of the drugs. Hydrophilicity is an important parameter that controls the release rate. Hydrophobic

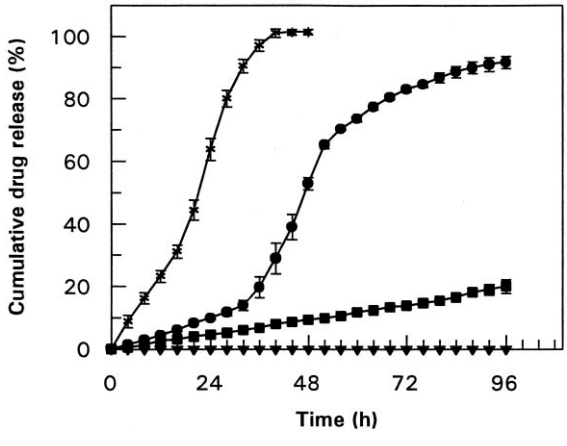

Fig. 1. Cumulative in vitro release of 5-FU (*), DEX-B (●), DEX-A (▼), and DEX-P (■) from POE (8 kDa) (phosphate buffer pH 7.4; 37°C; $n = 6$, mean ± SD; drug loading 1% w/w).

POEs become increasingly hydrophilic when compounds such as water-soluble drugs are incorporated in the polymeric matrix with consequent increase of the hydrolysis rate and drug diffusion. The hydrophilic 5-FU is released faster, particularly when compared to DEX-A whose extreme lipophilicity renders the polymeric matrix highly water-impermeable, which may hinder DEX-A dissolution and diffusion through the bulk. DEX-B possesses less marked hydrophobic properties, which explains its release rate which is slower than 5-FU but significantly faster than DEX-A. However, the acidobasic properties of the incorporated drug are even a more significant and influential parameter. Since 5-FU is acidic, it has a catalytic effect on POE hydrolysis, thus inducing a faster degradation and drug release principally controlled by polymer surface erosion. Though DEX-P is the most hydrophilic compound of the series, its basicity exerts a stabilizing effect on POE by buffering the whole system and protecting the ortho ester bonds from acidic hydrolysis. As previously reported (Merkli et al., 1995), the presence of basic compounds such as magnesium hydroxide within POE stabilizes the ortho-ester bonds and reduces the degradation rate, leading to a predominantly diffusion-controlled drug release. DEX-B and DEX-A are neutral, and have no such effect on polymer degradation.

It can be deduced that surface erosion does not solely control the release of the compounds used in this study. If surface erosion was the mechanism by which POEs erode, all compounds should be released at the same rate by a zero-order release kinetics, irrespective of the nature of the compound. Factors such as water solubility, lipophilicity and acidobasicity influence their release by affecting the dissolution and diffusion of the loaded drug from the matrix.

To determine whether the drugs have an influence on the release rate of each other, and because the combination of 5-FU and DEX is of therapeutic interest for the treatment of intraocular proliferative diseases, we have incorporated 1% of both 5-FU and one of the three forms of dexamethasone into the POE. Fig. 2 shows that the presence of any DEX significantly prolongs the

Table 1
Physicochemical characteristics of investigated drugs

Therapeutic agent	Abbreviation	Formula	Molecular weight	Aqueous solubility[a] (mg/ml)	Partition coefficient log K[b]	pH of a 1% solution
5-Fluorouracil	5-FU	$C_4H_3FN_2O_2$	130.1	10	−0.47	4.5
Dexamethasone	DEX-B	$C_{22}H_{29}FO_5$	392.5	1	1.33	7.0
Dexamethasone acetate	DEX-A	$C_{24}H_{31}FO_6$	434.5	0.1	2.65	7.0
Dexamethasone phosphate	DEX-P	$C_{22}H_{28}FNa_2O_8P$	516.4	500	−0.54	9.0

[a] At 37°C.
[b] Measured by octanol-phosphate buffer solution pH 7.4 partition at 37°C.

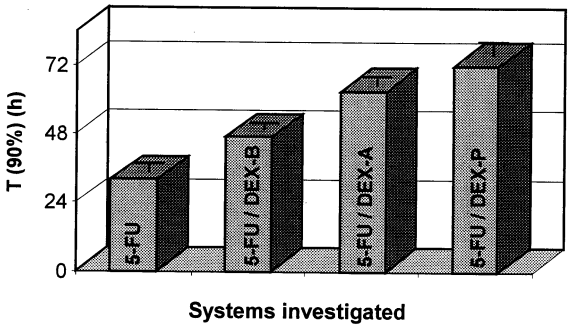

Fig. 2. Time required for the release of 90% of 5-FU when incorporated alone or in combination with the different DEX (POE 8 kDa; phosphate buffer pH 7.4; 37°C; $n = 6$, mean ± SD; drug loading 1% w/w).

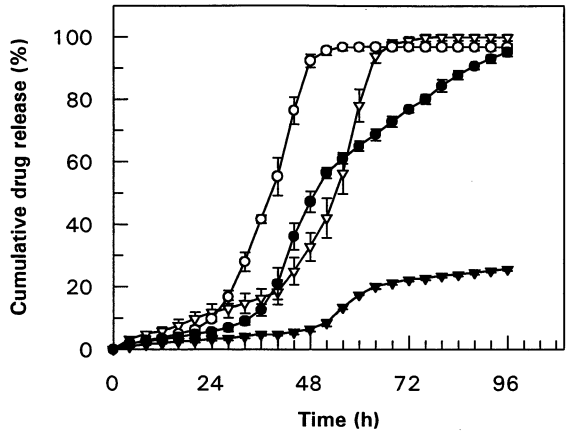

Fig. 3. Cumulative in vitro release of combined 5-FU (○) and DEX-B (●) as well as 5-FU (▽) and DEX-A (▼) from POE (8 kDa) (phosphate buffer pH 7.4; 37°C; $n = 6$, mean ± SD; drug loading 1% w/w).

release of 5-FU. The hydrophobic nature of DEX-B and, more markedly, DEX-A makes the polymeric matrix more hydrophobic, and hence delays 5-FU release by preventing water uptake. On the other hand it is the basic—though hydrophilic—character of DEX-P which allows the most sustained 5-FU release.

It has also been observed that 5-FU accelerates the release of the three forms of DEX. This hydrophilic and acidic compound makes the polymer matrix more water permeable and catalyzes hydrolysis, enhancing polymer degradation and drug release.

Figs. 3 and 4 show the combined release of both 5-FU and DEX. In the case of the 5-FU and DEX-B combination (Fig. 3), as mentioned above, 5-FU release is slowed (100% released in 48 h) by the presence of the lipophilic DEX-B compared to the release of 5-FU alone, whereas the latter is released slightly more rapidly than when incorporated alone in the matrix. Both drugs are not released at the same rate, this may be due to the hydrophobic and low water soluble nature of DEX-B which makes it less available to be released. This phenomenon is more evident when 5-FU is mixed with DEX-A (Fig. 3). 5-FU release is slower (100% released in 68 h), whereas DEX-A comes out very slowly from the polymeric matrix, only 25% is released after 96 h. It has been shown that DEX-A possesses the more marked hydrophobic character of all the drugs used here. The presence of 5-FU makes the polymeric matrix more hydrophilic and more susceptible to degradation, allowing thus DEX-A to be released, whereas very little is released when DEX-A is incorporated alone in POE. Degradation of the polymer is so slow, without the incorporation of a hydrophilic or acidic substance such as 5-FU, that no DEX-A is released. However, when 5-FU is added into the polymer, a sustained release of DEX-A is obtained. Finally, the incorporation of both 5-FU and DEX-P within POE shows a very interesting release profile (Fig. 4).

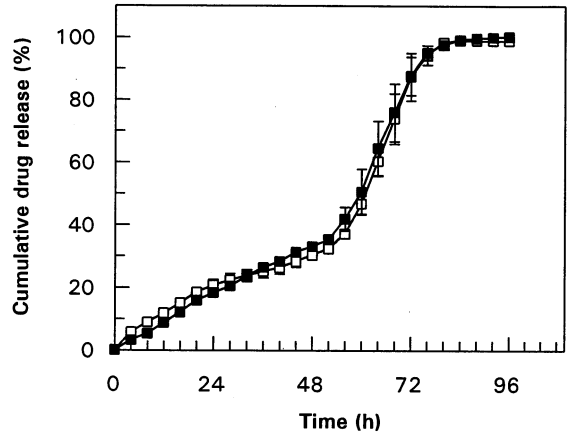

Fig. 4. Cumulative in vitro release of combined 5-FU (□) and DEX-P (■) from POE (8 kDa) (phosphate buffer pH 7.4; 37°C; $n = 6$, mean ± SD; drug loading 1% w/w).

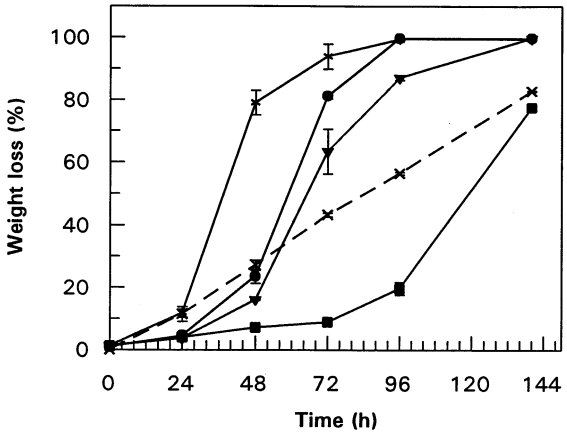

Fig. 5. Erosion profiles of matrices made of POE (8 kDa) alone (X), or loaded with 5-FU (*), DEX-B (●), DEX-A (▼) and DEX-P (■) (phosphate buffer pH 7.4; 37°C; $n = 6$, mean ± SD; drug loading 1% w/w).

The release of both substances is achieved in a concomitant and almost linear way in about 84 h. Release rate constants have been calculated according to a zero order kinetics. For the 5-FU data, the release rate constant for the initial part of the curve, up to 52 h, is of 0.57 (h^{-1}), whereas afterwards, the release becomes partially diffusion-controlled, which brings the rate constant to a value of 3.02 (h^{-1}). Concerning DEX-P, the same observations can be made with values of release rate constants of 0.69 (h^{-1}) for the erosion-controlled portion of the release, then when diffusion becomes the significant release mechanism, the constant is of 2.78 (h^{-1}). Surprisingly, the hydrophilic nature of these two products does not lead to an increased hydrophilicity of the polymeric matrix, and, as would be expected, acceleration of drug release; on the contrary this combination provides a sustained and concomitant drug delivery. Since DEX-P is basic in addition to its hydrophilic character, this basicity seems to be dominant in influencing release profile.

The concomitant administration of both 5-FU (an antimetabolite) and DEX (an anti-inflammatory corticosteroid with some antiproliferative properties) represents a very interesting treatment of proliferative diseases affecting the eye such as glaucoma filtration surgery failure or PVR. These diseases are characterized by an inflammatory phase followed by a phase of cellular proliferation. Optimal control can be achieved if antiproliferative drugs are combined and concomitantly released with anti-inflammatory corticosteroids. This approach has recently been investigated by Yang et al. (1998) who synthesized a codrug of 5-fluorouracil and triamcinolone acetonide for the treatment of experimental PVR. The device containing both drugs chemically bound was found to be more effective than treatment with either agent alone.

The release profiles of all the model compounds could not perfectly be described by a single kinetic model. If POE underwent pure surface erosion which solely controlled release, a zero-order rate of release could be expected. If the polymer did not erode, it would thus behave like a non-disintegrating, non-bioerodible matrix and the release could be expected to follow square root of time kinetics, Higuchi's model. If the aqueous diffusion boundary layer offered resistance to drug release, first order release kinetics could have been expected. The fact that a single kinetic model could not adequately describe all the release profiles suggests that the release controlling mechanism is different for each compound. The kinetics of the release also indicate that all the processes, erosion, dissolution and diffusion are simultaneously contributing to the overall release and that the extent of contribution of each alters as a function of the nature of the incorporated compound.

3.3. Degradation studies

The erosion of POE matrices was determined by measuring weight loss of the matrices by gravimetric analysis. The percentage weight loss (% w/w) of unloaded and drug loaded matrices was plotted as a function of time in Figs. 5 and 6. The overall erosion profiles are greatly affected by the incorporated drug. Unloaded POE shows a linear erosion profile, resulting from regular surface erosion. However, in the presence of the drugs, this pattern changes radically. There is an induction period during the first 24 h, which may reflect the time required for an initially hydrophobic surface to reach a steady hydrophilic state from which

hydrolysis occurs, as demonstrated with polyanhydrides (D'Emanuele et al., 1992). During this period, no weight loss occurs while molecular weight begins to decrease (Fig. 7). When the POE is loaded with each drug individually (Fig. 5), the fastest weight loss is observed in the 5-FU loaded matrix. This fast degradation is catalyzed by the acidic character of 5-FU and its water solubility which facilitates water penetration into the polymer. The water penetration has a dual effect: first, it begins to dissolve the incorporated drug and allows diffusional release to occur, and, second, it allows ionization of the acidic adjuvants with consequent catalysis of polymer erosion. It has been demonstrated that a considerable amount of water may be taken up by the POE matrix (Merkli et al., 1996). The incorporation of a hydrophilic drug such as 5-FU provokes an increase in the rate of moisture uptake due to the osmotic attraction of water into the polymer. As water-soluble substances are released more rapidly, resulting in pores and channels, more water can penetrate the matrix and come in increased contact with the polymer backbone, thus accelerating hydrolysis and erosion. This accelerated erosion further facilitates drug release and thus a cyclical chain reaction of erosion and release is set up.

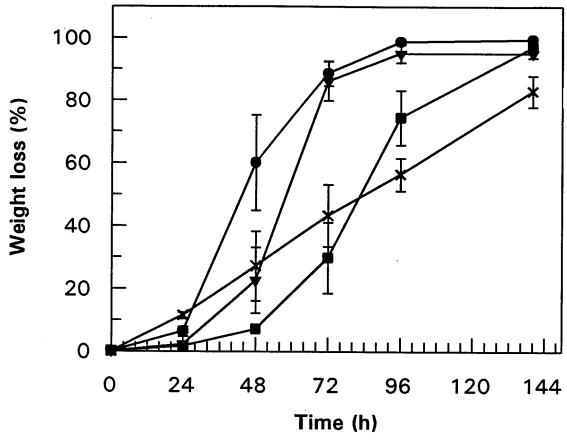

Fig. 6. Erosion profiles of matrices made of POE (8 kDa) alone (X), or loaded with combined 5-FU and DEX-B (●), 5-FU and DEX-A (▼) and 5-FU and DEX-P (■) (phosphate buffer pH 7.4; 37°C; $n = 6$, mean ± SD; drug loading 1% w/w).

The incorporation of the hydrophobic DEX-B slows down polymer erosion. Surprisingly, the POE containing DEX-A, though releasing almost no drug, shows a considerable degree of erosion. The very slow delivery of this compound is due to its water insolubility. Finally, matrices containing DEX-P erode very slowly (about 20%) up to 96 h, and then the erosion rate accelerates until final degradation occurs at about 10 days. These results confirm the fact that the basic properties, more than the hydrophilic/hydrophobic balance of DEX-P stabilize the polymer and prevent its degradation. Due to its high water solubility, DEX-P is dissolved rapidly as water penetrates into the bulk, and the resultant basic environment prevents hydrolysis of ortho ester bonds.

Fig. 6 represents the erosion profile of matrices loaded with both 5-FU and DEX. The fastest erosion rate is observed with matrices loaded with 5-FU and DEX-B. The fastest erosion rate corresponds to the fastest release rate; moreover, drug release and polymer erosion occur almost concomitantly. In this case, drug release seems to be predominantly erosion-controlled. With 5-FU and DEX-A loaded matrices, polymer lifetime is increased due to the marked hydrophobicity of the corticosteroid which prevents water penetration and thus polymer degradation. When compared to drug release rate, erosion profile follows 5-FU delivery; however, DEX-A remains within the hydrolysis medium as crystals, due to its water insolubility. Finally, POE containing 5-FU and DEX-P show the longest lifetime. The presence of the basic compound within the matrix stabilizes the ortho ester bonds and makes the polymer more stable. The erosion begins only after a 48-h induction period. By that time, about 30% of both drug has been released, which means that during this first part no erosion occurs and drug release is predominantly diffusion controlled. The presence of both water-soluble substances within the matrix renders it more hydrophilic, making water penetration easy and drugs may diffuse along the pores created by drug dissolution. After this initial phase, surface layers begin to be depleted in DEX-P, the ortho-

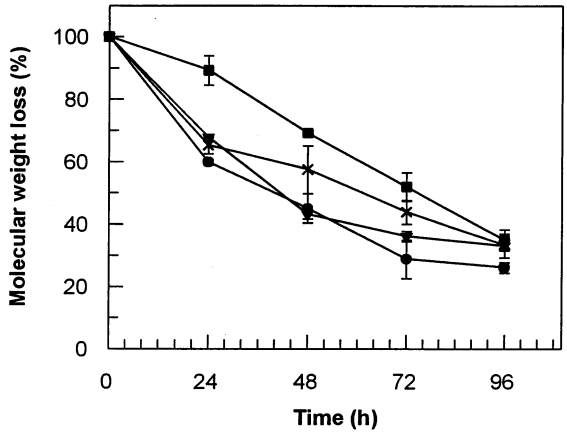

Fig. 7. Decrease in the weight average molecular weight of matrices made of POE (8 kDa) alone (X) or loaded with combined 5-FU and DEX-B (●), 5-FU and DEX-A (▼) and 5-FU and DEX-P (■) (phosphate buffer pH 7.4; 37°C; $n = 6$, mean ± SD; drug loading 1% w/w).

ester bonds are no longer protected against hydrolysis, and erosion takes place. Then, drug release is erosion and diffusion controlled.

Fig. 7 shows the decrease in weight-average molecular weight as a percentage of the initial molecular weight plotted against time for the systems containing both 5-FU and DEX. Here again, the results correlate with the former observations. During the first 24 h corresponding to the induction period of the erosion profile, a significant loss of polymer molecular weight occurs, except for the 5-FU and DEX-P system where chain scission is slower than in the other systems. The presence of both 5-FU and DEX-B induces the fastest reduction of molecular weight due to the fastest degradation rate of the polymeric matrix. The incorporation of 5-FU and DEX-A exhibits an intermediate hydrolysis rate, while the last system, containing 5-FU and DEX-P, shows a linear and slow molecular weight decrease. The polymer being stabilized by the presence of the basic compound, the polymer chains undergo a very limited hydrolysis, resulting in this limited overall degradation. It is only in this case that the decrease of molecular weight is slower than with POE alone.

4. Conclusion

The incorporation of drugs characterized by different physicochemical properties in a poly(-ortho ester) matrix shows that the nature of the therapeutic agent loaded into the polymer plays an important role in its release rate as well as in the degradation of the polymeric matrix. Incorporation of a hydrophilic drug decreases polymer lipophilicity and leads to a fast drug release predominantly diffusion-controlled and rapid polymer degradation. A hydrophobic substance tends to work against water penetration and thus decreases the overall degradation rate. However, such trends will be dramatically modified if the substance is acidic or basic, because of either catalytic or buffering effects. Dexamethasone phosphate is a basic substance, its release is markedly slowed down compared to the other compounds used in this study, despite its having the highest water solubility. In combination with 5-fluorouracil, which is though acidic, it was possible to release both drugs in a concomitant way and over an extended period of time. This biocompatible system may be a promising way to deliver concomitant and sustained drug levels for the pharmacological treatment of glaucoma filtration surgery failure after subconjunctival administration, intravitreally for proliferative vitreoretinopathy or subretinally for choroidal neovascularization.

Acknowledgements

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