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Note

Mechanisms of timolol release from monoisopropyl PVM-MA matrices with and without a basic salt

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Summary

Alkyl monoesters of poly(vinyl methyl ether-maleic anhydride) (PVM-MA) are bioerodible materials that can be used to control drug release. pH-dependent drug release from these polymers can be further modified with incorporated basic salts. This study shows that depending on mixing polymer erosion and drug release may be controlled either by polymer ionization or by hydrogen ion transport across the static diffusion layer. Timolol is released at a constant rate from the matrices with sodium acetate and, thus, they are preferred to those containing disodium phosphate.

Drug release can be controlled by acidic, bioerodible alkyl monoesters of poly(vinyl methyl ether-maleic anhydride) (PVM-MA) (Heller et al., 1978; Urtti, 1985; Urtti et al., 1985). The ionization of the carboxylic group increases the dissolution rate of these polymers (Heller et al., 1978), whereas the hydrophobicity of the ester group decreases penetration of water into the polymer. During polymer dissolution, dissociated hydrogen ions accumulate on the polymer surface and may partly inhibit ionization and polymer dissolution. Consequently, timolol release from the matrices of monoisopropyl ester of PVM-MA can be significantly increased in vitro (Finne et al., 1989) and in vivo (Finne et al., 1990) by adding basic salts to the matrices. Due to the poor buffering capacity of tear fluid (Longwell et al., 1976) drug release from the unbuffered matrices is slow and therapeutic concentrations in the target tissue are achieved only in 8 h after application to the rabbit eye (Finne et al., 1990). Basic salts added to the matrices neutralize and carry hydrogen ions from the polymer surface and in this way maintain the dissolution of the polymer in the tear fluid (Finne et al., 1990). Since the effect of a basic additive appeared to be greater in vivo (Finne et al., 1990) than in vitro (Finne et al., 1989), we studied the effect of mixing on timolol release from unbuffered and buffered matrices of monoisopropyl PVM-MA. The roles of polymer dissociation and the static diffusion

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layer in drug release and polymer dissolution are also discussed in this paper.

Films of monoisopropyl ester of PVM-MA containing 50 mg (0.12 mmol) of timolol maleate (INTER$_x$ Research Corp., MSDRL, Lawrence, KS, U.S.A.) with or without a basic additive (2.11 mmol of disodium phosphate or sodium acetate) were prepared by solvent casting using 5.0 g of 50% isopropanol solution of the polymer as described earlier (Finne et al., 1989). Circular matrices (diameter 13 mm, thickness 0.57 ± 0.06 mm) were cut from the film. Unmedicated, unbuffered matrices were prepared in the same way as the corresponding medicated matrices.

Timolol release from the matrices was studied using the rotating disk method at 35, 50, 75, and 100 rpm as described previously (Finne et al., 1989). Dissolution medium was 2 mM phosphate buffer pH 7.4 at 32 °C. Released timolol was analyzed with a UV spectrophotometer at 294 nm and the pH of the dissolution medium was monitored.

Polymer dissolution from the unmedicated matrices was studied using the rotating disk method at 50 and 100 rpm in 2 mM phosphate buffer. During the experiments, pH of the dissolution medium was maintained constant (7.35–7.45) by adding 0.1 N NaOH dropwise (20 μl) to the solution. Polymer concentrations in the samples were measured with a UV spectrophotometer at 220 nm. Release of timolol from the unbuffered matrices was also studied at constant pH and the drug concentrations were measured as above.

The surface structures of dry matrices and matrices presoaked in 2 mM phosphate buffer were examined by scanning electron microscopy (SEM) (JSM-35 scanning microscope, Jeol Ltd, Tokyo, Japan). The dried matrices were coated with gold before SEM.

Release rates of timolol (%/min) and the slopes (k) of the log (released drug) vs log (time) plots were calculated from the fitted linear regression lines. The statistical significance of the differences between the groups was tested with one-way analysis of variance (ANOVA).

The polymer surface pH was estimated with the dissolution model of Mooney et al. (1981). The model predicts the effects of the bulk solution pH, the pK_a of the dissolving acid, and the buffer concentration and pK_a on the surface pH and flux of the dissolving weak acid when rotating disc dissolution method is used. It assumes a diffusion layer-controlled mass transport and a simple, instantaneously established reaction equilibrium between all reactive acids and bases across the diffusion layer. The model was used to estimate the pH on the polymer surface at the observed values of bulk pH. The following values were used in the dissolution model of monoisopropyl ester of PVM-MA in 2 mM phosphate buffer (pH 7.4, 6.5 or 6.0; $\mu = 0.5$) at 32 °C: diffusivities of H^+ and OH^-, 3×10^{-5} cm^2/s; ionization constant of water at 32 °C, 1.8×10^{-14}; solubility of unionized PVM-MA, 8×10^{-6} M at pH 4.0; diffusivities of the ionized and unionized PVM-MA in water, 1×10^{-6} cm^2/s; dissociation constant of PVM-MA, 5×10^{-6} mol/l (Finne et al., 1989); diffusivities of the phosphates, 1×10^{-5} cm^2/s; dissociation constant of phosphate, 2.5×10^{-7} mol/l; viscosity of the PVM-MA solution on the matrix surface, 2 St.

Bulk pH in the end of the release experiment varied between 6.08 and 6.54 depending on the final amount of dissolved polymer. The speed of mixing affected neither the bulk pH nor the microclimate pH on the polymer surface as indicated by the dissolution model of Mooney et al. (1981). According to this dissolution model, equilibrium pH on the polymer surface was calculated to fall from 6.4 to 6.0 or 5.7, when the bulk pH fell from 7.4 to 6.5 or 6.0, respectively. The basic additives in the matrix had no effect on bulk pH as reported earlier, but obviously they increased the microclimate pH. The release rate of timolol at 35 rpm was increased by sodium acetate and disodium phosphate (Table 1) and, accordingly, it is possible to compensate for the poor mixing by adding a basic salt to the matrices.

Without a basic additive in the matrices timolol release increased from 0.11 ± 0.01 to 0.21 ± 0.01%/min when the speed of rotation was increased from 35 to 100 rpm (Table 1). Mixing accelerates the flux of hydrogen ions from the polymer surface by decreasing the static diffusion layer thickness. The diffusion layer thickness was calculated using the model of Mooney et al. (1981)

TABLE 1

Release of timolol from unbuffered (A) monoisopropyl PVM-MA matrices, and from matrices buffered with disodium phosphate (2.11 mmol) (B) or with sodium acetate (2.11 mmol) (C) in 2 mM phosphate buffer (pH 7.4; $\mu = 0.5$) at 32 °C using different speeds of rotation (35, 50, 75, and 100 rpm) (means ± SE of six experiments are shown)

	A	B	C
100 rpm *k* [a]	1.00 ± 0.06	0.88 ± 0.02	1.04 ± 0.04
b	0.21 ± 0.01	0.49 ± 0.03 [d]	0.30 ± 0.01 [f]
75 rpm *k*	0.85 ± 0.03	0.70 ± 0.01 [c]	
b	0.17 ± 0.002	0.36 ± 0.02 [d]	
50 rpm *k*	0.75 ± 0.01	0.70 ± 0.03	
b	0.12 ± 0.01	0.33 ± 0.02 [d]	
35 rpm *k*	0.83 ± 0.02	0.71 ± 0.02 [c]	0.94 ± 0.04 [e]
b	0.11 ± 0.01	0.17 ± 0.01 [d]	0.21 ± 0.01 [f]

[a] Slope of log(drug released) vs log(time) plot.
[b] Release rate (%/min).
[c,d] $p < 0.01$, 0.001 phosphate buffered vs unbuffered (variance analysis).
[e,f] $p < 0.01$, 0.001 acetate buffered vs unbuffered (variance analysis).

to be reduced from 95 to 56 μm when the speed of rotation was increased from 35 to 100 rpm. The release rate was increased in the same proportion as the reduction in diffusion layer thickness, as suggested also by the Noyes-Whitney dissolution equation. Thus, mixing accelerates H^+ flux to the bulk solution (Mooney et al., 1981) which leads to a faster dissolution of the polymer and increased release rate of timolol.

With an increase in the speed of rotation from 35 to 100 rpm the rate of timolol release from the sodium acetate and disodium phosphate matrices increased 43 and 188%, respectively (Table 1). Compared with the matrices containing disodium phosphate, the release rate of timolol was greater from the matrices with sodium acetate at 35 rpm, but slower at 100 rpm (Table 1). At a low speed of mixing, the static layer on the polymer surface is thicker and limits drug release more than at higher stirring rates. Thus, the role of H^+ transport by the buffer becomes more important relative to polymer dissociation. In this case, sodium acetate is more effective than disodium phosphate because acetic acid (pK_a 4.75) is almost completely ionized at the microclimate pH (5.7–6.4) whereas phosphate (pK_a 6.60) acts only partly as a proton acceptor at that pH. Consequently, a larger fraction of acetate ions than phosphate ions may carry H^+ across the diffusion layer into the bulk solution. Accordingly, the larger the fraction of the buffer in the bulk solution that is in the basic form, the faster is the dissolution of indomethacin (Mooney et al., 1981) and alkyl PVM-MA (Heller et al., 1978). In contrast, at higher speeds of mixing, the diffusion layer becomes thinner and the more basic additive (phosphate) increases timolol release more than acetate (Finne et al., 1989). This indicates that polymer ionization and surface pH, not its diffusion, is the rate-limiting factor in polymer dissolution. A lower speed of mixing (e.g. 35 rpm) corresponds better to the situation in the conjunctival sac than a higher speed (e.g. 100 rpm). Thus, addition of sodium acetate rather than disodium phosphate to the monoisopropyl PVM-MA matrices might prove more favourable in vivo in the eye.

In most cases, timolol release from the unbuffered matrices and those with disodium phosphate deviated somewhat from zero-order release kinetics ($k \neq 1.0$) (Table 1). Similar deviations from constant drug release were observed previously (Finne et al., 1989). The deviation may be explained by a decrease in bulk pH during polymer dissolution and diffusional leaching of timolol from the matrices (Finne et al., 1989). Diffusional leaching is a possible explanation in phosphate-buffered matrices, since the buffer is not dissolved, but dispersed in the polymer. Thus, pores build up to allow penetration of water upon dissolution of phosphate particles. Pore formation is supported by Fig. 1 and hydration of the phosphate-buffered matrix. The smooth, dry phosphate-buffered matrices were noticed to swell in contact with water. Release of timolol from the matrices containing disodium phosphate is faster than from the acetate buffered ones partly due to the greater number of release routes in the former. Mixing might loosen particles from the swollen phosphate-buffered polymer surface, thus increasing the dissolution area and the rate of

timolol release from the phosphate-buffered as compared with the acetate-buffered matrices.

In the case of the unbuffered matrices, accumulation of hydrogen ions on the polymer surface might explain the deviation from constant drug release when mixing is slowed down.

Timolol release from the matrices containing sodium acetate showed close to zero-order kinetics at 35 and 100 rpm (Table 1). Accordingly, timolol release from the acetate-buffered matrices occurs via surface erosion or by a Case II transport mechanism (Korsmeyer and Peppas, 1981). In contrast to phosphate-buffered matrices, no pore formation or swelling was seen in unbuffered or acetate-buffered matrices upon contact with aqueous medium.

Under constant pH, both timolol release ($k = 1.00 \pm 0.03/50$ rpm; $k = 1.03 \pm 0.02/100$ rpm) and polymer dissolution ($k = 0.86 \pm 0.02/50$ rpm; $k = 1.11 \pm 0.01/100$ rpm) from unbuffered matrices obeyed zero-order kinetics. The dissolution rate of the polymer ($0.18 \pm 0.006/50$ rpm; $0.27 \pm 0.002/100$ rpm) was fairly close to the release rate of timolol ($0.22 \pm 0.003/50$ rpm; $0.30 \pm 0.001/100$ rpm) (Fig. 2). Timolol might affect the dissolution of the polymer: the drug molecules may loosen the polymer network and decrease its organization which makes it easier for the polymer chains to dissolve. This accelerates the release of timolol and may cause the difference between timolol release and polymer dissolution from the unmedicated matrices. The data in Fig.

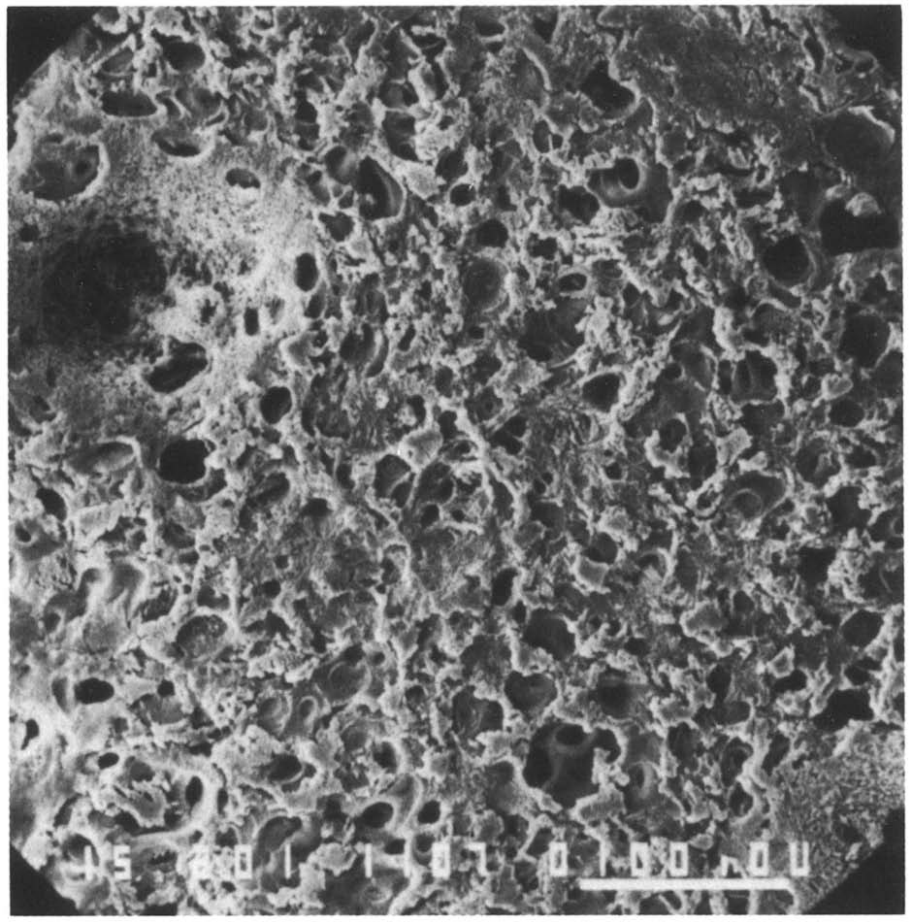

Fig. 1. Scanning electron micrograph of monoisopropyl PVM-MA matrices buffered with disodium phosphate after a 180 min soaking period in 2 mM phosphate buffer at 32 °C. Magnification: ×200.

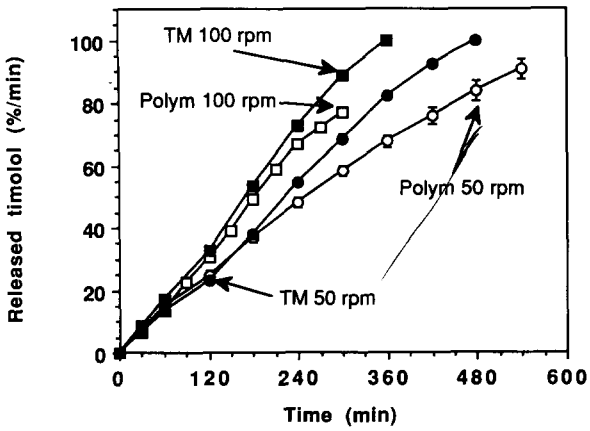

Fig. 2. Release of timolol maleate (TM) and the polymer in 2 mM phosphate buffer at 32 °C under constant pH (7.4). Means ± SE of five experiments are shown.

2 suggest a Case II type zero-order release mechanism for timolol at constant pH. However, due to the above-mentioned possible timolol-polymer interactions, the possibility that release is controlled by surface erosion cannot be ruled out either.

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