Crystal dissolution-controlled release systems. II. Metronidazole release from semicrystalline poly(vinyl alcohol) systems

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Abstract: Novel semicrystalline, poly(vinyl alcohol) (PVA)-based phase erosion systems were developed. The rate of drug release from these systems is controlled by the rate of crystal dissolution. PVA devices loaded with metronidazole were exposed to temperatures ranging from 90 to 120 C for times of 10–90 min to obtain samples with different degrees of crystallinity. Degrees of crystallinity were measured by differential scanning calorimetry and attenuated total reflectance Fourier transform infrared spectroscopy. *In vitro* release of metronidazole from such systems into deionized water at 37°C was monitored. The influence of parameters such as polymer molecular weight, annealing time and temperature, and surface pretreatment on the crystal dissolution, and hence the drug release rate, were investigated. Measurements of water-front movements were carried out to study the effect of parameters such as drug solubility on the release rate. The drug release rate was found to be dependent on the crystallization conditions of the samples. Surface pretreatment was found to reduce the burst effect observed during the release. © 1997 John Wiley & Sons, Inc. *J Biomed Mater Res,* **36,** 125–130, 1997.

Key words: poly(vinyl alcohol); controlled drug delivery; swelling controlled-release systems; hydrogels; crystallinity; dissolution; metronidazole

INTRODUCTION

State and phase erosion systems[1] have been used in the past to obtain non-Fickian release behavior of drugs from polymeric materials. Crystal dissolution-controlled release systems rely on the change of the polymer phase from crystalline to amorphous.

Poly(vinyl alcohol) (PVA) is a hydrophilic, nontoxic, and biocompatible polymer. It crystallizes to a considerable extent when annealed at temperatures slightly above its glass transition temperature ($T_g \simeq 85$°C). The use of crosslinked PVA for controlled release applications[2–6] has been extensively investigated in the past. Drug release from crosslinked polymers is controlled[7–9] by the degree of crosslinking of the polymer, and consequently the mesh space available for drug diffusion. In most cases, samples with varying degrees of chemical crosslinking are used to control the drug release rates. A shortcoming of this method is that chemical crosslinking uses crosslinking agents which are usually toxic and may leach out when exposed to biological fluids. Toxicity due to leachables may be avoided by using semicrystalline crystal dissolution-controlled release systems, where the drug release rates are controlled by heat treatment conditions, which in turn control the crystal dissolution rates.

In this work, we demonstrate the feasibility of using semicrystalline PVA for crystal dissolution-controlled release systems. Matrix systems of semicrystalline PVA with metronidazole, an antitrichomonal drug, were prepared and the mechanism of release of the drug was studied. The influence of various parameters such as polymer molecular weight, annealing temperature and time, and surface pretreatment on the release rate of metronidazole from PVA were investigated.

To obtain a better understanding of the mechanism of drug release, the water transport in these polymer

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discs was investigated, especially in relation to the formation of distinct fronts and the possible dissolution of the crystalline PVA phase during the release. Such front position movement could be compared to similar studies with noncrystalline, soluble hydrophilic matrices.[10] It can be concluded that in samples with higher initial degrees of crystallinity, the rate of crystal dissolution is much slower. As a result of this, the drug diffusion rate would also be much slower.

MATERIALS AND METHODS

Preparation of controlled release systems

Poly(vinyl alcohol) of four different molecular weights ($\overline{M}_n$ = 17,600, 35,740, 48,240, and 64,000; Elvanol®, E. I. duPont de Nemours, Wilmington, DE) was used for the experiments. The PVA samples had a degree of hydrolysis varying from 99.0 to 99.8% and polydispersity indices of 2.7, 2.16, 2.15, and 2.02, respectively. To a 10% (w/v) solution of PVA in deionized water, the desired amount (typical loading of 2–4 wt %) of metronidazole (Aldrich Chemical Co., Milwaukee, WI) was added. The solutions were cast on siliconized glass plates or petri dishes. The films were air-dried at room temperature for 5 days and crystallized by annealing at temperatures ranging from 90 to 120°C and for times varying from 10 to 90 min. No crosslinking agent was added at any point in this preparation.

Degree of crystallinity measurements

Differential scanning calorimetry (DSC) (Model 2910; TA Instruments, New Castle, DE) tests of the controlled release systems were conducted at a scanning rate of 10°C/min from 30 to 250°C. The heat of melting of PVA crystals was calculated from the DSC thermogram, and its ratio to the heat required to melt a 100% crystalline PVA sample[11] (138.6 J/g) gave the degree of crystallinity of PVA. The drug melting peak did not overlap with the PVA thermal history, nor did the presence of the drug affect the polymer peak.

Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) was used to qualitatively verify the increase in the degree of crystallinity of the PVA sample upon heat treatment. Spectral analyses of the crystalline regions in PVA and of the drug distribution within polymer samples have been widely used[12–16] in the past. In the case of PVA, this is possible owing to a change of the intensity of the 1141-cm^{-1} band, which occurs as a result of a symmetric C-C stretching mode,[13] which increases as the degree of crystallinity of the polymer increases.

In the present experiments, an FTIR spectrometer (Model 800; Nicolet, Madison, WI) was used equipped with a 45° trapezoid germanium ATR plate (Wilmad Glass Co., Buena, NJ), 50 × 10 × 2 mm^3, was used. An MCT-A detector cooled with liquid nitrogen was used to obtain the spectra. The chamber was continuously purged with dry air to reduce water vapor and carbon dioxide content. The background spectrum was first collected. Then, a 10 wt % PVA solution loaded with the desired amount of metronidazole was cast on the germanium crystal and allowed to dry at 25°C for 5 days. The thickness of the deposited films was obtained using a profilometer (Alpha-Step 200; Tencor Instruments, Santa Clara, CA). First, the spectrum of this sample was obtained. The films were then crystallized at 90, 110, and 120°C for 30 min and the spectra of all samples were obtained again.

Release studies

The release of metronidazole from PVA samples cut in the form of discs was investigated by immersing the drug-loaded systems in 1 L of deionized water in USP cells under constant stirring of 100 rpm at 37°C. The release was monitored by measuring the absorbance of the solution using a UV-Vis spectrophotometer (Model 558; Perkin Elmer, Norwalk, CT) at 317 nm. Influence of parameters such as polymer molecular weight, annealing temperature and time, drug loading, and surface pretreatment of the samples on the release rate of metronidazole were studied.

To determine the concentration of PVA dissolved and released, a 50-mL sample of the solution was complexed with 25 mL of 0.65*M* boric acid solution and 3 mL of 0.05*M* I_2/0.15*M* KI solution at 25°C. The concentration of the complexed PVA in the solution[17] was obtained by measuring the absorbance of visible light at 671 nm. Using this, the weight of PVA dissolved was calculated. This procedure was repeated at regular intervals.

Water-front measurements

A PVA sample containing metronidazole was cut in the form of a disc and placed between two Plexiglas® discs, as shown in Figure 1. The disc was then immersed in a dissolution cell containing 1 L of deionized water and agitated at 250 rpm, and dissolution in the radial direction was followed at 37°C. The agitation precluded interference from boundary layer effects. The samples were also removed from the solution at regular intervals and the front positions were recorded as a function of time using a videocamera, and measured.

RESULTS AND DISCUSSION

The main objective of this work was to establish that crystal dissolution-controlled PVA systems can be

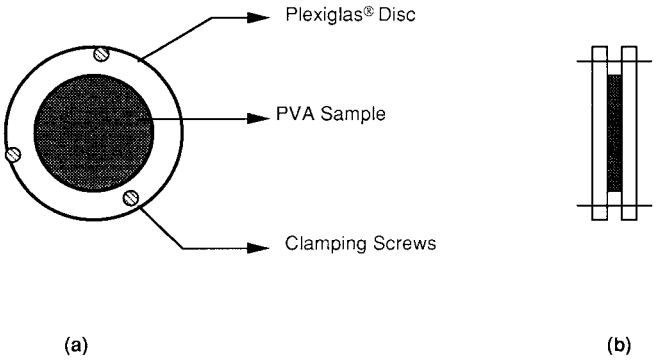

Figure 1. Sample holder for water-front measurements; (a) front view and (b) side view.

effectively used for release of drugs. As demonstrated by the experimental results, the release rate of metronidazole can be readily controlled by modifying parameters such as the polymer degree of crystallinity, the annealing temperature and time, and the polymer molecular weight.

The degrees of crystallinity of the polymer were obtained from DSC thermograms. The melting of PVA samples was found to occur from 200 to 240°C. The melting point of metronidazole is 178°C. The heat required to melt the crystals was measured by integrating the area under the melting peak on the DSC thermogram. The degrees of crystallinity of the devices were found to increase with increase in annealing time and temperature. For instance, for a sample of molecular weight of $\overline{M}_n$ = 35,240, annealing at 90°C for 30 min caused an increase in its degree of crystallinity from 19.8 to 38%. The measured values of the degrees of crystallinity were found to vary within 0.5%.

Proof of increase in the degree of crystallinity due to swelling was provided by ATR-FTIR spectra. Figure 2 shows the spectrum for an uncrystallized sample; Figure 3 presents the spectrum for the same sample crystallized at 90°C for 30 min. The height of the peak at 1141 cm^{-1} as compared to the height of a peak at 854 cm^{-1}, which remains constant, is indicative of changes in the crystalline phase of PVA. Figure 3 shows a significant increase in the height of the peak at 1141 cm^{-1} compared to the height of the same peak in Figure 2, thereby indicating an increase in the degree of crystallinity upon heat treatment. This is in agreement with the trends observed for the changes in the degree of crystallinity using DSC measurements.

The fraction of drug released, M_t/M_∞, was plotted as a function of time. Here, M_t is the weight of the drug released at time t, and M_∞ is the weight of the drug released after infinite time. The plot of the fraction of metronidazole released as a function of time (Fig. 4) shows an initial burst. This was attributed to the migration of drug to the surface ofthe polymer during storage. This burst effect was eliminated by washing the sample initially with water for 5 min before carrying out the release experiments. It is interesting to note that the profile of both the curves is very much the same, and after the initial burst is eliminated the drug release follows the same pattern.

The effect of polymer molecular weight on the rate of drug release was also studied. Increase in PVA molecular weight led to faster release of metronidazole from semicrystalline PVA samples, as shown in Figure 5. This is because PVA samples with higher molecular weight, when crystallized under identical conditions, have smaller number of crystals but larger crystals.[18] However, the overall degree of crystallinity of higher-molecular-weight samples crystallized under identical conditions is lower. This leads to decreased obstruction for drug diffusion, thereby leading to faster drug release rates. The plot of the fraction of drug released as a function of time shows a biphasic behavior. There are two distinct mechanisms of release here. The initial release profile of the drug is, of course, due to the burst effect, as well as to the precipitation of the drug both at the surface and within the sample. This initial release behavior can be attributed to the low solubility of metronidazole in water, as well as to the conversion of the crystalline to the amorphous phase. Once the movement of the fronts reaches steady state, the release profile is almost linear, as seen by fitting the second part of the curve to a straight line. Thus, zero-order release can be achieved by using these systems under suitable conditions.

The influence of annealing conditions on the release rate of the drug is shown in Figure 6. The sample

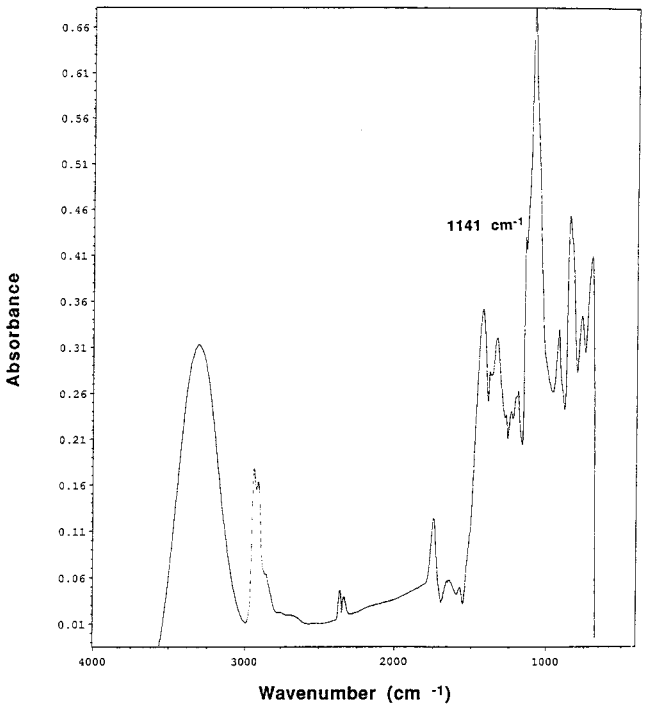

Figure 2. ATR-FTIR spectrum of an uncrystallized PVA sample ($\overline{M}_n$ = 17,600) loaded with metronidazole (4 wt %).

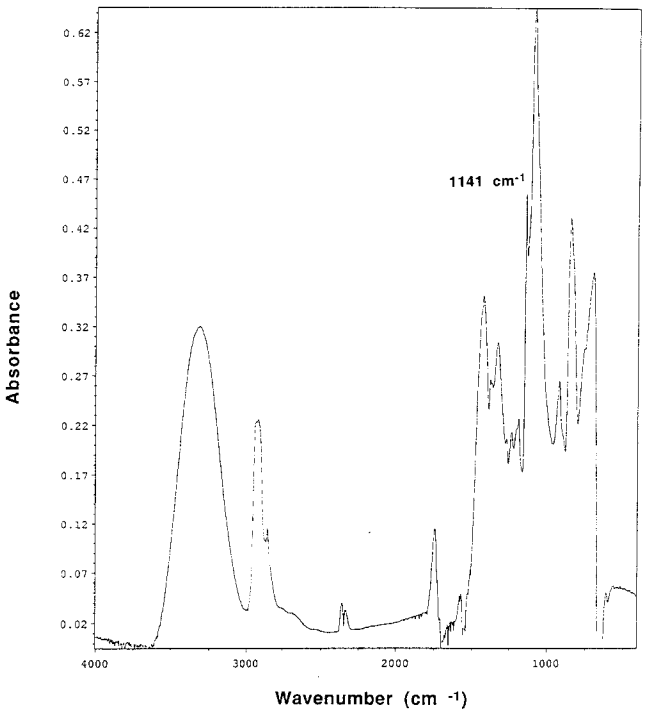

Figure 3. ATR-FTIR spectrum of the PVA sample ($\overline{M}_n$ = 17,600) loaded with metronidazole (4 wt %) and crystallized at 90°C for 30 min.

crystallized at 120°C for 1 h released metronidazole much more slowly than the sample annealed at 110°C for 10 min. As the crystallization temperature or time is increased, the degree of crystallinity of PVA increases. As a result, the hindrance for drug diffusion is higher, leading to lower drug release rates. Therefore, it is evident that controlling annealing conditions implies controlling the degree of crystallinity of the polymer, and hence the drug release rate. The plot of the fraction of drug released as a function of time exhibits biphasic behavior as in the previous case.

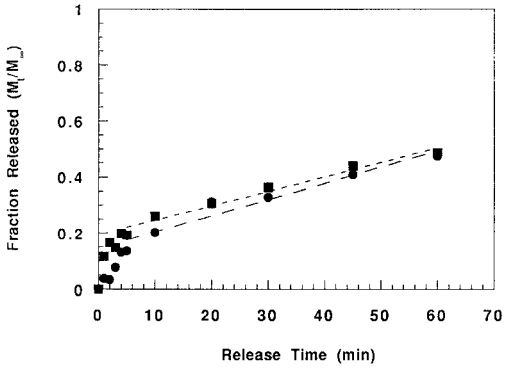

Figure 4. Elimination of burst effect by surface extraction of drug. Comparison of results for metronidazole release at 37°C from PVA ($\overline{M}_n$ = 17,600; annealed at 110°C for 20 min; metronidazole loading, 2 wt %); (●) Sample with surface extraction ($M_t/M_\infty = 0.14 + 0.006\,t$, $r^2 = 0.97156$). (■) Sample without surface pretreatment ($M_t/M_\infty = 0.19 + 0.005\,t$, $r^2 = 0.9861$). The standard deviation is too small to be drawn.

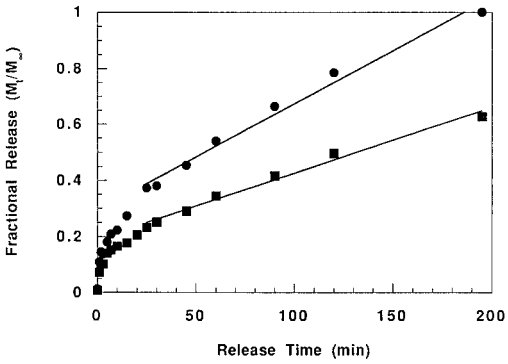

Figure 5. Influence of PVA molecular weight on metronidazole release at 37°C from PVA controlled release systems (metronidazole loading; 2 wt %; annealed at 120°C for 1 hr); (●) $\overline{M}_n$ = 64,000 ($M_t/M_\infty = 0.29 + 0.004\,t$, $r^2 = 0.98552$); and (■) $\overline{M}_n$ = 17,600 ($M_t/M_\infty = 0.19 + 0.002\,t$, $r^2 = 0.98504$). The standard deviation is too small to be drawn.

State-erosion[1] systems have been shown to exhibit zero-order release. These systems depend on polymer relaxation during transformation from a glassy to a rubbery state, to obtain zero-order release. In these systems, the glassy–rubbery transition is very fast because of the small degree of thickness of these samples. However, the unfolding of the crystals to form amorphous regions in the presence of water, or phase erosion, is presumed to be the controlling factor in this case. As a result, linear release profiles are obtained in the latter portions of the release.

Figure 7 shows the various fronts observed in the system when exposed to water. All the positions of the fronts were defined with respect to the initial diameter of the sample. The erosion front represents the polymersolvent interface; the diffusion front represents the boundary between the dissolved drug and the undissolved drug in the rubbery portion of the polymer. The swelling front represents the glassy–

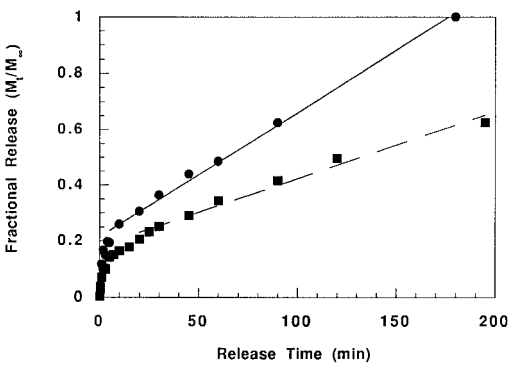

Figure 6. Influence of annealing conditions on metronidazole release at 37°C from PVA controlled release systems (PVA $\overline{M}_n$ = 17,600; metronidazole loading, 2 wt %); (●) annealed at 110°C for 20 min ($M_t/M_\infty = 0.18 + 0.002\,t$, $r^2 = 0.99124$); (■) annealed at 120°C for 1 h ($M_t/M_\infty = 0.22 + 0.004\,t$, $r^2 = 0.99663$). The standard deviation is too small to be drawn.

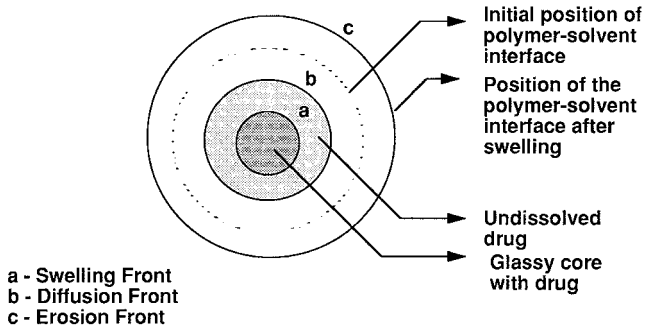

Figure 7. Schematic representation of the fronts observed as a function of time in semicrystalline PVA samples loaded with metronidazole (4 wt %) and immersed in deionized water at 37°C.

rubbery interface. The positions of the fronts were measured using a photographic technique. A typical plot of the positions of the various fronts observed as a function of time is shown in Figure 8. The swelling and diffusion fronts move inward as time progresses; therefore, they are represented as negative quantities. The erosion front moves outward as the polymer swells and is represented as a positive quantity.

The influence of the polymer degree of crystallinity on the positions of the various fronts was studied (Fig. 9). The movement of the erosion front progressed to a lesser extent in the sample with a higher degree of crystallinity. This is due to the lower degree of swelling, as opposed to the sample with a lower degree of crystallinity. The positions of the swelling fronts show that the solvent has penetrated within the sample to a much greater extent for the sample with a lower degree of crystallinity, as evidenced by the greater propagation of the swelling front in this case. The positions of the diffusion front are not markedly different in both cases. This is because metronidazole is sparingly soluble in water and its solubility in water is a controlling factor in determining drug release rates.

The difference in release rates of the drug from both samples is not markedly different, as expected from the

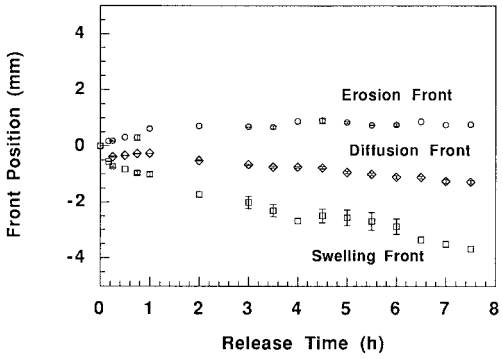

Figure 8. Water-front positions in semicrystalline PVA ($\overline{M}_n$ = 35,240) loaded with metronidazole (4 wt %) and immersed in water at 37°C. Error bars indicate standard deviation.

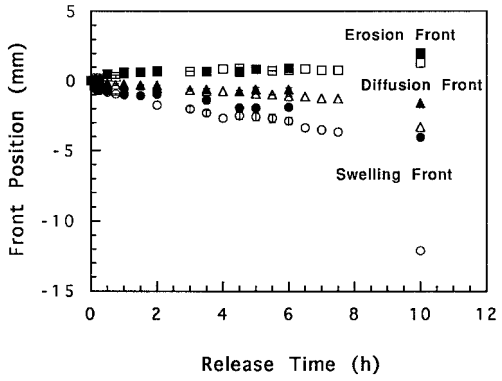

Figure 9. Influence of the degree of crystallinity of PVA samples loaded with metrronidazole (4 wt %) and immersed in deionized water at 37°C, on the positions of the fronts observed as a function of time; open symbols represent a sample with degree of crystallinity of 19.8%, and filled symbols represent a sample with degree of crystallinity of 41.2%. Error bars indicate standard deviation.

significantly different positions of the swelling fronts depicted in Figure 10. Therefore, not only is the degree of crystallinity of the polymer an important factor, the solubility of the drug also needs to be taken into consideration while determining the release rates. Moreover, owing to the release being restricted to the radial direction only, the release from such systems was found to be more non-Fickian as the exponent n in the power law model,[19] was > 0.5 in such cases.

Therefore, the degrees of crystallinity of these systems measured by both DSC and ATR-FTIR showed an increase upon heat treatment. This is because at temperatures slightly higher than the glass transition temperature, the polymer chains have just enough mobility to align themselves to form crystals.

Varying crystallization conditions caused corresponding variations in drug release rates. Increasing

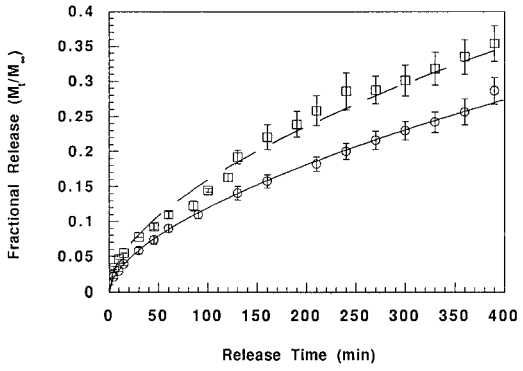

Figure 10. Influence of the degree of crystallinity of PVA samples on metronidazole release at 37°C from PVA controlled release devices containing 4 wt % metronidazole and allowing release only in the radial direction. (○) Sample with degree of crystallinity of 41.2% ($M_t / M_\infty = 0.0077 * t^{0.595}$, $r^2 = 0.9986$); (□) sample with degree of crystallinity of 19.8% ($M_t / M_\infty = 0.011 * t^{0.5627}$, r^2 0.9861). Error bars indicate standard deviation.

polymer molecular weight led to faster drug release. Surface pretreatment was found to reduce the burst effect observed in such systems.

The crystals impede the diffusion of water into the sample, as observed from the positions of the erosion front in the front measurements. The diffusion of water is also greatly decreased upon increasing the degree of crystallinity, as observed by the marked change in the position of the swelling front upon crystallization. The position of the diffusion front is, however, not dependent on the polymer; it depends mainly on the solubility of the drug and is an important factor in determining release rates.

CONCLUSIONS

In this work, we have outlined the development and characterization of novel systems based on semicrystalline PVA for controlled, non-Fickian release of metronidazole *in vitro.* The advantage of these systems is in the ease of controlling drug release rates by varying annealing conditions and by eliminating the use of any leachable, toxic crosslinking agents. Changing annealing conditions and the polymer molecular weight led to changes in metronidazole release rates. These systems exhibited a biphasic behavior during release of metronidazole.

These systems are soluble in water; their rates of dissolution depend on their annealing conditions. In actual oral or other applications, such systems will dissolve. As the polymer molecular weights are high enough to prevent absorption of the dissolved polymer by the tissues,[6] this may be considered a safe, effective way of releasing drugs at controlled rates. However, only drugs which do not lose their potency on exposure to the annealing temperatures of about 90°C can be released using these systems.

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