
● Short Communication

SELF-DIFFUSION AND MOLECULAR MOBILITY IN PVA-BASED DISSOLUTION-CONTROLLED SYSTEMS FOR DRUG DELIVERY

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Nuclear magnetic resonance (NMR) microscopy has been used to monitor the hydration of poly(vinyl alcohol) (PVA) samples of varying molecular weight. One-dimensional profiles weighted to predominantly show the variation of water concentration were acquired every 3 min during the first 30 min of hydration and subsequently at 1 and 2 h. Diffusion-weighted profiles obtained after 30 min and 1 and 2 h were used to calculate the spatial variation of the water self-diffusion coefficient. The resulting data provide supporting evidence for the hypothesis that phenomena such as reptation are important near the glassy/rubbery interface of polymers during dissolution, while the diffusion gradually changes to Zimm type near the rubbery/solvent interface. © 1998 Elsevier Science Inc.

Keywords: NMR microscopy; Poly(vinyl alcohol); Hydration; Diffusion; Reptation.

INTRODUCTION

Numerous controlled-release systems are based on polymers that swell and dissolve in the presence of a biological fluid. Dissolution of the carrier of such systems can be analysed in terms of a physical process consisting of transformation of the glassy polymer into a rubbery one, followed by chain disentanglement at the polymer solvent interface.¹ Understanding this process and the resulting polymer swelling allows for better characterisation of the likely process of drug release in these systems. Nuclear magnetic resonance (NMR) microscopy is a powerful, non-destructive technique for monitoring the hydration of controlled-release systems^{2,3} yielding information on the spatial and temporal variation of the state and concentration of water within the polymer. In this study, the hydration of one dissolution-controlled system, poly(vinyl alcohol) (PVA), was studied using an 11.7 T NMR microscope.

EXPERIMENTAL METHODS

Flat-faced tablets of 4.2-mm diameter and approximately 2-mm thickness were prepared using PVA (Elvanol grades 9050, 8582, HV, 133K supplied by DuPont) with four different average molecular weights (35,740, 48,240, 64,000 and 133,000). The tablets were formed by compression and subsequent machining of powder (particle size 200–800 μm), which was produced from cast polymer films. The films were subjected to a freeze/thaw process, which ensured that the degree of crystallinity in all samples was less than 5%. Each tablet was fixed onto a 4.2-mm diameter Nylon plug using cyanoacrylate adhesive. The plug was then glued inside a 5-mm NMR tube, with both the PVA tablet and Nylon making a tight fit inside the tube. Just before imaging, approximately 0.28 mL of distilled water was poured onto the surface of the tablet, forming a surface layer initially of about 5-mm depth.

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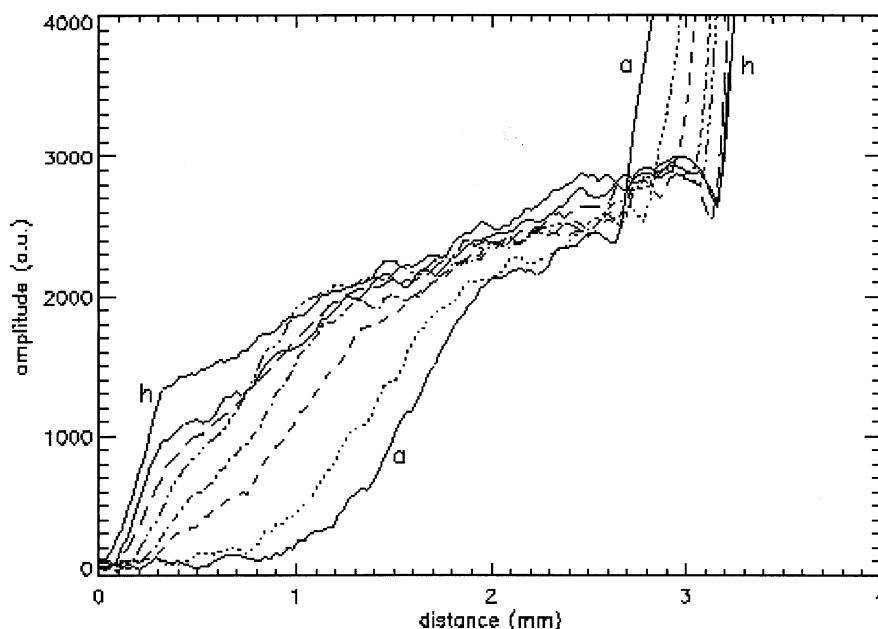


Fig. 1. One-dimensional profiles obtained from the PVA sample of molecular weight 35,740, using the spin-echo sequence which was applied after varying times of hydration (a: 2, b: 3.5, c: 5, d: 7, e: 9, f: 30, g: 60 and h: 120 min). The PVA/Nylon interface is located at the origin of these profiles and the portion of the profile at positions greater than 4 mm, showing the water layer on the surface of the sample, has been omitted for clarity.

Imaging was carried out on an 11.7 T NMR microscope⁴ using a 6-mm diameter radiofrequency saddle coil and a highly efficient gradient coil, capable of generating $1.73 \text{ Tm}^{-1} \text{ A}^{-1}$.⁵ One-dimensional profiles of $28\text{-}\mu\text{m}$ resolution, showing the variation of water concentration or self-diffusion coefficient, D , were generated after varying times of hydration using a spin-echo sequence (repetition time (TR) = 5 s, echo time (TE) = 2.75 ms). With the diffusion encoding gradients switched off, the resulting profile is mainly spin-density weighted, because in all samples T_2 is of the order of 10 ms and T_1 is approximately 1 s. Such concentration profiles were measured at approximately 3 min intervals during the first 30 min of hydration and then at 1 and 2 h. Each profile was formed from an average of eight experiments, giving a total acquisition time of 40 s. Diffusion measurements were made after 30 min, 1 h and 2 h, using 9 profiles generated with different diffusion weightings (b-values ranging from 10^3 to 2.5 smm^{-2}). The total time required to make a diffusion measurement was 6 min. All measurements were made at room temperature ($18\text{--}20^\circ\text{C}$).

RESULTS AND DISCUSSION

Figure 1 shows the concentration profiles measured in the sample of lowest molecular weight (35,740) during the process of hydration. The increasing penetration of

the water into the polymer with time and the accompanying polymer swelling is clear from these profiles. The concentration profiles obtained from all the studies were compared to those predicted by a theoretical model¹ and found to be qualitatively consistent.⁶

Figure 2 shows the spatial variation of the water self-diffusion coefficient in the same sample after 30 min of hydration. This profile displays a sudden reduction in the diffusion coefficient at the water/PVA interface and a gradual decrease in D for greater penetration distances into the polymer. The measured self-diffusion coefficients from all samples were quantitatively compared to model predictions. The models hypothesise a change in the diffusion mode as the dissolution proceeds. Initially, because the polymer chains are entangled ("concentrated" solution) phenomena such as reptation contribute to polymer motion and as disentanglement occurs, the chains have a higher mobility ("dilute" solution) and the diffusion mode changes to a Zimm type.⁷ Figure 3 shows a log-log plot of the diffusion coefficient measured close to the PVA/Nylon interface, after 30 min of hydration, versus PVA molecular weight. The slope of the line is -1.92 , which is in reasonable agreement with the predicted slope due to reptation of -2 .⁸ Figure 4 is a log-log plot of the diffusion coefficient measured at 30 min close to the water/PVA interface against PVA molecular weight. The slope in this case is -0.57 , while the Zimm

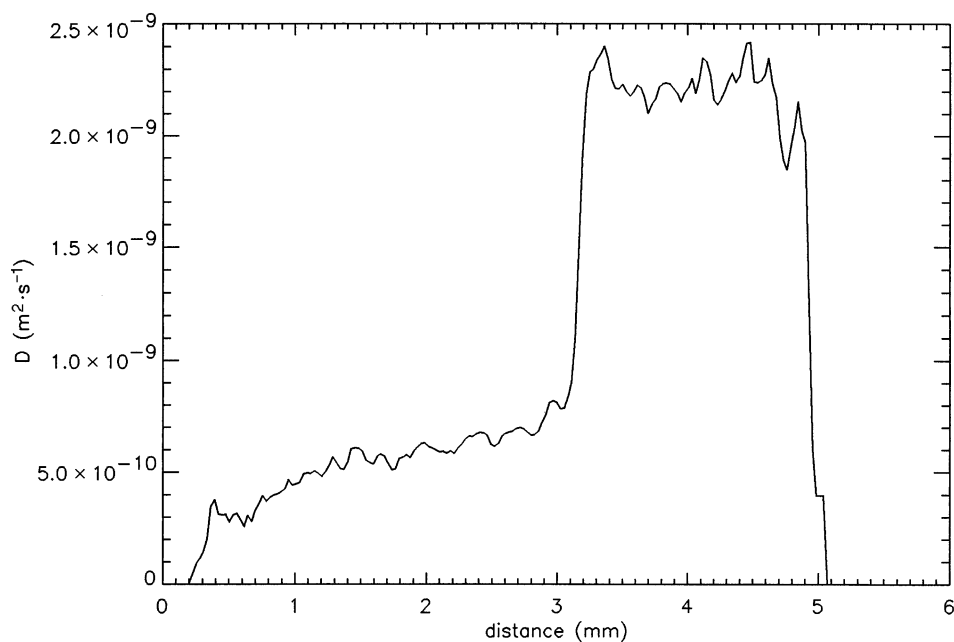


Fig. 2. One-dimensional profile showing the measured variation of self-diffusion coefficient in the 9050 PVA sample after 30 min of hydration.

analysis predicts a slope of -0.5 .⁹ These studies indicate the existence of a change in the mode of diffusion with dissolution time. It was also observed that the value of the diffusion coefficient at the water/PVA interface did

not change appreciably with time for all molecular weights. This is to be expected because the system at the interface can always be approximated as a dilute solution. The D -values close to the PVA/Nylon interface did

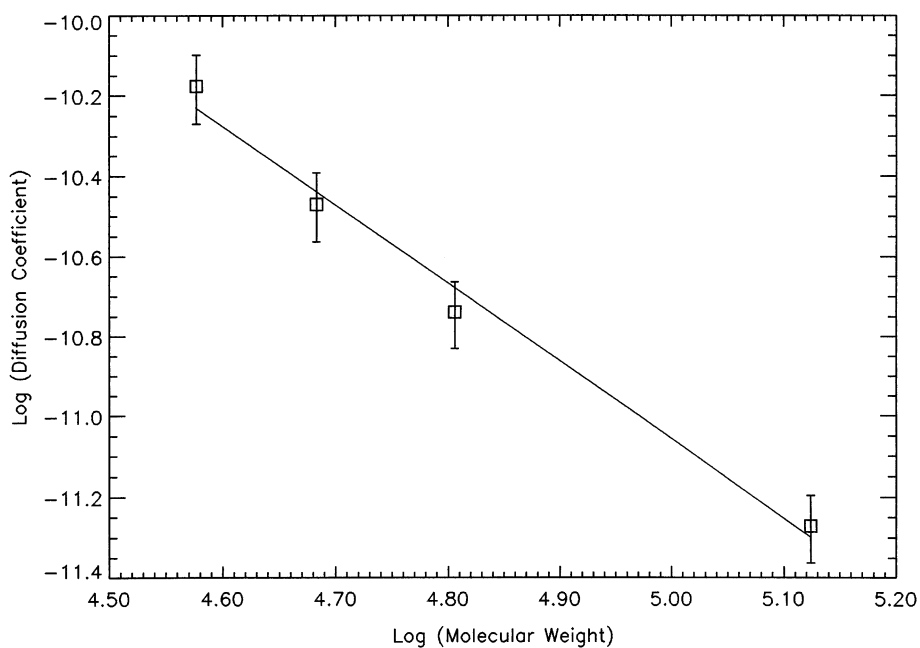


Fig. 3. Log-log plot of the self-diffusion coefficient measured near the PVA/Nylon interface as a function of the PVA molecular weight.

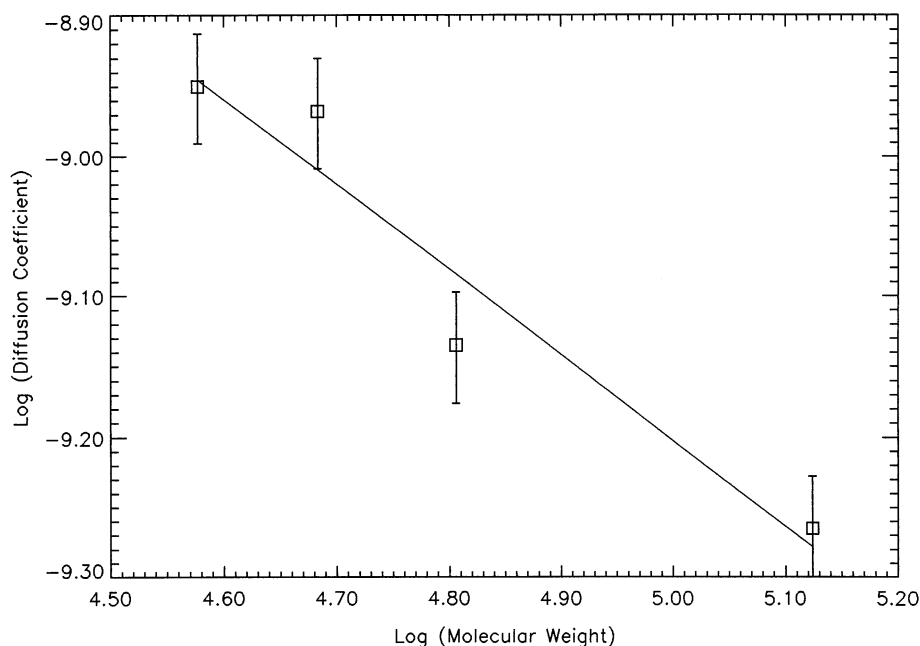


Fig. 4. Log-log plot of the self-diffusion coefficient measured near the water/PVA interface as a function of the PVA molecular weight.

show an increase with time for all molecular weights studied. This behaviour is consistent with the fact that as time elapses, water penetrates deeper into the polymer film, thus increasing the mobility of the polymer chains.

CONCLUSIONS

The present magnetic resonance imaging studies provide supporting evidence for the hypothesis that phenomena such as reptation are important near the glassy/rubbery interface of polymers during dissolution, while the diffusion gradually changes to Zimm type near the rubbery/solvent interface. The qualitative comparison of the concentration profiles with existing models is also favourable. The dramatic changes in diffusion behaviour during polymer dissolution can be taken advantage of in the design of sustained drug-delivery systems and the drug profiles can be made to mimic the polymer dissolution behaviour.¹⁰

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