Molecular Information on the Dissolution of Polydisperse Polymers: Mixtures of Long and Short Poly(ethylene oxide)

Anna Körner,[†] Anette Larsson,*[,‡] Lennart Piculell,[†] and Bengt Wittgren[§]

Department of Physical Chemistry 1, Lund University, Box 124, SE-221 00, Lund, Sweden, Department of Materials and Surface Chemistry, Chalmers University of Technology, SE-412 96, Gothenburg, Sweden, and AstraZeneca R&D, SE-431 83, Mölndal, Sweden

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A systematic study of the dissolution of dry, polydisperse poly(ethylene oxide) (PEO) samples, obtained from mixtures of low-molecular-weight and high-molecular-weight PEO, was made. During the dissolution process, the individual release of the low- and high-molecular-weight fractions was monitored. The high-molecular-weight/low-molecular-weight ratio controls the release rate, and the fraction of high-molecular-weight polymers dominates the effect on the overall release rate in mixed PEO tablets. Both fractions are released at the same rate during the main part of the dissolution process; however, during the initial dissolution period a fractionation occurs. The release rate is not a unique function of the average molecular weight of the polymer, but also depends on the polydispersity. By contrast, the average dimension of a polymer coil, as given by the intrinsic viscosity, gives a good prediction of the release rate irrespective of the polydispersity or details of the molecular weight distribution.

Introduction

The dissolution of a solid polymer in a solvent typically involves two characteristic moving boundaries (Figure 1). As in all dissolution processes, there is a boundary between the initial dry solid polymer phase and the neighboring concentrated solution phase (boundary "r", Figure 1). However, owing to the special nature of a concentrated polymer solution, where the polymer chains are highly entangled, the concentrated polymer solution bordering the solid phase typically appears as a high-viscous "gel layer" of macroscopic thickness, which remains stationary even if the surrounding solution is stirred. A second boundary may thus be identified, which separates the gel layer from the surrounding dilute solution (boundary "s", Figure 1). It is obvious, furthermore, that the two boundaries do not exist during the entire dissolution process. The development of a gel layer requires a finite time after the initial exposure of the solid polymer to the solvent. Conversely, toward the end of the dissolution process, all of the solid polymer has been consumed, and only a gel piece remains to be dissolved in the solvent (Figure 1e).

The fact that a concentrated polymer solution is highly entangled has at least two interesting consequences. First, the ultimate release of the polymer into the solution is typically very slow, and the release rate is strongly dependent on the molecular weight of the polymer.[1−3] This is of importance in all processes that involve the dissolution of a dry polymer. The second interesting consequence is the development of the gel layer, inside which the molecular diffusion is strongly dependent on the size of the diffusing molecule—as in all polymer gels. The slow (and tunable) polymer dissolution rate, and the existence of a molecular-size selective gel layer, makes a solid polymer matrix very useful for extended release formulations.[4,5]

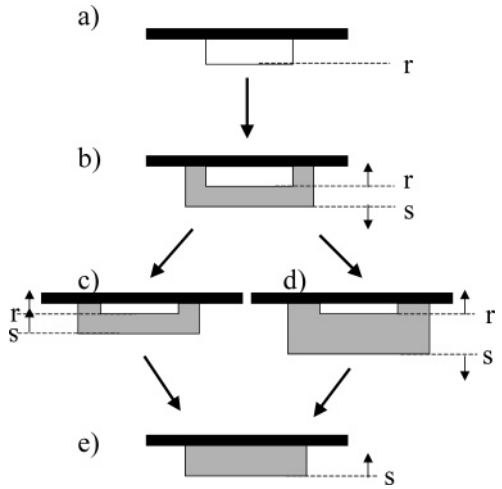

Figure 1. Schematic representation of the dissolution of a polymer tablet. (a) Dry polymer tablet mounted on a rotating disk. (b) Initial swelling step; the high-viscous gel layer develops and the gel/solvent interface, "s", moves away from the disk. At the same time the dry core/gel interface moves toward the disk. As the polymer is released from the gel, two scenarios may occur. (c) The two boundaries move toward the disk at the same rate, which yields a constant gel layer thickness. (d) Alternatively, the interface "s" continues to move away from the disk while the interface "r" moves toward the disk and the gel layer thickness continues to grow. (e) The final dissolution step when the gel layer is the only remaining part of the tablet.

Many experimental studies and modeling efforts have been performed to reveal the detailed physics behind the polymer dissolution process. Much of this work is summarized in recent review articles.[6−8] However, the models developed often contain parameters that are not available from published experiments. Therefore, they can only be used for qualitative comparisons. Moreover, the models typically consider monodisperse polymers. This limitation is unsatisfactory for two reasons. First, except for certain biological polymers, polymer samples are

* Corresponding author. E-mail: anettel@chem.chalmers.se.
[†] Lund University.
[‡] Chalmers University of Technology.
[§] AstraZeneca.

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intrinsically polydisperse. Second, mixtures of polymer fractions having different average molecular weights are used in applications to tune the dissolution rate of a dry polymer.[2,9,10]

The effect of polydispersity on the polymer release rate has not been studied extensively. Manjkow et al.[11] found that the dissolution rate of thin poly(methyl methacrylate) films was about twice as high for polydisperse samples compared to monodisperse samples with the same number-average molecular weight. Ramkisson-Ganorkar et al.[12] studied the release rate of insulin from poly(NIPAAm-*co*-BMA-*co*-AA) beads and found that increasing the polydispersity by adding long polymer chains to a low-molecular-weight fraction slowed the dissolution rate of the polymer. On the other hand, introducing polydispersity to a high-molecular-weight sample did not have a strong effect on the release kinetics.

The objective of the present work has been to gain molecular insight into the dissolution of dry polydisperse polymers. To that end, we have systematically studied the dissolution of dry "bimodal" polymer samples obtained from mixtures of low-molecular-weight and high-molecular-weight poly(ethylene oxide) (PEO) mixed in various proportions. During the release process, we have monitored the individual release of the low- and high-molecular-weight fractions. We have also compared the results from bimodal samples with those from normally polydisperse polymer samples. Finally, we have investigated whether there exists some average property of the polymer sample that may be used to predict its dissolution behavior, regardless of its degree of polydispersity.

The method used in this study was to make dry tablets of the polymers, and to study the release of polymer from the tablets when glued to rotating disks in a USP dissolution apparatus filled with water. The method has been described in a recent study of ours on the same type of bimodal tablets,[13] where only the overall release was studied. In that study it was found that a variation of the degree of crystallinity of the PEO samples, by 20% at most, did not have a significant effect on the dissolution rate of the PEO tablets. By contrast, it was found that the release rate of bimodal tablets under certain conditions depended on whether the two polymer fractions were mixed directly in the form of the original dry powders before tableting, or whether they were mixed on the molecular level in solution, followed by freeze-drying. In the present investigation, molecular mixing of the fractions is essential, and we have therefore used samples mixed in solution.

Experimental Section

Materials. Samples of Polyox WSR N-10 (hereafter referred to as PEO 0.1), Polyox WSR N-750 (hereafter referred to as PEO 0.3), Polyox WSR-1105 (hereafter referred to as PEO 0.9), and Polyox WSR N-60K (hereafter referred to as PEO 2.0) were supplied by Dow, Austria. Polyglykol 6000 (hereafter referred to as PEO 0.006) was purchased from Clariant. Other chemicals used in this work were sodium chloride (Merck), sodium azide (BDH Laboratory Supplies, Poole, UK), and 95% ethanol (Kemetyl, Haninge, Sweden).

Tablet Preparation. Tablets were made of PEO 0.1, PEO 0.3, PEO 0.9, and PEO 2.0 and of mixtures of PEO 0.1 and PEO 2.0 or PEO 0.006 and PEO 2.0 in different ratios. These mixed samples are denoted by the mass percentages of the two polymer components, starting with the low-molecular-weight component. Thus, a sample denoted PEO (0.1:2.0) 10:90 contains 10 wt % PEO 0.1 and 90 wt % PEO 2.0. The tablets were made according to a method described in detail earlier.[13] To obtain a homogeneous mixing of the two polymers on the molecular level, a 1% w/w aqueous solution was made of the polymer. The PEO solutions were freeze-dried using a HETO CD 13-2 freeze-drier. The freeze-dried material was milled before tableting. Differential scanning calorimetric measurements showed only one melting transition for the freeze-dried material, confirming that the two fractions were mixed on the molecular level.[13] The tablets were made in a single-punch tableting machine (Kilian SP300, Kilian & Co, GmbH) equipped with 12.0 mm flat-faced punches. The distance between punches was set to 2.0 mm. A 315.5 mg sample of polymer was introduced into the die, and the automatic compression cycle was run. All tablets weighed 315.5 ± 1 mg.

Dissolution Experiments. The dissolution experiments were carried out and analyzed according to a method described in detail earlier.[13] The polymer release was studied in a USP dissolution apparatus (Dissolutest, Prolabo) equipped with rotating disks (diameter 50 mm, height 5 mm). A tablet was mounted at the center of a disk using water-impermeable glue, and the disk was rotated at 100 rpm in the dissolution medium (deionized water, 25 °C). Aliquots of 2 mL for analysis (here referred to as "dissolution samples") were withdrawn from the dissolution medium at defined times. The dissolution samples were analyzed using size exclusion chromatography (SEC) on a TSK-GEL $GMPW_{XL}$ 7.8 × 300 mm, particle size 13 μm, linear mixed bed size exclusion column (TosoHaas, Montgomeryville, PA) connected online to a differential refractometer (Waters 410, Waters, Milford, MA). A solution of 10 mM NaCl with 0.02% NaN_3 was used as mobile phase, the flow rate was set to 0.3 mL/min, and the sample volume injected was 200 μL. The Millennium 32 software (Waters, Milford, MA) was used for analysis of the obtained RI chromatograms, and the polymer content in the dissolution medium was calculated using a calibration curve obtained from polymer samples of known concentration. The percentage polymer dissolved at each sample time was calculated from the known tablet weight using the relation

$$\%\ \text{released} = \left(\frac{c_n(V_0 - V_s(n-1)) + V_s \sum_{n=0}^{n-1} c_n}{w_{tbl}} \right) \times 100 \qquad (1)$$

Here c_n is the polymer concentration in dissolution sample n, V_0 is the total volume of the dissolution medium at time $t = 0$, i.e., 500 mL, V_s is the volume of the dissolution sample, i.e., 2 mL, n is the sample number in the dissolution series, and w_{tbl} is the tablet weight. Since the release profiles indicated that slightly more than 100% polymer had been released by the end of the experiment (partly due to evaporation of the dissolution medium during tempering and during the experiment), all dissolution profiles were normalized to reach 100% dissolved at the end of the experiment ($t = \infty$).

Figure 2 shows a representative chromatogram of a bimodal polymer sample. Two maxima are apparent, but there is no baseline separation between the peaks corresponding to the 2.0 and 0.1 fractions. The retention time at the minimum between the two polymer peaks for the final dissolution sample in each tablet dissolution series was therefore used as the border separating the two fractions, defined as the high-molecular-weight (HMW) and low-molecular-weight (LMW) fractions. By using this composition-specific borderline, the fraction of low-molecular-weight polymer could be determined in each dissolution sample from a given tablet.

Molecular Weight Distribution. The molecular weight distributions, the number-average molecular weights (M_n), and

TABLE 1: Number-Average Molecular Weight (M_n), Weight-Average Molecular Weight (M_w), Polydispersity Index (PI, M_w/M_n), and Intrinsic Viscosity [η] of the Polymers in the Tablets

tablet composition	$M_n/10^5$ [a]	$M_w/10^5$ [a]	PI	[η] (dL/g)
PEO 0.1	0.25 ± 0.01	1.22 ± 0.05	4.78	1.0
PEO (0.1:2.0) 90:10	0.36 ± 0.01	3.02 ± 0.08	8.39	1.6
PEO (0.1:2.0) 70:30	0.52 ± 0.01	6.95 ± 0.06	13.4	2.9
PEO (0.1:2.0) 50:50	0.64 ± 0.02	12.2 ± 0.33	19.1	4.3
PEO (0.1:2.0) 30:70	0.87 ± 0.01	14.5 ± 0.13	16.7	5.4
PEO (0.1:2.0) 10:90	1.56 ± 0.06	19.3 ± 0.37	12.4	6.8
PEO 2.0	2.34 ± 0.01	21.9 ± 0.07	9.37	7.8
PEO 0.3	1.01 ± 0.02	3.9 ± 0.03	3.88	2.7
PEO 0.9	1.56 ± 0.09	9.7 ± 0.11	6.28	4.9
PEO (0.006:2.0) 50:50				3.9
PEO (0.006:2.0) 30:70				5.6

[a] Deviations from the mean are one standard deviation.

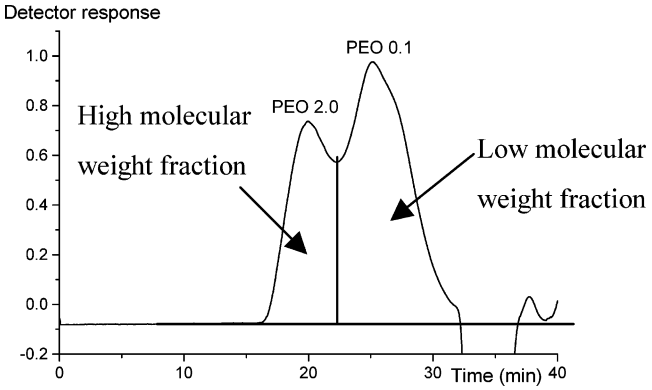

Figure 2. Representative chromatogram of a bimodal polymer sample. The fractions defined as high-molecular-weight fraction and low-molecular-weight fraction, respectivly, are indicated in the figure.

the weight-average molecular weights (M_w) of the various PEO samples and freeze-dried mixtures were determined using size exclusion chromatography (SEC) combined with both multi-angle light scattering (MALS) and refractive index (RI) detection according to a method described in ref 13.

Intrinsic Viscosity. The drainage times (t) in an Ubbelohde viscometer at 25.0 °C were measured for aqueous solutions of the PEO compositions used in the dissolution experiments. Four different concentrations of each composition as well as pure deionized water were measured using a Schott Geräte AVS 300. The viscometer was rinsed with deionized water before starting the measurements of a new composition and with the new solution before measuring a higher concentration of the same composition. The intrinsic viscosity, [η], was calculated using[14]

$$[\eta] = \lim_{c \to 0} \frac{t/t_0 - 1}{c} \qquad (2)$$

Here t is the drainage time for the PEO solution, t_0 is the drainage time for the solvent, and c is the concentration of the PEO solution.

Results

Characteristics of the Polymer Samples. Table 1 summarizes the determined number-average molecular weight (M_n), weight-average molecular weight (M_w), polydispersity index (PI), and intrinsic viscosity ([η]) of the polymers and polymer mixtures used in the study. The M_n, M_w, and intrinsic viscosity all increase with an increasing fraction of long polymer in the sample.

In Figure 3 the measured intrinsic viscosity is plotted against the measured weight-average molecular weight of the polymers in the mixed tablets. As expected, all the mixed samples fall

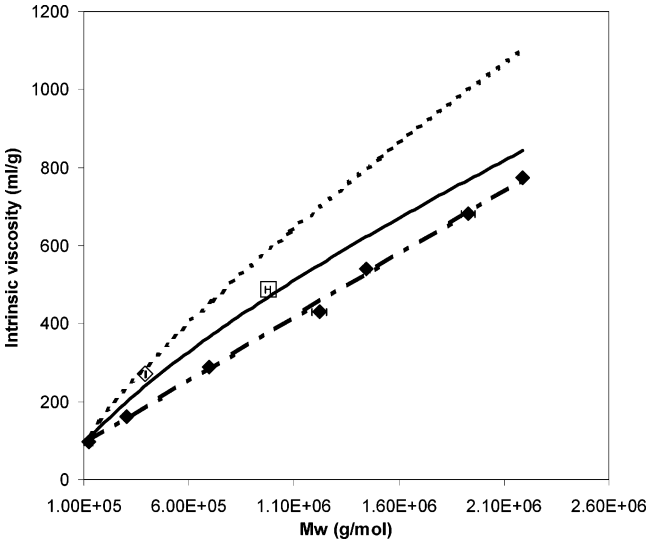

Figure 3. Intrinsic viscosity as a function of weight-average molecular weight for PEO 0.3 (unfilled diamond), PEO 0.9 (square), and the mixed PEO (0.1:2.0) series (filled diamonds). The bars indicate the standard deviation in the measurements. Lines represent linear fit to data for the mixtures (dot−dashed line), MHS fit to data for nonmixed samples (solid line), and MHS relation with $\alpha = 0.72$ and $k = 24.3 \times 10^{-3}$ mL/g (dotted line) according to literature results.[15]

on a straight line between the two endpoints. Since both the intrinsic viscosity (expressed in units of mass concentration) and M_w are linear functions of the mass fraction of (short) polymers in the mixtures, it follows that [η] must be a linear function of M_w for the mixtures. By contrast, the data for PEO 0.3 and PEO 0.9 samples deviate from the straight line. This is again expected, since for monodisperse polymers the relation between intrinsic viscosity and molar mass should follow a Mark−Houwink−Sakurada (MHS) power law, $[\eta] = kM^{\alpha}$,[16] where, typically, $\alpha < 1$. A power law fit to the data for the nonmixed samples (PEO 0.1, PEO 0.3, PEO 0.9, and PEO 2.0) is shown in Figure 3. The fit is only moderately good ($R^2 = 0.99$), presumably because the various "pure" fractions are quite polydisperse, and gives an exponent $\alpha = 0.72$ and $k = 24.3 \times 10^{-3}$ mL/g. These fitted MHS parameters can be compared to values found in the literature;[15] $\alpha = 0.78$ and $k = 12.5 \times 10^{-3}$ mL/g (PEO in the molecular weight range 20 000−5 000 000, and $1.8 \leq$ PI ≤ 2.4 at 30 °C).[16] The observed difference between our values and those found in the literature is probably due to the large polydispersity of our samples.

Dissolution Experiments. When a rotating tablet was exposed to the dissolution medium in the USP apparatus, it soon developed a swollen gel layer surrounding the tablet core, as illustrated schematically in Figure 1. The outermost part

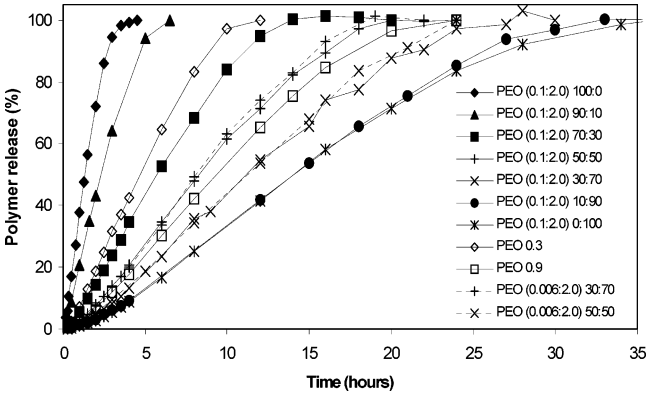

Figure 4. Release profiles for tablets in the study.

TABLE 2: Release Rates, Release Times, and Low-Molecular-Weight Fractions of the Mixed Tablets

tablet composition	t_{50}[a] (h)	r_{50}[a] (%/h)	LMW (%)
PEO 0.1	1.3 ± 0.0	37.8 ± 3.2	
PEO (0.1:2.0) 90:10	2.3 ± 0.0	21.8 ± 0.6	94
PEO (0.1:2.0) 70:30	5.8 ± 0.1	9.4 ± 0.1	82
PEO (0.1:2.0) 50:50	8.5 ± 0.1	6.8 ± 0.1	65
PEO (0.1:2.0) 30:70	11.2 ± 0.7	4.9 ± 0.6	46
PEO (0.1:2.0) 10:90	14.1 ± 0.1	4.0 ± 0.1	30
PEO 2.0	14.0 ± 0.0	4.0 ± 0.4	
PEO 0.3	4.7 ± 0.0	11.6 ± 0.4	
PEO 0.9	9.4 ± 0.1	5.9 ± 0.1	
PEO (0.006:2.0) 50:50	8.1 ± 0.1	7.3 ± 0.5	52
PEO (0.006:2.0) 30:70	11.3 ± 0.3	4.8 ± 0.2	32

[a] Deviations from the mean are the highest deviations determined for each composition.

(typically less than 1 mm) of the gel was transparent, whereas the major part of the gel was opaque, possibly due to a slow dissolution of (crystalline) regions of the PEO. Initially the thickness of the gel layer grew with time, but toward the end of the dissolution process the dimensions of a swollen tablet obviously decreased with time. The maximum thickness of the gel layer appeared to be an increasing function of the average molecular weight of the PEO in the tablets. The time for total dissolution of the tablet increased with increasing average molecular weight of the PEO, and varied in the interval 3−30 h.

Release profiles of the tablets in the study are presented in Figure 4. The profiles for the PEO (0.1:2.0) mixtures, but not those for the PEO (0.006:2.0) mixtures or for PEO 0.3 and PEO 0.9, have been published previously.[13] All tablets gave rise to smooth release profiles, and assuming no systematic measuring errors and normally distributed random errors with constant variance, the standard deviation was estimated to be 1.4%. The overall shape of the release profile was similar for all tablets, with a slower initial release, a linear release during the main release period (10−70%), and a slower release at the end of the experiment. For tablets containing a high percentage of PEO 0.1, the slower initial part of the release profile seemed to be over before the first measurement at 15 min. However, the presence of a slow initial release for these tablets is indicated by the fact that the linear parts of their release profiles extrapolate to finite times at 0% release.

The rate of dissolution of a tablet may be characterized either by the time t_{50}, where 50% of the tablet has been released into the solvent, or by the rate r_{50}, which is the rate of release obtained from the linear part of the release profile. These values are presented in Table 2 for the various tablets. The release rate decreases with increasing fraction of the long polymer, PEO 2.0, in the tablet except that PEO 2.0 has roughly the same

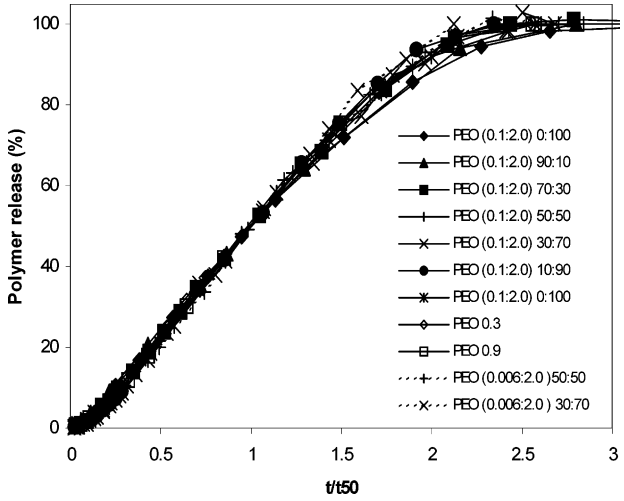

Figure 5. Release curves plotted against reduced time, t/t_{50}.

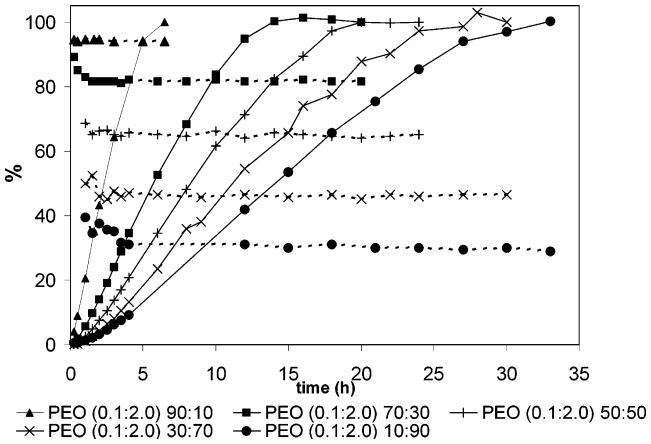

Figure 6. Released fraction low-molecular-weight polymer (dotted lines) together with release profiles 9solid lines) of mixed samples in the PEO (0.1:2.0) series as indicated in the legend beneath the plot.

release profile as PEO (0.1:2.0) 10:90. This can also be seen when comparing the r_{50} values or t_{50} values in Table 2.

The similarity in shape of all the release curves is illustrated by the fact that they very nearly superimpose when plotted against the reduced time, t/t_{50} (Figure 5). However, there are minor deviations toward the end of the superimposed profile, where the results for the two compositions with the lowest molecular weights (PEO 100:0 and 90:10) fall systematically below those of the other compositions.

We also made two compositions where at least 50% of the tablet consisted of PEO 2.0 and the remaining part of PEO 0.006. Mixing PEO 2.0 with PEO 0.006 instead of PEO 0.1 in these tablets did not alter the release profile much (Figure 4). Using 50% PEO 0.006 instead of 50% PEO 0.1 in the tablet resulted in a slightly faster release rate, but reducing the fraction of PEO 0.006 to 30% (PEO (0.006:2.0) 30:70) yielded a release profile almost identical to that for PEO (0.1:2.0) 30:70. This indicates that the overall polymer release rate in a mixed tablet is mainly governed by the longer polymer.

Fractionation. In Figure 6 the fractions of LMW polymer released from the PEO (0.1:2.0) mixtures into the solution are plotted against time. The release profiles are also included in the plot. Note that the overall fraction LMW, obtained in the final dissolution sample where the entire tablet has dissolved, is not the same as the fraction of PEO 0.1 originally mixed in the tablet; see Table 2, where the LMW fraction is given for each sample. This is due to the overlap between the PEO 2.0

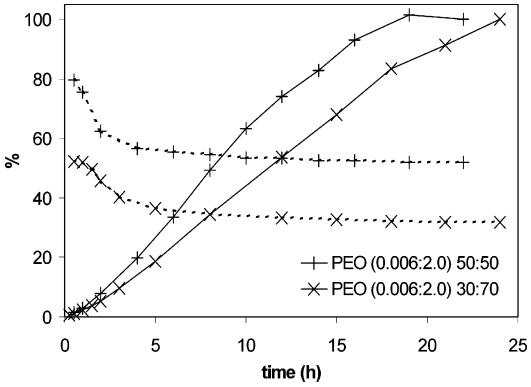

Figure 7. Released fraction low-molecular-weight polymer (dotted lines) together with the release profiles (solid line) of mixed samples in the PEO (0.006:2.0) series as indicated in the figure legend.

and the PEO 0.1 peaks in the chromatograms; see Figure 2. Clearly, the fraction defined as LMW on the basis of a chromatogram contains significant contributions from PEO 2.0 and vice versa. However, since the molecules from PEO 2.0 and PEO 0.1 were mixed on a molecular level in a tablet, a polymer molecule of a certain molecular weight behaves in the same way irrespective of which sample it originates from.

For each tablet, the fraction of LMW polymer is constant during the main part of the dissolution experiment. However, during an initial period of time, the fraction of LMW polymer is slightly higher than it is during the rest of the experiment. This initial period coincides rather well in time with the slower part of the release profile, occurring before entering the linear phase. For tablets where the polymer fractions were dry mixed as powders (ref 13, series D) rather than in solution, this initial fractionation was even more pronounced (data not shown). For the latter type of tablets, the release profiles were compared for freshly made dry-mixed 50:50 tablets and dry-mixed 50:50 tablets where the outermost layer of the tablet had been removed with help of a lathe. Both tablets showed the same behavior. This indicates that the enhanced initial fractionation of low-molecular-weight polymer in mixed tablets is due not to surface degradation of the polymer during tableting or storage, but to an enhanced initial release of the low-molecular-weight fraction of a mixed sample.

The corresponding plots for the two PEO (0.006:2.0) tablets are shown in Figure 7. Here the initial fractionation of the low-molecular-weight polymer in the released material is more pronounced than in the mixed PEO (0.1:2.0) tablets, supporting the conclusion that it is a real effect, not due to surface degradation. The fraction of LMW polymer is much higher in the beginning of the dissolution experiment, and then decreases with time. Since the data in Figures 6 and 7 refer to the accumulated LMW fraction in the dissolution medium, they do not directly give information on the release rate of the LMW fraction as a function of time. In Figure 8a, we have therefore converted the data for PEO (0.006:2.0) 50:50 in Figure 7 into release profiles for the LMW and HMW fractions. This conversion was made from the data in Figure 6 by multiplying each point in the overall release profile with the fraction LMW (or HMW) polymer obtained at that point and normalizing the thus-obtained release profile to 100% at full dissolution. The same is done in Figure 8b for the data of PEO (0.1:2.0) 50:50 from Figure 6.

In Figure 8 it can be seen that the release rate during the linear part of the release profiles for the two fractions, LMW and HMW, in each tablet is, within experimental uncertainty, identical. This was confirmed when calculating r_{50} for the

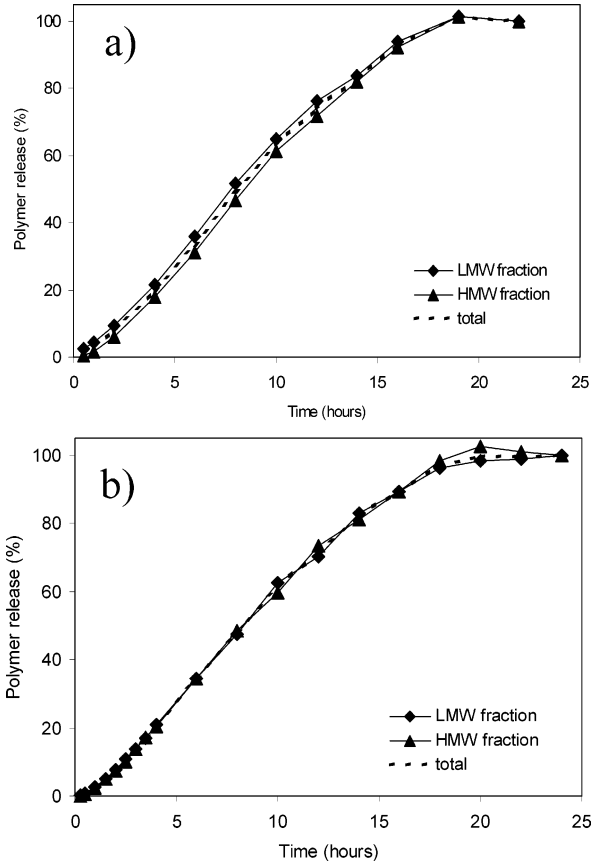

Figure 8. Release profiles for low-molecular-weight fraction (LMW) and high-molecular-weight fraction (HMW) together with total release profile, as indicated in the figure legend, for PEO (0.006:2.0) 50:50 tablets (a) and PEO (0.1:2.0) 50:50 tablets (b).

different fractions. For PEO (0.006:2.0) 50:50 r_{50} was 7.30%/h for the LMW fraction, 7.26%/h for the HMW fraction, and 7.29%/h for the total release profile. For PEO (0.1:2.0) the corresponding values were 6.86, 6.61, and 6.80%/h, respectively. Thus, during the linear part of the release profile there is no further fractionation occurring, but the LMW fraction and the HMW fraction are released at the same rate. This held true also for the PEO (0.006:2.0) 30:70 tablet (data not shown). This analysis therefore indicates that the enhanced release of LMW polymer only occurs during a quite short initial period of the tablet dissolution for all tablets studied here. One would expect, however, that, for a sufficiently low molecular weight of the low molecular fraction, the fractionation would persist over a longer part of the release profile. This was indeed confirmed in less extensive experiments (not shown) where 30% PEO with a molecular weight of 600 was mixed with PEO 2.0 in the tablets. Here, the release rates of the LMW and HMW fractions differed significantly also during the linear part of the release profile.

Discussion

Short and Long Chains Are Released at the Same Rate. Except for a short initial period during the dissolution process, short and long polymer chains are released at the same rate even from very polydisperse tablets. A possible explanation for this finding could be the development of a steady state where both the solid/gel and the gel/liquid boundaries move at the same rate.[10,17] In such a case, a gel layer with a fixed composition profile with respect to all components has developed, which is simply moving at a constant rate toward the interior of the tablet.

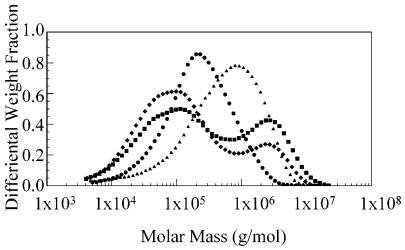

Figure 9. Molecular weight distributions for unmixed, monomodal, tablets PEO 0.3 (circles) and PEO 0.9 (triangles) and for mixed, bimodal, tablets PEO 70:30 (diamonds) and PEO 50:50 (squares).

In this limit, all substances contained in the solid matrix must be released at the same rate. Measurements of the gel layer thicknesses of our tablets have shown, however, that such a steady state only developed for the tablets dominated by short polymers; for most of the tablets, the gel layer thickness varied throughout the dissolution process.[18] We therefore propose that the reason all polymer fractions are released at the same rate is that the self-diffusion of water is much faster than the self-diffusion of any of the polymer components. Consequently, the latter components do not move significantly relative to each other during the dissolution of the tablet. The development of the gel layer is simply a penetration of water into an entangled polymer matrix that only swells, while retaining its original molecular weight distribution throughout the matrix. However, a molecular weight gradient should develop in the vicinity of the gel/liquid boundary, since short molecules should escape faster from this most dilute layer of the gel. This, we believe, is the origin of the initial fractionation observed for all samples. At the end of this initial period, a steady-state concentration profile has developed close to the gel layer surface, and this steady state is then maintained throughout the entire dissolution process.

Molecular Weight Dependence of the Overall Release Rate. Our study includes polydisperse samples with either monomodal or bimodal molecular weight distributions. The two distributions are quite different, as illustrated in Figure 9. Since all polymer fractions are, nevertheless, released at the same rate, it is of interest to see whether there exists a single average parameter that correlates with the overall release rate of the polydisperse samples, regardless of the details of the molecular weight distribution.

Figure 10a shows the release rates plotted as a function of the weight-average molecular weights for the investigated samples in the PEO (0.1:2.0) series together with PEO 0.3 and PEO 0.9. Figure 10b shows the corresponding plot of the release rate as a function of the number-average molecular weight. The data for the mixed tablets, including the pure 0.1 and 2.0 tablets, fall on smooth curves in both cases. The relationship between r_{50} and M_w for these tablets is well described by a power law with the prefactor $= 5.69 \times 10^5$ and the exponent $= -0.82$ ($R^2 = 0.99$). In Figure 10b the relationship for the M_n values cannot be described by a power law. However, we do not see any fundamental reason the mixed samples should follow such a law. PEO 0.3 and PEO 0.9, having a more narrow molecular weight distribution, do not follow the same relationship as the mixed samples in either plot. We recall that the same samples also deviated in the plot of the intrinsic viscosity versus weight-average molecular weight; see Figure 3.

The question then remains: is there some average property of a polymer sample that, regardless of the degree of polydispersity, correlates with the rate of release of the dry polymer to the surrounding solution? In Figure 11, we have plotted r_{50} against the inverse of the intrinsic viscosity for all investigated samples and mixtures. All data are seen to closely obey a universal, nearly linear, dependence.

An interpretation of the result in Figure 11 requires a more detailed analysis of the polymer dissolution process. The rotation of the disk gives rise to a stirring of the surrounding fluid. In a boundary layer, close to the gel−solution interface "s" (see Figure 12), the fluid velocity decreases sharply due to resistance from the polymer gel. The velocity decreases to zero at the gel surface "s", where the force originating from the movement of the fluid (which is dependent on the stirring rate) is balanced by the viscous resistance in the gel. As a consequence of this force balance, the viscosity at the swollen tablet surface, "s", is constant for all formulations at a certain rotation speed, regardless of the molecular weight of the polymer.

The mass transport (J) of polymer through the thin boundary layer separating the gel and the solution (Figure 12) can be expressed by a mass transfer equation as

$$J = kAc_s \tag{3}$$

where k is the mass transfer coefficient, A is the area over which the mass transfer occurs, and c_s is the polymer concentration at the gel surface, "s".[18,19] It is well established that the zero-shear viscosity of a polymer solution under good solvent conditions is a universal function (independent of molecular weight) of the reduced concentration, c/c^*, where c^* is the so-called overlap concentration.[20] Furthermore, to a good approximation, $c^* \approx 1/[\eta]$.[21] The assumption of a constant viscosity at the swollen

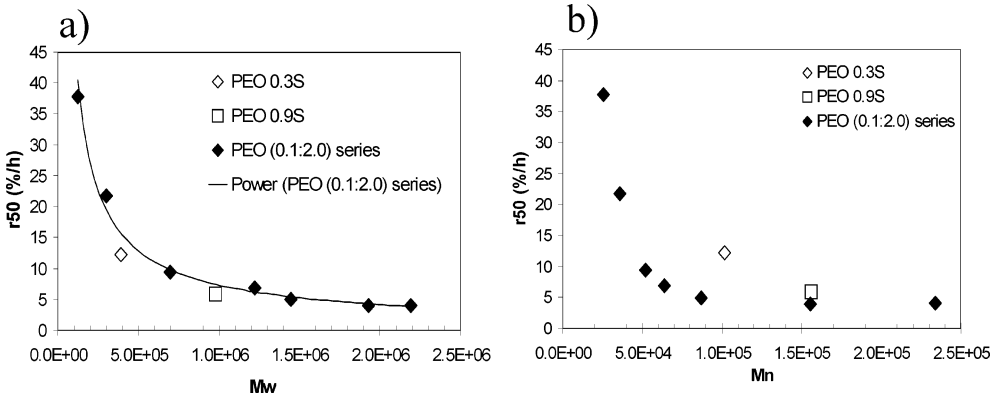

Figure 10. Release rate (r_{50}) for tablets plotted against (a) weight-average molecular weight and (b) number-average molecular weight of the polymer in the tablet.

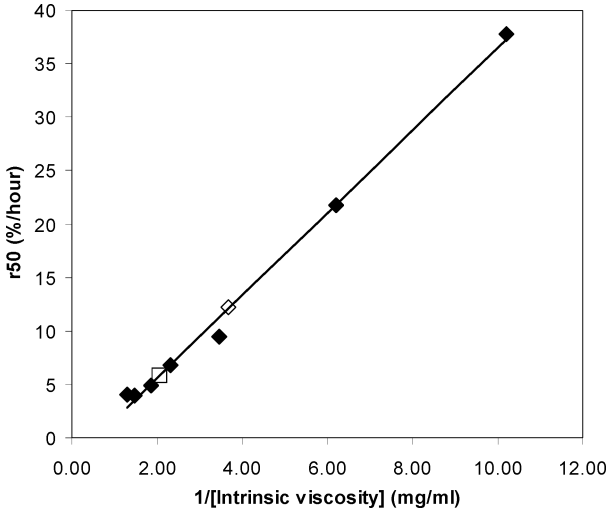

Figure 11. Release rate plotted against $1/[\eta]$ ($\approx c^*$) of investigated samples. The line is a linear fit to the data for the mixed samples. Symbols as in Figure 10.

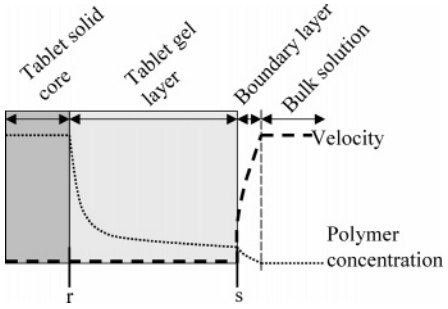

Figure 12. Schematic picture of the proposed dissolution process, including the proposed solvent velocity and polymer concentration profile.

tablet surface, independently of the molecular weight, thus yields

$$c_s[\eta] = x \tag{4}$$

where x is a constant. For the release rate at 50% dissolution (where $J = r_{50}$ and $A = A_{50}$), we arrive at

$$r_{50} = \frac{kA_{50}x}{[\eta]} \tag{5}$$

If the product kA_{50} is independent of the molecular weight distribution for samples with a common intrinsic viscosity, we may then understand why all data fall on a single relation in Figure 11. This seems reasonable; in fact, we may anticipate that k and A_{50} individually would not depend strongly on polydispersity. According to eq 5, the linearity of the plot in Figure 11 suggests, furthermore, that the product kA_{50} is, in fact, constant for all tablets, regardless of their average molecular weight. This is more difficult to understand, but it would seem to be due to a cancellation of two opposite effects. The area of the tablet depends on the degree of swelling of the tablet, which increases with increasing molecular weight.[1,18] The rate constant k, on the other hand, depends on the polymer diffusion coefficient, which decreases with increasing molecular weight.

Large Polymers Are Most Important for the Release Rate. Comparing the release profiles (or r_{50} values) of PEO 100:0 and 90:10, we find that the 10% PEO 2.0 in the 90:10 tablet gives a large effect on the release profile. Mixing in long polymer chains to PEO 0.1 leads to a substantial increase in the average coil volume (the intrinsic viscosity showed an increase of about 60%); see Table 1. Hence, the number of contact points (entanglements) between the molecules is increased, and this slows the release rate of the polymer tablet. By contrast, introducing a similar fraction of short polymer molecules in PEO 2.0 does not have a very significant effect on the average coil dimensions (the intrinsic viscosity increases by about 15%) or on the release rate. Similarly, when the tablet contains 70% PEO 2.0, the release rate (r_{50}) is almost the same irrespective of whether the remaining 30% is PEO 0.1 or PEO 0.006 (Figure 4). The intrinsic viscosities are about the same in these two tablets, but the polydispersity is increased in the sample containing PEO 0.006. This increase in polydispersity does not affect the release rate. These results are in good agreement with the results presented by Ramkissoon-Ganorkar et al.[12] when studying the dissolution kinetics of poly(NIPAAm-*co*-BMA-*co*-AA). They found that removing the largest chains from a polymer sample by fractionation resulted in an increase in release rate. On the other hand, polymer samples that all had a high weight-average molecular weight but different polydispersity indexes (i.e., different numbers of short chains) resulted in similar release profiles.

Conclusions and Outlook

In this work we showed that both molecular weight fractions in a bimodal, polydisperse, polymer tablet were released at the same rate during the dissolution process. We also found a good correlation between the polymer release rate and the intrinsic viscosity of the polymer in the tablet, irrespective of the polydispersity or details of the molecular weight distribution. This correlation supports the idea of a constant viscosity at the tablet surface as well as the use of a mass transport equation in describing the polymer release from the tablet. Further research is needed to investigate whether the intrinsic viscosity also can predict other properties of dissolving polymer tablets, such as their degree of swelling. Furthermore, one would like to know to what extent these conclusions apply also to other conditions (e.g., other stirring rates) and other polymers.

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