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Effect of terminal block on the microfluidization induced degradation of a model A-B-A block copolymer

Shawn Silvestri, Gustave Gabrielson and Li Li Wu

The University of Pittsburgh, Department of Pharmaceutical Sciences, 712 Salk Hall, Pittsburgh, PA 15261 (U.S.A.)

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Summary

The effect of high shear and turbulent processing on the mechanical degradation of a model series of A-B-A block copolymers was studied. Pluronic^R L64, L63 and L62 were microfluidized (80 lb/inch^2 (psi) inlet air pressure) zero to four volume passes through a Microfluidizer^R M110T equipped with a high-pressure pump and thermostatted to 23°C. Viscosity average molecular weight was determined for each copolymer after each cycle using intrinsic viscosity as estimated by capillary viscometry. All three polymers were observed to undergo mechanical degradation. The difference in initial average molecular weight of the A terminal blocks (L64 > L63 > L62) was found to have an effect on overall percent decrease in viscosity average molecular weight. Pluronic^R L64 was observed to be the most sensitive (20% decrease) and Pluronic^R L62 was found to be the least sensitive (5% decrease) to the high shear and turbulent forces encountered during microfluidization. The apparent first-order mechanical degradation constants for the polymers were calculated from the slopes of plots of reciprocal average molecular weight vs number of cycles. The apparent degradation constants were estimated as $1.48E{-}5$, $1.15E{-}5$ and $5.51E{-}6$ mol g^{-1} cycle^{-1} for Pluronic^R L64, L63 and L62, respectively. Differences in the mechanical degradation constants may be reflective of differences in the average molecular surface area exposed to shearing stresses and turbulence generated during the microfluidization process.

Introduction

The mechanical degradation of polymers induced by high shear and turbulent forces has been reported previously (Harrington et al., 1965; Moore et al., 1968; Silvestri et al., 1991). Shear and turbulent forces associated with mechanical degradation have previously been documented to originate from processes as subtle as viscous capillary flow to those as harsh as microfluidization. In general, polymers appear to be most susceptible to high shear degradation as either average molecular weight increases or exposure time is prolonged (Morawetz, 1983).

Microfluidization is a homogenization process which produces liquid-in-liquid dispersions from a combined effect of high shear, turbulence and cavitation (Korvstedt et al., 1984; Washington et al., 1988). The application of microfluidization to the production of pharmaceutical emulsions for drug delivery and parenteral nutrition has been

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Correspondence: S. Silvestri, The University of Pittsburgh, Dept. of Pharmaceutical Sciences, 712 Salk Hall, Pittsburgh, PA 15261, U.S.A.

addressed (Lostritto et al., 1987a,b). Polymers may be included in pharmaceutical dispersions as active ingredients, physical stabilizers or both. In any case, sensitivity of macromolecules to high shear and turbulence during microfluidization must be established a priori.

Recently, it was observed that a high molecular weight surface active agent (tragacanth) was sensitive to the high shear and turbulent nature of the microfluidization process (Silvestri et al., 1991). It was found that four volume passes through a Microfluidizer^R device at 23°C and interaction chamber pressures of 17500 psi provided sufficient energy and exposure time to decrease the apparent viscosity average molecular weight of tragacanth from 840000 to 43103 g mol^{-1}. These results were in agreement with photon correlation spectroscopy studies.

The exact mechanism of degradation induced by high shear and turbulent forces remains unclear. Previous work has shown that mechanical degradation of polymers requires simultaneous shear and turbulence (Harrington et al., 1965). In addition, the degradation has been postulated to be brought about by local increases in energy (temperature) associated with viscous heating effects (Harrington et al., 1965). However, this has yet to be experimentally verified.

Despite uncertainties about exact chemical mechanisms and processes involved in the mechanical degradation of polymers exposed to high shear and turbulent forces, theoretical mathematical models describing the apparent time dependence of the average molecular weight have been derived and tested for several types of devices which produce high shear and turbulent forces. According to the modified random scission theory (Harrington et al., 1965) if the shear stress to which a polymer chain is exposed lies above a critical value, the degradation may be described as a first order process in the number of bonds cleaved. As a result, theory predicts that reciprocal average molecular weight varies linearly with time.

In this study, the microfluidization-induced mechanical degradation of an A-B-A block copolymer was evaluated for the effect of varied molecular weight of A. The Pluronic^R surfactants are A-B-A block copolymers composed of hydrophilic polyoxyethylene (A) and hydrophobic polyoxypropylene (B) segments. Pluronic^R L64, L63 and L62 possess A terminal blocks of approximate average molecular weights of 517.5, 392.5, and 317.5 g mol^{-1}, respectively. However, the B block of the copolymer has identical molecular weight (1865 g/mol) for each of these Pluronics^R. Thus, studying the effects of microfluidization on each of these Pluronics^R may give useful information regarding the effect(s) of relative A block average molecular weight on the rate of (or sensitivity to) mechanically induced degradation.

Theory

The equations of viscosity describing the flow of polymer solutions are the Huggins equation (Huggins, 1942):

$$n_{sp}/C = [n] + k'[n]^2C \tag{1}$$

and the Kraemer equation (Kraemer, 1938):

$$\ln(n_{rel})/C = [n] + k''[n]^2C \tag{2}$$

where by definition (Sperling, 1986):

$$k' - k'' = 0.5. \tag{3}$$

In Eqns 1–3, n_{sp} is specific viscosity, n_{rel} is relative viscosity, C (g cm^{-3}) is concentration, $[n]$ is intrinsic viscosity (cm^3 g^{-1}), and k' and k'' are the Huggins and Kraemer constants. n_{sp} and n_{rel} may be further described by the relations:

$$n_{sp} = (n - n_0)/n_0 \tag{4}$$

and

$$n_{rel} = n/n_0 \tag{5}$$

with n (cps) representing the viscosity of the polymeric solution and n_0 (cps) the viscosity of pure reference material (Sperling, 1986). Eqns 1–5 provide the basic framework which describes the dependence of observed momentum flow of a polymer system on its concentration in solution, a polymer-solvent constant (k' or k''), and the hydrodynamic volume the polymer possesses in a particular solvent. Intrinsic viscosity is a physical constant that is independent of the model (Huggins or Kraemer) which is used to describe it.

The equivalent sphere model states that intrinsic viscosity is directly related to viscosity average molecular weight of the polymer (Flory, 1953) by the expression:

$$[n] = BM^{1/2}. \tag{6}$$

where B ($\mathrm{mol}^{1/2}\ \mathrm{cm}^3\ \mathrm{g}^{-3/2}$) is a constant dependent on polymer and solvent. From Eqn 6, a change in the intrinsic viscosity of a polymer on microfluidization may be directly correlated to a change in the square root of the viscosity average molecular weight of the polymer.

The theory of mechanical degradation of polymers has been described elsewhere in detail (Harrington et al., 1965) and has successfully been applied to microfluidization-induced degradation (Silvestri et al., 1991). In short, for polymers which undergo moderate to extensive shear degradation, the rate law expressed in terms of viscosity average molecular weight (M) is:

$$\frac{\mathrm{d}(1/M)}{\mathrm{d}t} = K/M_l = k \tag{7}$$

where t is exposure time (e.g. cycles or volume passes), K is a true first-order degradation rate constant (time^{-1}), M_l ($\mathrm{g\ mol}^{-1}$) is the limiting viscosity average molecular weight to which the substance will degrade on infinite exposure to a high shear force and k ($\mathrm{mol\ g}^{-1}\ \mathrm{time}^{-1}$) is an apparent first-order mechanical degradation constant. From Eqn 7, a plot of reciprocal viscosity average molecular weight vs time (cycles) should give a straight line with a slope equal to the apparent rate constant (k). The constant k serves as a direct measure of the sensitivity of a polymer to mechanical degradation where larger values of k may indicate an increased sensitivity.

The following procedure may be used to estimate intrinsic viscosity if absolute viscosity may be determined experimentally. Eqns 1–3 represent a series of three equations and three unknowns ($[n]$, k' and k''). This system of equations may be solved simultaneously as follows. Solving Eqn 3 for k' and substitution into Eqn 1 yields:

$$n_{\mathrm{sp}}/C = [n] + (0.5 + k'')[n]^2 C. \tag{8}$$

Subsequently, if Eqn 2 is subtracted from Eqn 8 one obtains:

$$n_{\mathrm{sp}}/C - \ln(n_{\mathrm{rel}})/C = 0.5[n]^2 C. \tag{9}$$

Eqn 9 may be solved directly for $[n]$ to give:

$$[n] = \left\{ \frac{2\{n_{\mathrm{sp}}/C - \ln(n_{\mathrm{rel}})/C\}}{C} \right\}^{1/2}. \tag{10}$$

Finally, if pure polymer in the liquid state is used, the concentration (C) of the polymer is the density (p) of the polymer. Thus, Eqn 10 becomes:

$$[n] = \left\{ \frac{2\{n_{\mathrm{sp}}/p - \ln(n_{\mathrm{rel}})/p\}}{p} \right\}^{1/2} \tag{11}$$

where the reference material may be assumed to be water. Therefore, intrinsic viscosity may be estimated from a single absolute viscosity estimate for a pure liquid.

Materials and Methods

Research grade (specification 100% pure) Pluronic$^{\mathrm{R}}$ L64, L63 and L62 (BASF Corp.) were used as received. For each of the block copolymers, approx. 200 ml was subjected to the following protocol.

Each Pluronic$^{\mathrm{R}}$ was microfluidized with a Microfluidizer$^{\mathrm{R}}$ M110T equipped with a high-pressure pump and thermostatted to 23°C. Compressed air was maintained at 80 psi at the inlet air pressure valve. This corresponded to an approximate interaction chamber of 17 500 psi. Aliquots (20 cm^3) were collected from the processed outflow tube after 0, 1, 2, 3 and 4 cycles through the Microfluidizer$^{\mathrm{R}}$ device for capillary viscometry measurements.

Efflux time for each aliquot was estimated with a calibrated Cannon Fenske Viscometer^R (Fisher ASTM Size 450). Efflux time was taken as the average of the first three recorded times within a 0.5 s range of one another. The tube constant at 23°C was estimated to be 2.691 by linear extrapolation of calibration results.

Results and Discussion

For these analyses the viscosity of water at 23°C was assumed to be 0.933 cps (CRC, 1985), the average molecular weights of Pluronic^R L64, L63 and L62 were taken as 2900, 2650 and 2500 g mol^{-1}, respectively (BASF specification sheet), and the densities at 23°C of Pluronic^R L64, L63 and L62 were taken as 1.05, 1.04 and 1.03 g cm^{-3}, respectively (BASF specification sheet).

Data was collected as efflux time and converted to absolute viscosity (cps) by use of the tube constant (Van Wazer, 1963). Table 1 depicts the dependence of the absolute viscosity on the number of passes through the Microfluidizer ^{R} device for Pluronic^R L64. It may be observed that as the number of cycles through the device increases, or equivalently, as exposure to the forces of microfluidization increases, the absolute viscosity of Pluronic^R L64 decreases consistently and substantially. Using the absolute viscosities for Pluronic^R L64 in Table 1, the density of Pluronic^R L64 and the viscosity of water (reference solvent) in Eqn 11, the intrinsic viscosity for each number of cycles was estimated (Table 1). As expected, intrinsic viscosity also decreased with increased microfluidization time.

TABLE 1

Mechanical degradation of Pluronic^R L64 induced by high shear and turbulent forces during microfluidization

Cycle	n (cps)	$[n]$ (cm^3 g^{-1})	M (g mol^{-1})
0	520.4	31.6	2900
1	465.0	29.9	2588
2	448.3	29.3	2494
3	434.5	28.8	2416
4	417.9	28.3	2322

Since intrinsic viscosity is proportional to the square root of the viscosity average molecular weight (Eqn 6), the estimates of $[n]$ may be correlated to M such that the relationship between M and exposure time may be critically examined. From Table 1 at zero passes M is assumed to be 2900 g mol^{-1} for Pluronic^R L64 and $[n]$ was estimated as 31.6 cm^3 g^{-1}. Substituting these values in Eqn 6 and solving for the constant B, one finds that B is approx. 0.587 cm^3 mol$^{1/2}$ g$^{-3/2}$ for Pluronic^R L64. If B is assumed independent of average molecular weight (Flory, 1953; Sperling, 1986), then Eqn 6 and the intrinsic viscosity estimates in Table 1 may be used to estimate the viscosity average molecular weight for 1, 2, 3 and 4 volume passes. This data is also listed in Table 1 and depicted graphically in Fig. 1.

Overall, a 20% decrease in the viscosity average molecular weight is observed when Pluronic^R L64 is subjected to four volume cycles through the Microfluidizer^R. However, this decrease is nonlinear in time as reflected in Fig. 1. In order to estimate the apparent first order degradation constant (k) for Pluronic^R L64, a plot of $1/M$ vs number of cycles (Eqn 7) was constructed (Fig. 2). The slope (k) of the linear regression of this data for 1–4 passes was calculated to be $1.48E-5$ mol g^{-1} cycle^{-1} ($r = 0.9987$). An unexpectedly large increase in $1/M$ from 0 to 1 pass was observed for Pluronic^R L64. Biphasic behavior has been observed for other polymers exposed to microfluidization (Silvestri et al., 1991). This may represent either an approach to random scission kinetics or a change in the mechanical degradation mechanism. Available information does not conclusively support either argument. Inclusion of this point in the Zimm Harrington analysis for Pluronic^R L64 gives an apparent rate constant of $1.99E-5$ mol g^{-1} cycle^{-1} and a correlation coefficient of 0.9651. These values are qualitatively similar to the values obtained for cycles 1–4. The best-fit line from the linear regression results where the initial time point was excluded appear to be in much better agreement with the experimental data. For these reasons, the terminal portion (cycles 1–4) apparent rate constant would appear to best describe the mechanical degradation kinetics of Pluronic^R L64 on exposure to microfluidization forces.

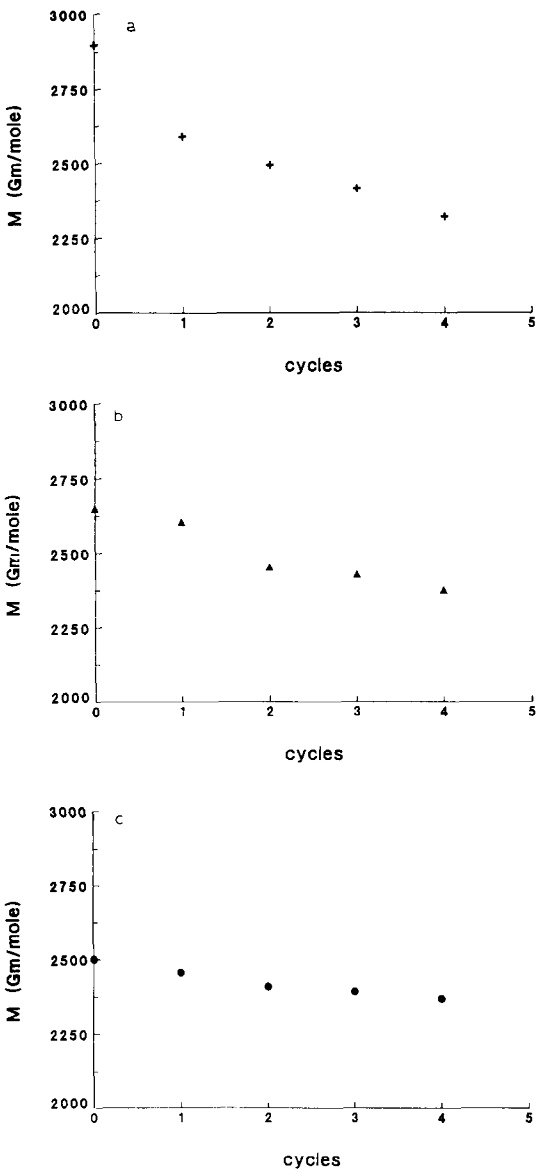

Fig. 1. Effects of high shear and turbulent forces during microfluidization on the apparent viscosity average molecular weight of Pluronic^R surfactants. L64 (+), L63 (▲) and L62 (●).

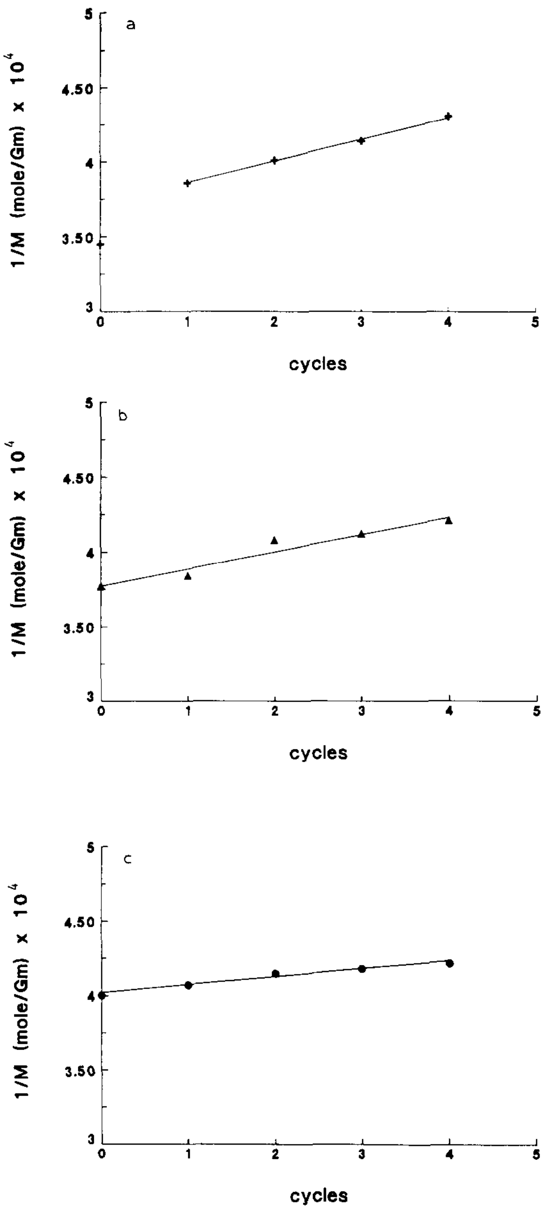

Fig. 2. Zimm Harrington plot for the mechanical degradation of Pluronic^R surfactants during microfluidization. L64 (+), L63 (▲) and L62 (●). Solid lines are the linear regressions of the data.

Finally, the constants k' and k'' were estimated for Pluronic^R L64. The intrinsic and absolute viscosity data in Table 1 was used in Eqn 1 to estimate k' for each volume pass in Table 1. Similarly, the intrinsic and absolute viscosity data in Table 1 was used in Eqn 2 to estimate k'' for each cycle through the device. The value for k' was estimated as 0.47 and for k'' as -0.03. Note that k' and k'' are independent of intrinsic viscosity and therefore independent of viscosity average molecular weight. Further, $k' - k''$ was

TABLE 2

Mechanical degradation of Pluronic^R L63 induced by high shear and turbulent forces during microfluidization

Cycle	n (cps)	$[n]$ (cm^3 g^{-1})	M (g mol^{-1})
0	417.3	28.5	2650
1	410.3	28.3	2605
2	386.6	27.4	2453
3	382.9	27.3	2428
4	374.8	27.0	2376

in all cases 0.50. This is consistent with the starting equation (Eqn 3) which describes the relationship of k' and k″.

Tables 2 and 3 depict the results for Pluronic^R L63 and Pluronic^R L62 shear degradation studies. In both cases, exposure-dependent decreases in the absolute and intrinsic viscosity estimates were observed. The constant B was estimated for Pluronic^R L63 and L62 by the same procedure used to estimate B for Pluronic^R L64. Estimated values for B were 0.554 and 0.530 cm^3 mol$^{1/2}$ g$^{-3/2}$ for Pluronic^R L63 and L62, respectively. Using these estimates of B and viscosity average molecular weight, the apparent first-order degradation constant, k', and k'' were estimated for each copolymer after each cycle. Several interesting points may now be addressed.

The constant B appears to depend on the starting polymer. As the overall percent of hydrophilic chain in the starting polymer is decreased, the value for B also apparently decreases. Based on the equivalent sphere model (Flory, 1953), the observed decrease may be related either to differences in the ratio of the squared effective radius ($R_{e\theta}$) in a theta solvent to the average molecular weight, or differences in the solvent expansion coefficient. Assuming that each of these Pluronic^R surfactants serve equally well as solvents for their own molecules, the former is more likely. Since M is decreasing as the Pluronic^R series goes from L64 to L62, a corresponding simultaneous and even larger decrease in $R^2_{e\theta}$ must occur. Indeed, chain statistics predicts that for a series of chemically similar polymers that the effective radius should decrease in a nonlinear fashion as average molecular weight decreases.

TABLE 3

Mechanical degradation of Pluronic^R L62 induced by high shear and turbulent forces during microfluidization

Cycle	n (cps)	$[n]$ (cm^3 g^{-1})	M (g mol^{-1})
0	354.6	26.5	2500
1	348.4	26.3	2456
2	341.7	26.0	2408
3	339.6	25.9	2392
4	336.3	25.8	2369

Trends in viscosity average molecular weight decreases as a result of microfluidization were similar for all three Pluronic^R surfactants. In a fashion analogous to the behavior of Pluronic^R L64, viscosity average molecular weight decreased nonlinearly with increasing cycles for Pluronic^R L63 and Pluronic^R L62 (Fig. 1). When comparing all three of the A-B-A copolymers, the overall decrease in viscosity average was greatest for Pluronic^R L64 (20%) and least for pluronic^R L62 (5%).

Zimm Harrington plots of $1/M$ vs cycles for Pluronic^R L63 and L62 were also constructed (Fig. 2). In both cases the data exhibited high linear correlation ($r > 0.969$). The apparent first-order degradation constants were estimated from the slopes of these plots to be $1.15E-5$ and $5.51E-6$ mol g^{-1} cycle^{-1}, respectively. The corresponding solid lines in Fig. 2 represent the best-fit line for the entire experimental range of exposure times. Comparison among this Pluronic^R series reveals that as the viscosity average molecular weight of the starting copolymer decreases, a corresponding decrease in sensitivity to mechanical degradation is observed. Specifically, k (mol g^{-1} cycle^{-1}) $= 1.48E-5$ (Pluronic^R L64) $> 1.15E-5$ (Pluronic^R L63) $> 5.51E-6$ (Pluronic^R L62).

It appears that an increase in initial average molecular weight of the A terminal blocks increases the molecular surface area exposed to the high shear and turbulent forces of the Microfluidizer^R resulting in an increase in the apparent mechanical degradation rate constant.

Finally, the physical constants k' and k'' were estimated for Pluronic^R L63 and L62 by the same procedure used for Pluronic^R L64. In both cases, after each cycle the values of k' and k'', were 0.47 and -0.03, respectively. Similar to Pluronic^R L64, these values were found to be independent of viscosity average molecular weight to two decimal places. Further, they appear to be independent of the number of repeat units in the A chain for this particular set of chemically similar copolymers.

Summary

The mechanical degradation of a model series of A-B-A block copolymers induced by the high shear and turbulent forces of microfluidization has been studied. Using a combined form of the Huggins and Kraemer equations in addition to a modified form of the equivalent sphere model, a novel approach to estimating the effects of microfluidization on viscosity average molecular weight through changes in absolute viscosity has been described.

It has been shown that exposure of pure Pluronic^R L64, L63 and L62 to the high shear and turbulent processing conditions encountered during microfluidization may result in apparent decreases in the viscosity average molecular weight of each of these surfactants. The sole chemical difference in this series of Pluronic^R copolymers is the average molecular weight of the terminal blocks (L64 being the highest and L62 being the lowest). Estimation of the apparent first-order degradation constant via Zimm Harrington plots revealed that Pluronic^R L64 was most sensitive to mechanical degradation induced by microfluidization and Pluronic^R L62 was least sensitive to mechanical degradation induced by microfluidization.

Finally, the physical constants associated with the Huggins and Kraemer equations (k' and k'') were calculated. These values were observed to be independent of viscosity average molecular weight for a given Pluronic^R surfactant as well as independent of the initial block copolymer average molecular weight for this series of surfactants.

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