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Mechanical degradation of drag reducing polymers in suspensions of blood cells and rigid particles

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Abstract. Natural and synthetic soluble drag reducing polymers (DRP) have been shown to produce beneficial effects on blood circulation in various animal models and may represent a novel bioengineering way to treat cardiovascular disorders. These polymers are known to degrade when subjected to high shear stresses which could be a part of the process of their elimination from the vascular system. However, the relative rate of their degradation was not known especially in the presence of blood cells or particles. The hydrodynamic tests in this study demonstrated that DRP mechanical degradation was significantly increased by the presence of red blood cells (RBC) and even more so by the presence of rigid particles of similar size. Degradation rates increased with an increase in RBC or particle concentration. The natural DRP (derived from aloe) was shown to be much more resistant to flow-induced degradation than polyethylene oxide in the presence or absence of RBC.

Keywords: Drag reducing polymers, mechanical degradation, blood circulation, red blood cells, particles

1. Introduction

Certain long-chain soluble polymers, known as drag reducing polymers (DRP), significantly reduce resistance to a flowing fluid when added to the fluid at minute concentrations. This phenomenon, known as the Toms effect, occurs in turbulent flow with polymers that have certain characteristics including high molecular weight and a fairly linear structure [18,26,44]. DRP have been investigated and used for various industrial and engineering applications including crude oil transport through pipelines, firefighting, and reducing drag on ships and submarines [5,11,19]. The same polymers which reduce resistance

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to turbulent flow also have been shown to beneficially affect blood flow, increasing cardiac output, tissue perfusion and oxygenation in several animal models including enhancement of microcirculation in diabetic animals, treatment of cardiac ischemia and hemorrhagic shock, and others [12,14–17,22,29,31, 32,34,35,38,39]. While DRP have demonstrated promise as a potential therapy for many pathological states, some of these polymers show a tendency to mechanically degrade over time when exposed to high stress conditions. This could limit potential clinical use of these DRP to treat chronic conditions such as microcirculatory impairment caused by diabetes or atherosclerosis since the effect might diminish too quickly for practical use. Therefore, before DRP are proposed for clinical use to treat chronic pathologies (diabetes, heart ischemia, atherosclerosis), the degradation behavior of these polymers must be investigated in detail. For clinical use, it is important to know how quickly the polymer will degrade in order to determine how often the treatment would need to be given. Since DRP preparations have to be delivered via intravenous injections, selection of slow degrading DRP for chronic administration would be necessary. Although DRP degradation has been intensively studied for decades [1–4,7,9,13,20,21,23, 24,27,28,30,37,40,42,47], and dilute suspensions of solid particles have been shown to produce a drag reducing effect [26,37], the effects of red blood cells (RBC) or similar size particles on the dynamics of this process have not yet been identified. Mechanical degradation of DRP can be defined as the chemical process by which the activation energy for the scission of a polymer chain is imparted by mechanical stresses on the polymer molecules [20]. The DRP degradation process can be quantified by the loss of a polymer's drag reduction effectiveness [40]. Among commonly used DRP, high molecular weight polyethylene oxides (PEO) are known to be the most effective drag reducers [23]. At the same time, it was shown that the polymers of this class quickly degrade due to exposure to mechanical stress in turbulent flow in a pipe or rotating disk causing the drag reducing effect to diminish over a short exposure time [13,21,42]. Polyacrylamides were shown to degrade more slowly than PEO [13]. Certain high molecular weight polysaccharides were also found to be good drag reducers that are much more resistant to mechanical degradation than PEO [9,23,24]. In addition, poly(N-vinylformamide) was recently found to be a comparatively effective DRP and to be more resistant to degradation than PEO [30]. The degradation of DRP solutions is likely caused by chain scission; however, there is evidence that degradation occurs, at least in part, due to the breakup of molecular aggregates or network structures formed in the DRP solution [21,27,47]. The objective of the current study was to find out whether the presence of particles in flowing DRP solutions, especially those of a biological nature such as RBC, affects DRP degradation. We tested the effects of particulate matter, including RBC and small rigid glass particles of similar size, on the rate of degradation of both polyethylene oxide and a natural DRP extracted from the aloe vera plant in solutions flowing in a recirculating turbulent flow system.

2. Materials and methods

The shear stress-induced degradation dynamics of two drag reducing polymers, PEO and an aloe derived DRP (AVP) which was discovered in our laboratory [22], were investigated in a turbulent flow system. Test fluids were normal saline and suspensions of RBC or rigid particles in saline. The tested polymer solutions (2.5 mg/ml (2500 ppm) in saline) were added to the flowing test fluids to give a concentration of 0.1 mg/ml (100 ppm).

PEO (Polyox WSR-301, $M_w = 4.5 \times 10^6$ Da) was provided as a sample by The Dow Chemical Co., and AVP was extracted from aloe vera leaves using a standard procedure established in our laboratory [22]. Briefly, the aloe derived DRP was extracted from the viscous gel portion of the aloe leaves with

ethanol and then reconstituted in saline. It is known that the ethanol insoluble portion of the aloe gel is a polysaccharide consisting of mannans of varying molecular weights, degrees of acetylation and mannose–glucose ratios [8,10,33,43]. A structure for the major component of aloe vera gel, consisting of a linear β-1,4-linked mannose backbone with β-1,4-linked glucose substituting for mannose approximately every 30 residues, was proposed by Chow et al. [8]. We characterized our aloe-based polymeric preparation using rheological, hydrodynamic and gel permeation chromatography (GPC) methods and proved it to be a very effective DRP with average M_w of $(6-8)\times 10^6$ Da.

Bovine blood was obtained from a local slaughterhouse and centrifuged for 15 min at 3600 rpm to remove plasma and buffy coat. The thrice washed RBC were resuspended in saline at a concentration of 5, 10 or 20%. The age of bovine blood in the studies varied from one day to one week. RBC were stored at 4°C. No difference in pressure vs. flow curves or in DRP degradation was observed with variation in blood age. Since thoroughly washed RBCs were used in the study, the results were well reproducible in spite of potential changes in whole blood properties due to storage. A rigid particle suspension was prepared by adding glass particles (Potters Industries Inc., equal volume mixture of 110P8 and 60P18 with mean diameters of 11 and 18 μm and densities of 1.1 and 0.6 g/cm^3, respectively) to saline at a concentration of either 1 or 5% by volume.

The asymptotic viscosity of the 20% RBC suspension was $\sim$1.8 cP at 22°C as measured using a capillary viscometer (Cannon-Manning) at a shear rate of $\sim$600 s^{-1}. The capillary viscometer diameter was two orders of magnitude larger than that of the RBC. Although the RBC suspension exhibits non-Newtonian properties, at the high shear rates present in the turbulent flow system used in these studies, the use of the asymptotic viscosity is valid. To determine whether the effects of RBC on polymer degradation were due to the particles (cells) themselves or due to the increase in viscosity, a 15% glycerol solution with viscosity of $\sim$1.7 cP (at 22°C) was prepared as an equiviscous but single-phase analog for the 20% RBC suspensions.

The turbulent flow system [30] consisted of a centrifugal pump (BioMedicus, Inc.), a flow meter and clamp-on flow probe (Transonic Systems, Inc.), a pressure transducer (PCB Piezotronics, Inc.), a glass tube (either 0.44 cm ID, 91.5 cm length or 0.56 cm ID, 120 cm length), and a one liter open fluid reservoir connected with $3/8$ inch Tygon tubing (Cole-Parmer). The smaller diameter glass tube was used in the experiments where saline was the test fluid, and the larger tube was used for the suspensions of RBC or particles in order to obtain flow conditions necessary to study the Toms effect. The fluid reservoir was filled with saline, a red blood cell suspension in saline, a suspension of rigid glass particles in saline, or a glycerol solution. Wall shear stress in the glass tube was maintained at 45 Pa throughout the degradation experiments. A decrease in a polymer's ability to reduce hydrodynamic resistance during circulation in the system, detected by a decrease in flow rate at the fixed wall shear stress, indicated mechanical degradation of the polymer. Reynolds numbers (based on the diameter of the glass tube) ranged from 10,000–25,000. Pressure and flow rate were recorded throughout a five-hour period or until the polymer completely lost its drag reducing ability and compared to these parameters at the baseline. For the experiments with PEO, the first data point was recorded at 30 s after PEO addition since, due to its lower M_w, PEO completely dissolved much faster than AVP and since there was already visible polymer degradation recorded at this point. For the experiments with AVP, the first data point was not recorded until one minute after AVP addition to allow for the polymer to completely dissolve in the flowing water. Aloe DRP definitely exhibited much stronger molecular entanglement than the PEO solution at the concentration which was used in the injected solutions. The AVP's molecular entanglement was supported by the fact that at the same polymer concentration in solution the viscosity of AVP solutions was disproportionally higher than that of PEO solutions at low shear rates. For example, at a shear rate

of 25 s^{-1}, the AVP solution had a viscosity three times higher than that of the PEO solution (45 cP vs. 15 cP). In the same solutions, the viscosities were much closer at high shear rates (10.4 cP vs. 7.6 cP at a shear rate of $\sim$500 s^{-1}). One can infer that moleculars entanglement played the major role in the much higher viscosity of AVP solution at low shear rates.

Drag reduction at constant wall shear stress (and, therefore, constant pressure drop) was calculated at each time point using the formula:

$$DR_{WS} = \frac{Q_p - Q_0}{Q_0} \times 100, \tag{1}$$

where Q_p is the flow rate of polymer solution and Q_0 is the flow rate of saline or particle suspension alone.

Number average, weight average, and a higher order z average molecular weights (M_w) and intrinsic viscosity (*IV*) of the DRP during degradation were determined using a Viscotek Triple Detector Array gel permeation chromatography (GPC) system (Viscotek, Houston, TX). The separation was performed on a methacrylate-based column with an exclusion limit of 5×10^7 Da. The system combines a refractive index detector, a right angle laser light scattering detector, and a differential viscometer in order to determine average M_w, *IV* and M_w distribution in a single experiment. Column and detector temperatures were maintained at 30°C and the mobile phase was 0.1 M $NaNO_3$ with 0.01% NaN_3. Polymers (100 μl) were injected into the GPC at a concentration of 100 μg/ml (100 ppm). Samples were not dried prior to injection, but were diluted and dialyzed against the GPC eluent using 7000 Da M_w cut-off membrane prior to injection.

In order to quantitatively compare the degradation behavior between two DRPs or between DRPs in the presence or absence of particles, the mechanical degradation behavior of DRPs in the turbulent flow system, both in saline solution and in the presence of RBCs or rigid particles, was examined by fitting it to a previously developed single relaxation decay model [7,20,42] as:

$$\frac{DR(t)}{DR(0)} = \exp(-k \times t),$$

where t is exposure time of the polymer to flow, $DR(0)$ and $DR(t)$ are drag reduction at time 0 and t respectively, and k, while not a true rate constant, is a property that quantifies rate of loss of a polymer's drag reducing ability.

3. Results

3.1. Accelerated degradation of PEO

The addition of PEO to the fluids initially caused a significant reduction in the resistance to flow of the saline and of RBC suspensions. Since the viscosity of the RBC suspensions was higher than that of water, the Reynolds numbers obtained in the RBC flow were lower than those in the saline flow and, therefore, the drag reducing effect in RBC suspensions was not as strong as that in saline. It is known that drag reduction increases with increasing Reynolds number [46]. However, the drag reducing efficiency of PEO decreased rapidly with increasing time of exposure to flow. In saline, the PEO completely lost its drag reducing ability after about an hour of flow. The presence of RBC, however, significantly

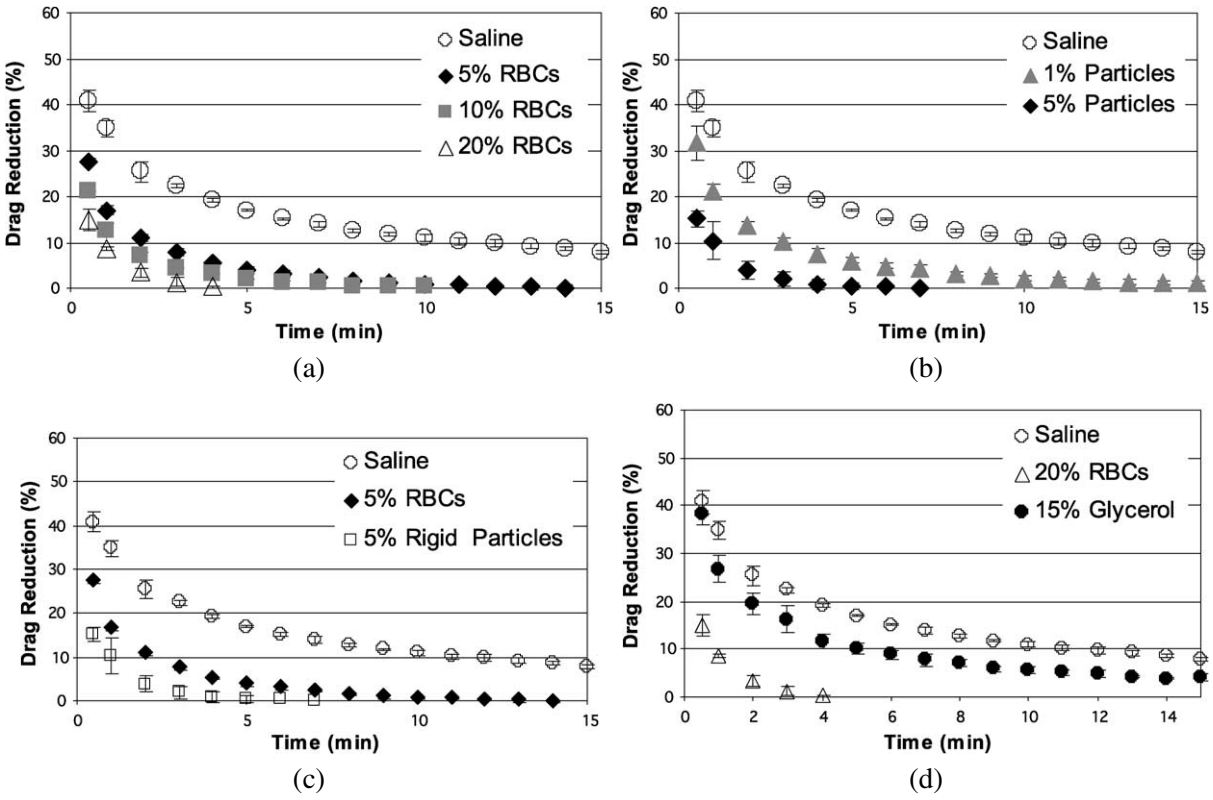

Fig. 1. Rate of PEO degradation at 0.1 mg/ml (100 ppm) increases with increasing RBC (a) or rigid particle (b) concentration. Degradation rate of PEO is higher in a rigid particle suspension than in a RBC suspension (c). Rate of degradation of PEO in a glycerol solution, having the same viscosity as a 20% RBC solution is slightly higher than in saline, but much lower than in the 20% RBC suspension (d). Data are presented as mean $\pm$ standard deviation.

accelerated the PEO degradation rate, as shown in Fig. 1(a). An increase in RBC concentration led to an increase in degradation rate. In a 20% suspension of RBC, the PEO completely lost its drag reducing effectiveness in $\sim$3 min, compared to $\sim$60 min in saline alone.

A similar effect was seen for PEO degradation in suspensions of rigid glass particles. Polymer degradation rate increased with increasing particle concentration (Fig. 1(b)). While the polymer degraded much faster in both suspensions than in saline, rigid particles caused a greater increase in PEO degradation rate than deformable RBC at the same concentration (Fig. 1(c)). The matching viscosity control tests showed that while PEO degraded slightly faster in a 15% glycerol solution than in saline, the degradation was significantly slower in glycerol than in 20% RBC of the same viscosity (Fig. 1(d)).

The nominal M_w of PEO decreased significantly with increased duration of exposure to flow. Nominal weight average molecular weight (M_w) of the PEO was initially $(4.7 \pm 0.8) \times 10^6$ Da, but decreased to $(2.5 \pm 0.1) \times 10^6$ Da within one hour and $(1.6 \pm 0.2) \times 10^6$ Da following five hours of exposure to turbulent flow in saline. It is known that, as the molecular weight of DRP decreases, the onset of drag reduction occurs at higher Reynolds numbers [46]. Therefore, although polymers with molecular weights above 10^6 Da can generally produce drag reduction, the Reynolds numbers in our case (Re $<$ 15,000) may not be high enough for the PEO with a molecular weight of 2.5×10^6 Da to produce significant drag reduction at the applied concentrations. A more significant decrease was observed in the z average mole-

cular weight (M_z), which represents the high end of the molecular weight distribution, showing that the largest molecules were degrading fastest. This fact further explains the loss in drag reduction since it is known that the molecules in the distribution with the highest M_w are most influential in determining the polymer's drag reducing efficiency [36]. In addition to polymer chain scission, the breakup of molecular aggregates likely contributes to the decrease in drag reduction. *IV* also decreased significantly throughout the five hour study: the *IV* of PEO was initially (10.6 ± 1.1) dl/g but decreased to (7.7 ± 0.2) dl/g within one hour and to (6.0 ± 0.3) dl/g in five hours. Table 1 shows molecular weights, *IV*, polydispersity index (PDI) and drag reduction values for PEO degradation in turbulent flow at several time points.

The single relaxation decay model fit the data well for PEO degradation in all of the tested solutions or suspensions (saline, RBCs, rigid particles, glycerol) for short term exposure to flow. The DRP degradation rate (k) increased linearly with an increase in particle concentration as seen in Fig. 2.

Table 1
Molecular characteristics and drag reduction (*DR*) of PEO at 0.1 mg/ml (100 ppm) during turbulent flow degradation in saline

Time (min)	Nominal M_w (Da)	Nominal M_z (Da)	*IV* (dl/g)	Rg (nm)	PDI (nm)	*DR* (%)
1	4.7×10^6	22.1×10^6	10.6	108	2.9	34
5	3.6×10^6	16.5×10^6	9.6	96	3.3	18
15	3.2×10^6	10.4×10^6	8.9	90	3.4	8
30	2.8×10^6	7.3×10^6	8.2	84	3.2	3
60	2.5×10^6	7.6×10^6	7.7	80	2.9	1
120	2.1×10^6	5.3×10^6	7.0	73	2.9	0
180	1.8×10^6	6.7×10^6	6.4	68	2.7	0
240	1.8×10^6	3.9×10^6	6.3	67	2.8	0
300	1.6×10^6	3.5×10^6	6.0	65	2.8	0

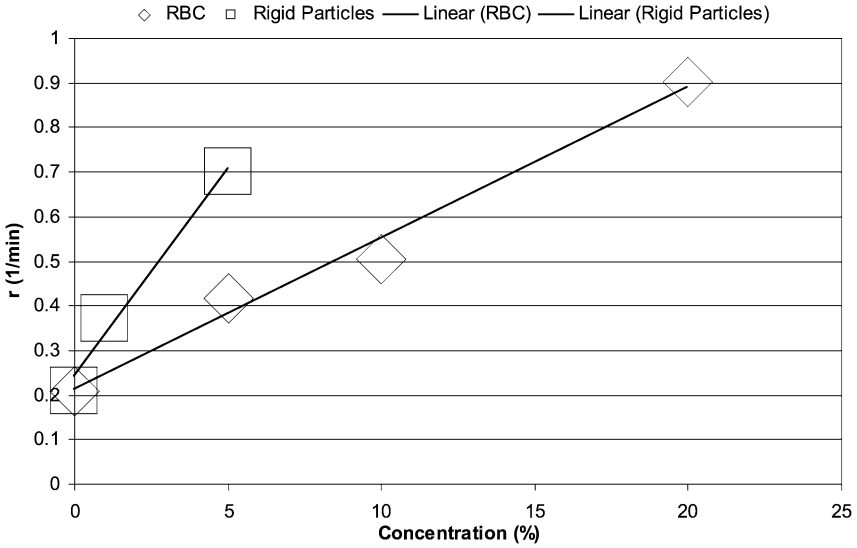

Fig. 2. The rate of PEO degradation rate increases linearly with an increase in particle concentration. Rigid particles cause a larger increase in degradation rate than flexible RBCs for a given concentration increase.

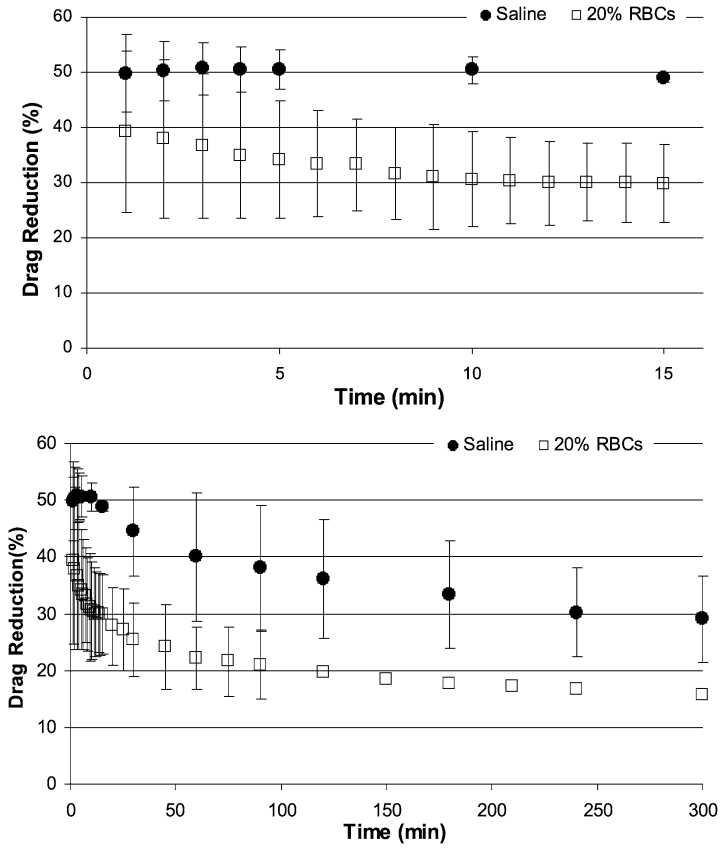

Fig. 3. The rate of degradation of AVP at 0.1 mg/ml (100 ppm) is higher in an RBC suspension than in saline, but AVP is much more resistant to mechanical degradation than PEO. Data is shown for degradation over the first 15 min of exposure to flow (top) and for the entire five hours of exposure (bottom). Data are presented as mean ± standard deviation.

3.2. Accelerated degradation of AVP

AVP was found to be much less susceptible to mechanical degradation than PEO in both saline and in RBC. Figure 3 shows that only slight degradation of AVP occurs during the first 15 min of exposure to flow.

However, the presence of RBC did accelerate the degradation of AVP. In saline, AVP retained most of its original drag reducing efficiency after five hours of exposure to turbulent flow. The degradation rate of AVP was slightly accelerated in a 20% RBC suspension, but ∼40% of its original drag reduction level still remained after five hours of exposure to turbulent flow.

Table 2 shows times needed to decrease the *DR* to 25% of the original value for PEO and AVP in various test fluids. The times needed for *DR* to be reduced to 25% of original are much longer for AVP than for PEO.

The nominal M_w of the AVP was initially $\sim 8.4 \times 10^6$ Da and *IV* was ∼29 dl/g. The molecular characteristics of AVP did not change significantly during five hours of exposure to flow.

The single relaxation decay model, which fit the PEO degradation data well, was also tried for AVP degradation, where it could be used to predict degradation over longer time periods

Table 2
Times needed to decrease the *DR* to 25% of original *DR* for various DRP and test fluid combinations. Data are presented as average time ± standard deviation

Polymer/test fluid	Time until *DR* is reduced to 25% of initial value (min)
PEO in saline	10.9 ± 1.6
PEO in 5% RBCs	3.4 ± 0.3
PEO in 10% RBCs	2.5 ± 0.5
PEO in 20% RBCs	1.9 ± 0.1
PEO in 1% rigid particles	3.9 ± 0.5
PEO in 5% rigid particles	2.1 ± 0.5
PEO in glycerol	5.5 ± 0.8
AVP in saline	>300
AVP in 20% RBCs	>300

than can be practically studied. However, this model was not a good fit for the AVP degradation data.

4. Discussion

Both RBC and rigid particles were found to significantly accelerate degradation of PEO. Using a glycerol solution as a viscosity control for the suspensions, it was determined that the increased degradation of the PEO in suspensions is likely due to the combination of increased viscosity and the presence of particles, with the particles playing the larger role.

It has been previously shown that the intensity of turbulence in flowing blood at a hematocrit below 30% is greater than that of plasma adjusted to the same viscosity at a given Reynolds number [41]. Collisions between cells result in changes of direction of motion and, thus, the development of additional vortices. Rigid RBC increase turbulence intensity even more than normal flexible RBC [41]. We assume that rigid particles increase turbulence intensity as well, compared to flexible cells. The shear deformation of flexible, viscoelastic RBC may absorb some of the kinetic energy from the turbulent flow and therefore reduce these additional vortices to some extent [41]. Therefore, the accelerated degradation rate of PEO molecules in the presence of rigid particles compared to PEO degradation rate in the presence of flexible RBC may be a result of this increase in intensity of turbulence in both the tube and the centrifugal pump.

Another potential mechanism of the observed particle effect might be related to the polymer degradation due to interparticle collisions. When a polymer molecule is trapped between colliding particles, the compressive forces as the particles approach, and the tensile (elongational) forces as they separate may be accelerating the degradation.

At the flow rate of 5 l/min, the pressure drop for the 5% rigid particle suspension with no polymer added (395 ± 24 mmHg) was larger than for the 5% RBC suspension with no polymer added (368 ± 17 mmHg). This was in spite of the fact that the viscosity of the rigid particle suspension (1.1 cP) was slightly lower than of the RBC suspension (1.2 cP). This increased pressure drop of the rigid particle suspension suggests an increased turbulent intensity, which may be at least partially responsible for the accelerated mechanical degradation.

Various water-soluble DRP have been shown to enhance blood flow in animal models of various pathological states including diabetes and hemorrhagic shock [12,14–17,22,29,31,32,34,35,38,39]. It

was shown that the effective biological half-life of one DRP, polyacrylamide (Separan AP-30), was about 35 h in rats [34]. The method of removal was suggested to likely be through break down of the polymer to molecules with molecular weights below 10,000 Da which could pass through the glomerular membrane and be excreted in the urine. PEO was shown to produce one of the strongest hemodynamic effects of any of other DRP tested for potential biomedical applications and, therefore, was used in many *in vitro* and *in vivo* studies. Mechanical degradation, however, is a serious concern when considering using DRP for potential treatment of chronic conditions. The stresses produced by cell motion in blood flow, as evidenced in the current studies, cause even more rapid degradation of PEO. AVP, on the other hand, was much more resistant to mechanical degradation in both saline and in the presence of RBC making it a much more promising candidate for the potential treatment of chronic circulatory disorders.

It has been previously hypothesized that certain polysaccharides may have increased resistance to degradation due to their strong bonds between monomer units as well as intra- and intermolecular interactions lessening the stresses on those bonds [23]. It has also been suggested that branches on a polymer molecule increase its mechanical stability [24]. Although the exact structure of the DRP component of aloe is not known, a structure proposed for the main component of the aloe derived polysaccharide may contain some branches [8] while PEO does not.

4.1. Study limitations

The degradation studies were performed in turbulent flow since it allowed for monitoring and characterization of the degradation using the decrease in polymer drag reducing efficiency. These flow conditions also provided the shear stresses necessary to compare degradation of different DRP in different media in a relatively short time period. The maximum shear stresses in the blood vessels of a healthy human do not exceed 10 Pa [6], although stenotic arteries can produce turbulence and shear stresses several times greater than this value [25]. The stresses in our test flow system were much higher than those generally found *in vivo*; therefore, it is expected that the DRP will degrade much more slowly in the body than in the experiments of this study. Indeed, it was previously shown that DRP could be effective for at least 35–48 h in rats ([34] and Kameneva et al., unpublished data). Although, studies of DRP degradation during laminar pulsatile flow would result in more accurate prediction of the DRP residence time in the circulating blood *in vivo*, such a study would be much more complex due to the inability to directly measure the reduction in drag-reducing efficiency of the tested DRP.

This study provides a comparison of the degradation behavior of various DRP or DRP in different suspensions. Undoubtedly, there was a certain contribution of the shear stress produced by the pump head to the mechanical degradation of DRPs. However, it was not considered in this study. Since all polymer solutions were exposed to similar flow conditions in the pump, the comparative study remains valid. However, the magnitude of this stress and the exposure time must be determined in order to accurately quantify the magnitude of the shear stress that caused the observed degradation. Future studies on DRP degradation in the pump vs. in the tube would help to quantitatively determine the stresses which cause DRP degradation.

In addition, future experiments investigating the effect of different sized rigid particles on the rate of degradation would provide valuable information on how the compressive and tensile forces between particles could stretch polymer molecules and lead to their scission. In a recent study, it was shown that prior to breaking, polymer molecules are stretched due to elongational strains in turbulent flows [45]. In the study presented here, the polymer molecules may be stretched to a size of the same order of

magnitude as the size of the RBC and particles, which can be related to one of the major mechanisms of the accelerated DRP degradation in their presence.

5. Conclusions

In summary, this study provides a comparison of the degradation of various DRP in different solutions and suspensions. AVP was demonstrated to be more resistant to mechanical degradation than PEO in either saline alone or in the presence of RBC. In addition, for the first time it was shown that the degradation rate of DRP increased with an increase in concentration of flexible RBC and even more so with an increase in concentration of rigid particles.

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