Poly(*N*-vinylformamide)—A Drag-Reducing Polymer for Biomedical Applications

Joie N. Marhefka,[†,‡] Philip J. Marascalco,[†,‡] Toby M. Chapman,[†,§] Alan J. Russell,[†,||,⊥,#] and Marina V. Kameneva*[,†,‡,⊥]

McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, Department of Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania, Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania, Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, Pennsylvania, Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania, and Department of Molecular Genetics and Biochemistry, University of Pittsburgh, Pittsburgh, Pennsylvania

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Water-soluble drag-reducing polymers (DRPs) were previously demonstrated to significantly increase blood flow, tissue perfusion, and tissue oxygenation when injected intravenously at nanomolar concentrations in various animal models. Turbulent flow drag-reducing ability was proven to be the most important factor defining the potential of polymers to favorably affect blood circulation. Several DRPs were applied in previous in vivo tests, but the search continues for suitable DRPs for biomedical applications. We demonstrated that poly(*N*-vinylformamide) (PNVF) with a molecular weight of 4.5×10^6 Da significantly reduced resistance to turbulent flow in a pipe and thus presents a DRP. We also found that the PNVF mechanical degradation is much slower than that of the most commonly used DRP, poly(ethylene oxide). PNVF is known to have low toxicity. Furthermore, our pilot in vivo study showed that PNVF had acceptable biocompatibility and hemodynamic effectiveness and thus could be considered as a DRP candidate for potential clinical use.

Introduction

It was discovered several decades ago that the addition of minute quantities of some special soluble polymers could significantly decrease resistance to flow without affecting viscosity or density of the fluid.[1] This phenomenon, known as the drag-reducing or Toms effect, occurs in developed turbulent flow with polymers (DRPs) which exhibit certain chemical and physical properties including high molecular weight (average molecular weight greater than a million Daltons), a long and flexible backbone, a high degree of polymerization, and at least a fairly linear structure.[2] The Toms phenomenon has been investigated and used for various industrial and engineering applications including crude oil transport through pipelines, firefighting, and reducing drag on ships and submarines.[3−5] Although turbulent conditions are not present in much of the vascular system, nanomolar concentrations of blood soluble DRPs injected in the vascular system have been shown to increase blood flow and reduce vascular resistance with no direct effect on blood viscosity or blood vessel tone.[6−8] In animal models of various pathological conditions, blood soluble DRPs have been tested and shown to produce beneficial hemodynamic effects including a significant increase in a number of functioning capillaries in diabetes[9] and a delay/prevention of the development of atherosclerosis in animals kept on an atherogenic diet and chronically injected with minute concentrations of DRPs.[10−13] Most recently it was shown that the DRPs, when used as a component of a resuscitation fluid, were able to significantly improve tissue perfusion and oxygenation and to reduce lethality in animals subjected to severe hemorrhagic shock.[15−16]

High molecular weight poly(ethylene oxides) (PEOs), polyacrylamides (PAMs), DNA, and plant-derived polysaccharides are some of the most effective water-soluble DRPs. These polymers were shown to produce beneficial effects on blood circulation with a considerable potential for clinical applications. PEOs, however, quickly mechanically degrade when exposed to turbulent flow or other relatively high shear stress conditions even for short exposure times.[16−17] DRP degradation is defined as the loss of a polymer's drag reduction effectiveness.[18] The degradation of DRP solutions is likely caused by chain scission, however, there is evidence that degradation may occur, at least in part, due to the breakup of molecule aggregates. PAMs, on the other hand, while being much more resistant to mechanical degradation, present apparent toxicity problems for potential biomedical applications.[7,11] Plant-derived DRPs are highly resistant to mechanical degradation and most likely nontoxic. However, they are not well chemically characterized and thus are not completely reproducible from preparation to preparation. In addition, these plant-based polymers are not easy to manufacture in industrial quantities. Thus, the search continues for other water-soluble DRPs, which would be more biocompatible and mechanically stable than the known synthetic DRPs and better defined, controllable, and easier to manufacture than the natural DRPs.

Water-soluble poly(*N*-vinylformamide) (PNVF) has become more available in the past decade due to the development of improved processes for synthesis and purification of the *N*-vinylformamide (NVF) monomer as well as the growing uses

* Corresponding author. E-mail: kamenevamv@upmc.edu. Phone: (412) 235-5125. Fax: (412) 235-5110.
† McGowan Institute for Regenerative Medicine.
‡ Department of Bioengineering.
§ Department of Chemistry.
|| Department of Chemical and Petroleum Engineering.
⊥ Department of Surgery.
Department of Molecular Genetics and Biochemistry.

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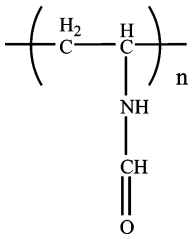

Figure 1. Structure of PNVF.

for PNVF and its derivatives in industrial applications.[19] The polymer has been proposed as a replacement for toxic acrylamide polymers[20] for industrial use. Potential applications for PNVF and its hydrolysis products include water treatment, papermaking, production of textiles, personal care items, adhesives, and coatings, and use in oil field industry and as a rheology modifier.[21] It was shown that very high molecular weight PNVF (up to 6.7×10^6 Da) could be synthesized using an inverse emulsion technique.[22] Due to its structural similarities with PAM, which is a well-known highly effective DRP, and its ease of polymerization,[22] high molecular weight PNVF could be a good candidate for a drag reducer. The high solubility of PNVF in water and very low toxicity of the NVF monomer, an isomer of acrylamide,[21] provide motivation for testing PNVF as a potential DRP for biomedical applications. Although hydrolysis products of PNVF, including poly(vinylamine), have been tested and shown to be effective DRPs,[23] to the best of our knowledge, the drag-reducing ability of PNVF was never tested before. This paper presents a comprehensive study of physicochemical, drag-reducing, viscoelastic, and mechanical degradation characteristics of PNVF and results of preliminary tests on the effects of small additives of PNVF to blood on hemodynamics in vivo.

Experimental Section

Synthesis. We used an inverse emulsion polymerization technique described by Badesso et al.[22] to synthesize high molecular weight PNVF. NVF monomer (Sigma-Aldrich) was distilled at 80 °C under vacuum. The distilled NVF monomer (25 mL), sorbitan monostearate (4.02 g), octane (145 mL), water (48 mL), and 2,2′-azobis(2,4-dimethylpentanenitrile) (Vazo 52, 0.048 g, DuPont) reacted in a high-speed stirrer (500 rpm) at 50 °C for 3 h under nitrogen. The reaction produced an emulsion, which was broken with excess acetone to yield high molecular weight PNVF. The PNVF was dried and then dissolved in distilled water at a concentration of 5 mg/mL. The PNVF solution was then dialyzed against distilled water using a Spectra/Por polyvinylidine difluoride membrane (Spectrum Laboratories, Inc.) with a 1×10^6 Da molecular weight cutoff to remove any unreacted monomer, low molecular weight polymer, and other impurities. The dialyzed PNVF was lyophilized and redissolved at a concentration of 5 mg/mL in distilled water. Three lots of the polymer were synthesized. Each preparation was characterized using the hydrodynamic, rheological, and chemical methods described below. The preparation which was shown to have the best drag-reducing properties was selected for further studies including in vivo biocompatibility tests. Several commercial PEOs, including PEO-1000 with molecular weight (MW) of 1000 kDa, PEO-2000 with MW of 2000 kDa, and PEO-4500 with MW 4500 kDa, were used in this study for comparison with the PNVF. The structure of PNVF is shown in Figure 1.

^{1}HNMR. ^{1}HNMR spectrum was recorded on a Bruker Avance 300 spectrometer, using deuterium oxide as a solvent.

Gel Permeation Chromatography. Molecular weight, intrinsic viscosity, radius of gyration, and polydispersity of the PNVF were measured 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 MW, intrinsic viscosity, radius of gyration, and molecular weight 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. The GPC characteristics obtained for PNVF were compared to those of a PEO-4500.

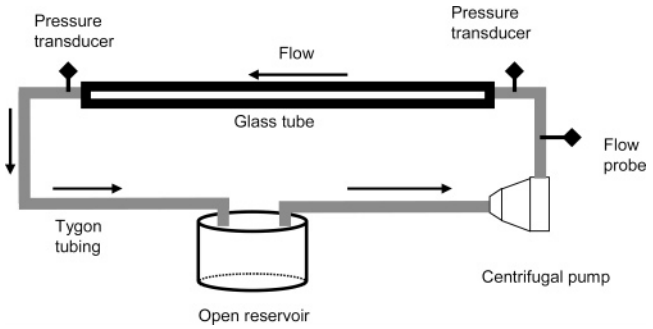

Figure 2. Schematic of system used for turbulent flow studies.

In Vitro Test of Drag-Reducing Ability. The ability of the PNVF to reduce resistance to turbulent flow was evaluated using an in vitro circulating system. The system (Figure 2) 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 1 L open fluid reservoir connected with 3/8 in. Tygon tubing (Cole-Parmer).

Flow rates of 2−6 L/min, which correspond to Reynolds numbers ranging from 10 000 to 25 000, were studied. PNVF was added to circulating saline to give concentrations of 0.1 and 0.5 mg/mL in solution. Pressure and flow rates were recorded before and after DRP addition. The in vitro flow experiments were performed at room temperature. Drag-reduction at a constant flow rate was calculated using eq 1

$$\mathrm{DR} = \frac{\Delta P_\mathrm{P} - \Delta P_0}{\Delta P_0} \times 100\% \qquad (1)$$

where DR is the drag-reduction (%), ΔP_P is the pressure drop across the tube for polymer solution (dynes/cm^2), and ΔP_0 is the pressure drop for saline alone (dynes/cm^2). Reynolds number (*Re*) was calculated using eq 2

$$Re = \frac{4Q}{\pi d \upsilon} \qquad (2)$$

where Q is the volumetric flow rate (cm^3/s), d is the tube diameter (cm), and ν is kinematic viscosity (cm^2/s). A dimensionless friction factor was also calculated for the DRP solutions and compared to that of saline alone using eq 3

$$\lambda = \frac{d^5 \pi^2}{8 l \rho} \frac{P}{Q^2} \qquad (3)$$

where λ is a friction coefficient, l is the tube length (cm), ρ is the density of the fluid (dynes·s^2/cm^4), and P is the driving pressure (dynes/cm^2).

Viscoelasticity. Rheological properties of concentrated PNVF solutions were studied since they have been previously shown to strongly correlate with a polymer's drag-reducing effectiveness. DRPs at relatively high concentrations in solutions have high viscosity and considerable elasticity and relaxation times compared to solutions of polymers of similar MW which do not possess drag-reducing ability. In addition, DRP solutions demonstrate non-Newtonian behavior (dependence of viscosity, elasticity and relaxation time on shear rate).

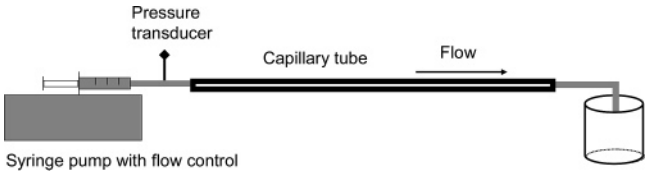

Figure 3. Schematic of laminar flow system.

Viscosity, elasticity, and relaxation time of concentrated polymer solutions (5 mg/mL) were measured at a wide range of shear rates using a Vilastic 3 viscoelasticity analyzer (Vilastic Scientific, Inc., Austin, TX), which employs controlled oscillatory flow in a cylindrical tube with diameter of 0.1 cm to measure these rheological parameters. Viscosity was also measured using a Brookfield cone and plate rheometer (Brookfield Engineering Laboratories, Inc.). In addition, viscosity was calculated from the data obtained in a laminar flow system employing Poiseuille's law. A schematic for the laminar flow system is shown in Figure 3.

Briefly, the polymer solution was driven through a capillary tube with an inner diameter of 1.3 mm and a length of 61 cm using a syringe pump. A wide range of flow rates from 1 to 10 mL/min which corresponded to Reynolds numbers from 2 to 25 and shear rates from 93 to 930 s^{-1} was applied. Pressure drop through the tube was measured, and Poiseulle's law (eq 4) was used to calculate viscosity

$$\mu = \frac{\pi \Delta P d^4}{128 L Q} \tag{4}$$

where Q is the volumetric flow rate (cm^3/s), ΔP is the pressure drop through the capillary (dynes/cm^2), d is the capillary diameter (cm), L is the capillary length (cm), and μ is the dynamic viscosity of the solution (dyne·s/cm^2).

Viscosity measurements using the various methods were compared in order to check for consistency and to measure viscosity, elasticity, and relaxation time in a variety of flow conditions and at a wide range of shear rates. Rheological parameters of PNVF were compared to those of PEOs that possess comparable drag-reducing ability (PEO-1000 and PEO-2000). Viscosities at low concentrations, where the solutions exhibit Newtonian behavior, were measured using a capillary viscometer (Cannon Instruments). All viscosities were determined at a temperature of 24 °C ± 0.5 °C.

Mechanical Degradation Studies. The circulating flow system that was used to test drag-reducing ability was also used to study mechanical degradation. A decrease in a polymer's ability to reduce hydrodynamic resistance during circulation in the system, detected by an increase in pressure or a decrease in flow rate, indicated mechanical degradation of the polymer. Wall shear stress in the glass tube was maintained at 45 N/m^2 throughout the degradation experiments. Two sets of degradation experiments were performed. In the first set, DRP was added to the system to result in a concentration of 0.1 mg/mL in solution. Pressure and flow rate were recorded throughout a 2-h period and compared to these parameters at the baseline. Drag-reduction at constant wall shear stress (and therefore constant pressure drop) was calculated at each time point using the formula

$$\mathrm{DR}_{\mathrm{WS}} = \frac{Q_{\mathrm{P}} - Q_0}{Q_0} \times 100\% \tag{5}$$

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

The rate of degradation of PNVF was compared to that of well-known DRPs, PEO-1000, and PEO-2000, which exhibited similar drag-reducing effectiveness to the tested PNVF. In the second set of experiments, GPC was used to determine the molecular weight of the polymer in the samples collected from the circulating loop during degradation tests. These experiments were performed at a slightly higher polymer concentration (0.25 mg/mL) in order to ensure that the refractive index detector on the GPC would generate an adequate response. PNVF concentration, determined by the refractive index detector on the GPC, was recorded for each sample to verify that the decrease in drag-reducing ability was not caused by polymer adsorbing to the tube wall.

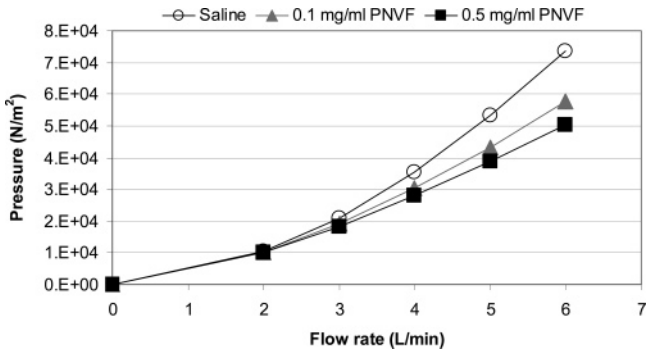

Figure 4. Pressure vs flow characteristics of PNVF solutions obtained in the turbulent flow system.

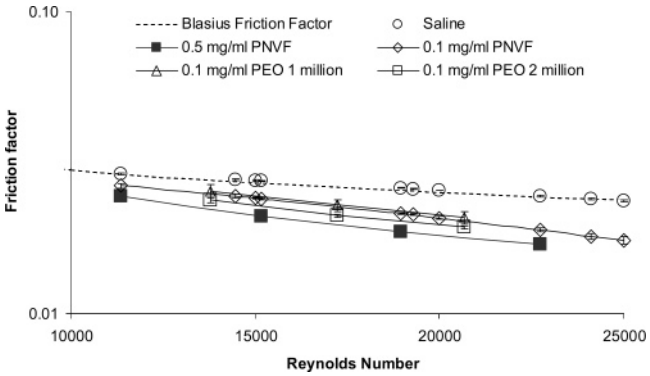

Figure 5. Dimensionless friction factor vs Reynolds number obtained for saline, PNVF (two concentrations) and two PEO solutions.

In Vitro Tests of Blood Biocompatibility. PNVF was added to whole rat blood at a concentration of 4 μg/mL. Blood was incubated for 1 h at room temperature. The effects of PNVF on red blood cell (RBC) morphology and aggregation were studied using a light microscope (Nikon). RBC images were obtained from a microscope slide and during slow flow in a capillary tube.

In Vivo Animal Tests. Four Sprague−Dawley rats (350−400 g) were used in the pilot tests of PNVF general biocompatibility and hemodynamic activity. The study was approved by the University of Pittsburgh's Institutional Animal Care and Use Committee. The animals were anesthetized and instrumented with arterial and venous catheters to measure arterial blood pressure and infuse fluids. A laser-Doppler flowmeter (Transonic Systems, Inc.) was used to continuously monitor tissue perfusion (TP) in the lip mucosa using a 3 mm laser Doppler needle probe. After animal stabilization and recording the base hemodynamic parameters for 10 min, 1 mL of PNVF solution (100 μg/mL) was injected over a 5 min period into the jugular vein to yield a final blood concentration of 4 μg/mL of PNVF in the animal. Blood volume was calculated as 60 mL/kg of body weight. Hemodynamic parameters were recorded for 60 min following PNVF injection. A paired *t*-test was applied to compare hemodynamic parameters before and after injection of PNVF.

Results

^{1}HNMR. The synthesis of PNVF was confirmed by NMR: ^{1}HNMR (D_2O) δ 1.68 (br s, 2H, methylene), 3.89 (br s, 1H, methine), and 8.0 ppm (m, 1H, formyl H). The shift at 8.0 ppm, which represents the formyl hydrogen, confirmed that the tested polymer is indeed PNVF and not the hydrolyzed form, poly(vinylamine).

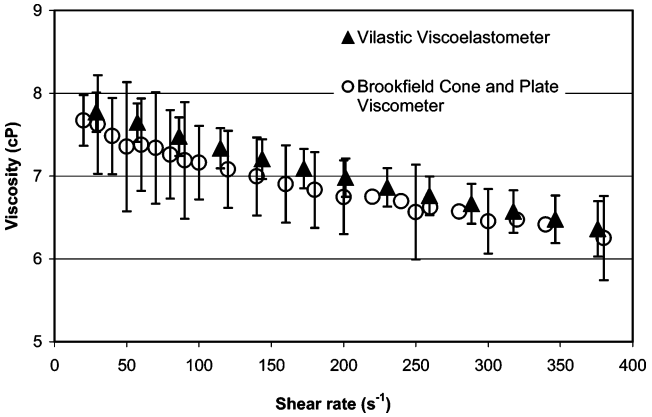

Figure 6. Viscosity of PNVF solution at the concentration of 5 mg/mL.

Gel Permeation Chromatography. The synthesized PNVF had a weight average molecular weight, measured by GPC, of $4.2 \times 10^6 \pm 1.7 \times 10^5$ Da with a polydispersity index of 4 prior to dialysis. Following dialysis against a membrane with a 1×10^6 Da molecular weight cutoff, the weight average molecular weight increased to $4.5 \times 10^6 \pm 3.1 \times 10^5$ Da, and the polydispersity index was reduced to 1.4. The intrinsic viscosity was 4 dL/g, and the radius of gyration was 80 nm. PEO with a molecular weight of 4.5×10^6 Da had a much higher intrinsic viscosity (13 dl/g) and radius of gyration (120 nm).

In Vitro Test of Drag-Reducing Ability. The addition of PNVF to turbulent flow produced a marked reduction in resistance to flow. Figure 4 shows the pressure vs flow relationship for water with 0.1 mg/mL PNVF and 0.5 mg/mL of PNVF compared to that of pure water.

At a given flow rate, the PNVF solution required a significantly lower driving pressure than that of saline alone, representing the Toms effect. PNVF reduced resistance to turbulent flow by a maximum of 20% at a Reynolds number of 20 000 when added into the circulating system at a concentration of 0.1 mg/mL and 32% at a concentration of 0.5 mg/mL. At a concentration of 0.1 mg/mL, PEO-4500 reduces drag by 36%, whereas PEO-1000 and PEO-2000 reduced drag by 17% and 23%, respectively. A dimensionless friction factor vs Reynolds number curve for these experiments is shown in Figure 5. Experimental data is compared to Blasius Friction Factor calculated using the formula $\lambda = 0.316/Re^{0.25}$.

Viscosity and Viscoelasticity. Concentrated PNVF solutions exhibited non-Newtonian behavior, a characteristic demonstrated by DRPs. High shear viscosity of a 5 mg/mL PNVF solution was ~6 cP at a shear rate of 400 s^{-1}, whereas low shear viscosity was ~8 cP at shear rates of ~20−30 s^{-1}. The viscosity vs shear rate curves for this solution, determined using a viscoelastometer and a cone and plate viscometer are shown in Figure 6. The viscosity, elasticity, and relaxation time vs shear rate curves for the PNVF, PEO-1000, and PEO-2000 solutions are shown in Figure 7. Viscosity of a 0.5 mg/mL PNVF solution is 1.3 cP, and viscosity of a 0.1 mg/mL solution is 1.05 cP as measured by a capillary viscometer at a temperature of 25 °C (compared to 0.9 cP viscosity of water at this temperature).

Mechanical Degradation Studies. The PNVF initially reduced resistance to flow by 15% when added into the flow loop at a concentration of 0.1 mg/mL and a Reynolds number of 15 000. However, the drag-reducing efficiency of the PNVF

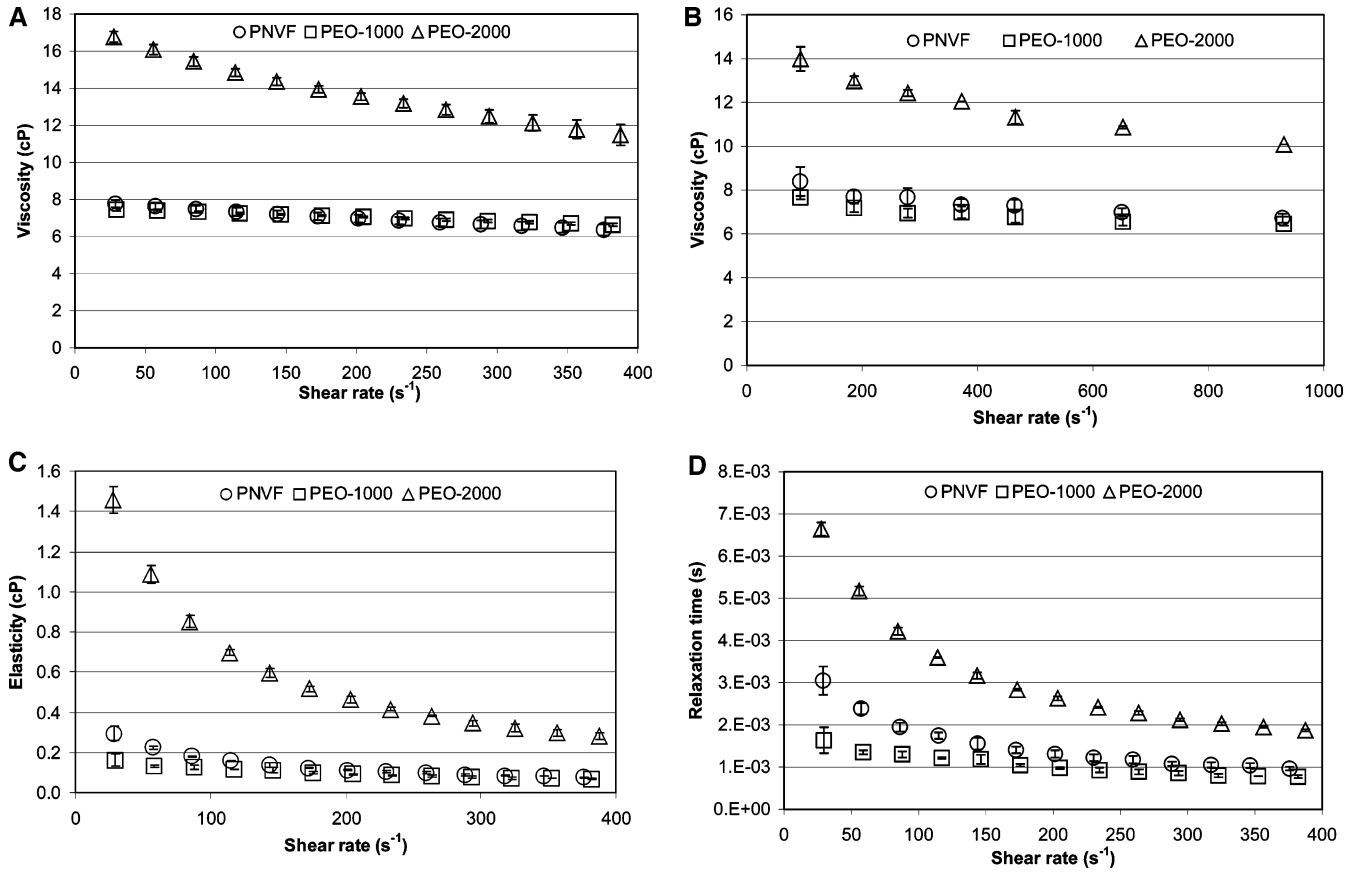

Figure 7. A. Viscosity measured in viscoelastometer at a concentration of 5 mg/mL. B. Viscosity measured a laminar flow system at a concentration of 5 mg/mL. C. Elasticity measured in viscoelastometer at a concentration of 5 mg/mL. D. Relaxation time measured in viscoelastometer at a concentration of 5 mg/mL.

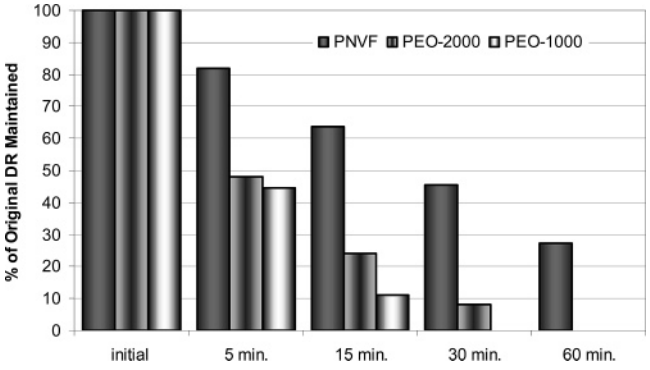

Figure 8. Percentage of original drag-reducing ability maintained after exposure to flow.

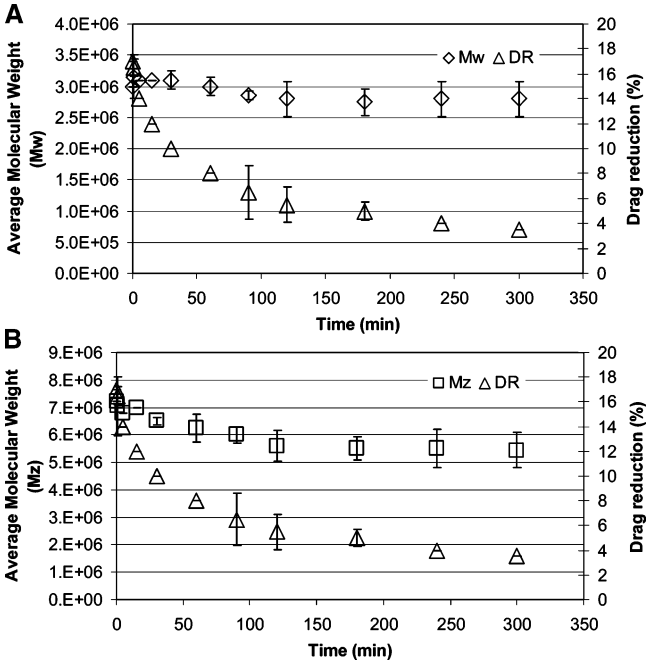

Figure 9. A. Weight average molecular weight decreases slightly as the PVNF drag-reducing ability degrades during exposure to turbulent flow. B. *Z* average molecular weight decreases slightly as the PVNF drag-reducing ability degrades during exposure to turbulent flow.

decreased with continuing exposure to flow, vanishing within 90 min of exposure. The degradation of PNVF was compared to that of PEO-1000 and PEO-2000, which exhibited similar initial drag-reducing efficiency. Figure 8 shows the percentage of the initial drag-reducing ability of these DRPs following exposure to flow induced shear stresses. PNVF retains over 40% of its ability to reduce resistance to flow after 30 min of exposure to flow induced shear stress and almost 25% after an hour of exposure, whereas PEO-1000 loses its drag-reducing ability completely within 30 min and PEO-2000 within 1 h. Average molecular weight of the PNVF, however, decreased only slightly over time. The change in molecular weight versus time of exposure to flow is shown in Figure 9. Both weight average (M_w) and *z* average (M_z) molecular weight, which represents the higher end of the molecular weight distribution, are shown. Finally, PNVF concentration in solution did not change throughout the experiment indicating that the polymer was not adsorbing on the tube walls.

In Vitro Tests of Blood Biocompatibility. PNVF did not change the morphology of RBCs. Figure 10 shows the RBCs incubated with PNVF compared to control RBCs both in static conditions on a microscope slide and slowly flowing in a capillary tube. The static picture also shows that the PNVF did not alter the aggregation of the RBCs.

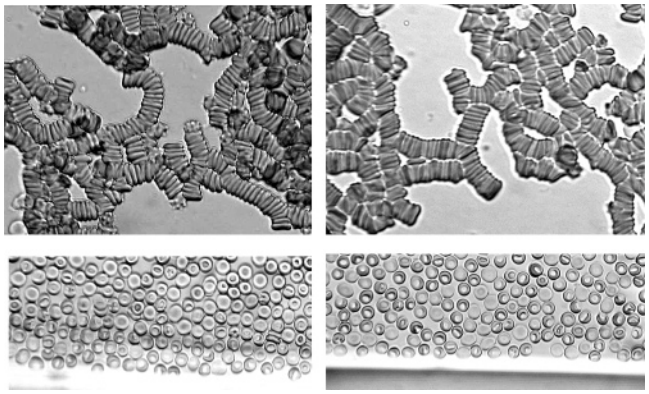

Figure 10. RBCs on a slide before (top left) and after (top right) PNVF addition and slowly flowing in a capillary tube before (bottom left) and after (bottom right) PNVF addition. PNVF did not affect the RBC morphology.

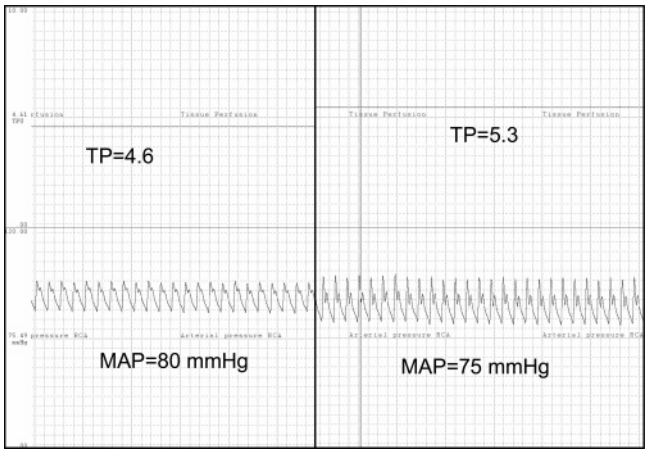

Figure 11. Record of hemodynamic parameters before and after a single injection of PNVF in a normal rat to give a concentration of 4 μg/mL in the blood. The PNVF caused an increase in tissue perfusion and a slight decrease in mean arterial blood pressure.

In Vivo Animal Tests. An intravenous injection of PNVF produced a statistically significant reduction in vascular resistance in a normal animal. The PNVF, at a concentration of 4 μg/mL in the blood, caused both an increase in tissue perfusion and a slight decrease in blood pressure. Thus, PNVF caused an average decrease in vascular resistance of 20% ($p = 0.016$, paired *t*-test vs the baseline). The animals tolerated the PNVF well. Figure 11 shows a record of hemodynamic parameters obtained in one of the tests, and Figure 12 shows the average tissue perfusion and blood pressure before and after the DRP injection for all four tests.

Discussion

DRPs have been shown to improve impaired blood circulation caused by numerous pathologies in animal models.[6−7,9−12,14−15] Although commonly used DRPs such as PEOs, PAMs, and plant derived polysaccharides are very effective in these models, they are not optimal for potential clinical applications. PEO is degraded quickly by high stresses,[16] PAM presents toxicity issues,[7,11] and natural polymers are often difficult to manufacture in the necessary quantities. Therefore, the search continues for better synthetic DRPs, which are resistant to mechanical degradation, biocompatible, and well reproducible, for potential clinical use.

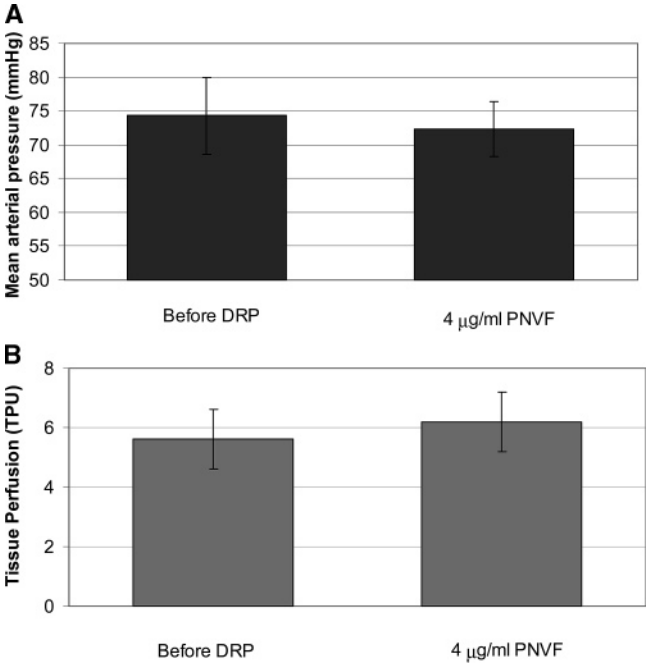

Figure 12. A. 30 min after intravenous injection, PNVF caused a slight decrease in mean arterial blood pressure. B. 30 min after intravenous injection, PNVF caused an increase in tissue perfusion, and therefore, reduction in peripheral vascular resistance.

High molecular weight PNVF (4.5×10^6 Da) was synthesized and tested as a DRP for potential biomedical applications. Our previous characterization of well-known DRPs (PEOs, PAMs, and plant-derived polysaccharides) demonstrated that all of these polymers have a MW greater than 10^6 Da, an intrinsic viscosity greater than 4 dL/g, and a radius of gyration greater than 50 nm. The synthesized PNVF had molecular properties characteristic of DRPs, including high molecular weight and relatively large intrinsic viscosity and radius of gyration, and was effective in reducing resistance to turbulent flow. Although the PNVF was shown to be an effective drag-reducer, reducing resistance to turbulent flow by over 30% at a concentration of 0.5 mg/mL, it was not as effective as PEO of the same molecular weight (4.5×10^6 Da). One possible explanation for this is that, since NVF polymerization is known to exhibit some chain transfer,[20] the PNVF is likely not entirely linear. This hypothesis is supported by the fact that its intrinsic viscosity (4 dL/g) is significantly lower than the 13 dL/g intrinsic viscosity of PEO-4500. Another factor that may contribute to this difference in drag-reducing efficiency is that the molecular weight of the NVF monomer is much higher than the molecular weight of the ethylene oxide monomer. It is well-known that, at the same polymer molecular weight, the polymer with the lower monomer molecular weight and therefore a higher degree of polymerization is a better drag-reducer.[2] The drag-reducing ability of the PNVF is close to that of PEO-1000 and PEO-2000 (at least in the applied range of Reynolds numbers). In addition, viscoelastic properties of the PNVF correspond well to these PEOs, indicating that the viscosity, elasticity, and relaxation time are important parameters in determining a polymer's drag-reducing activity.

Although PNVF was susceptible to mechanical degradation, losing all of its drag-reducing ability after 1.5 h of circulation in the turbulent flow system, its degradation rate was significantly lower than that of PEO-1000 and PEO-2000 which lost their drag-reducing ability after circulation for 20 and 45 min respectively at the same concentration and identical flow conditions. Although there was a significant loss of drag-reducing ability over time for both PNVF and PEO, the PNVF's molecular weight decreased only slightly. These results are consistent with previously published studies of mechanical degradation of drag-reducing polymers.[24−25] Two theories have been proposed to explain this phenomenon, which is also seen in polyacrylamide degradation. The first of these theories is the molecules at the high end of the molecular weight distribution are most influential in a DRP's efficiency[26] and scission of those molecules would account for loss in drag-reducing ability. This is supported by the decrease in M_z, which defines the high end of the molecular weight distribution (as seen in Figure 9b). The second hypothesis proposes that shear induced structure formation and molecule aggregation are partially responsible for the DRP effects, and therefore, the irreversible breakup of these structures is responsible for the declining drag-reducing effect produced by polymers.[24−25] We showed that the drag-reducing ability of the PNVF is not restored after stopping the flow for 1 h. This is consistent with the experiments of Liberatore et al., suggesting that that polymer aggregates contribute to the drag-reducing ability and irreversibly break up as the solution degrades.[25] The loss of the high molecular weight fraction of the PNVF during exposure to high mechanical stresses (Figure 9b) might also be responsible for the loss of ability to form structure since flow-induced structure formation is highly dependent on molecular weight.[27] Sellin et al. suggested a similar theory for PEO degradation, proposing that both chain scission and disentangling of molecular agglomerates could contribute to DRP degradation.[18] Although there is evidence that either of these theories or a combination of them could explain the loss of drag-reducing ability, the mechanisms behind the degradation of DRPs and the drag-reducing phenomenon itself are not completely understood, and therefore, it is likely that a combination of these theories and other factors may contribute to the degradation.

We considered the possibility that the decreased drag-reducing ability may be a result of the polymer adhering to the tube and pump walls and, thus, reduction of its concentration in the flowing solution. The concentration of polymer remained at 0.25 mg/mL throughout the experiment, and therefore the loss in drag-reducing activity was not caused by polymer adherence to the wall. More studies need to be done to further understand the DRP degradation mechanisms. However, these studies are out of scope of the present work.

For potential use in biomedical applications, it would be beneficial to have a DRP that degrades relatively slowly since it can last for a significant amount of time after intravascular injection. Considering that the blood flow in the cardiovascular system is not turbulent and that the shear stresses in the in vitro turbulent flow systems are significantly higher than physiological shear stresses, one can expect much a longer time of DRP circulation in vivo without degradation. Due to its higher stability against mechanical stress, PNVF might be a more favorable polymer for these uses.

In vitro and in vivo studies showed that the PNVF seemed to be biocompatible with blood. In vivo, the PNVF was found to be efficient in reducing vascular resistance without producing adverse effects, at least in acute experiments. However, further in vivo studies are necessary to prove beneficial effects of PNVF on normal and especially on pathological blood circulation. Nevertheless, due to its obvious drag-reducing effectiveness at both in vitro and in vivo flow conditions, relatively slow mechanical degradation, and its very low toxicity, PNVF can be considered as a DRP for potential biomedical applications.

Conclusions

High molecular weight PNVF was found to have pronounced drag-reducing properties and thus to belong to the class of water-soluble DRPs. PNVF was shown to significantly reduce resistance to turbulent flow in a pipe as well as to reduce vascular resistance in vivo. We also showed that PNVF was much less susceptible to mechanical degradation than the well-known drag-reducer poly(ethylene oxide). Our pilot in vivo study showed that PNVF had acceptable biocompatibility. Since PNVF is known to have very low toxicity, it warrants further studies as a DRP candidate for potential clinical use.

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