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# Spray Pattern and Droplet Size Analyses for High-Shear Viscosity Determination of Aqueous Suspension Corticosteroid Nasal Sprays

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**Aqueous suspension corticosteroid nasal sprays exhibit the rheological property of shear thinning, meaning they exhibit a decrease in viscosity upon application of shear. Most rheological methods are limited in the amount of shear that can be applied to samples (~1,000 $s^{-1}$) and thus can only approximate the viscosities at the high-shear conditions of nasal spray devices (~$10^5$–$10^6$ $s^{-1}$). In the current work, spray area and droplet size were shown to demonstrate viscosity dependence. Three Newtonian fluids were used to determine equations to approximate viscosity at the spray nozzle from correlations to spray area and droplet size using a standard 100 µL Pfeiffer® nasal spray pump. Several shear-thinning solutions, including four commercial aqueous suspension corticosteroid nasal sprays and three aqueous Avicel® (1, 2, and 3%, wt/wt) samples, were analyzed to demonstrate the ability of spray area and droplet size analysis to estimate high-shear viscosities. The calculated viscosity values trend in accordance with the rheometer data along with the ability to distinguish differences between all samples analyzed.**

**Keywords** rheology; Avicel; spray area; droplet size; viscosity; shear thinning

## INTRODUCTION

Corticosteroid nasal sprays have been prescribed to treat the symptoms of allergic rhinitis. The effectiveness of drug delivery is influenced by the formulation in combination with its spray device. The formulation of these drugs is designed to effectively disperse and suspend lipophilic drug particles within an aqueous medium and the spray device is designed to efficiently atomize the formulation for delivery into the nasal cavity. A useful formulation requires a high viscosity to sustain drug particles in suspension, though for effective delivery it must thin under the application of shear (in this case caused by the nasal spray delivery devices) in order for the spray to atomize efficiently (Sharpe et al., 2003). The formulation must then return to a more viscous state after application so that the formulation does not drip easily out of the nose. This reversible loss of viscosity can be quantified by pseudoplasticity (rapid reversibility) and thixotropy (slower time dependence).

Most commercial nasal sprays exhibit the rheological property of shear thinning, which is defined as a decrease in viscosity upon the application of shear. This behavior is attributed to the incorporation of a blend of microcrystalline cellulose (MCC) and carboxymethyl cellulose (CMC) (commercial name: Avicel®) in many commercial products. The microcrystals of MCC are weakly cross-linked by chains of the water-soluble CMC in an aqueous medium causing an increase in apparent viscosity. On the application of shear these weak threadlike polymer chains can slip past one another resulting in a lower apparent viscosity. When shear is then reduced or removed, the cross-links can reform, thereby increasing the apparent viscosity back to the original state. Therefore, the incorporation of MCC and CMC allows for ease of atomization (due to lower viscosity) out of a nasal spray pump followed by a reversal to near the initial viscosity upon removal of stress (Sharpe et al., 2003). The amount of time required for the return of viscosity close to its initial state of common nasal sprays has been shown to be greater than 5 min, implying that the remaining viscosity present after shear thinning is primarily responsible for the prolonged residence in the nasal cavity (Eccleston, Bakhshaee, Hudson, & Richards, 2000).

Viscosities of nasal sprays have been determined previously by collection of dispensed samples and evaluation in either a viscometer (Dayal, Sudhan Shaik, & Singh, 2004), which may not allow for shear determination, or a rotational rheometer (e.g., TA Instrument's AR-1000 and 2000 series) with practical upper shear rate limitations of approximately 1,000 $s^{-1}$ (Eccleston et al., 2000; Sharpe et al., 2003). Whereas standard rheological methods measure accurately the viscosity and shear-thinning behavior of the nasal formulation within their respective operating range, they are limited in measuring the

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values at the actual spray conditions generated by nasal delivery devices that can be in upwards of $10^5$–$10^6$ $s^{-1}$ (Barnes, 2000). Research using capillary rheometry has been used to calculate viscosities under high-shear (maximum $10^6$ $s^{-1}$) and extensional flow conditions (Eccleston & Hudson, 2000). However, these measurements are still only approximating the high-shear conditions experienced by the formulation while spraying out of nasal spray devices.

Viscosity has been shown to affect other important formulation parameters, including droplet size and spray geometries (Dayal et al., 2004; Harris, Svensson, Wagner, Lethagen, & Nilsson, 1988). Dayal et al. (2004) investigated the relationship between physical properties of nasal formulations and their spray characteristics (droplet size and spray areas). They observed a linear relationship between droplet size ($Dv_{50}$ as measured using Malvern's Spraytec®) and viscosity (measured using a Brookfield viscometer; Brookfield, Middleboro, MA) for nasal pumps using CMC as the viscosity modifier. They also noted that the spray area (measured using paper chromatography technique) decreased in a power-law manner with increasing viscosity. They concluded that the characteristic of nasal aerosol generation is dependent on a combination of actuation force, viscosity, rheological properties, surface tension, and pump design.

The current work shows the utility of spray area and droplet size analyses to approximate the high-shear viscosities of non-Newtonian shear-thinning nasal sprays. This was accomplished through correlation of spray area and droplet size to standard curves generated by using three Newtonian fluids over a wide range of concentrations and viscosities.

## MATERIALS AND METHODS

### Materials

Three Newtonian viscosity agents were used in this study, which included polyethylene glycol (PEG) average molecular weight of 400, propylene glycol (PG) molecular weight of 76.09, and glycerin molecular weight of 92.09. Four corticosteroid aqueous nasal sprays with varying degrees of viscosity and shear thinning were used and will be referred to as NS-A, NS-B, NS-C, and NS-D. NS-B contained higher levels of MCC and CMC than NS-A or NS-C. The levels of MCC and CMC present in nasal spray NS-D were unknown at the time of the study. All products were evaluated within their respective shelf lives. Avicel® RC-591 stabilizer is a commercial blend of MCC and CMC used in many pharmaceutical nasal sprays as a thixotropic suspending agent and was obtained from FMC® (FMC, Philadelphia, PA) BioPolymers for use in this study. Samples containing only Avicel® in water were formulated at 1, 2, and 3% levels (wt/wt).

### Nasal Spray Pump

All spray area analyses were carried out using a standard 100-µL Pfeiffer® (Pfeiffer, Radolfzell, Germany) nasal spray pump on a screw-top plastic bottle. The use of a screw-top actuator pump allowed for a convenient method to refill the device with different test solutions without requiring permanent sealing as in the case of crimp-top actuator bottles. Use of the same spray pump also removed device-to-device variability among manufactures and lots. Other spray pump designs were tested, which also produced comparable overall trends. However, spray area was dependent on spray pump design and thus absolute spray areas differed significantly. The 100-µL Pfeiffer® pump was determined to deliver the lowest relative standard deviation (RSD) for the samples used in this study (<2%) and was chosen accordingly for the remaining part of the work.

### PEG, PG, and Glycerin Sample Preparation

PEG, PG, and glycerin samples were prepared at 25, 50, and 75% (vol/vol) in deionized water. Deionized water was used as the reference standard for 0% modifier. Samples were thoroughly mixed and analyzed in a TA instrument's AR-2000 rheometer, Malvern's Spraytec, and a SprayVIEW® NSP analyzer.

### Corticosteroid Aqueous Nasal Spray Preparation

Nasal sprays NS-A, NS-B, NS-C, and NS-D were removed from their original bottles with care to minimize the amount of shear generated during sample loading for spray area and viscosity analyses.

### Avicel® Samples (1, 2, and 3%) Preparation

Avicel® samples were prepared by adding 1, 2, and 3% Avicel® by weight in water, gradually over a period of 2 min (for a small batch) while mixing. Samples were stirred at 2,000 rpm for a total of 15 minutes using a Caframo® (Caframo, Wiarton, Ontario) BDC2002 digital mixer. The samples were then homogenized for 5 min using a Silverson® (Silverson East Longmeadow, MA) L4RT homogenizer operating at 4,000 rpm. The samples were allowed to stand at room temperature for a period of 1 week to ensure that the final Avicel® structure was formed and the sample was rheologically stable (Rudraraju & Wyandt, 2005a, 2005b). All Avicel® samples were subjected to rheometer, droplet size, and spray area analyses.

### Viscosity Measurements (Rotational and Capillary)

Shear-thinning behavior was evaluated using an AR-2000 rheometer (TA Instruments, New Castle, DE, USA) using a concentric cylinder geometry and was operated at room temperature. Each 20-mL sample was loaded carefully into the cylinder to minimize the amount of shear caused during loading. All samples were subjected to an upward linear shear rate ramp from 1 to 1,000 $s^{-1}$. A downward ramp from 1,000 to 1 $s^{-1}$ was performed immediately following the upward ramp. Viscosity measurements used for correlation to spray area were obtained at a shear rate of 1,000 $s^{-1}$, the practical limit of the rotational rheometer used.

To estimate viscosity at high-shear rates, Avicel® samples were analyzed using a Rosand® RH10 capillary rheometer (Malvern, Westborough, MA, USA). The samples were analyzed by shearing in the $10^5$–$10^6$ $s^{-1}$ range at room temperature using a constant shear test. In this test the samples were sheared through a very fine tube (145 μm diameter) so that a high-shear rate could be obtained while keeping the Reynolds number low. All the testing was conducted using a single die/pressure transducer combination, 300 mm long × 0.145 mm × 180° diameter die and 20,000 psi transducer.

### Spray Area Analysis

Sample spray analysis was carried out on a SprayVIEW® NSP analyzer with an integrated SprayVIEW® NSx actuation system (Image Therm, Marlborough, MA). Spray area was selected as the recorded parameter instead of plume geometry due to the variability in plume geometries caused by bottle orientation, ellipticity of spray, and required manual user input during calculation. Spray areas were calculated automatically in gradient mode by the SprayVIEW® 4.0 data management and analysis software. Spray area analysis was optimized for actuation parameters and imaging setup. Great care was taken to eliminate outside influences such as light and air disturbances to ensure reproducibility of spray areas. Spray areas were calculated at a laser-to-orifice distance of 30 mm with actuation parameters 3,000 mm/s$^2$ for acceleration and 50 mm/s for velocity, which allowed for the RSD of the spray area analyses to be less than 1.0%.

### Droplet Size Analysis

Droplet size analysis was performed using a Malvern® Spraytec Model STP5313 particle size analyzer with an integrated SprayVIEW® NSx actuation system. Upon actuation of the nasal spray device, data were collected that consisted of average particle sizes from the region of low transmission. The data collection was performed at 100 Hz with an autotrigger for data acquisition when transmission dropped below 95%. Air was used as the dispersant and water was chosen as the particle of comparison. Particle size actuation parameters were 3,000 mm/s$^2$ for acceleration and 50 mm/s for velocity, the same parameters used for spray area. Each experiment was performed in triplicate.

## RESULTS

### SprayVIEW® NSx Actuation Reproducibility

Actuation reproducibility was examined by spray area analysis using stock PEG solutions at 25, 50, and 75% concentrations (vol/vol) with water as a reference. All samples were analyzed in triplicate at acceleration rates of 1,000, 1,500, 2,000, 2,500, 3,000, 3,500, and 4,000 mm/s$^2$ and velocities of 45, 50, 55, and 60 mm/s in all possible combinations. The RSD for each acceleration and velocity data point was averaged and contour plotted to estimate points of minimum actuation related RSD. As shown in Figure 1, the point of lowest RSD was determined to be at an acceleration of 3,000 mm/s$^2$ and a velocity of 50 mm/s with a combined spray area RSD value less than 1%. Subsequently, as both the Imagetherm SprayVIEW® NSP and the Malvern Spraytec® utilize the same SprayVIEW® NSx actuation system, an acceleration of 3,000 mm/s$^2$ and a velocity of 50 mm/s were used for all ensuing spray area and droplet size analyses to provide the most consistent data for correlation to viscosity by minimizing actuation-related variations.

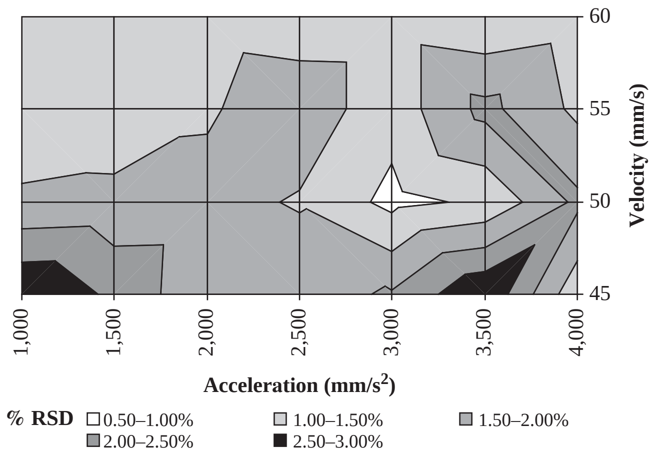


FIGURE 1. Combined PEG (0, 25, 50, 75%, vol/vol) relative standard deviation (RSD) of SprayVIEW® NSP analyzer spray area data plotted versus the actuation parameters of acceleration and velocity. The point of lowest RSD was located at an acceleration of 3,000 mm/s$^2$ and a velocity of 50 mm/s and used for all subsequent analysis.

### Newtonian Fluids

Newtonian fluids by definition do not express shear-thinning behavior upon application of stress. This attribute makes them ideal candidates to determine if there is a dependence of spray area and/or droplet size with viscosity in nasal spray devices. PEG was selected as the primary model of a Newtonian viscosity agent with stock solutions at 25, 50, and 75% PEG (vol/vol) with water as a reference. Rotational rheometry analysis was performed using a TA Instruments AR-2000® rheometer on all PEG-containing samples to demonstrate that PEG solutions can be used as Newtonian viscosity standards. No shear-thinning behavior was observed across a broad range of shear rates (15–100 $s^{-1}$), as shown in Figure 2. The concentrations of PEG analyzed were determined to be in a relevant range with regard to the nasal sprays used in this study and displayed a viscosity coverage of over an order of magnitude.

#### *Spray Area Analysis*

Spray areas, obtained utilizing a SprayVIEW® NSP analyzer, were determined for each PEG sample (25, 50, and 75% vol/vol) with water as a reference, demonstrating an inverse proportionality of spray area on viscosity. Figure 3

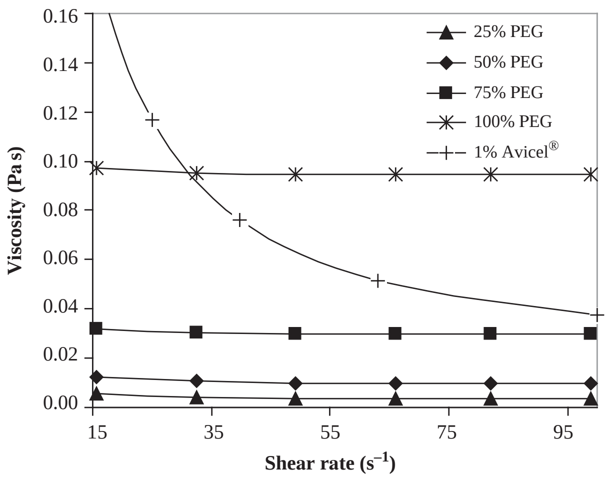


FIGURE 2. Shear rate ($s^{-1}$) versus viscosity (Pa s) plotted for 25, 50, 75, and 100% (vol/vol) PEG solutions showing the lack of shear-thinning behavior for Newtonian fluids. 1% Avicel® is shown as a non-Newtonian shear-thinning solution with significant reduction in viscosity upon increase of shear rate.

illustrates the significant decrease in observed spray area with introduction of rising levels of PEG. Spray areas were analyzed in triplicate at each concentration of PEG and used to create a calibration plot of percentage PEG as a function of the observed spray area ($mm^2$). Linear regression was employed to fit the data and found to have a strong correlation with $R^2$ = .9985, as shown in Equation 1. To determine the viscosity dependence on the percentage of PEG in a sample, rotational rheometry data were correlated to the percentage of PEG using a first-order exponential function with $R^2$ = .9967, as shown in Equation 2. Whereas empirically derived, the observed exponential relationship was consistent with previously observed behavior of Newtonian fluids (Figure 4).

$$\%\mathrm{PEG} = -412.37 \times \mathrm{spray\,area} + 421.94, \tag{1}$$

$$\eta = 0.0013e^{-0.0422 \times \%\mathrm{PEG}} \tag{2}$$

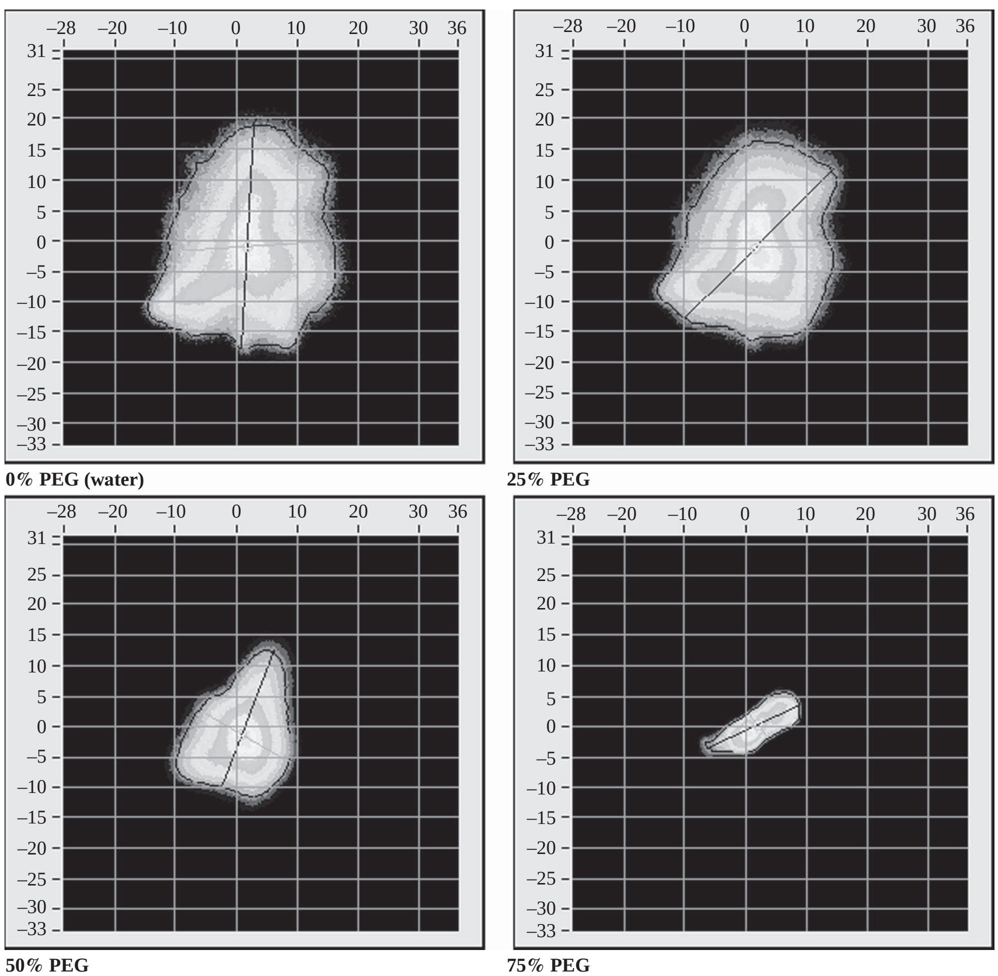


FIGURE 3. Spray Area of PEG Solutions (0, 25, 50, and 75%, vol/vol) analyzed at an orifice-to-laser distance of 30 mm using a standard 100-µL Pfeiffer® nasal spray pump on the SprayVIEW® NSP analyzer demonstrating inverse proportionality between percentage modifier and spray area.

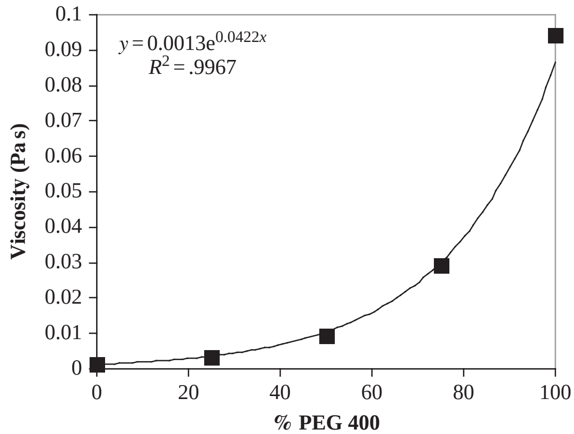


FIGURE 4. Viscosity (Pa s) plotted versus percentage of PEG (vol/vol). The viscosity was determined by an AR-2000 rheometer at a shear rate of 1,000 $s^{-1}$. A strong exponential correlation was determined between % PEG and viscosity with and $R^2 = .9967$.

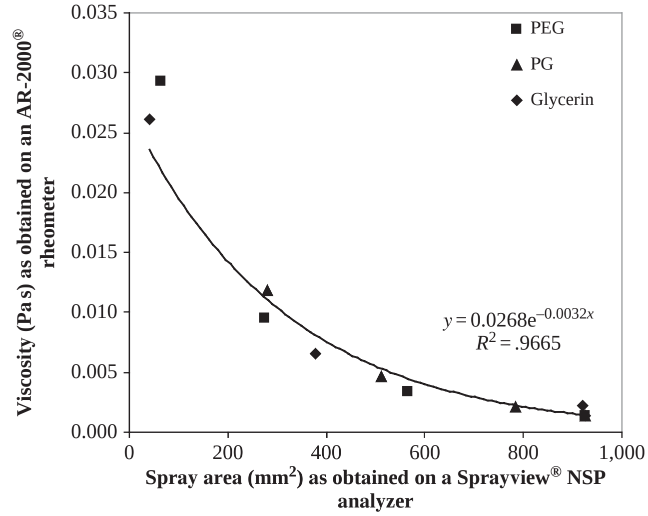


FIGURE 5. Viscosity versus spray area of three Newtonian fluids polyethylene glycol (PEG), glycerin, and propylene glycol (PG). Spray areas were obtained on a SprayVIEW® NSP analyzer and viscosities were obtained from a TA instruments AR-2000® rheometer.

PG and glycerin were used as additional Newtonian model compounds to verify that the observed correlation between spray area and viscosity was not compound specific and constrained only to PEG containing solutions. Stock solutions of PG and glycerin (25, 50, and 75%, vol/vol) with water as a reference were analyzed using a rotational rheometer and, as expected, were found to lack shear-thinning behavior at all shear rates tested. Spray area analyses of PG and glycerin showed a similar linear dependence on the percentage of viscosity modifier with only slight variations in slope and $y$-intercepts corresponding to the water reference standard. All of the PEG, PG, and glycerin spray area data were combined and fit to an exponential function, shown in Figure 5. All three Newtonian fluids exhibited the same exponential dependence of viscosity and spray area with a combined exponential fit having $R^2 = .9549$, thus providing an equation to estimate viscosity (Pa s) directly from spray area ($mm^2$) as defined in Equation 3.

$$\eta = 0.0268e^{-0.0032 \times \text{spray area}} \tag{3}$$

*Droplet Size Analysis*

Droplet size analysis of PEG, PG, and glycerin were performed in triplicate on a Malvern Spraytec® analyzer to determine if droplet size ($Dv_{50}$) could be correlated to viscosity in a similar manner as shown for spray area in the previous section. Droplet sizes were obtained for PEG, PG, and glycerin samples (25, 50, and 75% vol/vol) with water as a reference and were found to be directly proportional to the viscosities obtained by rotational rheometry. The droplet sizes increased with addition of viscosity modifier, although they were not linear as was determined for spray area analysis (Equation 1). However, when droplet size data for PEG, PG, and glycerin were combined and directly correlated to viscosity, a clear logarithmic behavior was observed with $R^2 = .9841$, as shown in Figure 6. Equation 4 was constructed to approximate viscosity (Pa s) directly from droplet size (μm).

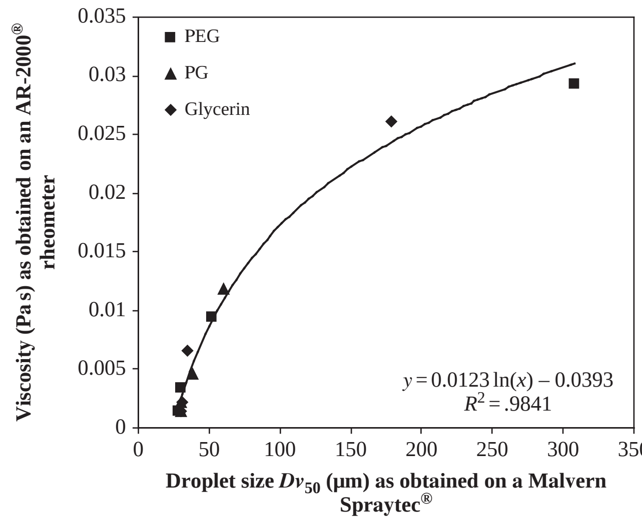


FIGURE 6. Viscosity versus droplet size ($Dv_{50}$) of three Newtonian fluids polyethylene glycol (PEG), glycerin, and propylene glycol (PG). Droplet sizes were obtained on a Malvern Spraytec® analyzer and viscosities were obtained from a TA instruments AR-2000® rheometer.

$$\eta = 0.0123 \ln \text{droplet size} - 0.0393 \tag{4}$$

## Non-Newtonian Fluids

### *Avicel® Samples*

Avicel® samples were used to eliminate other formulation factors (i.e., interaction with other excipients or the active pharmaceutical ingredient [API]) present in common nasal sprays and to examine effectively the results of shear-thinning viscosity agents on spray area and droplet size as they relate to high-shear viscosity. Avicel® samples were prepared at 1, 2, and 3% concentration by weight and were used to encompass a wide range of viscosities relevant to nasal spray formulations that are currently on the market (Sharpe et al., 2003). As shown in Figure 2, even the 1% Avicel® sample demonstrated shear-thinning behavior with a significant decrease in viscosity on application of small amounts of shear stress. Spray area and droplet size analysis were examined to estimate viscosities utilizing the previously derived Newtonian equations for spray area (Equation 3) and droplet size (Equation 4) analyses. The calculated viscosities for both spray area and droplet size were found to trend in the expected manner with regards to the percentage of Avicel®. As the percentage of Avicel® was increased, there was a significant increase in the calculated viscosities, demonstrating that Avicel® containing samples do not shear thin completely to the level of water and maintain some viscosity even at high-shear rates.

The spray area and droplet size calculated viscosities for 1, 2, and 3% Avicel® samples were compared with both rotational rheometry at a shear rate of 1,000 $s^{-1}$ and capillary rheometry at a shear rate of approximately 400,000 $s^{-1}$. The calculated values were 80–90% less than that determined by analyses on a rotational rheometer at its practical shear rate limit of 1,000 $s^{-1}$. In addition, the Avicel® samples demonstrated that as the percentage of shear-thinning agent was increased, the deviation from rotational rheometer data increased significantly (Figure 7, Table 1).

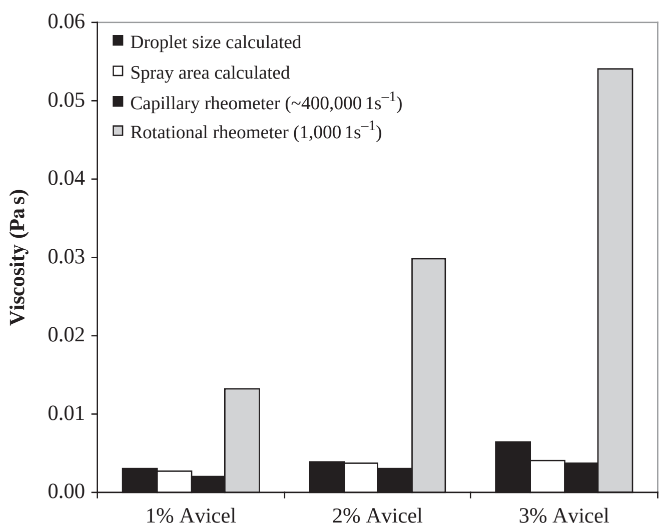


FIGURE 7. Viscosity of Avicel® samples at 1, 2, and 3% concentrations (wt/wt).

TABLE 1
Viscosity of Avicel® Samples at 1, 2, and 3% Concentrations (wt/wt) as Obtained by Spray area and Droplet size Predictions, and Rotational and Capillary Rheometer Experiments

| | Viscosity (Pa s) | | | |
|---|---|---|---|---|
| [Avicel] (%, wt/wt) | Droplet Size Calculated | Spray Area Calculated | Capillary Rheometry | Rotational Rheometry |
| 1 | 3.00E – 03 | 2.65E – 03 | 2.10E – 03 | 1.32E – 02 |
| 2 | 3.83E – 03 | 3.70E – 03 | 3.10E – 03 | 2.98E – 02 |
| 3 | 6.49E – 03 | 4.10E – 03 | 3.80E – 03 | 5.41E – 02 |

The Avicel® samples were analyzed by capillary rheometry at a shear rate of approximately 400,000 $s^{-1}$, which better approximated the high-shear rate occurring in nasal spray devices during actuation. At this high-shear rate, a clear trend was observed with a distinguishable increase in viscosity as the percentage of Avicel® was increased. Furthermore, the viscosity values were found to resemble closely those empirically calculated from the equations for spray area (Equation 3) and droplet size (Equation 4) analyses.

### *Aqueous Suspension Corticosteroid Nasal Sprays*

Spray area and droplet size analyses were used to calculate the spray nozzle actuation viscosities of four common commercial nasal sprays with varying degrees of shear-thinning behavior and Avicel® content, to demonstrate the utility of spray area and droplet size analyses for approximation of high-shear viscosities on currently marketed nasal spray formulations. As in the case of Avicel®, whereas the data was found to trend in accordance with data obtained from the rotational rheometer, the viscosities were significantly lower. The viscosity values determined from the equations for spray area (Equation 3) and droplet size (Equation 4) analyses were both determined to trend in the same manner as the rotational rheometer (Figure 8), and were on the order of previously published data for high-shear rate determination of commercial nasal sprays (Barnes, 2000). In addition, results from Figure 8 show that NS-B contains higher levels of CMC and MCC than NS-A or NS-C, which is in agreement with the formulated values.

## DISCUSSION

Aqueous suspension corticosteroid nasal sprays exhibit the behavior of shear thinning, which is highly dependent on the amount of shear applied to the sample. This shear-thinning behavior is caused by cross-linking of MCC and CMC in aqueous media. Although these interactions are strong enough to hold drugs in suspension and create a gel-like consistency, these bonds break upon application of the shear stress generated at the

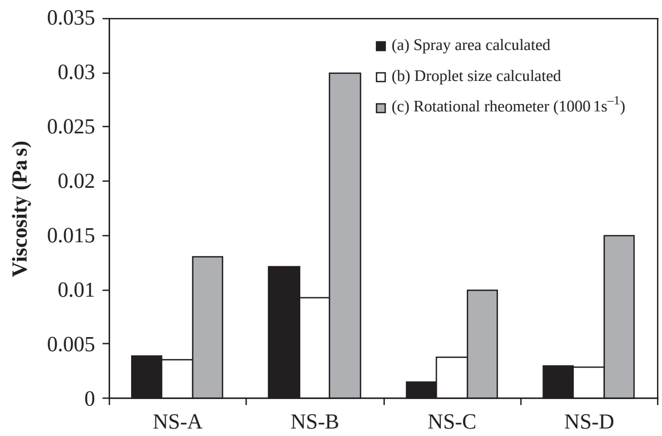


FIGURE 8. Aqueous suspension corticosteroid nasal spray viscosities by various analytical techniques. (a) Calculated using previously derived spray area correlation Equation 3. (b) Calculated using previously derived droplet size correlation Equation 4. (c) Determined on an AR-2000 rheometer at 1,000 s$^{-1}$ shear rate.

spray nozzle during actuation causing an instantaneous reduction in viscosity near the value of water. Upon removal of stress, the bonds re-form causing an increase in viscosity; however several minutes may be required for values to approach values present prior to the application of shear stress.

Analysis by rotational rheometry can not deliver high enough shear rates to correlate directly with the conditions occurring in nasal spray devices during actuation, and although capillary rheometry was capable of delivering the necessary high-shear rates ($10^5$–$10^6$ s$^{-1}$), the method still only approximates actual spray conditions. There is a potential for significant time savings by developing methods that can approximate viscosity values for solutions exiting a nasal spray device during actuation by correlating parameters that can be measured efficiently during spray actuation (i.e., spray area or droplet size analyses).

To approximate the viscosity generated at the spray nozzle, three Newtonian solutions (PEG, PG, and glycerin), which did not exhibit shear-thinning properties, were used to generate equations that directly related either spray area from the Imagetherm SprayVIEW® analyzer or droplet size ($Dv_{50}$) from a Malvern Spraytec®, with viscosity values obtained from a TA Instruments AR-2000 rotational rheometer. The standard Newtonian solutions were used at a broad range of concentrations corresponding to relevant viscosity values for commercial nasal sprays. The data obtained from all three solutions were combined and fit to an exponential curve for spray area (Equation 3), and logarithmic curve for droplet size (Equation 4) providing models that could approximate viscosity directly from either spray area (mm$^2$) or droplet size (µm) analyses.

The viscosities of shear-thinning nasal sprays were determined by both spray area and droplet size methods and were found to approach that of water at high-shear rates; however, the viscosities were still distinguishable and were shown to trend in accordance with data from the rotational rheometer. Furthermore, the calculated viscosity values were comparable with data obtained using capillary rheometry at a shear rate of approximately 400,000 s$^{-1}$. It was also determined that higher percentages of Avicel® caused greater deviations from the rotational rheometry that was not the case when compared with capillary rheometry. This can be explained by an increased amount of shear-thinning behavior found in samples with higher Avicel® content and the inability of rotational rheometry to achieve the necessary shear rates to mimic nasal spray actuation conditions.

## CONCLUSIONS

Spray area and droplet size analyses were both capable of estimating the viscosities of Newtonian fluids by using equations derived from standard viscosity sample calibration experiments. In addition, spray area and droplet size analyses were capable of approximating the viscosities of non-Newtonian shear-thinning solutions when used in empirically derived viscosity equations and were found to be in line with high-shear capillary rheometry values. Although these two approaches will not replace rotational or capillary rheometry-based viscosity measurements for nasal spray formulations, they may be used as an additional tool in gaining a better understanding of the viscosities generated at actual spray nozzle conditions during formulation development.

## ACKNOWLEDGMENTS

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