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RESEARCH PAPER

Comparison of the Flow Properties of Aqueous Suspension Corticosteroid Nasal Sprays Under Differing Sampling Conditions

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ABSTRACT

Many aqueous suspension corticosteroid nasal sprays become less viscous when shaken and sprayed, then return to a more viscous state after application. This time-dependent, reversible loss of viscosity under shear (e.g., shaking or spraying) can be quantified in the rheological property of thixotropy. The flow properties of 5 corticosteroid nasal sprays were measured over a range of shear rates. The formulations tested included Nasonex®, Vancenase® AQ, Nasacort® AQ, Rhinocort Aqua®, and Flonase®. The yield stress values, as well as an estimate of thixotropy, were compared by using three different sampling techniques, including one that simulated patient use (shaking for 30 sec, spraying, and immediately transferring the sample to the rheometer). The rheological properties of all products indicated that when initially shaken and dispensed, they flowed more freely, followed by recovery of viscosity that would likely inhibit the suspensions from flowing out of the nasal cavity. Under all three tested conditions, Nasonex exhibited the highest yield stress, the largest apparent initial and final viscosities, and the highest apparent thixotropy. The study protocol that simulated patient-use conditions produced the following rank order of measured thixotropy: Nasonex > Flonase > Vancenase AQ > Rhinocort Aqua > Nasacort AQ. The thixotropy of Nasonex was 3.4 to 21.4 times greater and the final viscosity was 3.2 to 17.4 times greater than the values of the other tested products.

Key Words: Corticosteroid; Nasal sprays; Rheological properties; Viscosity; Thixotropy.

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INTRODUCTION

Symptoms of allergic rhinitis can be effectively treated by local delivery of corticosteroids to the tissues of the nasal cavity.[1–4] Formulations of aqueous suspension corticosteroid nasal sprays are designed to efficiently disperse and suspend lipophilic drug particles within an aqueous medium, deliver these particles to the nasal cavity within an aerosol spray, and facilitate delivery of the drug to target tissues in the nasal cavity.[5] The effectiveness of drug delivery is affected by the formulation in combination with its spray device. The formulation must have a high viscosity to maintain the drug particles in suspension and to facilitate retention after application but should be easy to apply as an aerosol. Many corticosteroid nasal sprays become less viscous when shaken and sprayed, then return to a more viscous state upon sitting after application. This reversible loss of viscosity under shear (e.g., shaking or spraying) can be quantified in the rheological properties of pseudoplasticity, which measures rapid reversibility and thixotropy, which has a slower time-dependence.[6]

Measurable differences in rheological properties between selected aqueous corticosteroid nasal sprays have been reported.[5] In that study, rheometer measurements were made after samples were poured from their containers. Since thixotropic measurements are sensitive to the flow history of the tested sample, the measurements in this current study have compared the effects of three different sample preparation methods on the rheological properties of five different aqueous corticosteroid nasal sprays. One of the sample preparation methods attempted to mimic the pattern of patient application of the nasal spray.

MATERIALS AND METHODS

Materials

Five corticosteroid aqueous nasal spray formulations were tested: fluticasone propionate (Flonase®; GlaxoSmithKline), triamcinolone acetonide (Nasacort® AQ; Aventis), budesonide (Rhinocort Aqua®; AstraZeneca), beclomethasone dipropionate (Vancenase® AQ; Schering-Plough), and mometasone furoate (Nasonex®; Schering-Plough). All products were evaluated within their shelf-lives.

Sample Preparation

Three different sample preparation protocols were followed to study the effect of sample preparation in combination with the formulation and the spray device on the rheological properties of the products.

Sample Preparation Protocol I

The dispenser was shaken for 5 sec, then the top of the dispenser was removed to gain access to the product. The sample was removed from the dispenser by using a microspatula and was placed onto the plate of the rheometer. The sample was then tested as described below in "Shear Measurements."

Sample Preparation Protocol II

The sample was shaken for 30 sec. This step was followed by a priming step as described by the patient instructions in the package insert. The spray unit was actuated into a hood until a uniform fine mist was observed. The product then was sprayed through the nozzle into a collection beaker. The sample was left unperturbed in the beaker for 1 hr, then the sample was transferred onto the plate with a microspatula and tested as described below.

Sample Preparation Protocol III

The sample was shaken for 30 sec. This step was followed by a priming step as described by the patient instructions in the package insert. The spray unit was actuated into a hood until a uniform fine mist was observed. The product was then sprayed through the nozzle into a collection beaker and immediately transferred onto the rheometer plate by using a microspatula. The sample then was tested as described below.

Shear Measurements

Pseudoplasticity and thixotropy were evaluated at 25°C by using an AR 1000 rheometer (TA Instruments, Dorking, U.K.). Cone and plate geometry was used for rheological measurements. The cone was 40 mm in diameter and had an angle of 2° 0′ 51″ and a truncation of 50 μm. All experiments were run at a gap of 50 μm. The flat plate was temperature controlled by a Peltier thermoelectric unit. The use of the viscometer and the selection of the cone and plate

geometry, as well as the specific experimental conditions used, were justified empirically by the reproducibility of the data generated and the instrument's precision with the studied products. In addition, the use of rotational viscometers has been described previously in the literature.[5] The specific experimental conditions used in this study, where a conditioning step in shear rate is followed by a consecutive linear increase and decrease in shear rate, also have been described in the literature[7,8] and are considered suitable for thixotropic systems.

For measurements, a sample was placed onto the flat plate of the rheometer by using a microspatula. The cone was then lowered to form a gap of 65 μm between the cone and the plate. Excess sample was removed from the edge of the cone by trimming with a spatula, and the cone was lowered to a gap of 50 μm. The sample was conditioned with an equilibration time of 2 min. The shear rate was then increased in a linear ramp from 0 sec^{-1} to 100 sec^{-1} over a period of 8 min. A downward ramp of shear rate from 100 sec^{-1} to 0 sec^{-1} over 8 min immediately followed the upward ramp. The apparent viscosity was measured at 50 time points during the upward ramp and at 50 time points during the downward ramp.

The plate and cone were cleaned with isopropyl alcohol and dried between samples. A total of three sample runs were performed for each product in order to ensure precision.

Data Analysis

A graph of apparent viscosity vs. time was generated for each sample. Since shear rate was controlled to change linearly with time, as described above, shear rate also was plotted on the same graph to allow comparison of viscosities at different shear rates.

Data points were plotted on a graph of shear rate vs. shear stress. Thixotropy (area within the hysteresis loop) was calculated from the area between the curves of the upward and the downward ramps of the shear rate vs. shear stress curves. Yield stress was calculated for each product by using the Herschel-Bulkley model:

$$\tau = \tau_0 + k(\gamma)^n$$

where

τ = shear stress

τ_0 = yield stress

k = constant$_1$

γ = shear rate

n = constant$_2$

RESULTS

The following properties were evaluated: yield stress, apparent viscosity, and thixotropy. Figure 1(A–C) illustrates that shear thinning was observed for all five products during exposure to increased shear rates after the three different sample preparation protocols. All five products also showed pseudoplasticity, a reversible decrease in viscosity with increased shear rate. Table 1 shows the initial viscosities, final viscosities, and Herschel-Bulkley calculated yield stresses for all five formulations by using all three protocols. Table 2 shows the magnitude of thixotropy (integrated values) for all five formulations.

A plot of shear rate vs. shear stress allows visualization of time-dependent changes in rheological properties of the formulations due to exposure to shear. Figure 2 (A–C) shows that all formulations, with the exception of Nasonex, exhibited an initial yield stress at low shear rates and a curve concave to the shear rate axis that indicated shear thinning at higher shear rates. After each of the three sample preparation protocols, Nasonex exhibited more complex rheograms than the other formulations. During the early phase of the up ramp in shear rate, Nasonex showed a high yield stress followed by a decrease in shear stress. During the down ramp of shear rates, Nasonex showed a simpler relationship between shear rate and shear stress, similar to the properties of the other formulations. Alteration of shear stress vs. shear rate curves can indicate thixotropy of the tested formulation, and the area enclosed within the curves provides a measure of thixotropy under these conditions.

Sample Preparation Protocol I

This protocol avoided exposing the samples to the high shear rates generated during ejection through the spray nozzles. For sampling protocol I, Nasonex showed the highest yield stress and the highest initial (at highest shear rate) and final viscosities (Fig. 1A, Table1).

Nasonex and Flonase showed visible thixotropy in Fig. 2A and Table 2. The rank order of the thixotropy was as follows: Nasonex > Flonase > Nasacort AQ > Vancenase AQ > Rhinocort Aqua (Table 2).

A linear regression of the initial viscosities vs. the thixotropy values of the studied products indicated a good correlation ($R^2 = 0.97$). The terminal viscosities

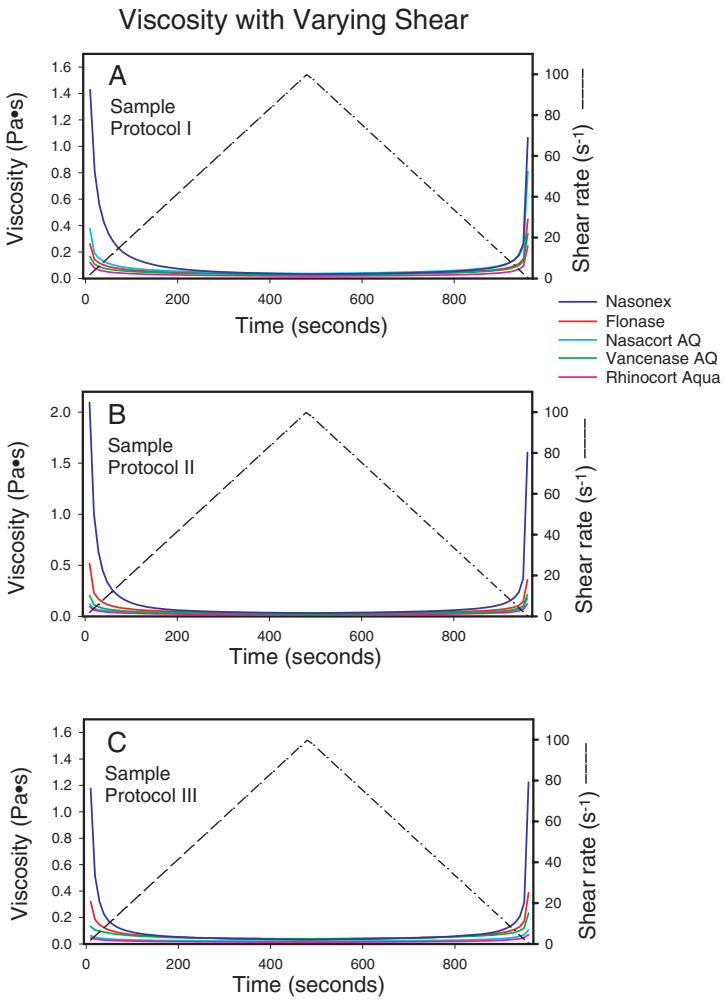

Figure 1. Effect of sample preparation and shear rate on viscosity. Apparent viscosity of nasal spray samples (left axis) and shear rate applied to samples (right axis) are plotted vs. time (horizontal axis). A. Viscosities after sample preparation protocol I. B. Viscosities after sample preparation protocol II. C. Viscosities after sample preparation protocol III.

Table 1. Effect of sample preparation on viscosity.[a]

		Flonase	Nasacort AQ	Rhinocort Aqua	Vancenase AQ	Nasonex
Protocol I						
Yield stress	(Pa)	0.118	0.177	0.074	0.058	0.228
Initial viscosity	(Pa·s)	0.263	0.380	0.122	0.165	1.43
Final viscosity	(Pa·s)	0.449	0.809	0.246	0.339	1.08
Protocol II						
Yield stress	(Pa)	0.230	0.048	0.026	0.074	0.478
Initial viscosity	(Pa·s)	0.518	0.121	0.096	0.206	2.10
Final viscosity	(Pa·s)	0.360	0.176	0.122	0.212	1.60
Protocol III						
Yield stress	(Pa)	0.006	0.058	0.001	0.027	0.310
Initial viscosity	(Pa·s)	0.321	0.062	0.047	0.132	1.18
Final viscosity	(Pa·s)	0.387	0.106	0.070	0.233	1.22

[a]$n = 3$ sample runs per product.

Table 2. Effect of sample preparation on thixotropy.[a]

	Flonase (Pa·s)	Nasacort AQ (Pa·s)	Rhinocort Aqua (Pa·s)	Vancenase AQ (Pa·s)	Nasonex (Pa·s)
Protocol I	15.5	9.31	7.39	7.50	107.4
Protocol II	27.1	7.89	6.46	14.3	65.1
Protocol III	6.73	1.07	1.14	1.17	22.9

[a]$n = 3$ sample runs per product.

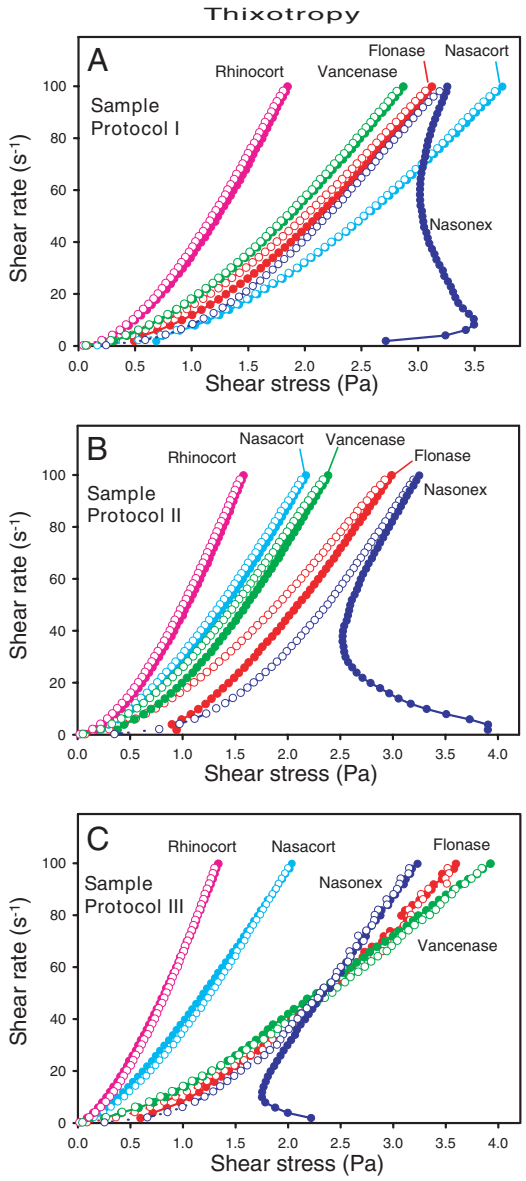

Figure 2. Effect of sample preparation on shear stress vs. strain rate curves. Shear stress on sample is plotted vs. shear rate. Data gathered during the up ramp of shear rate from 0 sec^{-1} to 100 sec^{-1} are plotted with solid symbols and data gathered during down ramp of shear rate from 100 sec^{-1} to 0 sec^{-1} are plotted with open symbols. A. Shear stress curves after sample preparation protocol I. B. Shear stress curves after sample preparation protocol II. C. Shear stress curves after sample preparation protocol III.

and the thixotropy values did not show a good correlation ($R^2 = 0.66$).

Sample Preparation Protocol II

Each sample was subjected to the high shear rate produced by its own spray unit, then was allowed to recover for 1 hr before testing. Under these conditions, all formulations again exhibited pseudoplastic behavior and exhibited a somewhat higher terminal than initial viscosities (Fig. 1B).

The difference in sample handling between protocol I and protocol II altered the magnitudes of the measured yield stresses, apparent viscosity. However, Nasonex again showed the highest initial and terminal viscosities and highest yield stress value (Table 1). Protocol II also changed the measured thixotropy of the formulations (Figure 2B, Table 2), resulting in a rank order of the thixotropies as follows: Nasonex > Flonase > Vancenase AQ > Nasacort AQ > Rhinocort Aqua.

A linear regression of the initial viscosities vs. the thixotropy values of the studied products again indicated a good correlation ($R^2 = 0.98$). Similarly, regression analysis of terminal viscosities vs. thixotropy values showed a good correlation ($R^2 = 0.96$).

Sample Preparation Protocol III

Rheological properties of the formulations were measured immediately following shaking and spraying from the sample units, handling that approximated normal patient use (Fig. 1C). There was no significant evaporation of liquid during the measurement, and losses (the difference between the initial and final weights) were found not to exceed 0.03%. These losses were attributed mostly to sticking of some of the sample to the metal surfaces of the cone and plate (verified by visual inspection). The magnitudes of the measured yield stress, apparent viscosity (Table 1), and thixotropy (Table 2) were again different from the results of protocols I and II. Nasonex and Flonase showed higher thixotropies than the other formulations (Fig. 2C). The rank order of the thixotropy values of the formulations were as follows: Nasonex > Flonase > Vancenase AQ > Rhinocort Aqua > Nasacort AQ (Table 2). These results highlight the importance of the sampling procedure when studying the rheological properties of a material.

All products exhibited somewhat higher terminal than initial viscosities. Nasonex showed the highest yield stress and highest initial and terminal viscosities. A linear regression of the initial viscosities and the thixotropy values of the studied products indicated a good correlation ($R^2 = 0.99$). Similarly, the regression analysis of the terminal viscosities and the thixotropy values yielded a good correlation ($R^2 = 0.98$). This suggests that the initial and terminal apparent viscosities as measured by using sampling protocol III and the time-dependent strength of the structural network are correlated.

DISCUSSION

A common ingredient used to build the viscosity of aqueous suspensions of corticosteroid nasal sprays is a blend of microcrystalline cellulose (MCC) and carboxymethylcellulose sodium (CMC). In aqueous solution, the microcrystals of MCC are weakly cross-linked by chains of the water-soluble CMC. These two components impart higher apparent viscosity through the entanglement of the long, thread-like polymers. The structural network formed by these weak and temporary cross-links offers some resistance to the slippage of polymer chains past one another when shear is applied. This weak lattice structure helps to suspend particles of corticosteroids, which are very insoluble in aqueous media. When the solution is exposed to shear stress, the polymer chains slip past one another freely and disentangle, reducing the apparent viscosity of the solution at higher shear rates. When shear rate is again reduced, the cross-links can reform, again increasing the apparent viscosity. The polymer structural network of MCC and CMC in an aqueous medium can exhibit both shear thinning (pseudoplasticity) and time-dependent recovery of structure (thixotropy).

The studied formulations containing a mix of MCC and CMC exhibit thixotropy because thixotropy reflects the finite time taken to move from any one state of microstructure to another and back again. The driving force for microstructural change in flow is the result of the competition between breakdown due to flow stresses, build-up due to in-flow collisions, and Brownian motion. A definition that covers the full extent of the phenomenon was provided by Bauer and Collins.[9] According to their definition, thixotropy is a phenomenon where a reduction in the magnitude of rheological properties of a system, such as elastic modulus, yield stress, and viscosity, occurs reversibly

and isothermally with a distinct time dependence on the application of shear strain.

Clearly all the studied formulations (nasal suspensions) exhibited thixotropy to some extent or another. The formulations containing higher concentrations of the structure-building components MCC and CMC sodium exhibited the highest level of thixotropy (i.e., Nasonex AQ). This high level of thixotropy is a direct consequence of the concentration of the structure-building element.

The physical behavior and advantages of thixotropic materials can be fully appreciated in nondrip paints, which are more viscous on the brush than on the wall. That is, they are thick when applied to the brush (initial viscosity), then thin or become less viscous as the brush is moved on the wall surface during painting (shear strain). Finally, the nondrip paints quickly thicken (final viscosity) and adhere to the surface of the wall when the painting motion (shear strain) is removed.[10,11]

This phenomenon is the same phenomenon exhibited by the studied formulations. When a nasal spray is sprayed, its initial viscosity drops, and as the shear rate is increased (i.e., shear strain applied) the viscosity keeps falling. When the shear rate is reduced (i.e., shear strain removed), the formulations start to thicken due to structure formation until the final viscosity is achieved. The faster the structural recovery of the formulation is achieved (i.e., the bigger the area under the hysteresis loop of the plot of shear rate vs. shear stress), therefore, the higher is the thixotropy and the less would the formulation drip from the surface of application.

For a given sample preparation protocol, each formulation showed a specific yield shear stress value and did not flow until this stress was exceeded. The differing yield stresses may be attributed to the different strengths of the polymer networks produced by components such as MCC and CMC, which are found in all five aqueous nasal sprays in this study.[12–16] Nasonex has a higher concentration of structure-building MCC and CMC (2% Avicel) than Vancenase (1.5% Avicel). Nasonex exhibited the greatest yield stress, initial viscosity, and terminal viscosity of the five tested aqueous nasal sprays under all three sample preparation conditions. These data suggest that the flow property differences are primarily due to a higher concentration of polymers in Nasonex than in the other nasal sprays.

Results of rheological analysis of polymer-containing solutions depend to a great extent on the method of sampling and sample preparation. For example, protocol I allows evaluation of a formulation without spraying through the delivery nozzle, a procedure that isolates the formulation properties from the application device. For completeness, it also is important to evaluate the effect of interactions between formulation and device and patient use conditions, as in protocols II and III. Previous investigations of aqueous corticosteroid nasal sprays have investigated shear stress at lower shear rates[5] and at very high shear rates,[17] which were intended to approximate the conditions during flow through a spray nozzle. As seen in the present study, the exact history of a thixotropic formulation may significantly affect its subsequent behavior. Thus a rheological study that includes the delivery of a formulation through its own spray device, as in protocols II and III, should give data that is most useful to predicting patient-use conditions. The studies reported here address, in particular, the flow properties of nasal spray formulations under low shear rate conditions after being exposed to the high shear rates typical of administration during patient use. The consistency of results suggests that the rheological properties of a formulation with high final viscosity and high thixotropy would support retention in the nasal cavity after application.

CONCLUSIONS

Formulation, sampling procedure, and device variables are critical factors that affect the rheological properties of aqueous nasal sprays. Nasonex exhibited the highest initial and final viscosities and highest thixotropy in three different sample preparation protocols, including one that approximated patient use. High final viscosity and thixotropy may support retention in the nasal cavity.

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