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COMMUNICATION

Rheological Behavior of Nasal Sprays in Shear and Extension

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ABSTRACT

The rheological profiles of commercial corticosteroid nasal spray suspensions (Beconase®, Nasacort®, Flixonase®, and Nasonex®) were compared using shear and extensional techniques. Thixotropy/shear thinning was investigated (Carri-Med CSL100, concentric cylinder geometry) by (a) the generation of flow curves at low (100 sec^{-1}) and high (1200 sec^{-1}) maximum shear rates and (b) determination of equilibrium shear viscosities at constant shear rates of 10 sec^{-1}, 100 sec^{-1}, or 1200 sec^{-1}. Extensional properties, on which droplet breakup and size depend, were examined using digital camera photography of droplet evolution and the length any trailing filament formed when the suspension was extruded from a 10-ml syringe at 500 μl/min. All the nasal suspensions were shear thinning and were also thixotropic to varying degrees. The absence of significant thixotropic recovery at short times (5 min) for all the sprays implies that thixotropy is not necessarily the controlling factor for prolonged residence of the spray in the nasal cavity, but rather that it is the high viscosities present in all four sprays, even after structure breakdown. Preliminary extensional flow data identified differences among the four sprays, with extensional filament lengths increasing in the same rank order as the lowest shear rate (10 sec^{-1}) equilibrium viscosities.

Key Words: *Droplet evolution; Extensional flow; Nasal spray; Shear thinning; Suspension; Thixotropy.*

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INTRODUCTION

The rheological properties of corticosteroid nasal spray suspensions, which are used extensively to relieve the symptoms of seasonal allergic or perennial rhinitis (1,2), will dramatically affect their overall performance (3). Such suspensions are generally formulated to be ''thixotropic'' as they require a high apparent viscosity at rest to inhibit particle sedimentation, but should thin down sufficiently when shear is applied (e.g., by shaking the container) to redisperse the drug before use. When the stress is removed, the formulation should remain thin while the dose is sprayed into the nose and then revert back to the original high consistency (4). The efficacy of once-daily dosing for these chronic conditions has been related to the thixotropic nature of a nasal spray. The high viscosity after thixotropic recovery was considered to allow prolonged adhesion to the nasal mucosa (5).

A quantitative determination of thixotropy is difficult because thixotropic materials are highly sensitive to their rheological history and to the conditions of the shear (6–8). In addition, thixotropy is frequently confused with other shear-thinning phenomena, such as pseudoplasticity and irreversible deformation (9). With thixotropy, the decrease in apparent viscosity with time of shearing is reversible, so that the fluid will rebuild itself and revert to its original state after cessation of shear. Thixotropic recovery is usually measured in tens of seconds to hours or even days. There is no question of time dependency in pseudoplasticity other than a small, but finite, time for the shear rate (at constant stress) or the shear stress (at constant rate) to come to equilibrium or to go to zero after the shear has been removed. This time, which is in the region of nanoseconds to seconds, can often be related to the relaxation time of the fluid. It is emphasized that, with both responses to shear, thixotropy, and pseudoplasticity, the apparent viscosity decrease with shearing is reversible. This is not the case with irreversible deformation, sometimes referred to as shear destruction, for which the underlying structure is destroyed, and the material will remain in the thinner state after the shear is removed. Rheological assessment is sometimes complicated when several different flow properties are superimposed in the same material. For example, complex multiphase formulations such as semisolid creams exhibit a mixture of reversible and irreversible deformation in shear; the apparent viscosity decreases with time of shearing, but then only partly recovers its original viscosity after resting (10,11).

The distinction among shear thinning, thixotropy, and irreversible deformation may be important when considering the therapeutic effect of such nasal sprays because the suspension must thicken immediately after spraying to prevent it from running out of the nose or down the back of the throat. This suggests that time-independent shear thinning such as pseudoplasticity, rather than thixotropy or irreversible deformation, is the required property.

Simple shear, as described above, is the customary mode of deformation used in the study of complex rheological fluids. Shear flow assessment alone, however, will not adequately describe the deformation during the use of a nasal spray because when the suspension is sprayed, the formulation will undergo an extensional or stretching flow as it accelerates through and exits from the nozzle. An understanding of such extensional flow is particularly important because droplet size and breakup, which will also influence the therapeutic effect, depend on this property (12,13).

The aim of this work was to compare the rheological profiles of four commercial corticosteroid nasal spray suspensions: Beconase® (Glaxo Wellcome, Middlesex, UK), Nasacort® (Rhone-Poulenc Rorer, Kent, UK), Flixonase® (Glaxo Wellcome), and Nasonex® (Schering-Plough, Herts, UK). In particular, the aims were first to evaluate the extent of shear thinning, thixotropy, and irreversible deformation in shear and second to perform a preliminary assessment of extensional rheology.

MATERIALS AND METHODS

Materials

Four corticosteroid nasal spray suspensions (Beconase batch B0777EB, Nasacort batch MN2378, Flixonase batch B3807NB, and Nasonex batch 97F12 04) were obtained directly from a local pharmacy with no knowledge of the previous histories or age profiles of the sprays. Thus, the data obtained give a snapshot of their rheological properties at a random point in time within the shelf life of each product.

Shear Measurements

The extent of shear thinning in the form of both thixotropy and pseudoplasticity was evaluated at 25°C using a Carri-Med controlled stress rheometer with concentric cylinder (Mooney Ewart CSL100, TA Instruments, Dorking, UK) geometry using two protocols: protocol 1, generation of two series of flow curves with maximum shear rates of 100 sec^{-1} (series 1) or 1200 sec^{-1} (series 2) and a sweep time of 480 sec; and protocol 2, determination of equilibrium viscosities at constant shear rates of 10 sec^{-1}, 100 sec^{-1}, or 1200 sec^{-1}. The shear rate was increased rapidly to its constant value, and the change in apparent viscosity at this maximum shear rate was monitored with time.

For all experiments, the spray nozzle was removed from the dispenser, and the sample was poured directly into the rheometer cup. Initial experiments were performed to establish reproducibility of results in relation to sampling and experimental conditions. After each flow curve experiment, the sample was left to rest in the rheometer for 5 min, and the test was repeated. Samples were then returned to the original dispenser and retained for structure-recovery investigations performed over extended times for up to 1 week.

Extensional Measurements

Extensional deformation was followed using digital camera photography (Olympus 800L, Olympus Optical Co., Melville, NY) of droplet evolution when the suspension was extruded at 500 μl/min through a 23-gauge needle from a 10-ml syringe attached to a perfusor pump. As each droplet formed, its evolution and any trailing filament formed were photographed. The length of the trailing filament before break gives a good approximation of extensional viscosity (14).

RESULTS AND DISCUSSION

The standard protocol when investigating shear-thinning phenomena such as thixotropy, pseudoplasticity, nd shear destruction is to derive flow curves of shear stress versus shear rate using a standardized shearing cycle. With such curves, however, it is not possible to separate the contributions of each type of response. The area of the hysteresis loop that is formed from the up-and-down curve of the rheogram is often used as a measure of thixotropic breakdown (4,6–8). This area, however, is dependent on both the maximum shear rate used and the time it takes to make the measurement. The trends shown for these sprays at one maximum shear rate will not necessarily be shown when they are compared at a different maximum shear rate. Thus, to cover a wide range of conditions, two series of standardized shearing cycles were used with maximum shear rates of either 100 sec^{-1} and 1200 sec^{-1}. The equilibrium viscosity at each maximum shear rate (and also at 10 sec^{-1}) was also determined by a separate set of experiments (protocol 2), providing an alternative method of assessing shear-thinning behavior.

All the flow curves were anticlockwise hysteresis loops. Reproducibility, as shown by the extent of superimposability of flow curves (see Fig. 1) was satisfactory for all

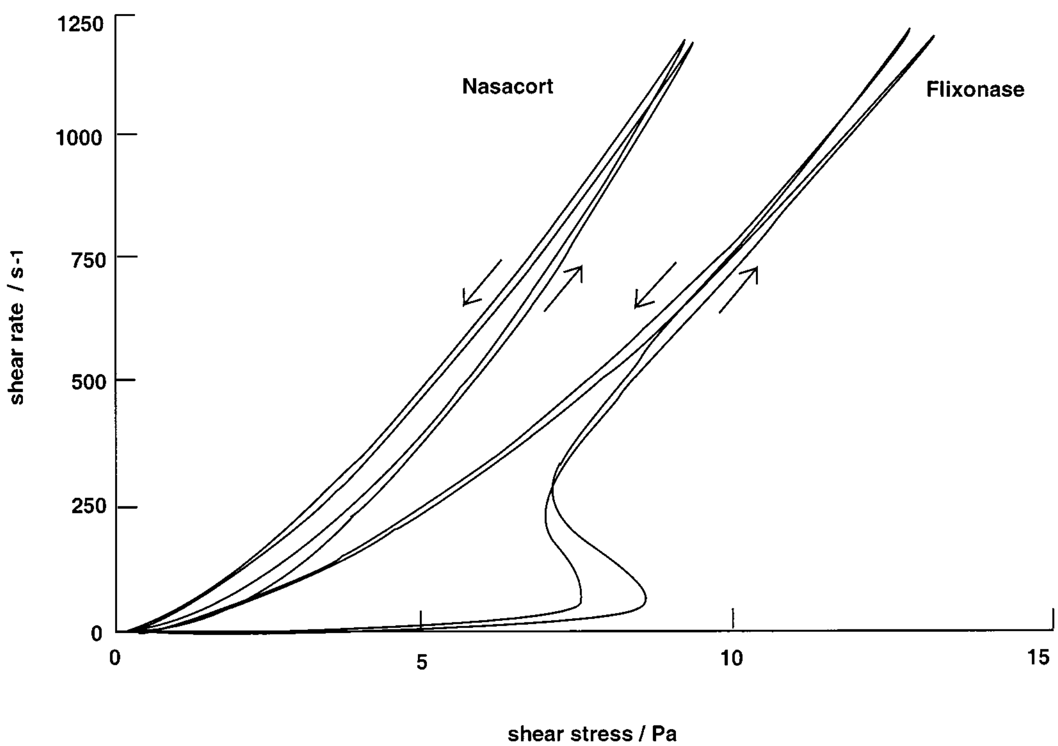

Figure 1. Typical rheograms at a maximum shear rate of 1200 sec^{-1} for two of the nasal sprays to illustrate reproducibility of results. Each experiment used a fresh sample.

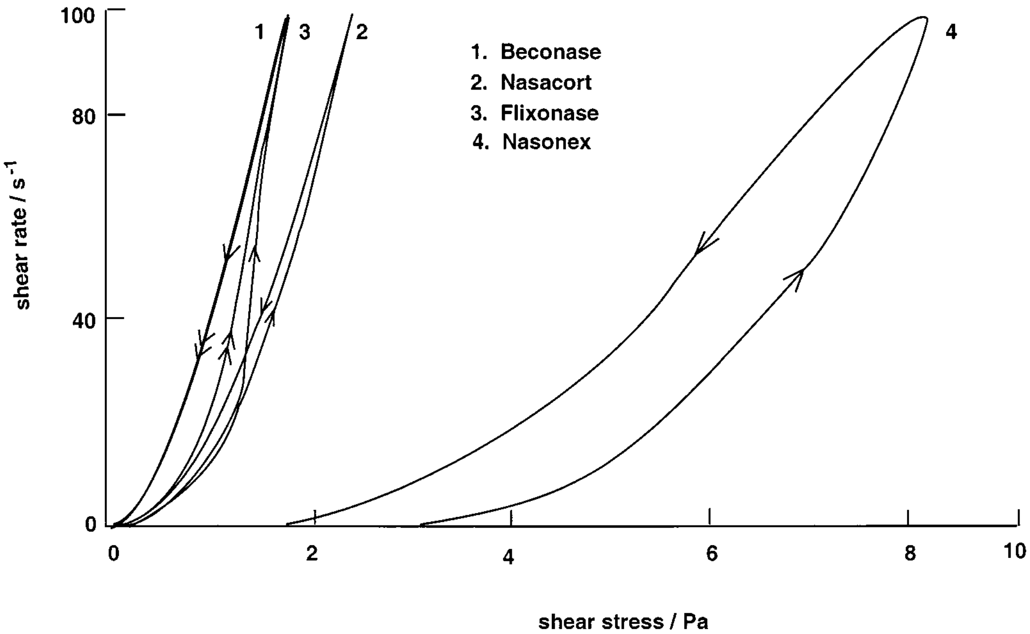

Figure 2. Typical rheograms for the four nasal sprays at a maximum shear rate of 100 sec^{-1}.

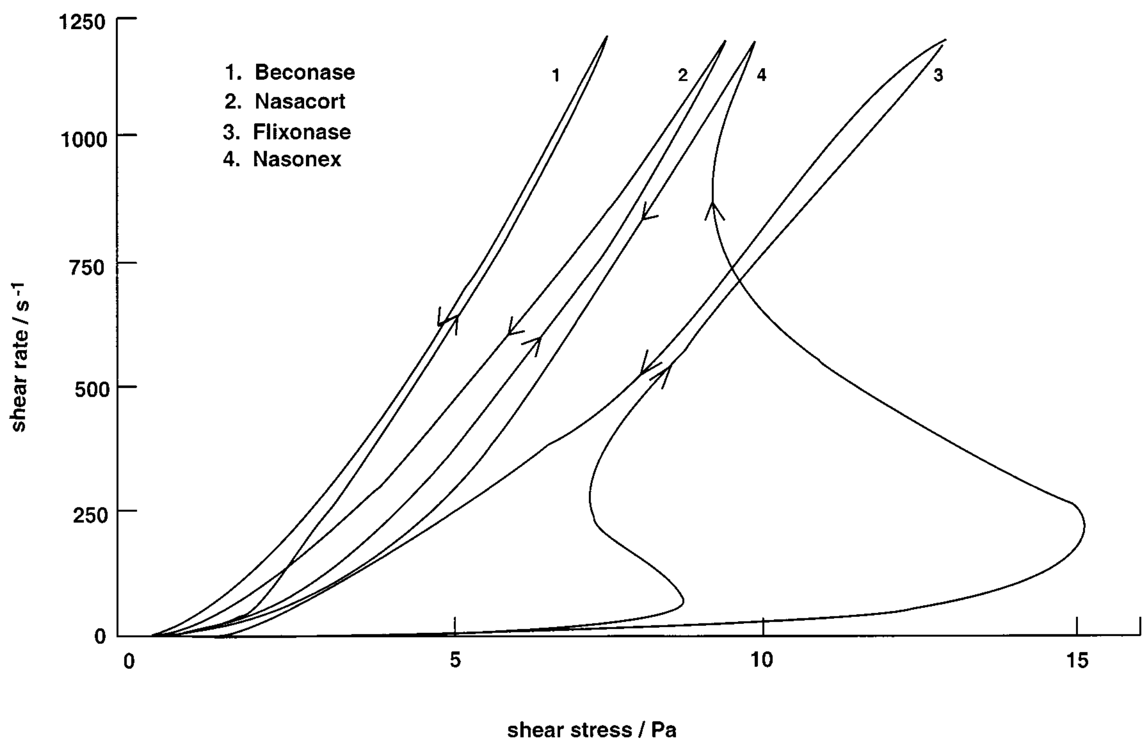

Figure 3. Typical rheograms for the four nasal sprays at a maximum shear rate of 1200 sec^{-1}.

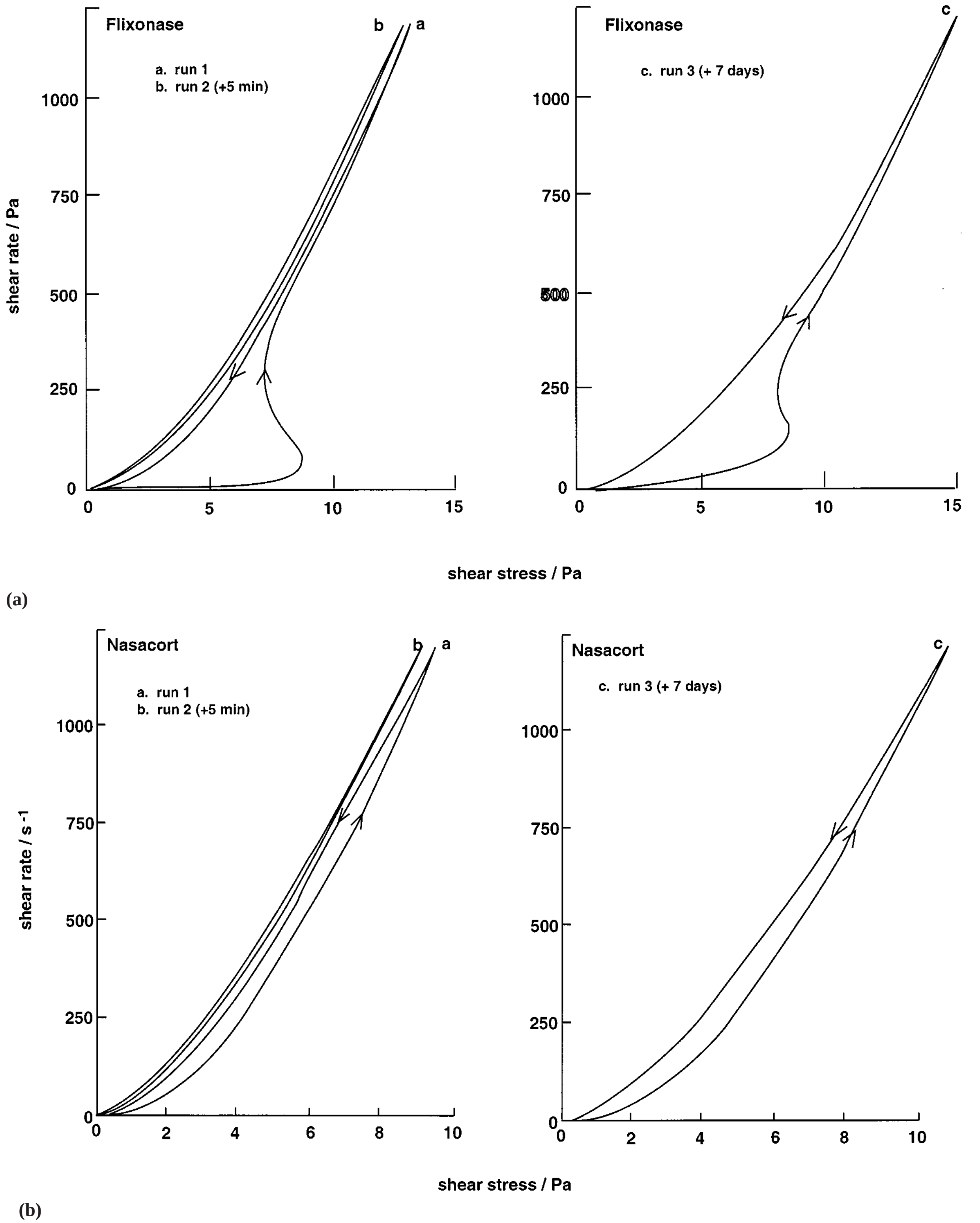

Figure 4. Typical rheograms for two representative nasal sprays (a) Flixonase and (b) Nasacort to illustrate thixotropic recovery. The first run a was with fresh sample; run b was after 5 min, and run c was after 1 week.

the suspensions except Nasonex, which was rather lumpy in the dispenser, although it sprayed with ease. Typical rheograms for each suspension at maximum shear rates of 100 sec^{-1} or 1200 sec^{-1} are shown in Figs. 2 and 3, respectively. They illustrate that all the suspensions were shear thinning and thixotropic, with the extent of thixotropy in series 2 (Fig. 3) (as measured by the loop area in Pa sec^{-1}) increasing in the order Beconase (3.5 Pa sec^{-1}), Nasacort (5.5 Pa sec^{-1}), Flixonase (15.9 Pa sec^{-1}), and Nasonex (58.6 Pa sec^{-1}). This trend was not as marked under the shearing conditions of series 1 (Fig. 2, maximum shear rate of 100 sec^{-1}), although the loop area for Nasonex was still considerably greater than the loop areas of the other sprays.

Relatively simple flow curves were obtained for all suspensions under the shearing conditions of series 1. Under the stronger deformation of series 2, both Flixonase and Beconase exhibited rather complicated flow curves, with distinct yield values at low shear rates. The appearance of such yield values has been the subject of much debate over the years. It is generally agreed that they are in part due to instrumental factors (e.g., possible slippage with concentric cylinder geometry) and in part due to a structural yield in the sample (15).

To determine whether there will be some irreversible deformation superimposed on the thixotropic behavior, the nasal formulations were retested under the same conditions after a suitable rest time. Typical flow curves for two of the sprays to illustrate structure recovery are shown in Fig. 4. All the sprays showed complete recovery, indicating thixotropy with negligible shear destruction. However, recovery was relatively slow because the second rheogram obtained 5 min after the first always had a markedly reduced loop area. Samples were partially recovered within hours, and all sprays were fully recovered when tested after storage for 1 week. Thus, it was concluded that shear thinning was reversible for each spray and mainly thixotropic with little or no irreversible deformation.

The time to reach an equilibrium viscosity varied with each sample (Figs. 5–7). For example, at 100 sec^{-1} (Fig. 6), Beconase and Nasacort reached equilibrium within 40 sec, Flixonase took nearly 120 sec, while Nasonex had not reached equilibrium even after 240 sec. The time to reach equilibrium for each suspension also decreased as the shear rate increased.

Two quantities with the dimension of viscosity η_{eq}, which is the value obtained at equilibrium at the given shear rate, and η_{app}, the apparent viscosity obtained from

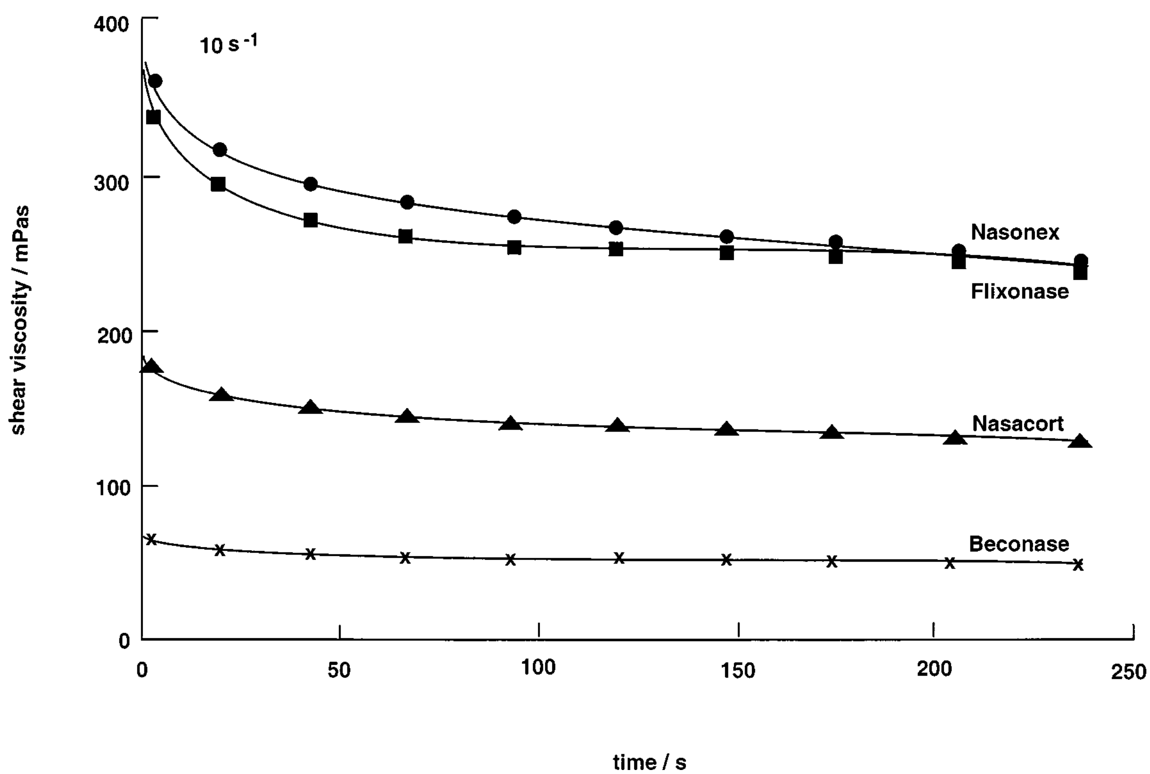

Figure 5. Change of apparent viscosity as a function of time at a constant shear rate of 10 sec^{-1} for all four sprays: Beconase, Nasacort, Flixonase, and Nasonex.

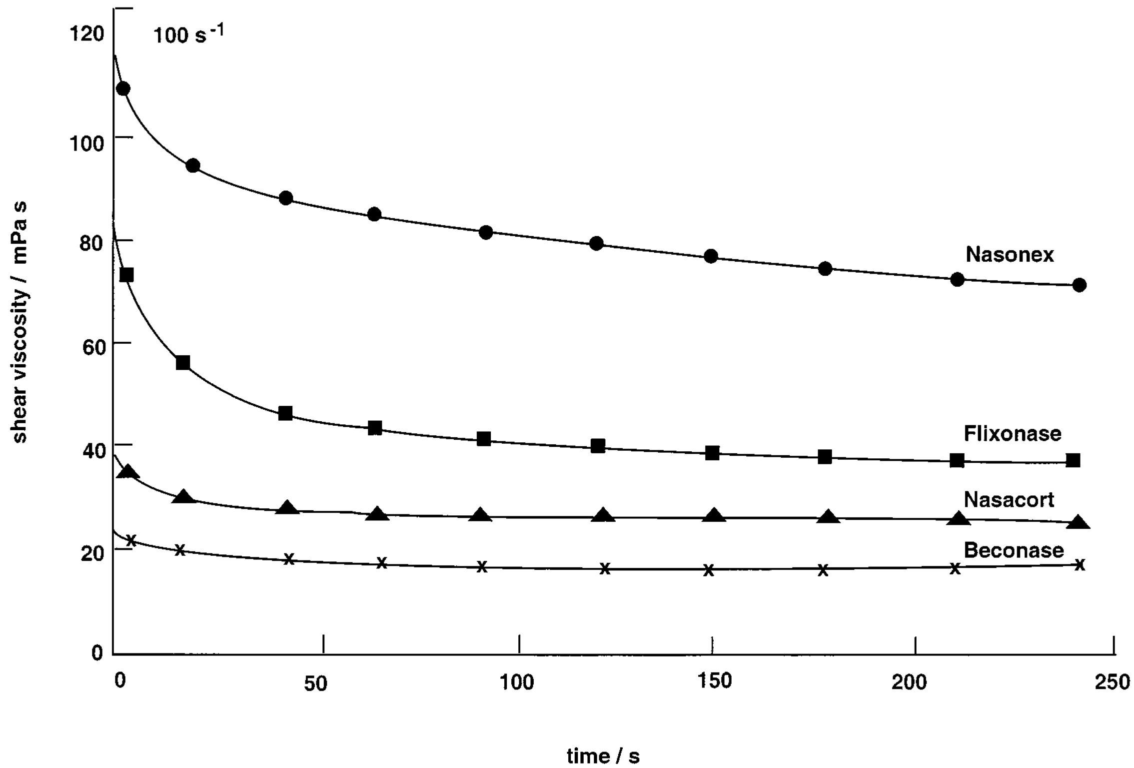

Figure 6. Change of apparent viscosity as a function of time at a constant shear rate of 100 sec^{-1} for all four sprays: Beconase, Nasacort, Flixonase, and Nasonex.

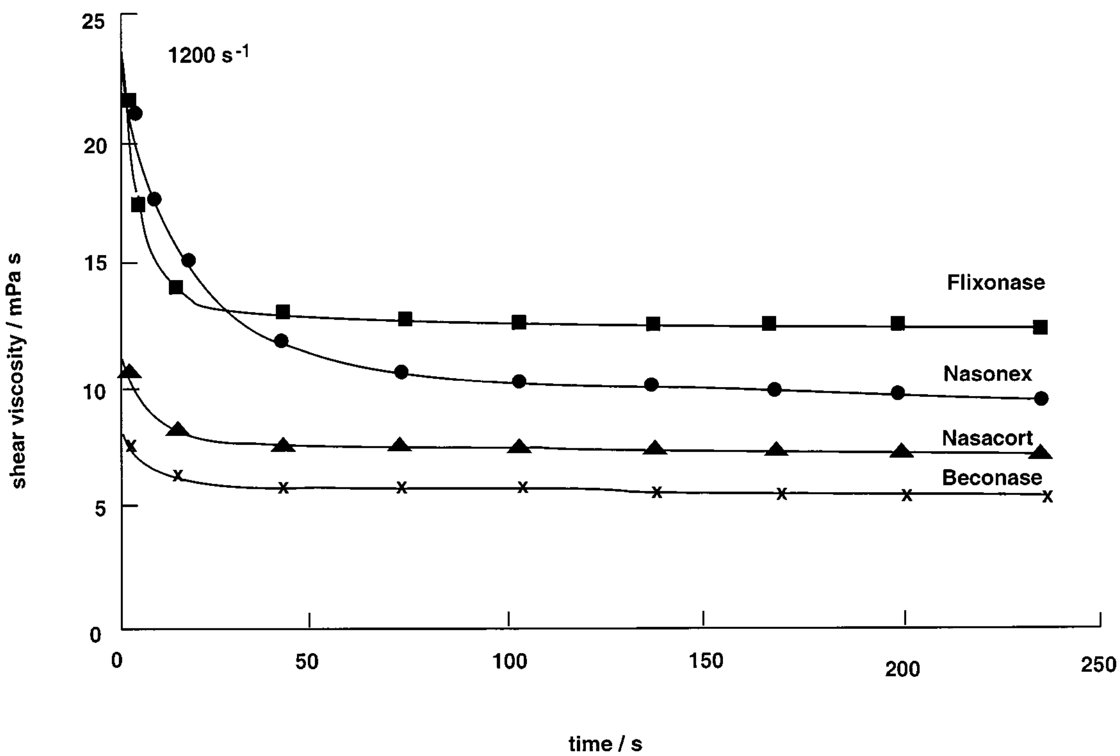

Figure 7. Change of apparent viscosity as a function of time at a constant shear rate of 1200 sec^{-1} for all four sprays: Beconase, Nasacort, Flixonase, and Nasonex.

Table 1

Apparent Viscosities η_{app} and Equilibrium Viscosities η_{eq} (mPa sec)

		100 sec^{-1}		1200 sec^{-1}	
Shear Rate	10 sec^{-1}, η_{eq}	η_{app}	η_{eq}	η_{app}	η_{eq}
Beconase	48.9	17.4	16.7	6.21	5.87
Nasacort	129	24.0	25.2	7.82	7.54
Flixonase	243	17.2	36.5	10.7	12.7
Nasonex	244	81.2	72.0	8.22	9.85

the corresponding apex of the flow curve, were defined and are compared in Table 1. If the material is thixotropic and the flow curve is performed at suitably slow rates, then these two viscosity values will be equal. If the flow curve is performed too quickly, then the measuring system may not be able to respond as quickly as the fluid, and hysteresis will occur. Equilibrium values were similar to, but not identical with, the corresponding flow curve apparent viscosities, the differences probably being due to their somewhat different shear histories. This suggests that the reversible structures had almost, but not completely, broken down during the shear cycle.

Figure 8 and 9 shows representative graphics of droplet evolution for Flixonase and Nasonex. As it was diffi-

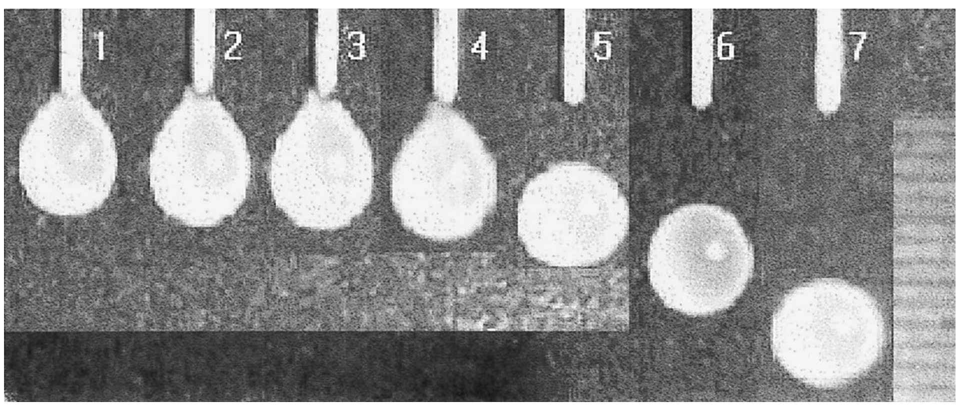

Figure 8. Droplet evolution for Flixonase spray. The filament has just broken at exposure 6.

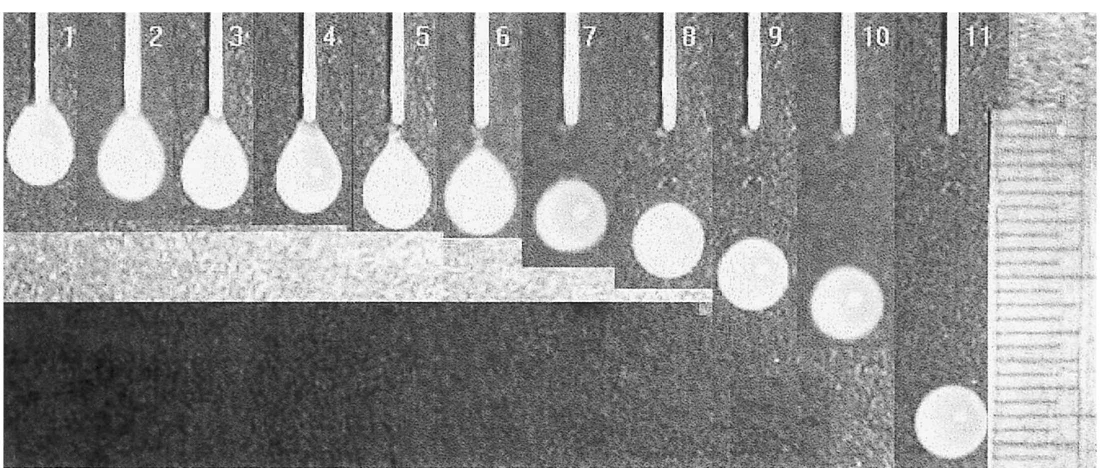

Figure 9. Droplet evolution for Nasonex spray. The filament has just broken at exposure 9.

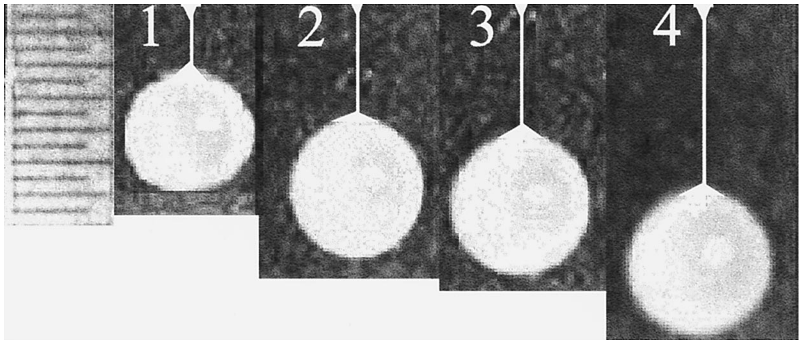

Figure 10. Formed droplets with associated filaments just prior to break for the four nasal sprays: 1, Beconase; 2, Nasacort; 3, Flixonase; and 4, Nasonex.

cult to distinguish filaments from the background, a certain amount of photographic enhancement was used, but the diameters and breakup configurations are preserved. A characteristic feature of such filaments of viscoelastic fluids is their uniformity—the filament stretches as a cylinder. This makes the determination of the extensional stress and strain rate relatively simple (14). A comparison of formed droplets with their associated filaments just before the droplet breaks for the four sprays is given in Fig. 10. It is evident that very short filaments only were shown by each sample prior to breakup and the droplet falling freely under gravity.

This preliminary extensional flow data indicates that Nasonex gives the longest filaments, Nasacort and Flixonase are similar with intermediate lengths, and Beconase gives the shortest filaments. Filament length, which is a good indication of extensional viscosity on which droplet size and breakup depend, increases in the same order as the lowest shear (i.e., 10 sec^{-1}) viscosities (see Table 1). This is not unexpected since, at low strain rates for elastic fluids and at all strain rates for Newtonian liquids, the extensional viscosity is three times the uniaxial extensional viscosity (16).

CONCLUSIONS

All the nasal spray suspensions were shear thinning and thixotropic to different degrees. To remain in the nasal cavity, the spray formulation must be thick enough not to run out of the nose or flow down the back of the throat. Although the correlation of such in vitro experiments with the in vivo situation must be approached with extreme caution, the absence of significant thixotropic recovery at short times (5 min) for all sprays implies that thixotropy is not necessarily the controlling factor, but rather it is the high viscosities present in all four sprays even after structure breakdown.

The preliminary elongational data suggest that there are differences in extensional properties, which correlated with the low shear viscosities. These differences will be determined by a more detailed series of experiments using direct extensional viscosity measurements (16).

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