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The Use of a Capillary Rheometer to Determine the Shear and Extensional Flow Behaviour of Nasal Spray Suspensions

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Abstract

The rheological profiles of four commercial nasal spray suspensions (Beconase, Flixonase, Nasacort and Nasonex) were compared using rotational viscometry. Two of the nasal sprays (Beconase and Nasonex) were further examined in both shear and extension using a capillary rheometer under conditions similar to those experienced at the spray nozzle (i.e. extremely high shear rates with significant stretching or extensional flow).

In rotation, the shear viscosity fell rapidly with increase in shear rate. Plots of the viscosity derived at the lower shear rates in rotation were extrapolated to include the high-shear rate capillary values. At very high shear rates, the shear viscosity of Beconase was higher than that of Nasonex with the cross-over occurring in the extrapolated region at approximately $10\,000\,s^{-1}$. In the transition region between laminar and turbulent flow (shear rate $6–8 \times 10^4\,s^{-1}$) there was a minimum in the shear viscosity to less than that of water for Nasonex and similar to water for Beconase, and a plateau region in extensional viscosity for Beconase but not Nasonex. These anomalies were due to the extensive aeration of both samples when sprayed. Whereas Beconase had de-aerated within 30 min of the experiment, Nasonex had not de-aerated completely after six weeks. The very low viscosity at the shear rates at the nozzle imply that it is unlikely that the low viscosity of the spray on delivery to the nose is a key factor in prolonging its residence time.

The extensional viscosity for these rather fluid samples was over 1000-times the shear viscosity (not 3-times as with Newtonian fluids) and both sprays exhibited strain hardening over the range covered. The high extensional stress in the nozzle enables the fluid to form as reasonably sized droplets rather than fine atomized droplets, which rather than settling in the nose, would be prone to redistribution through the normal respiratory function. Both sprays resisted degradation despite the high shear rates and extensional stresses experienced.

The rheological properties of corticosteroid nasal spray suspensions, used to treat seasonal allergic or perennial rhinitis (Mygind & Lund 1996; LaForce 1999), will affect their overall performance. In a recent study of four commercial nasal sprays, it was found that all were shear thinning and thixotropic to various degrees (Eccleston et al 2000). The relatively long times for thixotropic recovery implied that the viscosity of the spray after structure breakdown might be the controlling factor and not thixotropy, for the residence time in the nasal cavity. This rheological study, which was confined to shear experiments performed in the laminar region and at relatively low shear rates (typically $< 1500\,s^{-1}$), did not represent the conditions prevalent at the nozzle of a typical spray dispenser, where the flow is expected to be turbulent and shear rates are substantially higher. In addition, simple shear experiments, whatever the shear rate, do not adequately describe the deformation when the suspension is sprayed, because it will also undergo a stretching flow as it accelerates through and exits from the nozzle (Hudson et al 1992). Droplet size and break-up, which would also be expected to influence the therapeutic effect, depend on this property.

A preliminary assessment of extensional rheology of the sprays using digital camera photography of droplet evolution and filament length, identified

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differences between the four sprays, with filament lengths increasing in the same rank order as the lowest shear rate equilibrium viscosity (Eccleston et al 2000). However, very short lengths only were shown by each sample before break-up and the droplet falling freely under gravity, and it was not possible to obtain accurate extensional viscosity values from the measurement of filament dimensions. Therefore, a different method of determining extensional properties is required. For very thick materials, a number of instruments are available, such as the Rheometrics RME (Meissner & Hostettler 1994). However, these instruments are not suitable for thin materials, and alternative strategies need to be used for nasal spray formulations.

Capillary rheometers (as distinct from glass gravity capillary viscometers) are generally used for the determination of the shear viscosity of polymer melts at high temperatures using high pressures. It is not always appreciated, however, that it is also possible to adapt the rheometer to measure both the shear and extensional viscosity of highly mobile fluids at very high deformation rates (10^5–$10^6\,s^{-1}$ in aqueous fluids).

The aim of this work was to investigate the use of capillary rheometry to examine the rheological properties of two typical nasal spray suspensions under the conditions estimated to occur at or near the nozzle of a typical nasal spray device. Rotational rheometry was also used to extend the shear rate range used previously for four corticosteroid nasal sprays (Eccleston et al 2000), and to re-test capillary samples at lower shear rates, to determine whether degradation of the polymeric excipients had occurred which could induce particle flocculation or aggregation. Since a capillary rheometer is not usually used in this way in formulation research, the procedures adopted are illustrated stepwise, theoretically and graphically, using the raw data obtained for one of the nasal sprays.

Theory

In recent years it has been recognized that extensional (elongational) deformation rather than shear deformation is the dominant mode of deformation in many industrially important processes such as fibre spinning and flow through porous beds (Ferguson & Hudson 1985). In pharmacy, as in other disciplines, simple shear (usually at rather low shear rates) is the customary mode of deformation in the study of rheologically-complex materials and there are few reports on extensional flow. This is because of the experimental convenience of making simple shear measurements and the considerable difficulty in conducting high strain rate elongational flow experiments. Elongational deformation, however, is particularly important in pharmaceutical operations that involve polymer spraying, such as the film coating of tablets and the use of therapeutic sprays.

Extensional flow

There are three main forms of extensional flow, uniaxial, biaxial and planar. These give rise to extensional viscosities, η_E, η_B and η_P, respectively. Since Trouton (1906) first showed that $\eta_E = 3\eta_0$ for Newtonian fluids, where η_0 is the zero shear rate viscosity, the vast majority of the literature on extensional flow has been concerned with the uniaxial extensional viscosity, η_E, of very viscous materials. The equation defining extensional viscosity is:

$$\eta_E(\dot{\varepsilon}) = \lim_{t\to\infty} \eta_E(t, \dot{\varepsilon}) = \lim_{t\to\infty} \frac{\sigma_E(t, \dot{\varepsilon})}{\dot{\varepsilon}} \qquad (1)$$

where σ_E is the extensional stress and $\dot{\varepsilon}$ is the extensional rate of strain. This means that at a given strain rate the true extensional viscosity will be the equilibrium value (i.e. will not change with time).

A variety of techniques are available to measure the extensional viscosity of non-Newtonian fluids. For very thick materials, instruments, such as the Rheometrics RME (Meissner & Hostettler 1994), rely on the extension of a cylindrical specimen in equilibrium experimental conditions (after transient effects have disappeared). The ratio of the steady extensional stress to the steady extensional rate of strain then gives the required extensional viscosity. These controllable measurements enable η_E to be calculated with some confidence. Such experiments are not suitable for fluids of low consistency, such as the nasal sprays, and non-controllable experiments where the stress and/or extensional strain rate are not constant must be performed. Since it is not possible to maintain a cylindrical specimen of such fluids, alternative methods have been used, in which the fluid is allowed to flow in a particular manner, and an extra extensional deformation needs to be imposed. These non-controllable experiments are difficult to interpret. An extensional viscosity is still defined by the ratio between suitably defined (local) stress and strain rate variables and these can be used to yield a transient extensional viscosity (i.e. not steady state) which provides a measure of the fluid's resistance to the extensional flow in question.

There are different methods for non-controllable experiments such as the pendent drop (Jones &

Rees 1982), triple-jet (Oliver & Bragg 1974), fibre spinning (Hudson et al 1974; Ferguson & Hudson 1975; Hudson & Ferguson 1976) and converging flow (Binding 1988) techniques. The converging flow technique of investigating extensional flow can be realized within the contraction between the barrel and die of a capillary rheometer and is the one used in this study.

Flow in a capillary rheometer

Capillary rheometry is used as a method of characterizing the rheological properties of a test fluid. The fluid is forced through a cylindrical tube with a smooth inner surface (Figure 1). The flow parameters have to be chosen such that the flow may be regarded as steady state, isothermal and laminar. Knowing the dimensions of the capillary (i.e. diameter and length), the functional dependence between the volumetric flow rate of the fluid and the pressure drop due to friction can be determined. For Newtonian fluids, these raw data can be converted into shear rate and shear stress values at the wall of the capillary, since the relationships between the measured data (flow rate and pressure drop) and rheological data (shear rate and shear stress) are linear. However, for non-Newtonian fluids, the relationships are no longer linear, and so corrections have to be made to establish the dependence between the flow rate and the pressure drop, and to calculate the shear rate and shear stress.

The flow of fluids from a reservoir, into and through a capillary tube is quite complex, and may be divided into three distinct regions (Figure 1). The first is the fully developed laminar flow in the reservoir. This leads into the second region, the entry region, where large stresses are developed due to the funnelling effect of the liquid as it emerges from the reservoir and enters the capillary. The third region is the capillary itself, that is the region where laminar flow is again fully developed. This is usually the part of immediate concern, which can be identified with a steady, simple shear flow. The constancy of the stress with distance along the capillary is associated with a constant axial pressure gradient, and the relevant length is defined as the viscometric region. There is a fourth, exit region (not shown), which was not considered in this work. The shear properties of the fluid in question are determined in the viscometric region. The extensional properties however dominate in the entry region containing the contraction between the reservoir and the capillary, where the fluid must experience a converging flow. In this entry region, the streamlines of flow change direction giving an increase in energy. At this point of directional change the molecules stretch, giving extensional flow. This dominant extensional flow will decay and return to shear flow in the capillary proper, where, for many thin materials, shear rates are extremely high and apparent viscosity can be close to that of water. For inelastic fluids, such as Newtonian liquids, the streamlines at the boundary of the fluid stay close to the walls, and are unlikely to undergo high extensional stresses, even when they are forced towards the capillary at the contraction (Figure 1A). This will be true for all the fluid across the contraction. However, if the fluid has elasticity due, for example, to polymer or particle interactions (Figure 1B), then much higher extensional stresses will be generated. Close to the wall, the streamlines will be forced into the central region much further from the contraction. Some fluid will

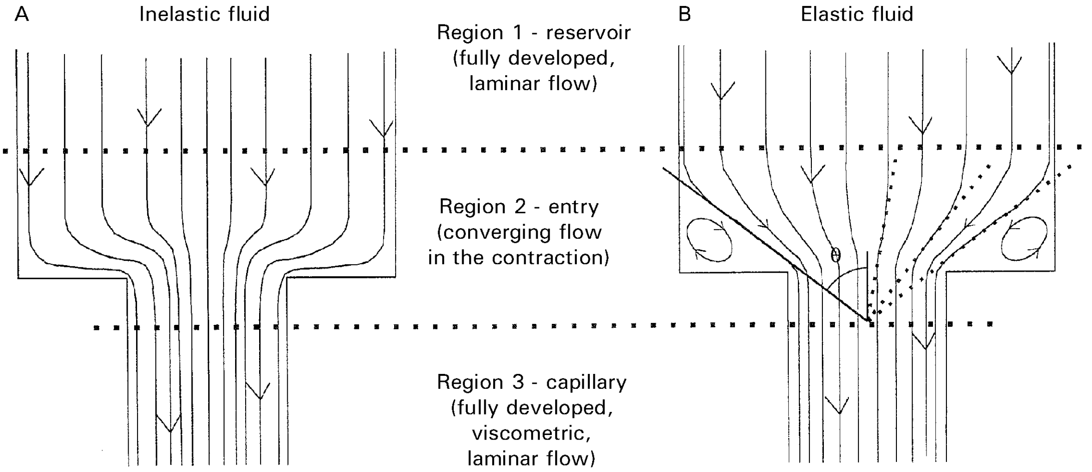

Figure 1. Schematic diagram of capillary tube flow for an inelastic (possibly Newtonian) fluid (A), and an elastic fluid (B). The three main regions of interest are indicated.

be trapped in a recirculating vortex between the streamlines and the walls of the reservoir. The size of this vortex will depend on the rate of flow of the fluid, as well as the geometry of the contraction. Flow visualization experiments (Chisholm 1999), indicated that the fluid flowing through the contraction has a wineglass shape, the diameter of the rim is the diameter of the barrel and the stem is the capillary. The volume of interest within this shape is a right circular cone with half angle θ.

Shear and extensional stresses

Ignoring exit pressure losses, the total pressure drop (P) in a capillary rheometer is given by:

$$P = P_{entry} + P_{capillary} \tag{2}$$

where P_{entry} corresponds to pressure losses in the convergence just before the capillary. By performing measurements with a range of dies of different capillary lengths, but having the same diameter and entry geometry, a plot of total pressure drop against die length to diameter ratio, the Bagley plot (Bagley 1961), can be made. The entry pressure drop, determined from the intercept of this graph, is then subtracted from the total measured pressure drop to give the capillary pressure drop, which is related to the shear stress at the wall. When performing shear experiments, the entry pressure loss is not considered further. However, this entry pressure drop is essentially the extensional stress generated by the converging flow in the contraction.

Shear and extensional strain rates

For Newtonian fluids, the shear rate at the wall can be determined from the standard equation:

$$\dot{\gamma}_w = \frac{32Q}{\pi D^3} \tag{3}$$

where Q is the volume flow rate and D is the diameter of the nozzle. However, for elastic fluids, corrections need to be applied to allow for the changing flow profile developed.

To determine the extensional viscosity, the corresponding extensional strain rate is required. Several studies have considered this difficult problem by using an estimated value of the cone angle to interpret the experimental results (Metzner et al 1969; Cogswell 1972; Binding 1988). A reasonably simple, yet accurate method to calculate this strain rate was reported by Metzner & Metzner (1970). If the volumetric flow rate is Q, the die diameter is D, and the cone half angle (at the tip) is θ, then the extensional strain rate is defined by:

$$\dot{\varepsilon} = \frac{8Q}{\pi D^3}\frac{\sin^3\theta}{1-\cos\theta} = \frac{8Q}{\pi D^3}f(\theta) \tag{4}$$

Some values of $f(\theta)$ are shown in Table 1. It can be seen that it takes values between 0 and 1·3, and is greater than 1 for angles of $33^\circ < \theta < 90^\circ$. Before actual values of the extensional strain rate can be determined, the cone angle, which may change with flow rate, is determined. The ideal method is to measure the cone angle, θ, visually. However, this is not that simple as the barrel of a capillary rheometer is usually made of metal, preventing direct viewing. A reconstruction of the flow dynamics inside the capillary rheometer was created using a glass barrel (Chisholm 1999), and an Instron tensile tester in the compression mode used to recreate the series of velocities of the ram used in the capillary rheometer. To allow the flow lines of the fluid to be perceived, fine particles were suspended in the fluid before the experiment. These particles would not effect the flow of the fluid which can then be filmed, and the angle visualized and measured. Using this set-up, for many flows observed in our laboratory, it has been found that $40^\circ < \theta < 80^\circ$, although the angle does change slightly with flow rate. At 40°, $f(\theta) = 1{\cdot}14$, whereas the maximum value is 1·30 (Table 1). Therefore, assuming $f(\theta) = 1{\cdot}22 \pm 0{\cdot}08$, and using a die of radius 0·255 mm, Equation 4 then gives an expression for the extensional strain rate which only depends upon the volumetric flow rate ($mm^3\,s^{-1}$).

$$\dot{\varepsilon} = (23.4 \pm 1.5)Q \tag{5}$$

Materials and Methods

Materials

Four commercial corticosteroid, metered nasal spray suspensions, Beconase (batch no. B0777EB;

Table 1. Values of $f(\theta)$ (defined by Eqn 4) as a function of the cone angle of the convergent flow (θ).

θ°	2·05	14·3	22·5	30·7	45·0	51·1	59·3	65·5	69·6	73·6	77·7	81·8	85·9	90·0
$f(\theta)$	0·07	0·49	0·74	0·95	1·21	1·27	1·30	1·29	1·26	1·23	1·18	1·13	1·07	1·00

Glaxo Wellcome, UK), Nasacort (batch no. MN2378; Rhone-Poulenc Rorer, UK), Flixonase (batch no. B3807NB; Glaxo Wellcome, UK) and Nasonex (batch no. 97F12 04; Schering-Plough, UK) were obtained directly from a local pharmacy with no knowledge of their age or previous history. Therefore the data obtained in this study is within the shelf life of each product at a random point in time. According to the labels, all suspensions contained cellulose suspending agents. For example, Beconase is an aqueous suspension of beclomethasone dipropionate containing microcrystalline cellulose and sodium carboxymethyl cellulose, and Nasonex is an aqueous suspension of mometasone furoate monohydrate in Dispersible Cellulose BP.

Shear rate at the nozzle of the nasal sprays

Experiments to estimate the shear rate at or near the nozzle were performed using a strobe (Irwin EA0374; Cambridge, UK) to time the standard metered-dose of known mass. The average diameter of the nozzle was also measured. Since the flow through the nozzle is essentially Poiseuille (laminar flow through a pipe), the equation for the shear rate of a Newtonian fluid (Eqn 3) was used.

Rotational rheometry

A CarriMed controlled stress rheometer (CSL2500; TA Instruments, Dorking, UK) with cone-and-plate geometry (2°, 40 mm) was used to determine the equilibrium shear viscosity for each formulation at constant shear stresses over the range 0·25 to 15 Pa, at 25°C. In a previous study, the rheometer was used in shear rate mode to obtain flow curves under standardized conditions (Eccleston et al 2000). Some equilibrium values were also obtained at the maximum flow curve shear rates used. In this study, where a wider range of equilibrium values was required, the instrument was used in a shear stress mode throughout to identify any initial transients. The spray nozzle was removed from the container and the sample poured directly onto the rheometer base platen. The platens were brought together with the minimum compressional stress being applied to the sample, and a period of 20 min was allowed for the sample to relax from any such stress. At each shear stress, shearing was continued for at least 15 min for the shear rate to reach equilibrium. Two of the sprays were re-tested using the above protocol, after they had been tested at very high shear rates in the capillary rheometer to determine the extent of degradation after such high shear rates.

Capillary rheometry

An advanced capillary extrusion rheometer (ACER 2000; Rheometrics, UK) was adapted for this study. The capillaries used were not those usually supplied with such instruments (which are normally used for polymer melts), but had to be specially made for these highly mobile nasal fluids. The modified capillaries were made by welding a series of syringe needles (Coopers Needle Works, UK), of varying lengths and diameters, into brass dies. For the following experiments, the diameter of each capillary was 0·51 mm (21 gauge), which was close to that of the nasal spray nozzles. Lengths of 50, 100 and 20 mm were used, in that order.

Approximately 100 mL of fluid was required for each experimental run. Consequently, only two of the four sprays were used, chosen from a previous study because they appeared to provide the extremes of extensional viscosity, with Beconase giving the shortest filaments and Nasonex the longest filaments (Eccleston et al 2000). The selected nasal spray was poured into the temperature-controlled barrel of the rheometer, and allowed to rest for 30 min at the set temperature of 25°C. It was then pushed through the die at a series of preset piston velocities, with the pressure in the converging flow at the bottom of the barrel being monitored by a transducer. The sample extruding from the capillary was collected in a suitable beaker. A small volume of the sample remained at the bottom of the barrel after the run was completed. The collected sample was then reintroduced into the barrel, and the procedure repeated twice more (using the same rest period between runs). After this, the 50-mm die was replaced by the 100-mm die (and subsequently by the 20- mm die), and the series of experiments repeated with the same sample. Hence, for each die length, the computer software supplied with the instrument produced three sets of points of two parameters (piston velocity and pressure drop).

Results and Discussion

Shear rate at the nozzle of a nasal spray

Typically, the nozzles had internal diameters over the range 400–800 μm. Delivery of each metered dose (0·075–0·120 mL fluid) took place within 0·05–0·10 s. These figures give shear rates over the range 24 000–240 000 s^{-1}. For a fluid with a viscosity approximately equal to that of water, these parameters give a Reynolds number (Re) of approximately 900–3100. The upper end of this range is in the transition region between laminar and turbulent flow. This confirms that rotational instruments cannot be used to determine the shear rheology of sprays in the region of delivery, since their maximum shear rates fall below those given above, and capillary rheometry is therefore essential.

Rotational rheometry

The results of the experiments for all four nasal sprays are shown in Figure 2. The experimental errors associated with these results are contained within the size of the symbol indicating a data point. It can be seen that, as shear rate increases, the shear viscosity falls quite rapidly. However, at higher shear rates, the viscosity of three of the sprays tends to a constant value of the same order as water at 25°C (i.e. $\eta_\infty \approx 0{\cdot}89\,\mathrm{mPa\,s}$). Hence, these three sprays can be modelled using the power law model described by Sisko (1958):

$$\eta = \eta_\infty + k\dot{\gamma}^{n-1} \tag{6}$$

with $n \approx 0{\cdot}4$. This model has been reported as being ideal to describe the behaviour of a number of polymeric and particulate dispersions (Barnes et al 1989).

The data for Flixonase was parallel to that for Beconase, which is not surprising as they both contain the same polymer suspending agent, but at slightly different concentrations. The curve for Nasonex was slightly different to that of the other three sprays, in that it is convex rather than concave. This is not normal behaviour. However, it was observed that at the end of the experiments, when the upper platen was raised, the Nasonex was aerated, even at these relatively low shear rates. This would have the effect of reducing the viscosity at higher shear rates, resulting in the flow curve shown in Figure 2.

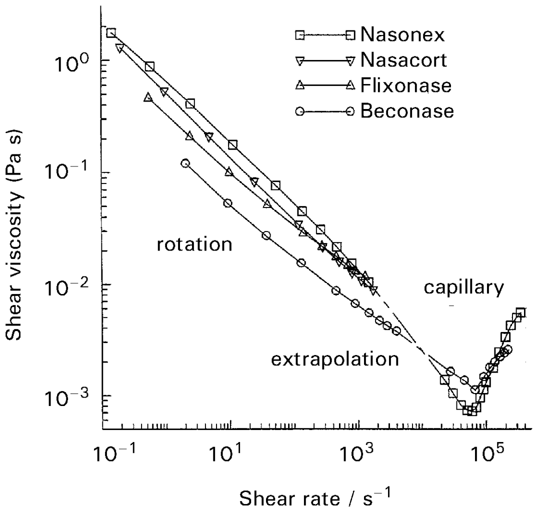

Figure 2. Beconase and Nasonex nasal sprays. The apparent shear viscosity as a function of shear rate derived from both rotational and capillary rheometry. The extrapolations from the rotational data between the two methods are shown using broken lines. Also shown are the data from rotational rheometry for the other two sprays, Flixonase and Nasacort.

Capillary rheometry

The calculations take place in three stages, the details of which are shown step-by-step for one of the sprays (Beconase).

Determination of the shear rate at the wall and the extensional strain rate. Starting with a fresh sample, the spray was pushed through the capillary at a series of piston velocities. The data in Figure 3A show the measured pressure drop as a function of the set piston velocity, with the 50-mm die. Again, the experimental error is contained within the size of the symbol used. The sample collected beneath the die was immediately re-introduced into the barrel, and the procedure repeated, after the 30-min rest period. Whereas the first three points were almost coincidental with those of the first run, subsequent points were somewhat lower. All points on the third run were lower than those on the first. This effect can be attributed to the thixotropic nature of the fluid. Structure had been sheared out of the fluid, and it takes a number of hours for the consistency to fully return (Eccleston et al 2000). The first three points of the second run were obtained using the still pure sample left in the dead space in the rheometer from the first run. Subsequent series of runs with the other two dies (100 and 20 mm) showed that all curves within a series are practically coincidental, confirming that structure had not reformed.

The piston velocity is converted to volumetric flow rate ($Q/\mathrm{mm^3\,s^{-1}}$) as:

$$Q = \frac{V}{60}\frac{\pi d^2}{4} \tag{7}$$

where d = 25 mm is the diameter of the barrel. Figure 3B shows the data pairs of (Q, P) for all three dies. To determine the change from laminar to turbulent flow, the Re is also plotted on Figure 3B. The Re is given by:

$$\mathrm{Re} = \frac{4\rho\rho}{\pi\mu D} \tag{8}$$

In Equation 8, the assumption is made that the density is approximately $1000\,\mathrm{kg\,m^{-3}}$, and that the viscosity is 1 mPa s (which is of the order of η_∞ seen in Figure 2). The diameter of the capillary is D = 0·51 mm. The transition from laminar to tur-

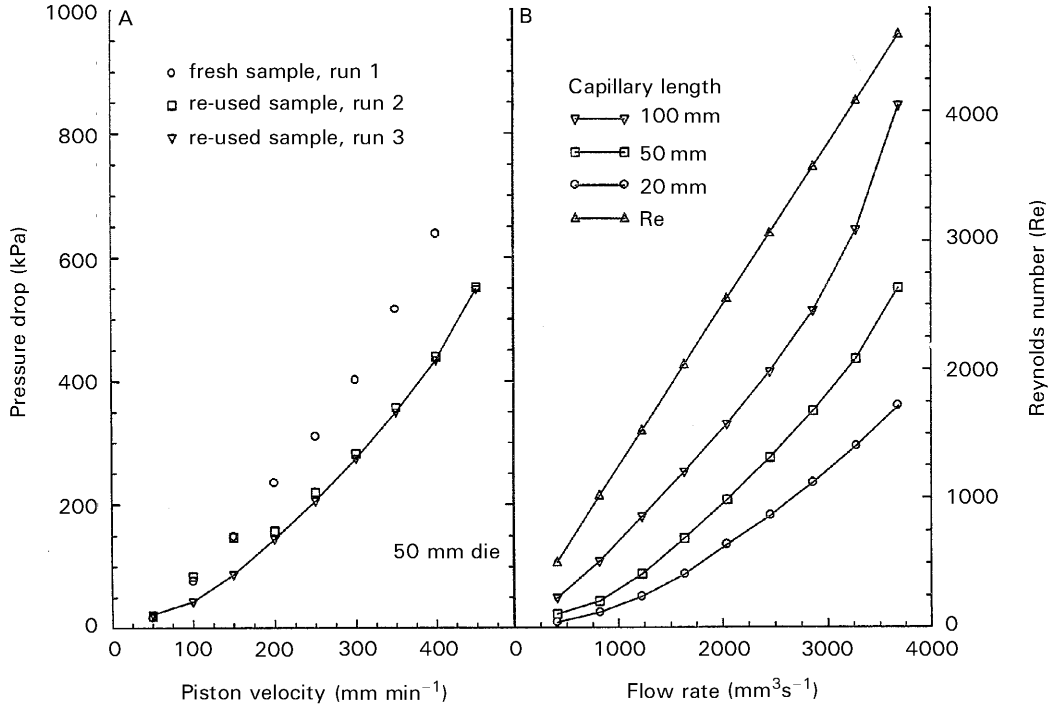

Figure 3. Beconase nasal spray. A. Pressure drop as a function of piston velocity for the capillary of 50-mm length. The results of three separate experiments are shown. B. Pressure drop as a function of flow rate for each capillary. The Reynolds number as a function of flow rate is also shown.

bulent flow takes place between Re values of 2100 and 3000. It can be seen from Figure 3B that this corresponds to flow rates of between 1400 and 2200 $\mathrm{mm^3\,s^{-1}}$.

For Newtonian fluids, the shear rate at the wall is given by Equation 3. The Rabinowitsch correction for non-Newtonian fluids (Brydson 1981) is then applied:

$$\dot{\gamma}_{\mathrm{w}} = \frac{8}{\pi D^3}\left(3Q + P\frac{dQ}{dP}\right) \qquad (9)$$

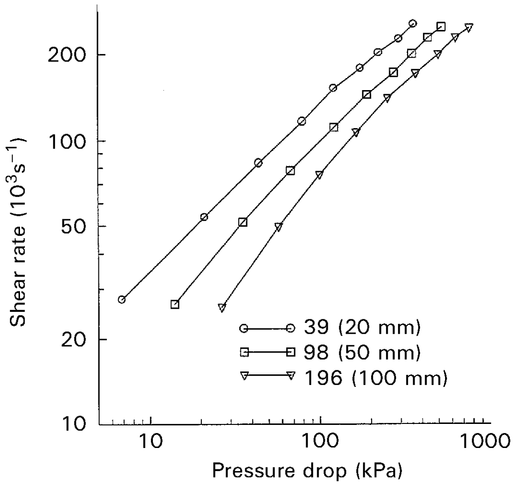

Figure 4. Beconase nasal spray. The shear rate as a function of pressure drop for each of the three capillary lengths.

In order to manipulate the data mathematically, it is necessary to reverse the data to give pairs of (P, Q). This means that they can then be differentiated numerically to give dQ/dP as a function of P, which is then inserted into Equation 9 to give the shear rate at the wall as a function of P. This was done for each of the three values of L/D, as shown in Figure 4. Finally, the original flow rate can then be assigned a corrected shear rate, as shown in Table 2. The extensional strain rate at this given flow rate was calculated from Equation 5, and is also shown in Table 2 where the associated experimental errors are given.

Determination of the shear and extensional stresses. For any given value of shear rate, and for each of the three values of L/D, the pressure drop can be read from Figure 4, and then used to determine the parameters a and b in the expression:

$$P = a\,(L/D) + b \qquad (10)$$

This is the Bagley correction. For each of the plots found from Equation 10, the slope $a = 4\sigma$, and so the shear stress is given by $\sigma = a/4$. The intercept b is therefore the extensional stress, σ_E. The values of a and b at given values of shear rate are given in Table 2.

Determination of the shear and extensional viscosity. The shear viscosity defined by $\eta = \sigma/\dot{\gamma}_{\mathrm{w}}$, and

Table 2. The shear rates corresponding to given flow rates, after application of the Rabinowitsch correction (Eqn 9), for Beconase and Nasonex nasal sprays tested in the capillary rheometer.

Nasal spray	Flow rate ($mm^3 s^{-1}$)	Shear rate (s^{-1})	a (Pa)	b (Pa)	Extensional strain rate (s^{-1})
Beconase	409	27980 ± 320	183 ± 15	2640 ± 160	9570 ± 614
	818	46140 ± 480	251 ± 21	17940 ± 440	19140 ± 1227
	1227	67360 ± 650	300 ± 36	40150 ± 720	28710 ± 1840
	1636	91680 ± 780	535 ± 44	56350 ± 1110	38280 ± 2450
	2045	115200 ± 950	818 ± 58	101300 ± 1320	47850 ± 3070
	2454	137900 ± 1070	1102 ± 71	143900 ± 1580	57420 ± 3680
	2863	165100 ± 1120	1460 ± 77	188200 ± 1630	66990 ± 4300
	3272	195400 ± 1230	1860 ± 83	244100 ± 1720	76560 ± 4910
	3682	224600 ± 1310	2280 ± 90	296100 ± 1880	86160 ± 5520
Nasonex	280	22 560 ± 280	125 ± 9	2130 ± 190	6770 ± 430
	336	30 300 ± 360	127 ± 12	3860 ± 330	9100 ± 580
	403	40 160 ± 410	131 ± 15	6180 ± 540	12 060 ± 770
	484	50 120 ± 480	148 ± 20	9310 ± 690	15 050 ± 960
	684	59 900 ± 570	172 ± 24	13 500 ± 810	17 980 ± 1150
	854	69 870 ± 640	217 ± 28	18 000 ± 1070	20 980 ± 1340
	1068	79 990 ± 710	305 ± 33	23 600 ± 1220	24 010 ± 1540
	1335	89 960 ± 780	407 ± 39	28 700 ± 1540	27 000 ± 1730
	1669	99 820 ± 840	525 ± 46	34 300 ± 1790	29 970 ± 1920
	2086	126 900 ± 900	894 ± 59	52 600 ± 2060	38 090 ± 2440
	2608	157 300 ± 940	1526 ± 71	82 200 ± 2440	47 230 ± 3030
	3260	200 400 ± 990	2649 ± 90	133 000 ± 2980	60 170 ± 3860
	4074	242 400 ± 1050	4065 ± 110	187 000 ± 3380	72 780 ± 4670
	3762	293 300 ± 1110	5772 ± 130	252 000 ± 3870	88 040 ± 5640
	4385	341 900 ± 1170	7488 ± 165	315 000 ± 4410	102 600 ± 6580

Also shown are the values of the parameters a and b in the linear expressions (Eqn 10) for the pressure drop, as a function of L/D, for these shear rates (i.e. the Bagley plot), together with the corresponding extensional strain rates.

the extensional viscosity defined by $\eta_E = \sigma_E/\dot{\varepsilon}$, can then be determined. For the two nasal sprays tested in the capillary rheometer (Beconase and Nasonex) the results are also shown in Figure 2, together with an extrapolation to meet the values obtained on the rotational instrument. In the region of approximately $6\text{–}8 \times 10^4\,s^{-1}$, the capillary plots go through a minimum as the flow through the die changes from laminar to turbulent. From this shear rate on, the normal definition of viscosity ($\eta = \sigma/\dot{\gamma}_w$) does not remain valid, but it is still instructive to plot these values for comparison purposes. Although Beconase has a lower shear viscosity in rotation, the capillary results indicate that at very high shear rates the shear viscosity of Beconase is higher than that of Nasonex, with the cross-over occurring at approximately $10\,000\,s^{-1}$ in the extrapolation region. This minimum viscosity is actually less than that of water for Nasonex, and very similar to that of water for Beconase ($\eta = 0{\cdot}89$ mPa s for water at 25°C). The reduction of shear viscosity to that less than water is probably due to the extensive aeration of both samples. Whereas Beconase had de-aerated within the 30 min between each experiment, Nasonex had not de-aerated completely after six weeks. The polymeric excipients were different for the two sprays, with Beconase containing microcrystalline cellulose and sodium carboxymethyl cellulose, whereas Nasonex contains Dispersible Cellulose BP. Further work is required to determine whether this is responsible for the different rates of aeration. In any case, the data suggest that the liquid sprayed into the nose is of a similar viscosity to that of water.

The extensional viscosity, given by $\eta_E = \sigma_E/\dot{\varepsilon}$, can now be calculated, and is shown in Figure 5. Also shown in Figure 5 for comparison, are the values of shear viscosity obtained on the capillary rheometer and the viscosity of water at the test temperature. The extensional viscosity increases with strain rate (strain thickening) over the range covered. Some molecular theories predict that the extensional viscosity reaches a maximum value as the polymer chain becomes fully extended (Bird et al 1977). This would appear to be the case with Beconase, at approximately $3 \times 10^4\,s^{-1}$. However, above this value there is a further increase in viscosity, probably due to the turbulence. This temporary plateau region was not noticeable for the Nasonex sample, but that may be because of the high level of aeration which may have caused some slipping in the capillary. It was noted, however, that the extensional viscosity for these non-Newtonian, but still rather fluid samples, was over 1000 times the shear viscosity (not 3 times, as with Newtonian fluids; Trouton 1906) at equivalent shear/strain rates, as shown in Figure 5. The high extensional

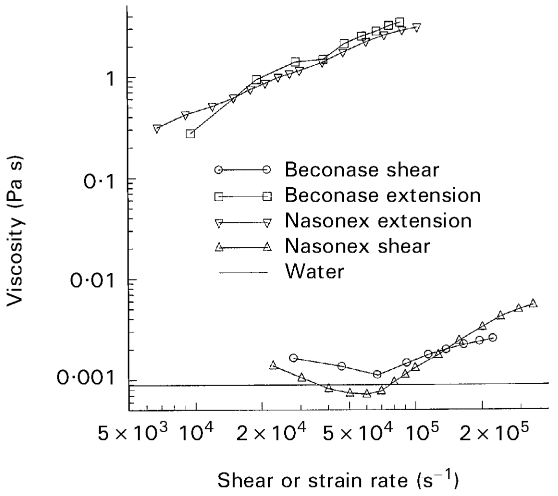

Figure 5. Beconase and Nasonex nasal sprays. The extensional viscosity as a function of strain rate and the shear viscosity as a function of shear rate, both obtained on the capillary rheometer, together with the viscosity of water at the test temperature.

stress in the nozzle enables the fluid to remain as reasonably-sized droplets rather than fine atomized droplets (Hudson et al 1992), which may not settle in the nose.

Degradation

The two sprays which were re-tested in the rotational rheometer after the high shear rate experiments in the capillary rheometer had virtually the same flow curves as those shown in Figure 2, with only a small deviation at the higher rates. This suggests that the polymeric excipients are well able to withstand the high shear regime in the capillary, and by inference, in the nozzle of the spray dispenser.

Conclusions

The rheological conditions at the nozzle of a nasal spray have been identified. They suggest that shear rates are extremely high, that the flow is in the transition between laminar and turbulent flow, and that extensional flow is also important. To simulate these conditions, a capillary rheometer was used to investigate both shear and extensional flow of two commercial nasal spray suspensions. Apparent viscosities derived at lower shear rates using rotational rheometry, were extrapolated to the capillary data to cover a wide range of shear rates. At the estimated shear rates at the nozzle, the apparent shear viscosity of both sprays was extremely low (of the same order as water) with little difference between the sprays. As thixotropic recovery is slow, it seems unlikely that the low viscosity of the spray on delivery to the nose is a key factor in prolonging its residence time. In contrast, the extensional viscosities, on which droplet size depend, were high and of the same order of magnitude for each spray. The droplet sizes consequently will be larger than would be expected on the basis of the shear viscosity alone, which would produce fine atomized droplets. The droplet size will affect the therapeutic effect in that atomizers might disperse the formulation into the air, and would be prone to redistribution through the normal respiratory function, rather than deposited onto the nasal mucosae. However, although extensional viscosity was similar for each spray, droplet sizes may not be the same, since different excipients in the formulations, for example surfactant, will also tend to influence droplet size. Further work is necessary to identify the influence of excipients on droplet size at each extensional viscosity.

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