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Development and application of a micro-capillary rheometer for in-vitro evaluation of parenteral injectability

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Abstract

A micro-capillary rheometer was developed to determine the rheology and injectability of parenteral formulations. The rheometer consisted of a micro-capillary and a glass syringe attached to an Instron that drove the syringe plunger at predetermined speeds and measured resulting forces on the plunger. The cross-head speed and the measured force were used to calculate the shear rate and the shear stress respectively, according to the Hagen–Poiseuille equation. The resulting rheograms of several Newtonian standards showed excellent linearity over a broad range of about 10×10^3 to 160×10^3 s^{-1} and produced accurate and reproducible viscosity determinations over the viscosity range of about 10×10^{-3} to 100×10^{-3} Pa.s. The developed methodology focussed primarily on the minimization of errors associated with the determination of the wall frictional force using both direct measurement and linear regression to determine this parameter from the data. The effect of micro-capillary diameter, syringe cross-sectional area and micro-capillary length was explored in an effort to increase the measured force so that wall frictional force errors could be minimized. The micro-capillary rheometer gave reproducible and accurate rheograms over a range of shear rates consistent with the shear rate range used in clinical practice, and showed that Newtonian and non-Newtonian rheological behaviours could be evaluated quantitatively.

Introduction

Injectability refers to the performance of a suspension or liquid during the injection process and incorporates factors such as the pressure or force required, evenness of flow, aspiration qualities and freedom from clogging (Akers et al 1987). Good injectability is an important characteristic of parenteral injection formulations. Poor drug injectability characteristics can lead to patient discomfort or to dysfunctional formulations (Marriott 1999). The injectability of dilute suspensions and solutions may not be as critical as that of more concentrated disperse systems where the viscosity is greater and the rheology more complex (Barnes et al 1989). Most methods used for testing injectability have been qualitative (Floyd & Jain 1996). For example, simple ejection of a suspension into an open container, performed very slowly with intermittent application of pressure to the plunger, can provide useful information about the injectability of the suspension. Force profiles from a materials testing device such as an Instron provide more a quantitative estimate of the injectability of parenteral formulations (Floyd & Jain 1996). An instrument was developed to assess the injectability of parenteral formulations by measuring the time required to smoothly inject a solution or suspension into a meat sample under a specified pressure (Suzuki 1979). Regression equations were obtained for syringes of given types and sizes using needles of various gauges when a test solution was injected. These expressions permitted the calculation of the expected injection time for a given syringe-needle system and for a given vehicle of a certain viscosity (Suzuki 1979). The injectability of parenteral suspensions was closely related to the viscosity and particle characteristics of the suspensions (Akers et al 1987). The viscosity and rheology can be measured using a number of conventional techniques, including rotational viscometers. The major problem in using these viscometers for the determination of the injectability of parenteral formulations is their limited shear rate range. For example, rotational

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viscometers employ shear rate ranges below $1000\,s^{-1}$. However, injection of fluids through needles into human tissue is a high shear process that is estimated to occur at more than $4000\,s^{-1}$ (Hans 1990). Using fine needles will lead to further high shear rates; for example, injecting 1 mL of a liquid from a 1 mL syringe through a fine needle with an internal diameter of 350 μm in a period of 2 to 5 s will result in a shear rate range of about 47 500 to $118\,800\,s^{-1}$. In addition, the geometry of the rotational rheometer and its method of application of shear are very different to the processes involved in the injection of a fluid through a syringe and needle into human tissue or blood.

For suspensions, an increase in the particle–capillary radius ratio was found to change and indeed to blunt the velocity profile under plug flow, where the particles became non-rotational, when observed in the central region of the tube (Cox & Mason 1971). The deviation of the velocity profile from that of the Newtonian profile was principally due to the dependence of the rheology on the particle-to-tube radius, the solids concentration and the interactions between the particles and the tube wall. The capillary flow of concentrated suspensions prepared from non-micronized particles with diameters greater than 10 μm through relatively large capillaries with diameters greater than 1 mm has been well covered in the literature (Yilmazer & Kalyon 1989; Yaras et al 1994; Mayadunne et al 1996; Carley et al 1997; Butler et al 1999; Lukner & Bonnecaze 1999). Other authors have discussed the flow of concentrated suspensions containing micronized particles (<10 μm) through smaller capillaries (diameter < 1 mm) (Tsao et al 1993; Suwardie et al 1998). Therefore, injection of concentrated complex parenteral dispersions, many involving large particle-to-capillary diameter ratios in a syringe–needle system, brings some technical challenges that the development of a corresponding micro-capillary rheometer can address quantitatively. In addition, measuring high viscosity liquids using the micro-capillary rheometer might result in two principal potential sources of error (Cogswell 1981): the end effects (Bagley correction) and the deviation from an ideal parabolic velocity profile for non-Newtonian samples (Rabinowitsch correction). These, together with the impact of piston friction, are covered in the appropriate sections.

The aim of this work was to develop a reliable micro-capillary rheometer able to measure and quantify the injecting force and to predict the rheological behaviour of fluids during clinical injection using a corresponding syringe-needle system with injection rates and applied forces quantified with an Instron device.

Materials and Methods

Materials

The following Newtonian liquids were used in the development and validation of the micro-capillary rheometer: three silicon oils, Brookfield 100 (B100), Brookfield 50 (B50) and Brookfield 10 (B10) (Brookfield Engineering Laboratories Inc., USA). Celestone Chronodose injection (Schering-Plough Pty Ltd, Australia), in which 1 mL contains betamethasone 5.7 mg, as betamethasone sodium phosphate 3.9 mg in solution, and betamethasone acetate 3 mg in suspension in an aqueous vehicle, and Propofol emulsion for injection (Mayne Pharma, Australia), containing propofol 10 mg per millilitre, were selected as commercial pharmaceutical injections to be evaluated in the micro-capillary rheometer.

Micro-capillary rheometer measurements

Glass gas-tight Luer lock and removable-needle syringes of capacities 1 mL and 2.5 mL (SGE Australia Pty Ltd, Australia) were used as the barrel of the micro-capillary rheometer. Different types of stainless-steel needles were employed as the micro-capillaries attached to the barrel of the Luer lock syringe (capillary designated N) or removable-needle syringe (capillary designated NR). Capillary diameters ranged from 345 to 660 μm and were cut using a quartz cutting tool. All micro-capillaries used in the experiments had a length of 22.9 mm except for the NL520 and NRL345 micro-capillaries, which were 36.5 and 65.0 mm long, respectively (Table 1). The internal diameters of all the capillaries used were measured using a Carl Zeiss camera microscope Ultraphot II (Zeiss, Germany) with a 1 mm scale divided into 100 divisions.

The micro-capillary rheometer was attached to a material-testing instrument (Instron Corporation, USA) using a 100 N load cell in compression mode. A locally developed aluminium holder was manufactured to hold the syringe rigidly during the injection. Temperature control (Eurotherm Controls, USA) was maintained in the holder using a cartridge heater and thermocouple inserted inside the holder (Figure 1). The temperature was programmed to $25 \pm 0.3\,^{\circ}C$, and validated regularly using a digital thermometer. The cross-head speed of the upper grip of the Instron ranged from 11 to $970\,mm\,min^{-1}$ and depressed the plunger of the syringe to a constant distance prior to contact with the end of the barrel (equivalent to 0.8 mL in the 1 mL syringe and 2 mL in the 2.5 mL syringe). The force measurements were captured at a rate of 30 to 40 points s^{-1} for the same displacement each time. Data collected in the first 10 mm displacement were not considered since they contained the starting transient data. Five replicates were taken for each liquid at each cross-head speed. The fluid to be evaluated was loaded into the syringe barrel directly by the micro-capillary syringe or by a syringe with large internal diameter needle (18 gauge), depending on its viscosity. The syringe was then inserted into the holder and 5 min was allowed for it to reach the required temperature. To measure the wall frictional force, the barrel wall was lubricated with a small amount of that fluid.

Table 1 Internal diameter and length of micro-capillaries

	N380	N525	N660	NR347	NRL345	NL520
Diameter (μm)	380	525	660	347	345	520
Length (mm)	22.9	22.9	22.9	22.9	65.0	36.5

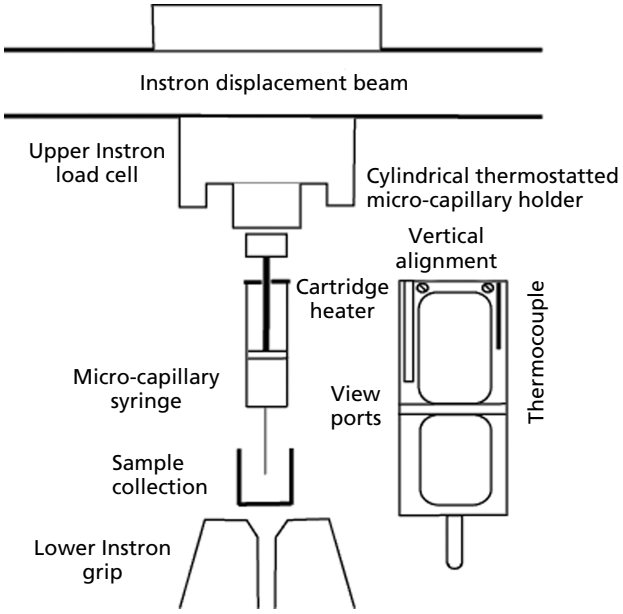

Figure 1 Micro-capillary syringe within the Instron arrangement together with the thermostatted holder (shown separately).

Validating the viscosity of the Newtonian standards

The viscosity of each Newtonian standard was validated using a Rheometrics Fluids Spectrometer RFS II (Rheometric Scientific, USA) with a 100-g transducer using five replicates. A steady-state mode was chosen to conduct the measurement using parallel plate geometry with a gap within a range of 0.8 to 1.2 mm.

Viscosity calculations using the micro-capillary rheometer

For the capillary rheometer, viscosity can be expressed in relation to shear rate as:

$$\text{Viscosity } (\eta) = \frac{\tau_w}{\dot{\gamma}_{app.}} = \frac{(\Delta P D/4L)}{(32Q/\pi D^3)} \quad (1)$$

where $\dot{\gamma}_{app.}$ (s^{-1}) is the apparent shear rate, τ_w (Pa) is the shear stress, ΔP is the pressure resulting from driving the plunger, Q is the volumetric flow rate of the fluid passing through the capillary needle, and D and L are the internal diameter and length of the capillary, respectively.

In order to correct for the apparent shear rates measured for fluids showing non-Newtonian behaviour, the power-law model was applied:

$$\eta = \dot{\gamma}_{true}\, K_2^{n-1} \quad (2)$$

where K_2 is the consistency constant, n is the power-law index and $\dot{\gamma}_{true}$ is the actual shear rate rather than the apparent shear rate. According to the Rabinowitsch procedure (Carreau et al 1997), $\dot{\gamma}_{true}$ is determined according to the following expression:

$$\dot{\gamma}_{true} = \dot{\gamma}_{app.} \frac{(3n' + 1)}{4n'} \quad (3)$$

where n′ is the flow behaviour index as determined from the slope of log τ_w vs log $\gamma_{app.}$ (Barnes et al 1989; Nair et al 2000). Thus, for non-Newtonian fluids, the shear stress depends on the shear rate to the nth power (Nielsen 1977).

Statistical analysis of data

Data sets were compared employing either a one-way analysis of variance with the Student–Newman–Keuls test or the Kruskal–Wallis one-way analysis of variance on ranks using SigmaStat version 2.0. Linear regression was undertaken using the same software.

Results and Discussion

Viscosity of the Newtonian standards

Newtonian standards (B100, B50 and B10) were chosen to validate the micro-capillary rheometer. The viscosity of B100, B50 and B10 was measured over the general shear rate of 0.1–1000 s^{-1} using the Rheometrics rotational rheometer. The viscosity measurements were as follows: $94.7 \pm 0.5 \times 10^{-3}$ Pa.s for B100, $46.4 \pm 0.5 \times 10^{-3}$ Pa.s for B50 and $9.3 \pm 0.1 \times 10^{-3}$ Pa.s for B10. Measurements in the initial part of the rheogram (< 0.6 s^{-1}), where the shear rate was small and consequently the error in torque readings was greater than the sensitivity of the transducer, were excluded. Force measurements in the latter part of the rheograms (>631 s^{-1}), where the shear rate was high and consequently the torque deformed the liquid between the plates, were also excluded. The measured viscosity values were 98.0×10^{-3} Pa.s for B100, 48.6×10^{-3} Pa.s for B50 and 9.8×10^{-3} Pa.s for B10 at 25°C, which are different from the nominal values provided by the supplier.

Force–speed measurements

Rigidity and alignment of the micro-capillary rheometer were essential to obtain reproducible force measurements. The use of a glass barrel instead of a clinical plastic syringe, a rigid attachment to the upper grip of the Instron and a temperature-controlled holder for the syringe reduced coefficients of variation (CV) from about 14 to 1%.

Force measurements were collected at cross-head speeds ranging from about 100 to 1000 mm min^{-1} using glass barrel syringes and micro-capillary diameters from 380 to 675 μm. Force decreased with a decrease in speed for the three Newtonian oils as, expected. This is illustrated in Figure 2 for the force measurements of B100 fluid using the 1 mL Luer lock and the removable-needle syringes. Figure 2A shows the total force together with the directly measured wall frictional force obtained with the Luer lock syringe and the N380 micro-capillary, while Figure 2B shows the total force using the removable-needle syringe and the NR347 micro-capillary, which will be used to

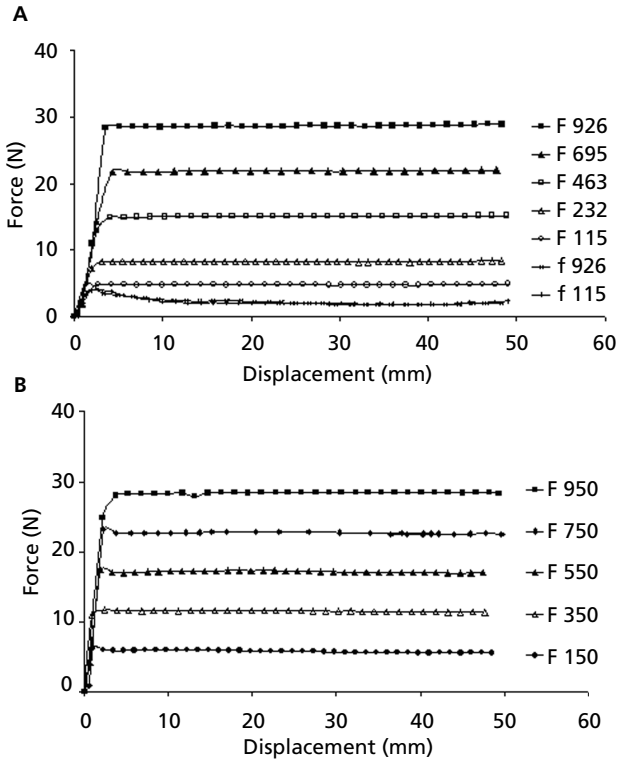

Figure 2 Force–displacement data collected at different speeds (mm min^{-1}) at 25°C for B100 using (A) 1 mL Luer lock syringe and the N380 micro-capillary and (B) 1 mL removable-needle syringe and the NR 347 micro-capillary, where F is the total force measured at the indicated speeds when the barrel is filled with the liquid and f is the frictional force when the barrel is wetted only with the same liquid.

estimate the wall frictional force component in the next section. Once beyond the initial transient data, reproducibility across the five replicates can be seen to be very high. Wall frictional forces (f) were determined for all Newtonian standards. The determination of wall frictional force is discussed in more detail below.

The net force required to expel the liquid from the syringe and micro-capillary at specific speeds was determined by subtracting the wall frictional force from the measured force. The net forces and speeds were used to calculate shear stresses and shear rates as discussed in the previous section. Representative rheograms of shear stress vs shear rate were constructed for the three Newtonian standards (Figure 3). The results demonstrated excellent linearity over the shear rate ranges with R^2 values of 0.999 or greater. The shear rate range is broad, with shear rate spans of at least $152 \times 10^3\,s^{-1}$. The viscosities of the standards were determined from the slopes of the linear regression and were 95.0×10^{-3} Pa.s compared to $94.7 \pm 0.5 \times 10^{-3}$ Pa.s measured using the Rheometrics rheometer for B100, 47.1×10^{-3} Pa.s compared to $46.4 \pm 0.5 \times 10^{-3}$ Pa.s for B50 and 9.3×10^{-3} compared to $9.3 \pm 0.1 \times 10^{-3}$ Pa.s for B10 at 25 °C, indicating that the viscosity values determined in the micro-capillary rheometer in the much higher shear rate range were not significantly different from the values

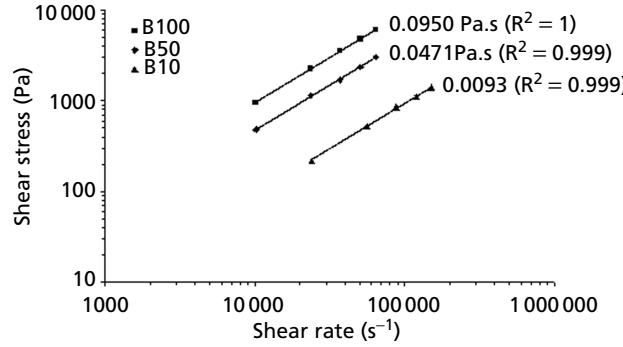

Figure 3 Shear stress–rate plots measured at 25°C for B100 and B50 using a 1 mL removable-needle syringe and NR 347 capillary, and for B10 using a 2.5 mL removable-needle syringe and NRL 345 capillary.

measured using the Rheometrics rotational viscometer ($P = 0.421$, ANOVA on ranks).

Wall frictional force determination

The frictional forces for the standards with the various micro-capillaries were determined over a range of cross-head speeds and were shown to be similar at high and low speeds. This is exemplified for B50 and the Luer lock syringe (1 mL) where the wall frictional force did not change over the cross-head speed range of about 100 to 950 mm min^{-1} (Figure 4A). The wall frictional forces for each of the standard fluids can be determined by averaging the frictional forces measured at low and high speeds. However, when the measured sample forces are low and are approaching the magnitude of the wall frictional forces, experimental errors in the determination of the wall frictional force, due to over or under lubrication of the syringe during measurement, can have an impact on the validity of the resulting rheogram. This will be seen in the following section, where the influence of capillary diameter and syringe diameter are examined.

Rather than experimentally measure the frictional force, approaches to determine the frictional force using an analytical expression proved successful. For Newtonian liquids, the wall frictional force (f) can be derived from equation 1 for the capillary rheometer. Shear stress (Pa) and shear rate (s^{-1}) are given by:

$$\text{shear stress } \tau_w = \frac{(F - f)D}{4AL} \text{ since } \Delta P = \frac{(F - f)}{A}$$

and

$$\text{shear rate } \dot{\gamma}_{app.} = \frac{32AS}{60000\pi D^3} \text{ since } Q = \frac{V}{t} = \frac{AS}{60000}$$

where F (N) is the force needed to inject the fluid, V (m^3) is the volume of liquid flowing in time t (s), A (m^2) is the cross-sectional area of the syringe connected to a capillary of diameter D (mm), and the cross-head speed is S (mm min^{-1}). The general equation of viscosity in the micro-capillary rheometer can be rewritten as:

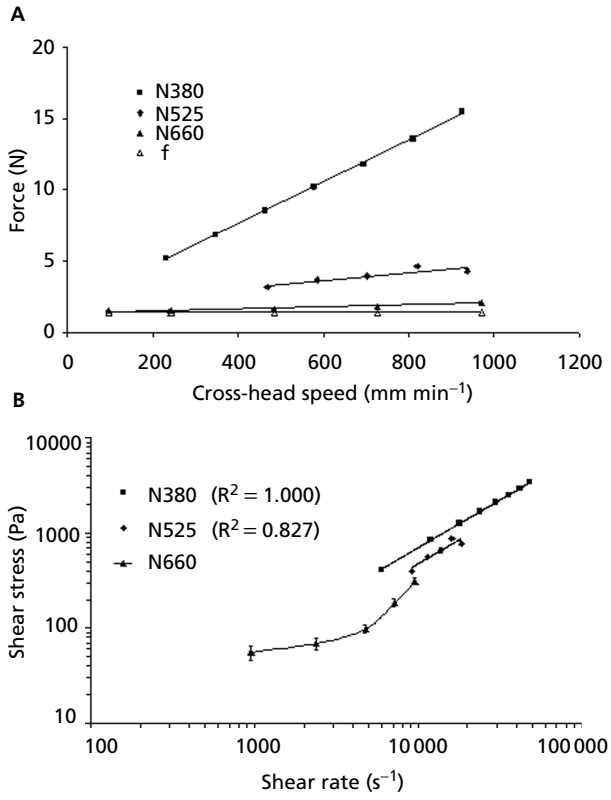

Figure 4 Measurements for B50 at 25°C using a 1 mL Luer lock syringe and N380, N525 and N660 capillaries. (A) Force–speed plots showing the wall frictional force (f); (B) shear stress–shear rate plots.

$$\frac{(F - f)D}{4AL} = \eta \frac{32AS}{60000\pi D^3} \quad (4)$$

Since $128A^2/60000\pi$ is constant and can be represented as K, the frictional force can be expressed as:

$$F = \eta K\left(\frac{L}{D^4}\right) S + f \quad (5)$$

The Wall frictional force can be estimated from the intercept of the regression between F and S using regression analysis. Wall frictional forces were determined in this manner for all rheograms in this study.

Influence of micro-capillary diameter

According to previously described micro-capillary equations, an increase in the micro-capillary diameter reduces the measured force. This effect was seen with all Newtonian standards when the viscosities were measured using the 1 mL Luer lock syringe and the following three capillaries: N380, N525 and N660. A typical decrease in force with increasing capillary diameter is seen in Figure 4A for the B50 Newtonian standard. Frictional forces, estimated from the intercept of the regression between force and speed, were 1.4 N, 1.8 N and 2.1 N for the N380 micro-capillary, 1.3 N, 2.1 N and 3.1 N for the N525 micro-capillary and 1.2 N, 1.4 N and 2.2 N for the N660 micro-capillary for the B100, B50 and B10 standards, respectively. These wall frictional forces were used to calculate net forces, and shear stress vs shear rate rheograms were constructed for the data in Figure 4A. Shear stresses vs shear rate regression for the smallest diameter micro-capillary (N380) showed excellent linearity with a regression coefficient of 1.0 (Figure 4B). The regression of shear stress vs shear rate for the N525 micro-capillary showed increasing deviation and there was clearly a non-linear relationship for the N660 micro-capillary.

As the force values decrease, the calculation of the net force and shear stress is subject to increasing error as the diameter of the micro-capillary increases due to the measured force approaching the value of the wall frictional force. Even when the wall frictional force is estimated from the data using linear regression, errors associated with force measurement in general will result in shear stress error and non-linearity of the shear stress vs shear rate rheograms.

Influence of syringe diameter

The influence of syringe diameter was evaluated for the three Newtonian oils B100, B50 and B10 with the 2.5 mL Luer lock syringe with the three capillaries N380, N525 and N660. Plots of force vs cross-head speed are shown in Figure 5A for the N525 micro-capillary. The difference in the magnitude of the force measured by the 2.5 and 1.0 mL syringes is clearly seen for the three Newtonian standards consistent with the micro-capillary expression in equation 4. Wall frictional forces, derived from the force–speed regressions of the 2.5 mL syringe, were greater than those estimated from the force–speed regressions for the experiment conducted using the Luer lock (1 mL) syringe as may be expected from the proportionality with plunger circumference. Wall frictional forces were in the range of 1.9 to 4.3 N. Shear stresses were calculated from the net force and the resulting rheograms are shown in Figure 5B. For the B100, the rheograms calculated from the data of the two syringes superimpose very closely for the higher viscosity B100 fluid. The greater shear rate range covered by the 2.5 mL syringe is also evident. The lower viscosity B50 fluid showed both a lower superimposition and a lower linear fit for the 1 mL syringe compared to the 2.5 mL syringe (i.e. R^2 was 0.827 in comparison with 1.000) due to the force values approaching the corresponding wall frictional forces for the 1 mL syringe. The rheograms for the two syringes with the B50 standard almost superimposed. The rheogram for the B10 standard using the 1 mL syringe was not produced since the measured force and wall frictional forces were comparable. The use of the larger-diameter syringe (2.5 mL) allowed a linear rheogram to be constructed with $R^2 = 0.973$ (Figure 5B).

Influence of micro-capillary length and end effect

To investigate the end effects on the measurements of the larger capillary diameters, B100 and B10 were measured

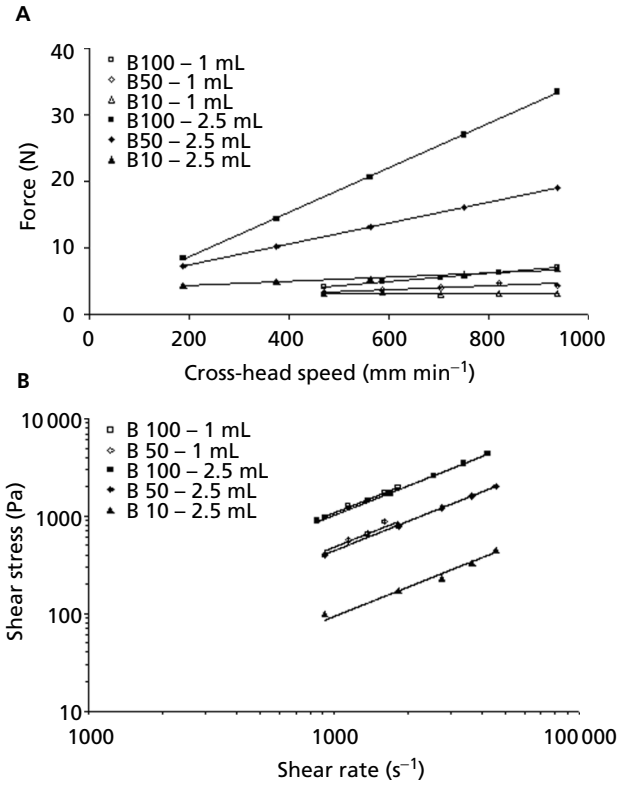

Figure 5 Force–speed (A) and shear stress–shear rate (B) for B100, B50 and B10 at 25°C using the N525 capillary using the 2.5 mL Luer lock syringe (closed symbols) and the 1 mL Luer lock syringe (open symbols).

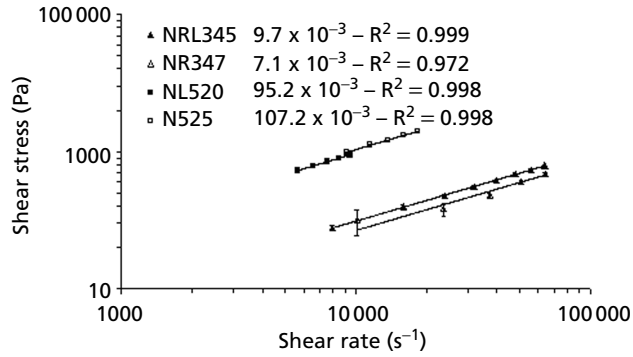

Figure 6 Stress–shear rate plots for B100 using the 1 mL Luer lock syringe and the NL520 (L = 36.5 mm) and N525 (L = 22.9 mm) micro-capillaries and for B10 using the 1 mL removable-needle syringe and the NRL345 (L = 65.0 mm) and NR347 (L = 22.9 mm) micro-capillaries (measured at 25°C).

using two micro-capillaries with almost the same internal diameter but different lengths. NL520 and N525 micro-capillaries were attached to the Luer lock (1 mL) syringe and used to measure the viscosity of B100 while the NRL345 and NR347 micro-capillaries were attached to the removable-needle (1 mL) syringe and used to measure B10 standard fluid. Force measurements were collected for the B100 and B10 fluid at five speeds. The estimated frictional forces for B100 were determined to be 0.6 and 1.3 N for the NL520 and N525 micro-capillaries, respectively, while they were 2.5 and 2.0 N for the NRL345 and NR347 micro-capillaries, respectively. Force–speed regressions were valid with good linearity ($R^2 > 0.972$) for all measurements. Shear stresses were plotted against shear rates and resulted in linear regressions with $R^2 > 0.972$ for the two fluids using both micro-capillaries. However, the error bars for B10 using the shorter micro-capillary NR347 indicated less reproducibility (Figure 6). The viscosity values for B100 from the shear stress rate regressions were 95.2×10^{-3} and 107.2×10^{-3} Pa.s using the NL520 and N525 micro-capillaries, respectively, while for B10 they were 9.7×10^{-3} and 7.1×10^{-3} Pa.s using the NRL345 and the NR347 micro-capillaries, respectively. Viscosity values for the longer micro-capillaries were very close to the actual values, while the measurements using the shorter micro-capillaries led to inaccurate results.

It has been suggested that the L/D ratio must be large to avoid the entrance and exit effects known as end effects in the capillary rheometer (Carreau et al 1997). Bagley (1957) developed a method of correction for this error based on the following expression for the corrected shear stress:

$$\tau_w = \frac{\Delta P D}{4(L + e_0 D)} \quad (6)$$

in which the parameter e_0 is determined by constructing curves of ΔP vs L/D at constant shear rates. Straight lines are obtained, and the values of e_0 are determined by extrapolation to zero pressure (Carreau et al 1997). It has also been suggested that if L/D > 50, the Bagley or end correction is small and can be neglected (Boger & Binnington 1977; Barnes et al 1989). Subsequently, a study of the significance of end effects on the viscosity of cellulosic and polymeric samples concluded that if the L/D ratio was >30, then end effects were negligible (Watson & Miller 1996). Tsao et al (1993) found that end effects were less than 7% when the rheology of silicon powder/silicon carbide formulations were evaluated with a conventional Instron capillary rheometer with an L/D ratio > 20.

In our experiment, the L/D ratios were 60 using the N380 capillary, 43.6 using the N525 capillary and 34.7 using the N660 capillary, and, since the L/D ratio was >30, the end effect was not investigated further.

Applications of the micro-capillary rheometer

To evaluate the micro-capillary rheometer, the rheological behaviour of two commercial parenteral formulations, Celestone Chronodose suspension and Propofol emulsion, was measured using the 2.5 mL removable-needle syringe and the NR347 micro-capillary. In contrast to the Newtonian standards, the wall frictional forces for the two parenteral formulations decreased with decreasing speed and therefore could not be estimated analytically from

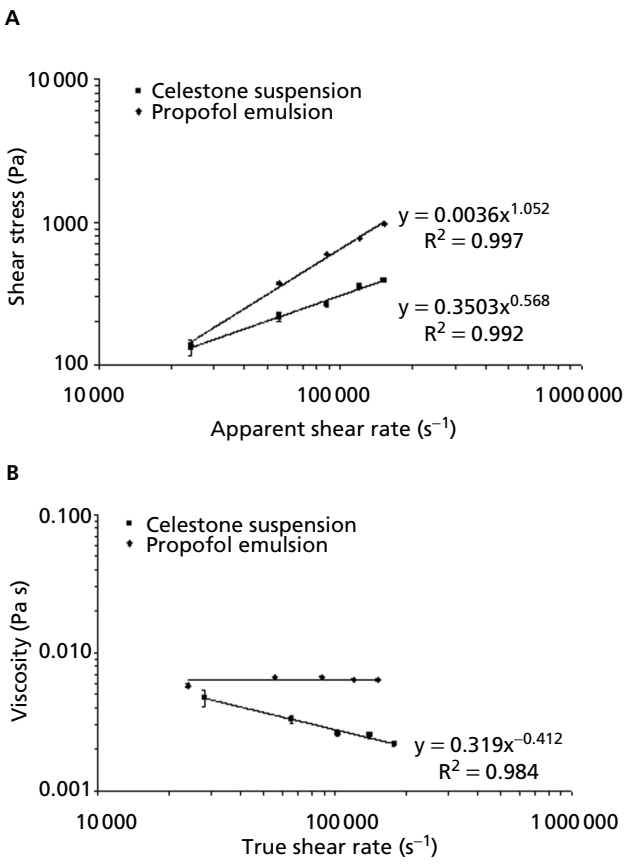

Figure 7 Measurements of Celestone suspension and Propofol emulsion at 25°C using the 2.5 mL removable-needle syringe and the NR347 capillary. (A) Force–speed and (B) viscosity–shear rate.

the force–speed data ($P < 0.001$, Student–Newman–Keuls method). Over the cross-head speed range of 150 to 950 mm min^{-1}, the measured wall frictional forces ranged from 4.7 ± 0.1 to 8.2 ± 0.1 N for the Celestone Chronodose suspension and from 2.1 ± 0.1 to 3.5 ± 0.1 N for the Propofol emulsion. The net force was obtained by subtracting the measured wall frictional force (f) from the total force (F) for each sample at each speed.

For both the Celestone Chronodose suspension and the Propofol emulsion, the relationship between the net forces and speeds was linear with $R^2 > 0.98$. Shear stresses were plotted against the apparent shear rate and corresponded to power-law behaviour with $R^2 > 0.992$ (Figure 7A). Newtonian fluids having shear stress independent of shear rate have a power-law index of $n = 1$. If $n < 1$, then a shear thinning or pseudo plastic behaviour is observed, and if $n > 1$, a dilatant or shear thickening behaviour can be observed. The flow index values (n) for Celestone Chronodose suspension and Propofol emulsion were 0.588 and 1.052, respectively. The Propofol emulsion, which has an n value very close to 1, indicates its behaviour as a Newtonian fluid with a viscosity of 6.6×10^{-3} Pa.s (Figure 7B). Since the flow index value of Celestone Chronodose suspension was less than 1, shear thinning behaviour occurred and a true shear rate range of 2.77×10^4 to 17.56×10^4 s^{-1} was calculated according to equation 3. The viscosity vs true shear rate was plotted for Celestone Chronodose suspension (Figure 7B). The viscosities of Celestone Chronodose suspension decreased from $4.8 \pm 0.6 \times 10^{-3}$ Pa.s at the lowest shear rate to $2.2 \pm 0.1 \times 10^{-3}$ Pa.s at the highest shear rates.

It is common to observe a Newtonian shear viscosity plateau at high shear rates, but this was not observed in the rheological behaviour of Celestone Chronodose suspension when examined in these micro-capillaries of clinical diameters and lengths even though the error bars of the replicates in this high shear rate region were very small, indicating good reproducibility. The injection speed range of 150 to 950 mm min^{-1} selected for these experiments was consistent with the practical clinical injection rate range of 1 mL in 5 to 30 s (Scarfone et al 1998). Quantitative data on the rheological parameters such as flow type, viscosity and applied force can be used to optimize the formulation variables in parenteral dose-forms, including drug particle size and distribution, particle stabilization mechanism and liquid vehicle rheology.

Conclusion

A micro-capillary rheometer consisting of a syringe–micro-capillary system and connected to an Instron instrument was developed and validated, initially with three standard Newtonian liquids of various viscosities and then with two commercial parenteral formulations that were shown to behave as Newtonian and non-Newtonian fluids. In contrast to conventional rotational viscometers, the methodology can be used to evaluate the injectability of parenteral formulations over a clinically significant shear rate range. The methodology is flexible since the micro-capillary rheometer system can be easily customized to suit a range of formulations by appropriate selection of micro-capillary diameter, syringe cross-sectional area and micro-capillary length to maximize measured force. The methodology can be used to evaluate parenteral formulations during development, providing information to help in excipient and drug property selection and optimization. Although many conventional capillary viscometers use an applied gas pressure to drive the fluid and thereby remove the plunger wall frictional component (Cogswell 1981), the syringe plunger configuration was maintained here and both the total force and the wall frictional force component were quantified since these are important aspects of clinical injectability. To determine the wall frictional force of the plunger in order to calculate the net force required to expel the liquid formulation, two approaches were evaluated. Estimation of the wall frictional force from the force/cross-head speed plots (eqn 5) using linear regression analysis proved superior to direct measurement using a syringe barrel wetted with fluid but without attachment of the capillary for Newtonian standards, but not for the two clinical formulations. The appropriate shear rate range is limited by the decrease in force that occurs at lower cross-head speeds and shear rates (below about 10×10^3 s^{-1}) if clinically significant capillary diameters and lengths are to be used. This shear rate range can be extended through smaller diameters

and longer length micro-capillaries, and syringes with larger cross-sectional areas to increase the measured force for more fundamental studies on flow characteristics. As noted above, the micro-capillary rheometer provided a very high degree of reproducibility across the five replicates and a high degree of fit ($R^2 > 0.99$) for linear flow behaviour. When the wall frictional force approached the total applied force (e.g. low viscosity fluids with large capillary diameters, low shear rates or short capillaries), the accuracy of the measurements fell, decreasing both the degree of reproducibility and the goodness of fit of the data (R^2) to linear flow behaviour models.

Two selected commercial pharmaceutical formulations, an emulsion preparation and an aqueous suspension were evaluated in the micro-capillary rheometer. Linear flow models of the Newtonian and non-Newtonian behaviour showed a high degree of fit (R^2), enabling confidence in identifying their rheological behaviour under clinical flow conditions. While the aqueous suspension showed shear thinning following a power-law model behaviour, the parenteral emulsion showed Newtonian behaviour over all shear rates studied.

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