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Flow and injection characteristics of pharmaceutical parenteral formulations using a micro-capillary rheometer

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Abstract

A micro-capillary rheometer consisted of a fine needle with an internal diameter of 347 μm attached to a 1 ml removable-needle syringe within an Instron device that operated in compression mode to provide various crosshead speeds ranging from 150 to 950 mm min^{-1} covering typical clinical injection rates, and that determined the resulting force on the plunger. The crosshead speed and the resulting force were used to calculate the shear rate and the shear stress respectively. These were used in standard capillary flow expressions together with an independent measurement of the wall frictional force and allowed the viscosity of parenteral Newtonian solutions and non-Newtonian suspensions to be measured quantitatively and their rheological behaviour in needles of clinical dimensions to be established. Commercial pharmaceutical parenteral formulations consisting of three oil-based solutions and three aqueous suspensions were chosen for this study. The net injection forces were also obtained and it was shown that both the oil-based solutions and the aqueous suspensions covered similar ranges. The viscosities for the parenteral solutions were determined from the slope of the linear regression ($R^2 > 0.97$) between shear stress and shear rate and ranged between 0.029 and 0.060 Pa s. For the aqueous suspensions examined, viscosities decreased from low shear rate to high shear rate, following a power-law model and indicating a pseudo plastic behaviour. Standardisation of the micro-capillary rheometer with Newtonian silicone oils calibrated with a Rheometrics Fluids Spectrometer showed viscosity values consistent between the rotational flow measurements and capillary flow measurements which were within 5% and showed very high degrees of reproducibility between replicate samples. This degree of reproducibility allowed differences in the contribution of the wall frictional force to the required plunger force for both the oil-based and aqueous parenteral formulations to be determined reliably. The wall frictional force values for all formulations were similar (0.6–1.6 N) but the frictional forces of aqueous systems were found to decline significantly with plunger speed. The micro-capillary rheometer has been used to evaluate the impact of concentration changes due to sedimentation on the injectability of one of the aqueous suspensions, where it was shown that not only the viscosity increased but the shear thinning behaviour ceased at higher shear rates. The micro-capillary rheometer which was able to operate in clinical shear rate ranges has been shown to detect deteriorations in the injectable rheology of suspensions, which in the case here was due to pre-injection sedimentation.

Keywords: Capillary rheometer; Injection characteristics; Parenteral; Viscosity; Shear thinning

1. Introduction

Pharmaceutical parenteral formulations can be classified into aqueous or oil-based solutions, emulsions

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and suspensions and are delivered in different ways including intravenous, intramuscular, intradermal, intralesional, intraarticular and subcutaneous injections (Chien, 1992). For injectable suspensions in particular, since they are thermodynamically unstable systems, physical stability becomes as important as chemical and biological stability. In addition, injectable suspensions require evaluation of their characteristics in the syringe (syringeability) and during injection (injectability), as well as the effectiveness of their isotonicity, sterility and preservation (Floyd and Jain, 1996). From a clinical viewpoint, behaviour in the syringe describes the ability to pass easily through a hypodermic needle from the vial prior to injection. It includes characteristics such as the ease of withdrawal, clogging and foaming tendencies and accuracy of dose measurements (Floyd and Jain, 1996). Important aspects of the behaviour during injection include factors such as pressure or force required during injection, evenness of flow, aspiration qualities and freedom from clogging (Akers et al., 1987). These characteristics of parenteral suspensions in the syringe and during injection are closely related to the viscosity and particle characteristics of the suspension (Akers et al., 1987). Poor responses of formulations result from an increase in the following factors: the viscosity and density of the vehicle, the size of the suspended material and the concentration of the suspended drug. Probably the most important of these factors are those that relate to viscous flow (Floyd and Jain, 1996). Most methods used for the evaluation of these phenomena are qualitative in nature. Simple ejection of the suspension into an open container, performed very slowly with intermittent application of pressure to the plunger, has provided useful information about the injection characteristics of such suspensions. Force measurements from a materials testing device such as an Instron have been reported by Floyd and Jain (1996). Ritschel and Suzuki (1979) developed a new instrument to assess the injection characteristics of parenteral materials by measuring the time required to smoothly inject a solution or suspension into a meat sample under specified pressure. Regression equations were obtained for different types of syringes and needle size when a test formulation was injected. These equations permit the calculation of the expected injection time for a given syringe-needle system and for a given vehicle of a certain viscosity (Ritschel and Suzuki, 1979). As such Ritschel and Suzuki introduced the idea of using the syringe-needle system as a viscometer, using viscometric equations to predict the injection flow time.

Here we apply a syringe-needle system with an Instron instrument to provide an evaluation of injection characteristics of commercial parenteral formulations. The aim of this research was to configure the force measuring Instron in conjunction with the syringe-needle assembly to provide a micro-capillary rheometer capable of quantitatively evaluating the rheological characteristics and forces needed to inject parenteral products within a range of clinical shear rates and conditions.

2. Materials and methods

2.1. Materials

The commercial oil-based solutions used were Fluphenazine decanoate® (10%; F H Faulding & Co., Australia), Haldol decanoate® (5%; Janssen-Cilag Pty Ltd., Australia) and Fluanxol concentrated® (10% from H. Lundbeck, Denmark). The following aqueous suspensions were used, Cilicaine® aqueous suspension (44%; Sigma Pharmaceuticals Pty Ltd., Australia), Depo-Ralovera® (15%) and Depo-Provera® (5%) (Pharmacia & Upjohn Pty Ltd., Australia). The formulations of the vehicles in the aqueous suspensions were obtained from the supplier and were as follows: Cilicaine® aqueous suspension vehicle contained: 86 mg sodium citrate, 33 mg polysorbate 80 and sufficient water to achieve a volume of 3.4 ml. Depo-Ralovera® vehicle contained: 28.5 mg macrogol 4000, 2.4 mg polysorbate 80, 8.6 mg sodium chloride, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and sufficient water to complete a volume of 1 ml. Depo-Provera® vehicle contained: 28.8 mg macrogol 4000, 1.9 mg polysorbate 80, 8.6 mg sodium chloride, 1.3 mg methyl hydroxybenzoate, 0.14 mg propyl hydroxybenzoate and sufficient water to achieve a volume of 1 ml. Materials used in the preparation of these vehicles were laboratory and analytical grade. Three silicon oils: Brookfield 100, 50 and 10 cP from (Brookfield, USA) were used as Newtonian liquid standards to validate the micro-capillary rheometer.

2.2. Micro-capillary rheometer development and validation

The micro-capillary rheometer consisted of a fine stainless steel needle, either 22.9 or 64 mm in length, depending on the force range examined, with an internal diameter of 347 μm which was attached to a 1 ml syringe (removable-needle gas tight syringe from SGE, Australia) and rigidly contained and vertically aligned in an aluminium holder which also had small electrical cartridge heaters controlled at 25 °C by a Eurotherm 2116 controller (Eurotherm Controls, UK). The micro-capillary rheometer was attached to an Instron 4465 (Instron, USA) to drive the syringe plunger, using a 100 N load cell, at the following five crosshead speeds: 150, 350, 550, 750 and 950 mm min^{-1} and consequently measured the resulting force on the plunger in the instrument's compression mode as input to the Hagen-Poiseuille capillary flow expression. The Instron was set to capture data at different crosshead speeds (shear rates) to produce 30–40 points at each measurement and to travel a total distance of 4.8 cm, which is equivalent to a volumetric displacement of 0.8 ml within the syringe. The micro-capillary rheometer was validated using standard oils that were characterized first in a rotational viscometer, Rheometrics RFS II Fluid Spectrometer (Rheometric Scientific, USA).

2.3. Force speed measurements

Three fresh samples were measured for each of the solutions and suspensions at each crosshead speed. Each sample was maintained in a water bath at 25 °C prior to use, stirred consistently for the same duration and transferred into the syringe using a large 18 gauge needle, and measured immediately to ensure that sedimentation did not occur. An average of the data, with standard deviation, was calculated for all samples from the same solution or suspension. The concentration of Depo-Ralovera® suspension was increased by allowing the suspension to sediment, after which a portion of the supernatant liquid was removed. Two concentrations were selected to evaluate the concentration dependence. The flow characteristics of the new concentrated suspensions were compared to the rheological behaviour of the original concentration of Depo-Ralovera® suspension (15% w/v) using the micro-capillary rheometer.

The wall frictional forces (f) for non-Newtonian samples, i.e. the aqueous suspensions, were determined by preparing a 10-ml sample for each vehicle of the suspensions and then used to determine the force at each crosshead speed needed to compress the syringe, without the needle, but wetted with the vehicle used in the preparation of the suspension. Ideally, the syringe should be wetted with the suspension not with the vehicle; however, significant variability resulted due to the inherent partial drying of the suspended particles on the walls of the syringe. The frictional force (f) was subtracted from the force needed to inject the aqueous suspension (F) at each crosshead speed. For the Newtonian standards, the frictional force (f) was determined from the intercept of the regression between shear stress and shear rate.

2.4. Calculation of viscosity using the micro-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 $\dot{\gamma}_{app}$ is the apparent shear rate, τ_w 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, D and L are the internal diameter and length of the capillary.

For Newtonian oils and solutions, the wall frictional force (f) can be derived from Eq. (1) for capillary rheometer considering that:

$$\text{Shear stress}\ (\tau) = \frac{(F-f)D}{4AL} \quad \text{since}\ \Delta P = \frac{F-f}{A},$$

and

$$\text{Shear rate}\ \dot{\gamma}_{app} = \frac{32AS}{60\,000\pi D^3}$$

$$\text{since}\ Q = \frac{V}{t} = \frac{AS}{60\,000},$$

where F is the force needed to inject the fluid, V is the volume of the liquid flowing in time t, and in terms of the cross sectional area of the syringe A in m^2, diameter of syringe reservoir D in mm, and cross head

speed S in mm min^{-1}, as a result, the general equation of viscosity in the micro-capillary rheometer can be rewritten as:

$$\frac{(F-f)D}{4AL} = \eta \frac{32AS}{60\,000\pi D^3} \quad (2)$$

Since $128A^2/60\,000\pi$ are constants and can be represented as K, the frictional force can be measured from the intercept of the regression between F and S according to the following expression:

$$F = \eta K \left(\frac{L}{D^4}\right) S + f \quad (3)$$

In order to correct for the apparent shear rates measured for aqueous suspensions, which tend to show non-Newtonian behaviour, the power-law model was applied:

$$\eta = K_2 \dot{\gamma}_{\text{true}}^{n-1} \quad (4)$$

where K_2 is the consistency constant and n is the power-law index, $\dot{\gamma}_{\text{true}}$ is the actual shear rate and not the apparent shear rate $\dot{\gamma}_{\text{app}}$. According to the Rabinowitsch procedure (Carreau et al., 1997), $\dot{\gamma}_{\text{true}}$ is determined according to the following expression:

$$\dot{\gamma}_{\text{true}} = \dot{\gamma}_{\text{app}} \frac{3n' + 1}{4n'} \quad (5)$$

where n' is a constant equal to the power-law index (n) as determined from the slope of $\log t_w$ versus $\log \dot{\gamma}_{\text{app}}$ (Barnes et al., 1989; Nair et al., 2000).

2.5. Statistical analysis of data

When comparison of two sets of data was required, two-way ANOVA with the Student–Newman–Keuls test (SNK test) was applied using SigmaStat version 2.0. Linear regression was undertaken using the same software (SigmaStat version 2.0).

3. Results

3.1. Micro-capillary rheometer development and validation

The micro-capillary rheometer has been developed and validated using the standard Newtonian oils as shown in Fig. 1. In the micro-capillary rheometer these standards demonstrated Newtonian behaviour over a broad shear rate range relevant to the injection process. The frictional forces (f) for these measurements were estimated from the intercept of the force-speed regressions. The measured viscosity values were found to

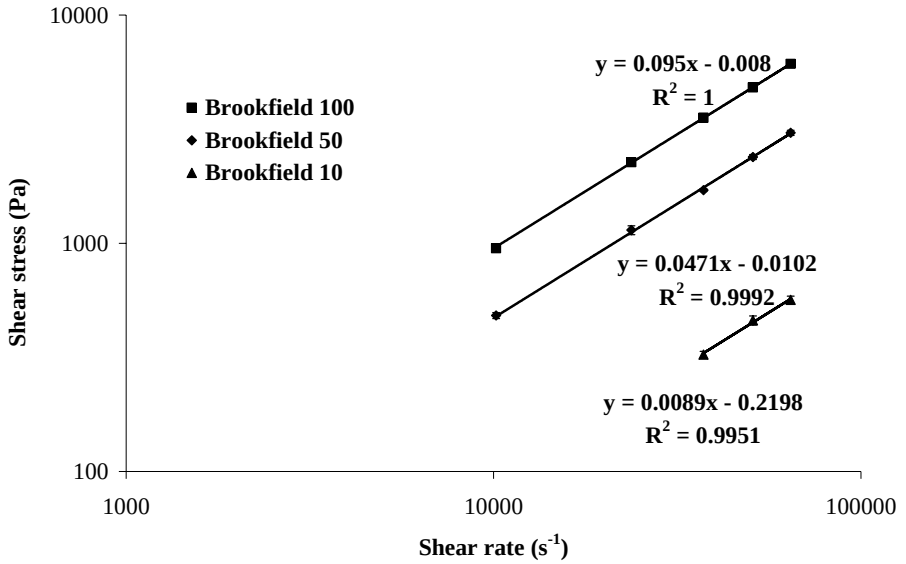

Fig. 1. Shear stress–shear rate rheograms of the three Newtonian standards measured using the micro-capillary rheometer at 25 °C with error bars showing standard deviations.

Table 1
Comparison between viscosity values measured in the Rheometrics RFS II viscometer and those measured in the micro-capillary rheometer for Brookfield 100, 50 and 10 cP at 25 °C

Standard oil	Viscosity ($\times 10^{-3}$ Pa s)	
	Using the Rheometrics viscometer	Using the micro-capillary rheometer
Brookfield 100 cP	94.6	95.0
Brookfield 50 cP	46.4	47.1
Brookfield 10 cP	9.3	8.9

be consistent with the viscosity values of these standards as measured with the RFS II rheometer within less than a 4% variation (Table 1). Fig. 1 provides the data with the error bars for five replicates for each data point. It can be seen that the degree of reproducibility of the micro-capillary rheometer arrangement is extremely high with consideration that the lowest two points were eliminated for B 10 because the force measured (F) was small and interfering with the frictional force (f).

3.2. Force-speed measurements

The forces needed to inject the oil-based solutions and the aqueous suspensions were measured at the specified crosshead speeds using the micro-capillary rheometer (Tables 2 and 3). The wall frictional forces were determined from the intercepts of the regression analysis of force versus speed for the three oil-based solutions and were 1.4 ± 0.1 N for Fluphenazine decanoate®, 1.0 ± 0.1 N for Haldol decanoate® and 1.2 ± 0.1 N for Fluanxol concentrated®. The wall frictional forces for the three aqueous suspensions were found to decrease with speed. For the speed range of 950–150 mm min^{-1}, the wall frictional forces were measured as follows: for Cilicaine® aqueous suspension; 1.6 ± 0.1 N decreasing to 0.9 ± 0.1 N, for Depo-Ralovera®; 1.1 ± 0.1 N decreasing to 0.6 ± 0.1 N and for Depo-Provera®; 1.1 ± 0.1 N decreasing to 0.8 ± 0.1 N. Here, with the suspensions, the wall frictional force (f) was subtracted from the total force (F) for each sample.

Net force was determined, where the net force is the force needed to inject the fluid after subtracting the frictional force. In both the oil-based solutions and the aqueous suspensions, the relationship between the net forces and speeds was linear ($R^2 > 0.98$). Net forces for the oil-based solutions were found to be in the range of 2.8 ± 0.1 N to 17.1 ± 0.1 N for Fluphenazine decanoate®, 2.7 ± 0.1 N to 16.2 ± 0.2 N for Haldol decanoate® and 1.3 ± 0.1 N to 8.2 ± 0.1 N for Fluanxol concentrated®. For the aqueous suspensions, the net force ranges were as follows: 6.7 ± 0.1 N to 16.3 ± 0.9 N for Cilicaine® aqueous suspension, 1.4 ± 0.2 N to 3.8 ± 0.2 N for Depo-Ralovera® and 0.7 ± 0.1 N to 3.2 ± 0.2 N for Depo-Provera®.

3.3. Flow characteristics of oil-based solutions

Over a shear rate of (10,159–64,342 s^{-1}), shear stress values for the three oil-based solutions ranged from 307 to 3874 Pa. Shear stress versus shear rate for each of the three oil-based solutions was plotted on a logarithm scale as shown in Fig. 2(A) and shown to fit a power-law model with $R^2 > 0.97$. The power-law indices for the three rheograms were 0.98 for Fluphenazine decanoate®, 0.97 for Haldol decanoate® and 0.98 for Fluanxol concentrated® indicating a near ideal Newtonian behaviour with n approaching 1. From the regressions of shear stress

Table 2
Force-speed data for the three oil-based solutions measured at 25 °C using the 1 ml removable needle syringe and a needle with internal diameter of 347 mm

Speed (mm min^{-1})	Fluphenazine decanoate®		Hadol decanoate®		Fluanxol concentrated®	
	F (N)	S.D. (N)	F (N)	S.D. (N)	F (N)	S.D. (N)
950	18.5	0.2	17.2	0.2	9.4	0.1
750	14.7	0.1	13.6	0.2	7.6	0.1
550	11.2	0.3	10.2	0.1	5.8	0.1
350	7.6	0.1	6.8	0.1	4.2	0.1
150	4.2	0.1	3.7	0.1	2.5	0.1

S.D. is the standard deviation for five replicates of the force measured in Newton.

Table 3
Force–speed data for the three aqueous suspensions measured at 25 °C using the 1 ml removable needle syringe and a needle with internal diameter of 347 mm

Speed (mm min^{-1})	Cilicaine®		Depo-Ralovera®		Depo-Provera®	
	F (N)	S.D. (N)	*F* (N)	S.D. (N)	*F* (N)	S.D. (N)
950	17.9	0.9	4.9	0.2	4.3	0.2
750	15.5	0.2	4.5	0.0	3.3	0.2
550	13.4	0.3	3.9	0.2	2.7	0.0
350	11.3	0.6	2.6	0.2	2.1	0.0
150	7.6	0.1	2.0	0.2	1.5	0.1

S.D. is the standard deviation for five replicates of the force measured in Newton.

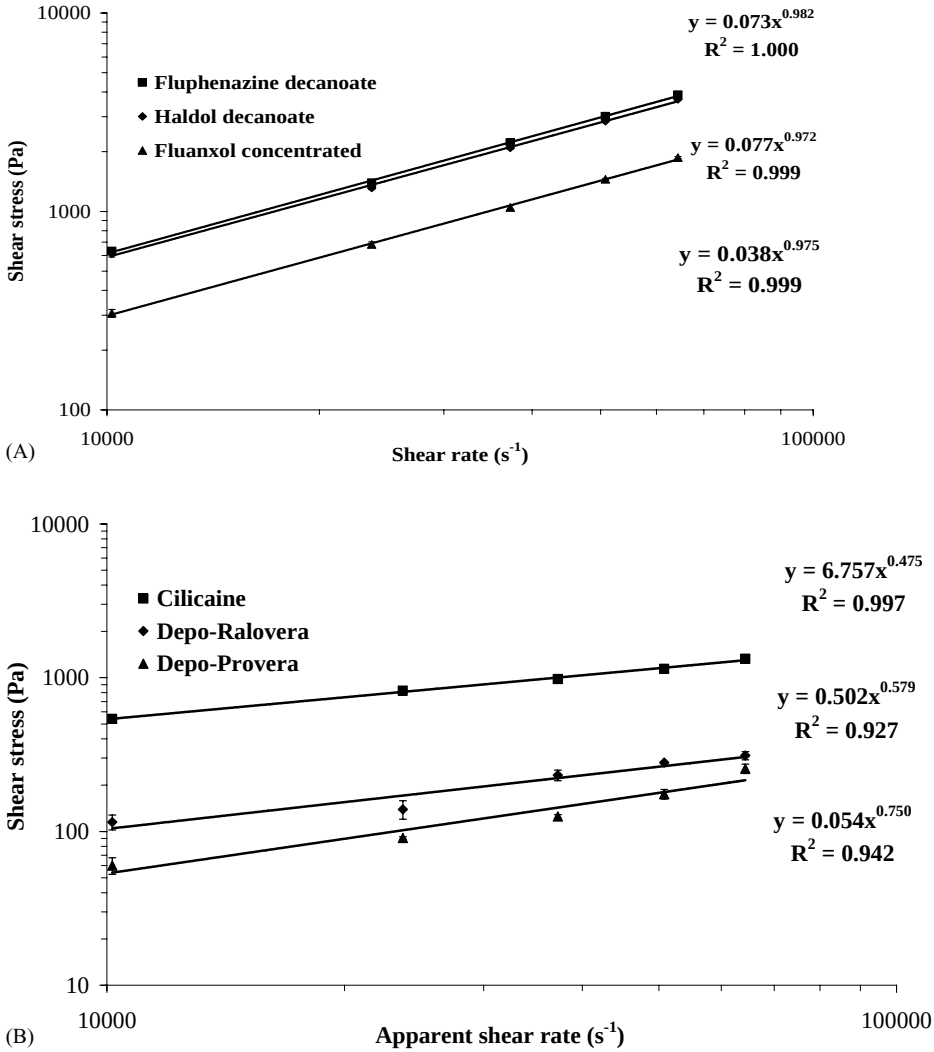

Fig. 2. Shear stress–shear rate rheograms for (A) oil-based parenteral solutions and (B) aqueous parenteral suspensions measured using the micro-capillary rheometer at 25 °C with error bars showing standard deviations.

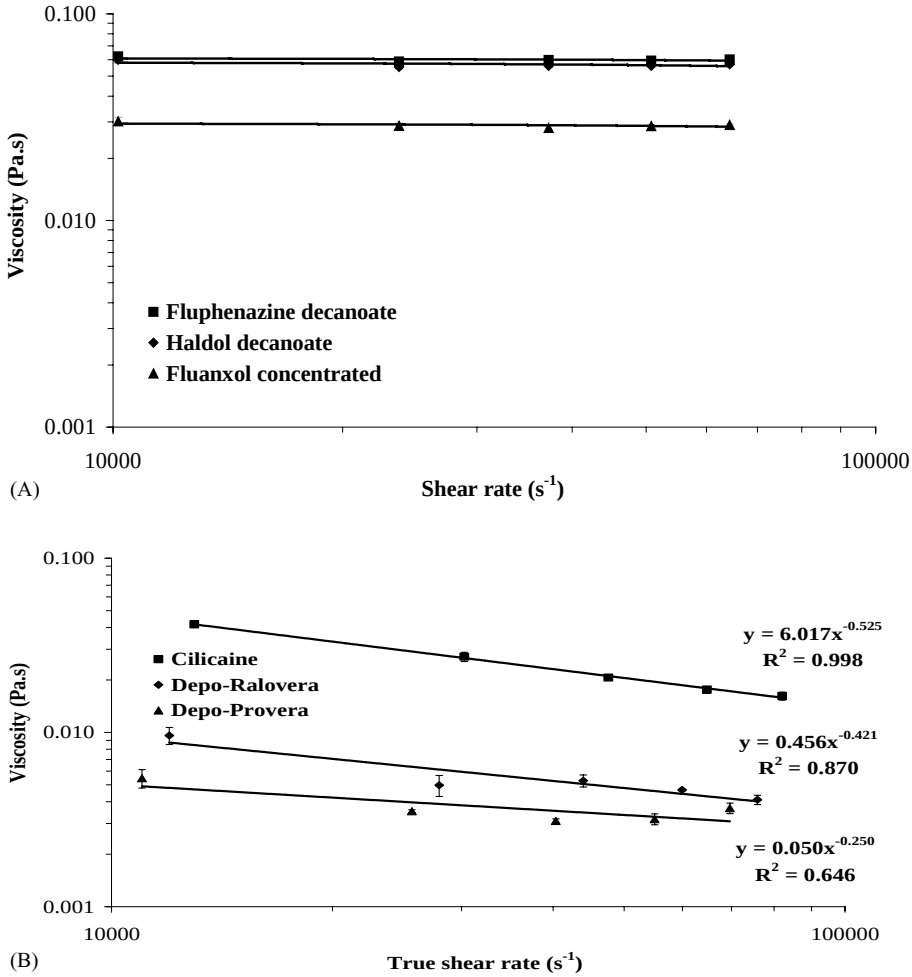

Fig. 3. Viscosity–shear rate rheograms for (A) oil-based parenteral solutions and (B) aqueous parenteral suspensions measured using the micro-capillary rheometer at 25 °C with error bars showing standard deviations.

versus shear rate for the three solutions, viscosity values (slopes of the regressions) ranged from 0.029 to 0.060 Pa s. These viscosities were plotted versus shear rate on a logarithm scale as given in Fig. 3(A).

3.4. Flow characteristics of the aqueous suspensions

Shear stresses were calculated from the force measurements for the aqueous suspensions and found to range from 60 to 1328 Pa. Shear stress for the three aqueous suspensions was plotted against apparent shear rate in a range of 10,159–64,342 s^{-1} on a log scale as given in Fig. 2(B) and shown to correspond to a power-law with $R^2 > 0.92$. The n values for the three rheograms were 0.48, 0.58 and 0.75 for Cilicaine®, Depo-Ralovera® and Depo-Provera® respectively indicating a shear thinning behaviour. Consequently, the true shear rate values were calculated and ranged from 12,978 to 82,128 s^{-1} for Cilicaine®, from 11,989 to 75,928 s^{-1} for Depo-Ralovera® and from 11,000 to 69,667 s^{-1} for Depo-Provera®. The viscosity versus true shear rate was plotted for the three aqueous suspensions on a log scale as shown in Fig. 3(B), where it can be seen to fit a power-law. The power-law indices (n) for viscosity—true shear rate plots were 0.48, 0.58 and 0.75 for Cilicaine®, Depo-Ralovera®

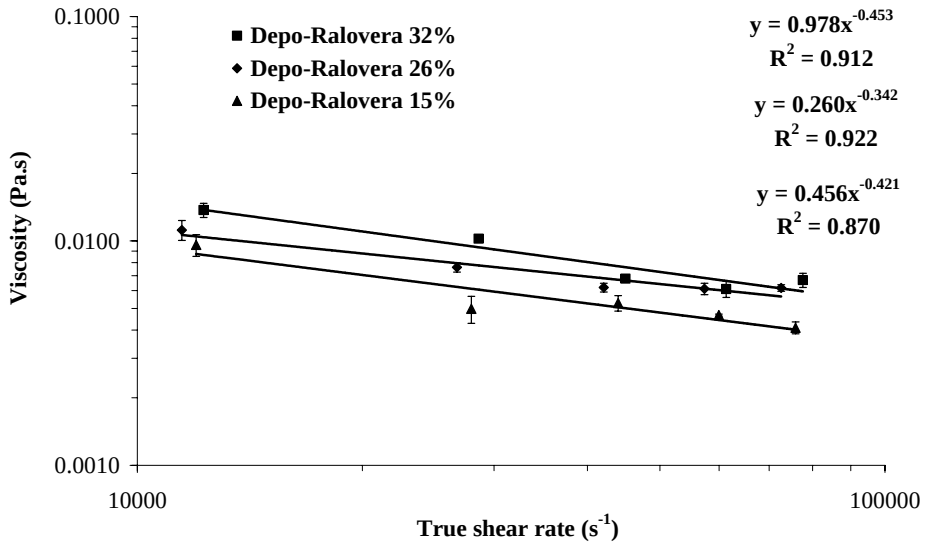

Fig. 4. Viscosity–shear rate rheograms for the three concentrations of Depo-Ralovera® suspension measured using the micro-capillary rheometer at 25 °C with error bars showing standard deviations.

and Depo-Provera® respectively (with a valid power-law regression of $R^2 > 0.87$ for Cilicaine® and Depo-Ralovera® but not for Depo-Provera® with $R^2 = 0.65$). The viscosities of Cilicaine® commenced with 0.042 ± 0.001 Pa s at the low shear rate and decreased to a value of 0.016 ± 0.001 Pa s at the highest shear rates and Depo-Ralovera® commenced with 0.010 ± 0.001 Pa s and decreased to 0.004 ± 0.001 Pa s while Depo-Provera® commenced with 0.005 ± 0.001 Pa s at the low shear rate, decreased to a value of 0.003 ± 0.001 Pa s and then increased slightly to 0.005 ± 0.001 Pa s at the highest shear rates.

3.5. Flow characteristics of a concentrated aqueous suspension

Sedimentation of the Depo-Ralovera® produced concentrations of 26 and 32% (w/v). Fresh homogeneous samples from these concentrations were evaluated in the micro-capillary rheometer at the same crosshead speeds as in Section 2.2. The net force ranged from 1.6 ± 0.2 N to 5.5 ± 0.2 N for the 26% suspension and from 2.1 ± 0.1 N to 6.4 ± 0.5 N for the 32% suspension. Shear stresses were calculated from the force measurements for the two suspensions and found to range from 128 to 519 Pa. Plotting the shear stress against the apparent shear rate for the two samples in the range 10,159–64,342 s^{-1} and applying the power-law model gave flow index values (n) of 0.66 and 0.55 for the 26 and the 32% concentrations, respectively ($R^2 > 0.91$). Consequently, the true shear rate values were corrected and ranged from 11,470 to 72,643 s^{-1} for the 26% suspension and from 12,262 to 77,661 s^{-1} for the 32% suspension. The viscosity versus true shear rate was then plotted for these samples and compared with the original (15%) Depo-Ralovera® suspension (Fig. 4), where it was seen to fit a power law. The viscosity of the 26% Depo-Ralovera® commenced with 0.011 ± 0.001 Pa s at the low shear rates and decreased to a value of 0.006 ± 0.001 Pa s at the highest shear rates and that for the 32% Depo-Provera® reduced from 0.014 ± 0.001 Pa s at the low shear rates to 0.007 ± 0.001 Pa s at the highest shear rates.

4. Discussion

Eq. (3) for Newtonian liquids indicates that the relation between the injecting forces for two Newtonian liquids will depend on their injecting speeds and vis-

cosities. Two approaches are possible in the use of the equation. First, if the injecting speed is constant, the injecting force ratio will be proportionally dependent on the viscosity ratio of the two Newtonian liquids. Second, when the injecting force for two Newtonian liquids is kept constant, the injecting speed will be proportionally dependent on the viscosity ratio for the two liquids. In the latter case, the time required for injection can be related to viscosity, because speed equals distance over time, and distance is constant. Thus, time required for injection is directly proportional with viscosity. The micro-capillary rheometer used in this study represents the first case while the methodology developed by Ritschel and Suzuki (1979) represents the second case.

Comparisons of the wall frictional forces for both oil-based and aqueous based samples were conducted by examining the Newtonian standard oil samples and the aqueous vehicle component of the suspensions at the different experimental speeds in a range corresponding to clinical injection speeds. These tests showed that there was no significant difference between the wall frictional forces measured at different speeds for the oil-based samples ($P = 0.757$), while there was a significant difference between the wall frictional forces measured for the three aqueous vehicles at different speeds ($P < 0.001$), with the vehicle for Depo-Ralovera® declining from 1.1 to 0.6 N over the speed range. Therefore, the methodology for calculating the flow behaviour of aqueous systems needs to account for this variation in wall frictional force.

The net force measurements indicated that the variability related to the oil-based solutions was less than that associated with aqueous suspensions, as shown by the standard deviations in the net force measurements. The net forces for injection of the commercial oil-based solutions ranged from about 1.3 to 17.1 N for the clinical injection speeds (shear rates) examined and were almost identical to the range found for the aqueous suspensions, which were from 0.7 to 16.3 N.

For non-Newtonian fluids shear stress depends on the applied shear rate, and hence an apparent shear rates and not an actual shear rates were measured. Therefore, in the simplest constitutive equation relating shear stress to shear rate these quantities are modelled according to a simple power-law, which when rewritten in terms of the viscosity becomes Eq. (4). As noted, Newtonian fluids having shear stress independent of shear rate have a power-law index $n = 1$, i.e. constant viscosity. These oil-based solutions had n values that were 0.98, 0.97 and 0.98 for Fluphenazine decanoate®, Haldol decanoate® and Fluanxol concentrated® respectively, which indicated that they were very close to Newtonian fluids. 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 n values for all these aqueous suspensions were found to be <1, which means that the three suspensions were shear thinning or pseudo plastic if they showed a yield point in the stress at very low shear rates and below which they would not flow. The highest n value was for the dilute aqueous suspension Depo-Provera®. This agrees with the expectation that highly diluted suspensions tend to approach Newtonian behaviour as the interactions between the particles of the suspension are reduced by dilution. At higher concentrations, their shear stress is no longer independent of shear rate due to increasing particle-particle interactions and they may adopt a shear thinning or pseudo plastic behaviour. Concentrated suspensions are expected to have the same shear thinning behaviour disrupted with a shear thickening interval. Barnes (1989) argues that all suspensions, whether they are dilute or concentrated, will experience this shear thickening interval. He suggests that the critical shear rate which represents the onset of this shear thickening for dilute suspensions will be too low for some rheometers to detect. The pharmaceutical aqueous suspensions examined here did not show a shear thickening interval within the clinical shear rate studied. This is probably because the shear rate range studied, from 1×10^4 to $7 \times 10^4\ s^{-1}$, was too high to detect it. In this micro-capillary rheometer, flow injection behaviour at very low shear rates cannot be examined because the measured applied force will be small and very close to the wall frictional force, and consequently the error will be significant.

Increasing the concentration of Depo-Ralovera® from 15 to 26% (w/v) concentration resulted in a progressive increase in the true viscosity in the lower shear rate range. In the high shear rate range, shear thinning of the samples ceased and a Newtonian plateau appeared with viscosities higher than those of the original commercial concentration.

The injection speed range chosen for the experiment was from 150 to 950 mm min^{-1} consistent with

the recommended clinical injection rate of 1 ml in 10 s (Dacre and Kopelman, 2002). This quantitative data on flow type, viscosity and applied force relate to the parameters for optimum intramuscular injection. The individual net force for flow can be used to assess new formulations and re-formulations for intramuscular injection and involve the effects of drug particle size, particle stabilisation mechanism and liquid vehicle rheology.

5. Conclusions

The micro-capillary rheometer was used to test the injectability of some commercial intramuscular injections, which are known for their good behaviour during injection. The data collected can be used to assess the injectability of any new parenteral formulation in a quantitative manner. Both the rheological behaviour and force measurements at different injection speeds can be used for this purpose. Concentration increases in the Depo-Ralovera® formulation resulting from sedimentation, was investigated. This was shown to produce a shear thinning behaviour similar to the original concentration but at higher viscosities in the low shear rate range and which ceased at higher shear rates above $45 \times 10^3\ s^{-1}$ to yield a Newtonian plateau with viscosities higher than the commercial formulations. Importantly the micro-capillary rheometer developed represents a device that resembles the actual geometry of needle and syringe assembly. It measures the rheological behaviour at very high shear rates, which include the clinical shear rates. The addition of an in vitro model for the human tissue resistance is envisaged to complete the model and to achieve better correlation between the in vitro and in vivo injectability.

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