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Rheological characterization of rbSt oil suspensions

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Abstract

The low shear rheology of numerous rbSt sustained release oil suspensions was studied in order to assess the impact of formulation variables on product characteristics. A Haake CV 100 was used to obtain rheograms of rbSt suspensions in a Miglyol 812/Tween 80 vehicle as a function of drug concentration, drug particle shape and Tween 80 concentration. Rheograms of active formulations revealed a drug-Tween-Miglyol complex which increased in structure as a function of Tween 80 concentration. However, corresponding placebo formulations failed to show any significant change in Miglyol rheology regardless of the Tween 80 concentration. The active formulations at 12.5% (w/v) rbSt showed increased deviation from Newtonian behavior as the Tween 80 concentration increased from 0 to 1.0% (w/v), but thixotropy was not apparent. Increasing the rbSt concentration to 24% (w/v) while keeping Tween 80 at 0.1% (w/v) caused slight thixotropy and a substantial deviation from Newtonian flow. The above tests were performed using a lot of spray-dried drug containing a high percentage of shattered particles. Further studies with a lot of spray-dried drug containing predominantly spherical particles showed similar rheology. Oil suspensions made from lyophilized drug exhibited Newtonian behavior and minimal viscosity. Photomicrographs of the suspensions made with spray-dried drug revealed a dense population of small particles consistent with a high degree of structural rheology while those of the lyophilized drug suspensions showed an open network of overlapping platelet structures consistent with the minimal viscosity observed.

Keywords: Rheology; Microscopy; Recombinant bovine somatotropin (rbSt); Somavubove; Parenteral oil suspensions; Syringeability; Particle morphology; Miglyol 812

1. Introduction

The physical/chemical forces influencing the properties of oil suspensions can be quite different from those of aqueous suspensions. Chief among these is the absence of electrical effects associated with the DLVO theory and the formation of boundary layers which have a stabilizing effect and prevent sedimentation of the particles in aqueous suspensions (Adamson, 1982; Falkiewicz, 1988). Without these electrical effects, the formulator must focus on other factors to produce a stable oil suspension. These factors include particle size, shape, concentration and wettability. Since these factors also determine the rheology of the suspension, rheological character-

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ization can be a valuable tool in evaluating formulation suitability.

Literature references of rheology studies on parenteral products are few and usually discuss aqueous suspensions such as penicillin (Ober et al., 1958; Boylan, 1965; Boylan and Robison, 1968). Sims and Worthington (1985) studied the effect of sterilization processes on the rheology of oleaginous suspensions gelled with aluminum monostearate and found that the addition of a model drug, micronized 5-fluorouracil, significantly reduced viscosity and thixotropy. In the present investigation, numerous rbSt oil suspensions have been examined to assess the influence of several formulation variables on product rheology and stability. These variables include the method of drying during manufacture of the drug, i.e., lyophilization vs two spray-drying techniques, as they influence particle size and shape, drug concentration and different surfactant concentrations. Rheograms were also used to evaluate the impact of drug particle shape on the characteristics of aged suspensions.

2. Materials and methods

2.1. Materials

The rbSt oil suspensions were prepared on a w/v basis in scintillation vials by adding the vehicle to bulk drug and homogenizing for less than 1 min with a Brinkmann homogenizer having probe generator PTA 20TS at a setting of 5–6. The vehicle consisted of a range of Tween 80 (0–1% w/v) dissolved in Miglyol 812. Lyophilized drug was prepared by bulk tray lyophilization in a Virtis Freeze Dryer Model 100-SRC-5 and was triturated using a Wedgewood mortar and pestle to reduce particle size. Spray-dried drug was prepared in a Bowen Spray Dryer Model BLSA using either a two fluid atomizer (BSD1) or a radial hole rotary atomizer (BSD5). A detailed discussion of the impact of spray-drying parameters on the physical characteristics of rbSt bulk drug has been presented by Foster and Leatherman (1994). Studies related to the effect of Tween 80 concentration and rbSt concentration on suspension rheology used spray-dried drug from BSD5.

2.2. Microscopy

Light microscopy photomicrographs were obtained with a Zeiss Universal microscope at 500 × magnification using transmitted light. Scanning electron microscopy was performed on a JEOL JSM-T300. A magnification of 350 × was used with the lyophilized drug while 750 × was used with spray-dried drug. Samples were prepared on aluminum stubs and sputter coated with gold at 12 Hv, 18–24 mA for 300 s on a Technics Hummer X. Scanning electron photomicrographs of lyophilized and spray-dried drug (BSD1 and BSD5) are presented in Fig. 1. Because of the spherical and shattered appearance of the particles, drug made using the two fluid atomizer (BSD1) and radial hole rotary atomizer (BSD5) will be referred to hereon, respectively, as spray-dried/spherical and spray-dried/shattered. Lyophilized drug appears as large, thin sheets while spray-dried drug appears as either spheres with blowholes or shattered aggregates. Note that the magnification of the lyophilized drug is nearly half that of the spray-dried drug. The role of this vast difference in size and shape of the drug will become apparent in the rheology of the suspensions.

2.3. Rheology

Rheograms were obtained on 5 ml samples at 25°C with a Haake CV 100 using the ZA30 rotor and a shear rate range of 0–3 s^{-1} in 3 min for low shear rheometry or 0 to a maximum of 300 s^{-1} in 3 min for higher shear rheometry. In order to minimize structural disturbance upon loading the viscometer and to ensure equivalent sample temperature and restructuring, samples were poured into the viscometer from a calibrated 5 ml beaker followed by a 3 min dwell time before initiating measurements. (Note: Some suspensions were too viscous and exceeded the capacity of the designated rotor system at the higher shear rate maximum. In these cases, the maximum shear rate was appropriately lowered and fresh samples

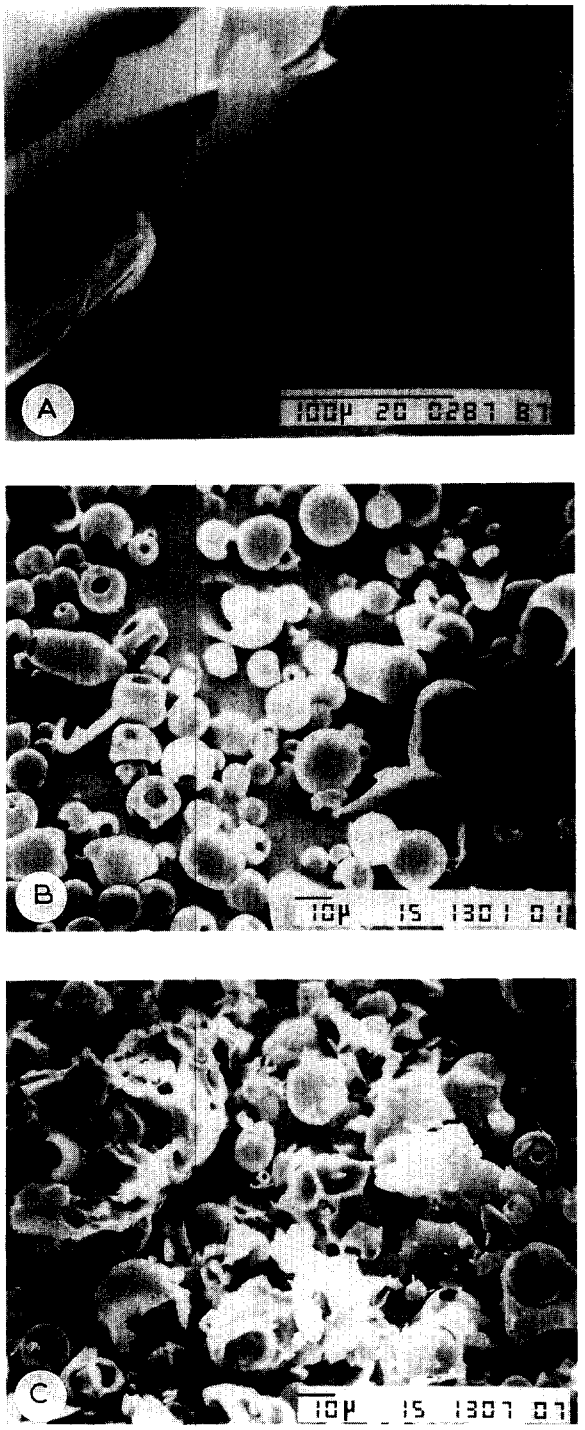


Fig. 1. Scanning electron microscope photographs showing the morphology of rbSt particles obtained from various drying processes. (A) Lyophilized 350×, (B) spray-dried/spherical (BSD1) (750×), (C) spray-dried/shattered (BSD5) 750×.

were tested.) All samples tested at the higher shear rates exhibited Newtonian flow, therefore, only rheograms from the low shear rate studies will be presented here.

3. Results and discussion

3.1. Effect of Tween 80 concentration

As Fig. 2 shows, increasing the concentration of Tween 80 in the 12.5% (w/v) rbSt suspension gradually increased its structural rheology. In the absence of Tween 80, the drug suspension in Miglyol 812 had a low viscosity and was strictly Newtonian in flow. Increasing the concentration of Tween 80 from 0.1 to 0.5% (w/v), resulted in a corresponding rise in viscosity and greater degree of pseudoplasticity. A further increase to 1% (w/v) Tween 80, provided a more dramatic increase in viscosity with formation of a yield value but no thixotropy. The rheograms at higher shear rates all showed Newtonian flow. The increased structural rheology produced by the successive increase in Tween 80 concentration suggested formation and strengthening of an rbSt-Tween 80-Miglyol 812 network. However, network bonding must be very weak since it is destroyed at the higher shear rates. This network structure would be consistent with the Tween 80, as a wetting agent, acting as a bridge between the Miglyol and

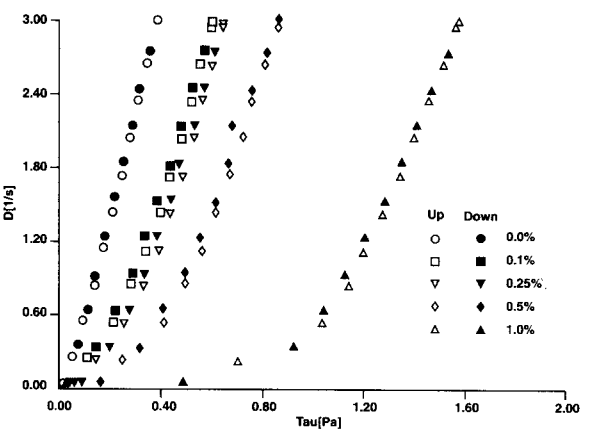


Fig. 2. Rheograms of 12.5% (w/v) rbSt suspensions in Miglyol 812 as a function of Tween 80 concentration.

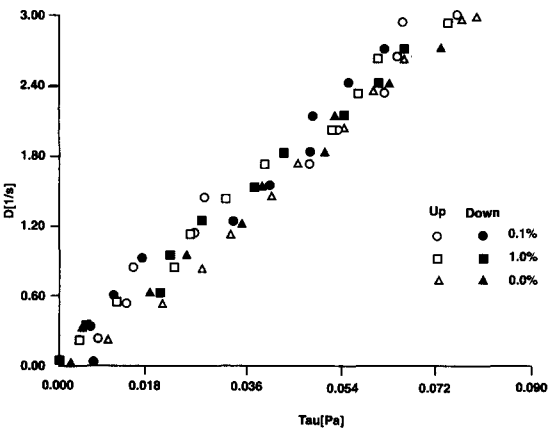


Fig. 3. Rheograms of Miglyol 812 containing varying amounts of Tween 80.

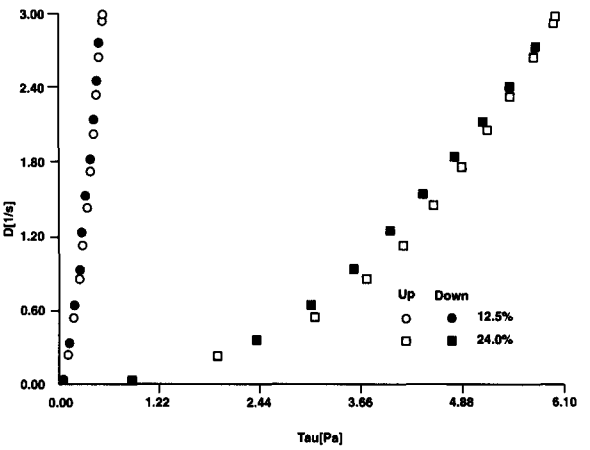


Fig. 4. Rheograms of rbSt suspensions in Miglyol 812 with 0.1% (w/v) Tween 80 as a function of drug concentration.

rbSt to provide better dispersion of the drug particles in the oil and a consequential increased effective number of particles/volume which in turn would provide increased resistance to flow.

The structure formation/increased wettability theory was supported by testing vehicles made of Miglyol 812 with Tween 80 added over the concentration range used in the rbSt suspensions. As Fig. 3 illustrates, all the rheograms were Newtonian and the viscosity did not change. Higher shear rates also produced the same results.

3.2. Effect of drug concentration

As Fig. 4 demonstrates, approximately doubling the drug concentration in the suspension resulted in a dramatic increase in viscosity with development of a yield value and slight thixotropy in the low shear rheogram. The viscosity of the 24% (w/v) rbSt suspension at the maximum shear rate (3 s^{-1}) is nearly 10-fold that of the 12.5% (w/v) rbSt suspension (2.0 compared to 0.2 Pa s, respectively). As Table 1 shows, the higher shear rate rheology provided Newtonian flow over the shear rate range 0–200 s^{-1} for the 12.5% (w/v) rbSt sample while the 24% (w/v) rbSt sample provided pseudoplastic flow and due to limitations in the viscosity range of the rotor system, permitted measurements of only 0–25 s^{-1}.

3.3. Effect of bulk drug size and shape

Fig. 5 compares the rheology of rbSt suspensions prepared with drug made from different drying processes. In order to eliminate variation due to differing rates of structure build up upon aging, the samples were allowed to age 7 weeks at room temperature before measurement to ensure that the equilibrium structure had been established. Lyophilized drug produced low viscosity Newtonian suspensions while spray-dried spherical and shattered drug both gave higher viscosity, thixotropic suspensions with yield values. Spray-dried/spherical drug produced slightly higher viscosities and yield values but otherwise retained the same rheogram shape as spray-dried/shattered drug.

Table 1
High shear rheological parameters of 12.5 and 24% (w/v) rbSt suspensions with 0.1% (w/v) Tween 80

rbSt % (w/v)	Shear rate (s^{-1})	Shear stress (Pa)	Viscosity (Pa s)
12.5	50	6.68	0.128
	100	12.59	0.125
	200	24.28	0.122
24.0	5	7.61	1.520
	10	11.2	1.110
	20	17.1	0.854
	25	19.9	0.795

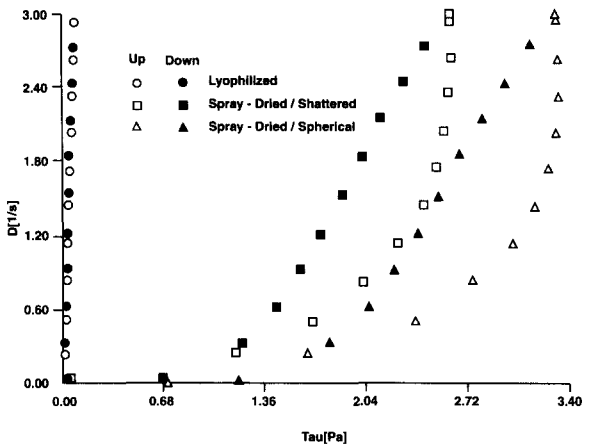


Fig. 5. Rheograms of 15% (w/v) rbSt suspensions in Miglyol 812 with 0.1% (w/v) Tween 80 showing the impact of drying processes on rheology.

An understanding of the rheology exhibited by these suspensions can be obtained upon examination of the drug particle size and shape. As Fig. 6 illustrates, the lyophilized drug suspensions contained an open network of large, overlapping platelets while both spray-dried drug suspensions had small, crowded spherical particles. Platelets tend to sediment, move as a unit and align easily in the direction of an applied shear. Hence, they provide little resistance to flow and have low suspension viscosities. In contrast, spherical particles tend to pack tightly which increases the resistance to flow and thus viscosity. Closer examination of the photomicrographs reveals smaller particles and tighter packing of the spray-dried/spherical drug and larger, irregular spheres with looser packing for the spray-dried/shattered drug. This variation in particle morphology would account for the maintenance of the overall rheogram shape while allowing for increased viscosities and yield values.

3.4. Effect of age

As an illustration of the variation in rates of structure formation, initial and 7 week rheograms of the suspensions made with drug from the various processes are presented in Fig. 7a–c. The rheology of the lyophilized drug suspensions remain unchanged, but the 7 week rheograms of both spray-dried drug suspensions show shifts in the rheograms to higher shear stress values and increases in thixotropy. The most dramatic change is seen in the spray-dried/shattered drug. These changes suggest increased structure formation in the spray-dried drug suspensions most likely in the form of improved wetting of the drug particles by the Tween 80. The lack of rheological change in the lyophilized drug suspensions suggests that the sedimentation associated with particle size and shape dominates its rheology.

3.5. Syringeability

The ability of a parenteral solution or suspension to pass easily through a hypodermic needle, i.e., syringeability, is an important attribute of injectable products. Chien et al. (1981) developed a device for testing the syringeability of non-aqueous parenteral formulations and found that syringeability was inversely proportional to viscosity for a given size hypodermic needle. Table 2 presents syringeability data through 18 and 20 gauge needles for Miglyol 812/Tween 80 suspensions of spray-dried rbSt. As would be expected, injection time for the larger bore needle is faster. Also, based on the similar rheology exhibited by spray-dried shattered and spherical drug, one might predict their similar injection times.

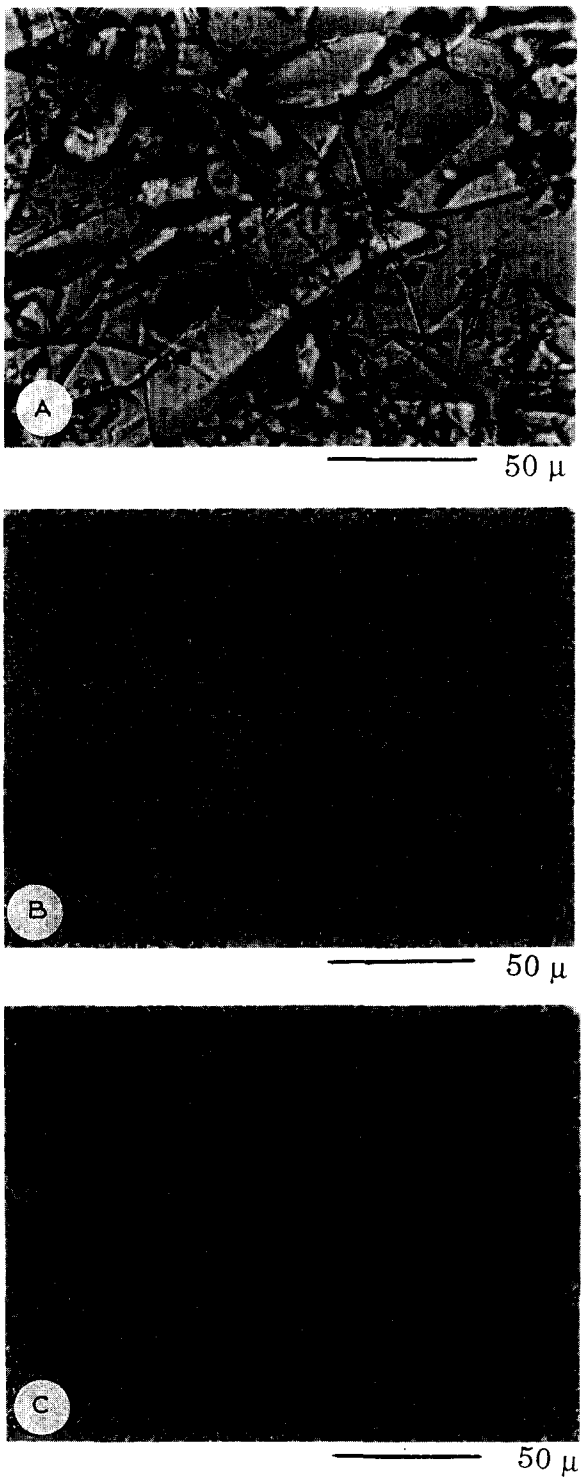
Henderson et al. (1961) described mathematical techniques by which the rate of shear could be estimated for liquids flowing through hypodermic needles of known dimensions at a known rate. Initial assumptions made are that the fluid is Newtonian and therefore its velocity distribution through a tube (i.e., needle) is parabolic. This being so, and since the parabolic volume is half that of the circumscribing cylinder, the mean velocity of the cylinder of fluid will be half the maximum velocity at the center of the paraboloid. The mean velocity can then be calculated from the equation:

$$\text{flow rate} = \text{volume of the cylinder} = \pi r^2 h$$

where flow rate = injection time,

r = needle internal radius and

h = mean velocity of the cylinder of fluid.



The maximum velocity at the center of the paraboloid (i.e., needle) then becomes $2h$. The shear rate (S) at the center of the needle is then calculated from the velocity gradient (dv/dr) as:

$S = dv/dr = \text{maximum velocity}/r$

The calculated mean velocities and shear rates corresponding to the injection times of the samples are listed in Table 2. The calculated shear rates range from 1792 to 2184 s^{-1}, but rheology studies at these high rates of shear are beyond the capability of the instrument. However, as Fig. 8 shows, both the 10 and 15% rbSt suspensions at the maximum shear rates of the rotor system produce Newtonian flow. Thus, rheology studies at the high shear rate range of the instrument should be representative of those at the actual shearing conditions encountered in the syringe.

4. Conclusions

The rheological studies of rbSt suspensions in Miglyol 812 with varying quantities of Tween 80 suggested formation of a drug-Tween-Miglyol network. As the Tween 80 concentration increased, the suspension rheology reflected the strengthened network with increasingly greater changes in viscosity and deviation from Newtonian flow. The network formation theory was verified in that samples of Miglyol 812 containing Tween 80 over the same concentration range as the rbSt suspensions produced low viscosity Newtonian rheograms which were essentially identical at all concentrations. The impact of drug concentration on suspension rheology and network formation was realized by dramatic changes in viscosity and formation of a yield value when the rbSt concentration was doubled.

The rheology of suspensions made with different bulk drug processes reflected particle size,

Fig. 6. Photomicrographs (500×) of 15% (w/v) rbSt Miglyol 812 suspensions with 0.1% (w/v) Tween 80 showing particulate characteristics of drug dried by various processes. (A) Lyophilized, (B) spray-dried/spherical (BSD1), (C) spray-dried/shattered (BSD5).

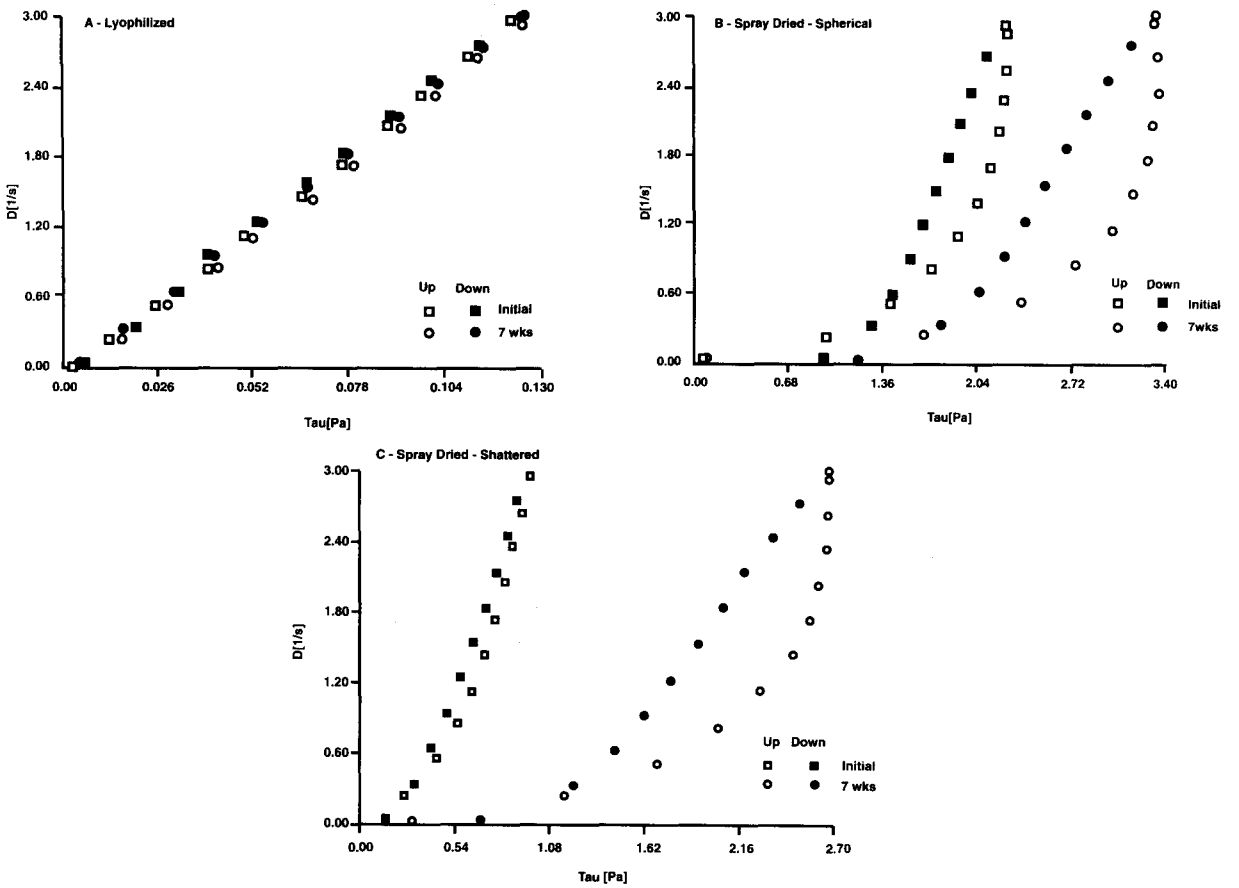


Fig. 7. Rheograms showing the impact of aging on 15% (w/v) rbSt suspensions in Miglyol 812 with 0.1% (w/v) Tween 80.

shape and packing. The large platelets of lyophilized drug readily sedimented resulting in minimal viscosity and Newtonian flow. In contrast, the close packing of the smaller spherical particles in the spray-dried material produced thixotropic flow and substantially greater viscosi-

Table 2
Injection time of spray-dried rbSt suspensions in Miglyol 812 with 0.1% (w/v) Tween 80

Particle morphology	Needle gauge	Needle internal diameter (cm)	rbSt concentration % (w/v)	Average injection time for 1 cm^3 (s)	Mean velocity (cm/s)	Shear rate (s^{-1})
Spherical	20	0.09	10	3.2 ± 0.4	49.15	2184
Spherical	18	0.12	10	1.6 ± 0.1	57.07	1902
Spherical	20	0.09	15	3.4 ± 0.3	46.26	2056
Shattered	20	0.09	15	3.9 ± 0.3	40.33	1792

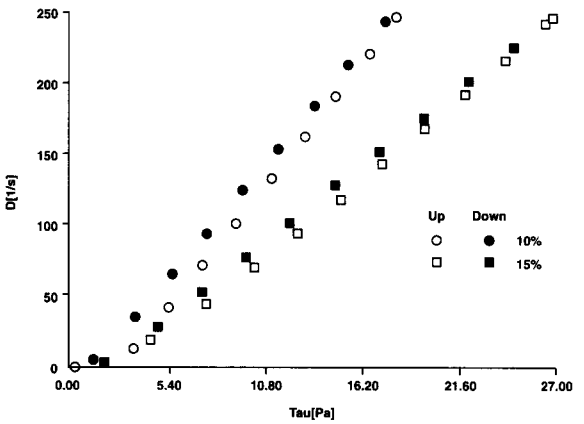


Fig. 8. High shear rheograms of 10 and 15% (w/v) rbSt suspensions in Miglyol 812 with 0.1% (w/v) Tween 80.

ties and yield values. When compared to spray-dried/shattered drug, the smaller particles and greater degree of crowding of the spray-dried/spherical drug resulted in greater viscosities and yield values while retaining the overall rheogram shape. Particle morphology also greatly influenced the rheology of aged suspensions in that lyophilized drug suspensions remained unchanged over the 7 week test period while spray-dried drug suspensions experienced apparent structural changes over the same period which resulted in increased viscosity, yield values and thixotropy. Finally, syringeability testing of the rbSt suspensions indicated that the similarity in the rheology of spray-dried spherical and shattered drug was reflected in the injection time.

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