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Influence of rheological behaviour of particulate/polymer dispersions on liquid-filling characteristics for hard gelatin capsules

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Abstract

Lactose/poloxamer dispersions were prepared by mixing under vacuum to achieve a de-aerated mix with good capsule filling properties and disperse phase uniformity at 70 °C. Satisfactory capsule filling of molten dispersions was achieved up to a limiting concentration of disperse phase, dependent on particle size distribution and continuous phase viscosity. Lactose/poloxamer dispersions exhibited thixotropic shear thinning behaviour with an abrupt increase in apparent viscosity above a limiting concentration of disperse phase. There was a good correlation between satisfactory filling of molten dispersions into capsules and apparent viscosity of the formulation, whereas, the pronounced increase in apparent viscosity resulted in unsatisfactory filling above a critical concentration of disperse phase. The rheological data was analysed in detail using empirical models and also used to identify capsule filling problems at extrudate shear rates for flow from hopper to pump ($12\,s^{-1}$) and from nozzle to capsule ($340\,s^{-1}$).

Keywords: Rheology; Capsule filling; Thixotropy; Poloxamer; Solid dispersion

1. Introduction

Liquid-fill formulations for hard gelatin capsules can be Newtonian liquids or more complex thixotropic or thermosoftened systems. Liquid filling of hard gelatin capsules using thermosoftened systems is a relatively simple process, which involves initially heating the solid polymer with the particulate drug at a temperature above the melting point of the polymer. This leads to two distinct possibilities; either the formation of a molten liquid phase (Betagiri and Makarla, 1995; Hawley et al., 1992) due to drug dissolution/melting, or a particulate dispersion of the drug in the molten polymer (Rowley et al., 1998; Sutananta et al., 1995). The formulation is normally filled into capsules at temperatures up to 70 °C, and on cooling, a solid dispersion plug is formed in the capsule. However, the formulation should crystallize rapidly after filling into capsules in order to avoid problems of leakage and non-uniform distribution of drug in the capsule due to sedimentation.

One of the main considerations in the development of thermosoftened formulations is the solubility of the drug in the molten polymer. The active substance may dissolve or melt in the excipient with little change in viscosity for a wide range of compositions of active and excipient, e.g. ibuprofen is miscible in molten poloxamer (Luterol F68) and PEG 10000 up to 90% (w/w) ibuprofen with satisfactory capsule filling (Hawley et al., 1992). However, for a dispersion of solid drug particles in the molten excipient, the rheology is affected by the properties of the disperse phase (particle size, concentration) and the continuous phase (molecular weight, viscosity), leading to filling limitations (Kattige, 2001).

Liquids and semi-solids can be easily and accurately filled into hard gelatin capsules provided that the formulation rheology is compatible with the liquid pumping capacity of the filling machinery. Filling problems are related to formulation viscosity and an approximate range of 0.1–25 Pa s has been proposed for satisfactory filling using automatic machinery, recently reviewed (Rowley, 2004). In addition, leakage can be overcome by sealing the capsules after filling, either by use of a separate sealing machine or as an integral part of the filling process.

Generally, thixotropic shear thinning behaviour is desirable for satisfactory capsule filling at ambient temperature such that the apparent viscosity of the formulation decreases during the

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high shear filling process, but increases after the formulation is filled into capsules (Walters et al., 1992). In cases, where shear thinning does not reduce the apparent viscosity of the formulation, to meet the requirement of the liquid dosing pump of the capsule filler, it would be necessary to reduce the concentration of solid disperse phase.

Drugs with different physicochemical properties but similar particle size distributions were shown to have different effects on apparent viscosity of triglyceride oil/silicon dioxide gels (Ellison, 1997). Changing the chemical nature of the gel formulations by using hydrophilic or hydrophobic silicon dioxide in liquid poloxamers of differing ratios of polyoxyethylene and polyoxypropylene groups, was shown to have a considerable effect on gel apparent viscosity and hence capsule filling properties (Saeed, 1999). These investigations provide evidence to show that the rheological characteristics of liquid-fill formulations at ambient temperature are influenced by the chemical nature of the drug and gel. However, the effect of disperse phase concentration on capsule filling, rheology and dispersion stability was not investigated.

This paper investigates the problems associated with filling of particulate/polymer dispersions in hard gelatin capsules with reference to the physicochemical properties of disperse and continuous phase, as well as rheology of the formulation during machine filling at 70 °C. In the latter case, values of shear rate for liquid transfer from hopper to pump and pump to capsule through the nozzle were estimated (Cogswell, 1981) and used to aid the interpretation of capsule filling data in relation to formulation rheology. It is envisaged that this investigation would provide information regarding the effect of disperse phase concentration, particle size distribution and poloxamer molecular weight on capsule filling. In addition, it would also help to establish the limiting concentration of disperse phase that could be filled into capsules using the semi-automatic capsule filler (Hibar) used in this work.

2. Materials and methods

2.1. Materials

Poloxamers (Synperonics PE/F68, PE/F88, ICI, UK), polyethylene oxide polypropylene oxide block copolymers with a range of viscosity and melting point suitable for liquid-filling at 70 °C were selected.

α-Lactose monohydrate, Granulac-230 (Meggle GMBH) mean 22.6 μm (10% <2.9 μm, 90% <47.6 μm) and Sorbolac (Meggle GMBH) mean 15.3 μm (10% <2.4 μm, 90% <31.1 μm) determined using a laser light scattering technique (Malvern Mastersizer 1000) was selected as a model disperse phase with negligible solubility in the molten poloxamers at the capsule filling temperature.

2.2. Methods

2.2.1. Preparation of lactose/poloxamer dispersions

The poloxamers were melted in a constant temperature water bath at 70 °C. The lactose particulate phase, either Granulac-230 or Sorbolac, was added to the molten poloxamer and mixed for 60 min under vacuum using a paddle mixer (Ika-Werk RW 20 DZM) at 100 rpm as described previously (Kattige and Rowley, 1999). Mixing under vacuum reduced the preparation time of the formulation and achieved a de-aerated mix. The formulation was poured into the hopper of the capsule filling machine with hopper and pump maintained at 70 ± 0.1 °C and allowed to equilibrate for 15 min before filling into size 1 hard gelatin capsules. Lactose 2.5–37.5% (w/w) dispersions in the poloxamers F68 and F88, were investigated for rheological properties, whereas, 10–37.5% (w/w) were investigated for capsule filling.

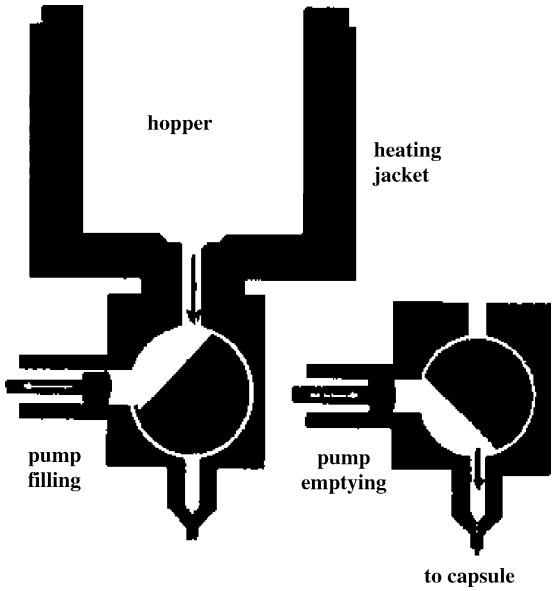

Fig. 1. Diagrammatic representation of the capsule-filling machine.

2.2.2. Capsule filling

The molten poloxamers and dispersions were filled into size 1 hard gelatin capsules using the Hibar capsule filler (Hi Tech Machinery). The semi-automatic capsule-filling machine used in this research is represented diagrammatically in Fig. 1 (Hawley, 1993) to show the direction of liquid flow from hopper to dosing valve. The formulation is placed in a thermostatically controlled hopper that is coupled at the base to a three-position valve. A pneumatically operated cylinder and piston arrangement controlled by an air compressor at 60 psi, is coupled to the valve at 90°. In the base of the three-position switch, is a circular orifice in which a circular nozzle of internal diameter (6 mm) is fitted. As the piston is retracted, a sample is drawn from the hopper into the valve. Mechanically coupled cams then rotate the valve through 90° at the instant the piston starts the return stroke. This extrudes the sample through the nozzle into the capsule shell. The filling operation can be done manually or automatically in batches of 24 capsules at a time and in this research the fill weight was adjusted micrometretically to 450 mg.

The filling operation took approximately 15–20 min for a batch size of 50 g and the filled capsules were allowed to cool to ambient temperature in the capsule tray. The filled capsules were tested for weight uniformity by a modified BP method using the

Table 1
Physical properties of selected poloxamers (ICI, 1994)

Poloxamers	Approximate molecular weight	HLB value	Melting point (°C)	Viscosity at 77 °C (Pa s)
F38	4800	30.5	48	0.31
F87	7700	24.0	52	0.77
F68	8350	29.0	55	1.33
F88	11800	28.0	58	2.80

fill weight of 20 capsules per batch, determined by weighing each capsule before and after the filling process. Initial studies revealed that to achieve a uniform fill weight for highly viscous formulations, the capsule filling machine had to be run for a longer time to remove air pockets from the system and therefore in all cases, the first 24 capsules were discarded and the remaining capsules were collected and sampled for weight uniformity testing. The capsule contents weighed more than 300 mg, therefore not more than two were allowed to deviate from the mean by 7.5% and none were allowed to deviate by more than twice that percentage, in order to comply with BP/EP specification.

2.2.3. Rheology

The controlled stress rheometer (Carrimed CSL 100) with a 4 cm parallel plate measuring system set at 70 ± 0.1 °C was used for these investigations. It is recommended (Carrimed, 1995) that the gap between the plates should be set 10 times greater than the largest particle size in the dispersion. In this research, the largest particle size of lactose was approximately 100 μm, therefore the gap between the plates was set to 1000 μm for all the formulations. The sample was placed on the rheometer plate and the ram raised to the preset gap. The formulation was allowed to equilibrate at 70 °C for 15 min and the shear stress was then uniformly increased from 0 to 795 Pa for 1 min and then decreased to 0 over 1 min. Three random samples of gel were taken from each batch and tested for reproducibility. The rheograms and the data reported are the mean results of three batches and in all cases the coefficient of variation was less than 5%. The rheograms were analysed using Bingham, Casson, Power Law, Herschel Bulkley and Sisko equations and best-fit determined.

3. Results and discussion

It has been reported previously (Kattige, 2001) that of the four poloxamers listed in Table 1, each filled satisfactorily into size 1 capsules. In addition, it was shown that satisfactory filling was achieved with 10% (w/w) dispersions of Granulac-230 in each poloxamer. In this work, the effect of disperse phase concentration for two different particle sizes was investigated in detail for the two poloxamers F68 and F88 with the highest molecular weight and viscosity.

3.1. The effect of lactose particle size and concentration on capsule filling of lactose/poloxamer F68 formulation

These experiments were undertaken to investigate the effect of disperse phase concentration on capsule filling properties of Granulac-230 and Sorbolac/poloxamer F68 dispersions. Previous work (Rowley et al., 1998) indicated that for mean capsule content of 300 mg, coefficient of variation (cv) values less than 3.5% would be satisfactory, although it is theoretically possible to comply with BP/EP specifications with cv values up to 8.7%. However, for the purpose of this investigation values less than 4% were regarded as acceptable for satisfactory capsule filling, although it was envisaged that in most cases much lower variation of liquid-fill weight would be possible.

The results for mean fill weight and cv for Granulac-230 dispersions (10, 15, 20, 25, 30 and 35%, w/w) in poloxamer F68 are presented in Table 2. In addition, limit A (±7.5% of the mean weight) and limit B (±15% of the mean weight) are given for all the formulations and the results show that each formulation complied with the BP limits for fill weight uniformity. The cv for dispersions 10–25% (w/w) were <1%, whereas, increasing the disperse phase concentration to 30 and 35% produced cv values of 1.29 and 3.36%, respectively.

There were significant differences in mean fill weights when compared by single factor ANOVA at a confidence level of 0.05, except (a) 10% (w/w) Granulac-230 formulation was not different from 30% (w/w) and (b) 25% (w/w) was not different from 10, 20 and 30% (w/w) formulations. Although there were statistical differences due to change of disperse phase concentration, practical differences with respect to capsule filling were

Table 2
Comparison of fill weight range and mean (g), coefficient of variation (%) and BP weight uniformity for Granulac-230/poloxamer F68 dispersions

	Granulac-230 concentration (%, w/w)					
	10	15	20	25	30	35
Range	0.434–0.443	0.446–0.449	0.442–0.447	0.437–0.444	0.425–0.446	0.381–0.430
Mean	0.439	0.447	0.443	0.442	0.439	0.405
cv (%)	0.44	0.17	0.27	0.31	1.29	3.36
BP limit A	0.472–0.406	0.481–0.414	0.476–0.410	0.475–0.409	0.472–0.406	0.435–0.375
BP limit B	0.505–0.373	0.514–0.380	0.509–0.377	0.508–0.376	0.505–0.373	0.466–0.344

Table 3
Comparison of fill weight range and mean (g), coefficient of variation (%) and BP weight uniformity for Sorbolac/poloxamer F68 dispersions

	Sorbolac concentration (%, w/w)				
	10	15	20	25	27.5
Range	0.449–0.459	0.450–0.458	0.442–0.454	0.411–0.439	0.400–0.439
Mean (g)	0.454	0.454	0.449	0.433	0.426
cv (%)	0.62	0.53	0.71	1.37	2.67
BP limit A	0.448–0.420	0.488–0.420	0.483–0.415	0.465–0.401	0.458–0.394
BP limit B	0.522–0.386	0.522–0.386	0.516–0.382	0.498–0.368	0.490–0.362

not apparent until the disperse phase concentration was >30% (w/w) for this formulation.

The smaller particle size lactose (Sorbolac) with a mean particle size of 15.3 μm (10% <2.4 μm and 90% <31.1 μm) was used to investigate the effect of disperse phase particle size distribution on capsule filling properties, by comparison with the results for Granulac-230 dispersions. Table 3 shows the mean fill weight and coefficient of variation values for Sorbolac/poloxamer F68 dispersions of concentrations 10, 15, 20, 25 and 27.5% (w/w). Application of the modified BP weight uniformity test showed that the capsule filling data complied with the required specifications. All formulations from 10 to 27.5% (w/w) disperse phase showed satisfactory filling at 70 °C with mean fill weight greater than 0.4 g and cv less than 2.7%. However, 30% (w/w) Sorbolac/poloxamer F68 dispersion could not be filled into capsules. The results in Table 3 confirm that the mean fill weight of the Sorbolac/poloxamer F68 dispersion decreased slightly up to 20% (w/w) and markedly above 20% (w/w). There were significant differences in mean fill weights when compared by single factor ANOVA at a confidence level of 0.05, except (a) 10% (w/w) dispersion was not different from 15 to 20% (w/w) and (b) there was no significant difference between 15 and 20% (w/w) dispersions. This implies that 25 and 27.5% (w/w) formulations behaved differently to other formulations. As the concentration of lactose was increased from 10 to 35% (w/w), the mean fill weight of the formulation decreased from 439 to 405 mg, for Granulac-230/poloxamer F68 dispersions and 454 to 426 mg for Sorbolac/poloxamer F68 (10–27.5%, w/w) dispersions, although the machine fill volume was kept constant for all the formulations. One of the reasons for weight decrease was the increase in apparent viscosity of the formulation (Section 3.3) with increase in concentration of disperse phase and this effect was more pronounced with the dispersion containing the smaller particle size lactose. In addition, the bridging nature of the formulation which occurred at higher disperse phase concentrations and shown in Fig. 2 (Hawley, 1993) indicated that the piston was unable to extrude the formulation completely from the cylinder into the capsule, as discussed later.

There are a number of factors including gel aeration and changes in rheology that contribute to increasing coefficient of variation of fill weight. The apparent viscosity of the formulation increased with increase in lactose concentration and the problem of aeration of the formulation, assessed qualitatively by hot stage microscopy, also increased. Quantitative rheological evidence will be used to discuss these differences in Section 3.5, however, qualitative differences were observed during capsule filling and these are summarized as follows. Bridging of the formulation between capsules as shown in Fig. 2 started at a concentration of 20% (w/w) of disperse phase, Granulac-230. The bridge was thin and it severed, leaving a drop at the side of the capsule, whereas, for 35% (w/w) Granulac-230 there was significant bridging of formulation between capsules. In the case of some formulations, the dispersion spiralled as a cylindrical extrudate into the capsule. This effect was first observed at a concentration of 20% (w/w) and became more pronounced with further increase in lactose concentration up to 35% (w/w), where the dispersion did not fill from the bottom of the capsule, indicating low fluidity of the formulation. These results indicate that despite these observable changes in fluid flow it is possible to fill Granulac-230 up to 35% (w/w) in F68 with mean fill weight greater than 0.4 g and coefficient of variation values less than 3.5%, however, formulations with 37.5% (w/w) and higher could not be filled into capsules. Although weight variation values were satisfactory for Granulac-230 dispersions up to 35% (w/w) filled by the Hibar machine, dispersions above 20% (w/w) exhibited rheological characteristics as described above which may be unsatisfactory for capsule filling using fully automated high speed machinery. However, controlled agitation to minimize aeration of the formulation in the hopper would also provide increased shear thinning to decrease the apparent viscosity of the dispersion and reduce the problems of bridging and spiralling.

In the case of Sorbolac/poloxamer F68 dispersions (Table 3), the cv was less than 1% for 10–20% (w/w) formulations, increasing to 1.37 and 2.67% for 25 and 27.5% (w/w) formulations, respectively. The higher cv for 25 and 27.5% (w/w) formulation are attributed to increasing viscosity and bridging

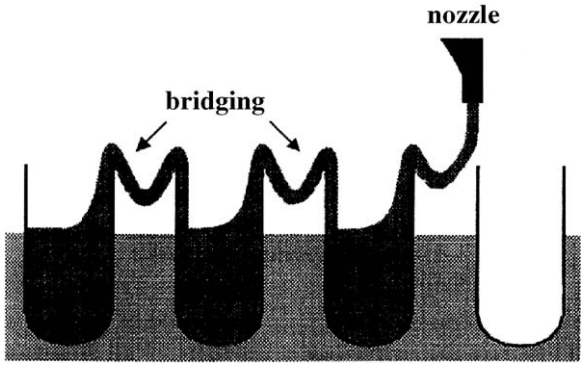

Fig. 2. Bridging of formulation between capsules.

Table 4
Comparison of fill weight range and mean (g), coefficient of variation (%) and BP weight uniformity for Granulac-230/poloxamer F88 dispersions

	Granulac-230 concentration (%, w/w)					
	10	15	20	25	30	32.5
Range	0.447–0.456	0.466–0.473	0.463–0.472	0.441–0.481	0.427–0.456	0.381–0.430
Mean (g)	0.453	0.470	0.468	0.456	0.444	0.410
cv (%)	0.66	0.38	0.54	1.73	1.99	3.84
BP limit A	0.487–0.419	0.505–0.435	0.503–0.433	0.49–0.422	0.476–0.410	0.440–0.378
BP limit B	0.521–0.385	0.540–0.400	0.468–0.398	0.524–0.388	0.509–0.377	0.470–0.348

nature of the formulation as explained previously for Granulac-230/poloxamer F68 formulation.

The evidence from these results indicate that the limiting concentration of disperse phase for Sorbolac/poloxamer F68 dispersions was reached at a concentration of 27.5% (w/w), whereas, for the larger particle size Granulac-230 dispersions the limiting concentration was 35% (w/w).

3.2. The effect of polymer viscosity on capsule filling of Granulac-230 and Sorbolac dispersions

The effect of continuous phase molecular weight and viscosity on capsule filling properties was investigated by comparing lactose dispersions in poloxamer F68 and F88. The results for capsule filling parameters of 10–32.5% (w/w) Granulac-230/poloxamer F88 dispersions reported in Table 4 show that mean fill weights ranged from 0.410 to 0.470 g with satisfactory filling up to a concentration of 32.5% (w/w) and cv values less than 4%, whereas, the 35% (w/w) formulation could not be filled. In comparison, the maximum concentration for filling Granulac-230 dispersion in F68 was 35% (w/w). Application of the BP specifications for weight uniformity (Table 4) indicate that the F88 dispersions up to disperse phase concentration of 32.5% (w/w) fall within the specified limits and therefore each batch passed the modified BP test. The reasons for high cv and low mean fill weight with increased concentration of disperse phase can be attributed to reasons previously explained for F68 dispersions in Section 3.1. The mean fill weight of the F88 (10–32.5%, w/w) formulations showed significant differences when compared by single factor ANOVA at a confidence level of 0.05, except that (a) the 10% (w/w) dispersion was not different from 25% (w/w) formulation and (b) 15% (w/w) was not different from 20% (w/w) dispersion. However, F88 has a more pronounced effect on the decrease in mean weight and increase in cv of Granulac-230 dispersions then the lower molecular weight F68.

The capsule filling data for Sorbolac/poloxamer F88 formulations (Table 5) show that the filling capacity of the pump was restricted to formulations with disperse phase concentration up to 25% (w/w). The mean fill weight of the formulations was in the range of 0.430–0.459 g and the coefficient of variation values were less than 2.5% for dispersions which filled satisfactorily at 70 °C.

Assessment of fill weight data using modified BP weight uniformity test revealed that all formulations except the 27.5% (w/w) Sorbolac dispersion, passed the test. 27.5% (w/w) Sorbolac/F88 dispersion had a coefficient of variation value of 7.6% with three of the fill weights outside the specifications of limit A and two were outside limit B of the BP test and therefore failed the test. Two fill weights from a second batch of 27.5% (w/w) Sorbolac/F88 dispersion were outside the specifications of limit A, of which one was outside limit B, the coefficient of variation was 6.45% and this batch was also unacceptable. In comparison, the maximum concentration of Sorbolac in F68 for satisfactory filling was 27.5% (w/w). The mean fill weight of the formulations was significantly different when compared by single factor ANOVA at a confidence level of 0.05. Analysis of mean fill weight using least square difference revealed that (a) 25% (w/w) dispersion was significantly different from 10, 15, 20% (w/w) dispersions and (b) 27.5% (w/w) formulation exhibited significant difference when compared with 10, 15, 20 and 25% (w/w) formulations.

The limiting capacity of the disperse phase in the same poloxamer decreased as the particle size distribution of lactose decreased. Granulac-230, mean particle size 22.6 μm can be filled satisfactorily at 70 °C up to a concentration of 35% (w/w) in F68, whereas, Sorbolac, mean particle size 15.3 μm can be filled up to 27.5% (w/w). A similar trend was observed

Table 5
Comparison of range and mean fill weight (g), coefficient of variation (%) and BP weight uniformity for Sorbolac/poloxamer F88 dispersions

	Sorbolac concentration (%, w/w)				
	10	15	20	25	27.5
Range	0.448–0.453	0.451–0.462	0.451–0.454	0.408–0.448	0.334–0.459
Mean (g)	0.450	0.459	0.452	0.433	0.430
cv (%)	0.35	0.61	0.23	2.2	7.6
BP limit A	0.484–0.416	0.493–0.425	0.486–0.418	0.466–0.401	0.462–0.398
BP limit B	0.518–0.383	0.528–0.390	0.520–0.384	0.498–0.368	0.495–0.365

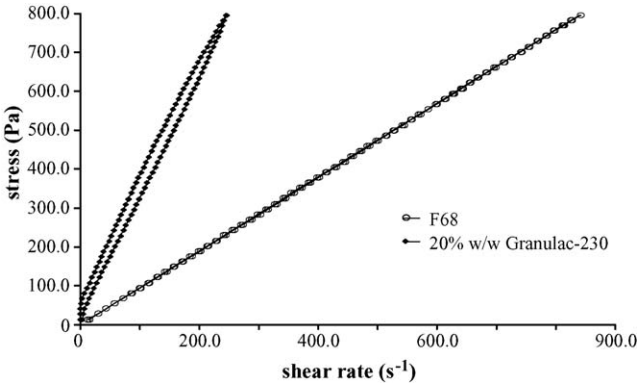

Fig. 3. Comparison between 20% (w/w) Granulac-230/poloxamer F68 dispersion and poloxamer F68.

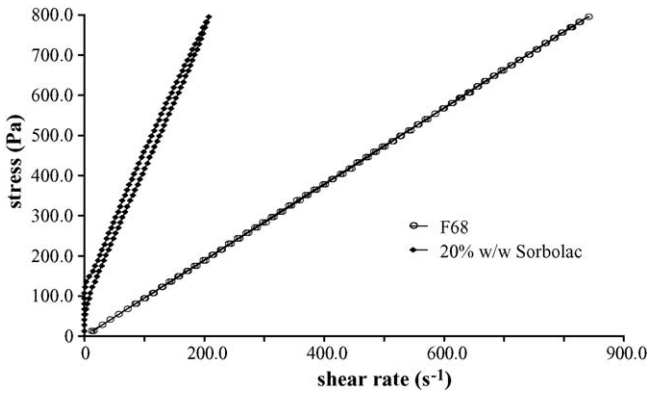

Fig. 4. Comparison between 20% (w/w) Sorbolac/poloxamer F68 dispersion and poloxamer F68.

for lactose dispersions in poloxamer F88 with the capacity decreasing to 32.5% (w/w) for Granulac-230 dispersions and 25% (w/w) for Sorbolac dispersions. As the molecular weight of poloxamer and disperse phase concentration increased, the interaction of lactose particles with poloxamer as well as increased entanglement of the poloxamer chains may be responsible for the observed effects, which are discussed in more detail in Sections 3.3–3.5 with reference to the rheological data.

3.3. Rheology of lactose/poloxamer F68 dispersions

Poloxamer F68 showed Newtonian behaviour in the shear rate range (14–841 s^{-1}) as shown in Fig. 3, whereas, it was anticipated that addition of lactose would confer non-Newtonian properties to the system due to interaction between lactose particles and poloxamer. Qualitative assessment of the Granulac-230 dispersions showed that with increase in lactose concentration from 2.5 to 37.5% (w/w), the rheology of the formulation changed from being fluid-like at low concentration to a thick paste at high concentration.

The addition of lactose produced thixotropy in the system as indicated by the presence of a well defined hysteresis loop as shown for the 20% (w/w) dispersion, given as an example in Fig. 3, in comparison to that for F68 melt. In addition, the apparent viscosity decreased with increase in shear rate indicating shear thinning behaviour. Fig. 4 shows the effect of smaller particle size lactose, Sorbolac on the rheological behaviour of Sorbolac/poloxamer F68 dispersions when compared to the flow curve of poloxamer F68 melt. The trend in rheological behaviour was very similar to that observed for Granulac/poloxamer F68 systems and the flow curves exhibited thixotropic shear thinning behaviour.

3.4. Rheology of lactose/poloxamer F88 dispersions

A comparison of the rheology of F68 and F88 dispersions was undertaken in order to investigate the effect of poloxamer molecular weight as well as disperse phase particle size and concentration on apparent viscosity of the molten dispersion. The rheology of suspensions is dependent not only on the properties of disperse phase but also on the characteristics of the dispersion medium, and it has been reported (Song and Evans, 1993) that high molecular weight fluids increase the shear stress imposed during mixing, thus enhancing dispersion. The movement of particles is reduced in a high viscosity medium due to viscous drag that reduces the rate of particle flocculation (Song and Evans, 1994) and as a result it is more difficult for particles to aggregate in a higher viscosity medium. In this work, the poloxamers F68 and F88 had viscosities of 0.94 and 2.8 Pa s, respectively, at 70 °C. Fig. 5 shows the rheological profile of 20% (w/w) Granulac-230/F88 dispersions along with poloxamer F88 melt which was Newtonian over the shear rate range investigated. There was a change in the magnitude of apparent viscosity with concentration of disperse phase, however, all lactose/poloxamer F88 dispersions exhibited similar rheological behaviour, which was thixotropic and shear thinning. This is similar and consistent with the results observed for Granulac-230/poloxamer F68 dispersions reported in Section 3.3. Fig. 6 for Sorbolac/poloxamer F88 dispersions showed thixotropic shear thinning characteristics similar to that observed for Granulac-230/poloxamer F88 systems.

A greater increase in apparent viscosity with disperse phase concentration was observed at low shear rates, for example, the values of η_a at shear rates 10, 20 and 30 s^{-1} were 8.9, 6.4 and 5.2 Pa s for 20% (w/w) Granulac-230/F68 and 30.9, 19.9 and 15.2 Pa s, respectively, for the 30% (w/w) dispersions. In comparison with the smaller particle size disperse phase η_a values at

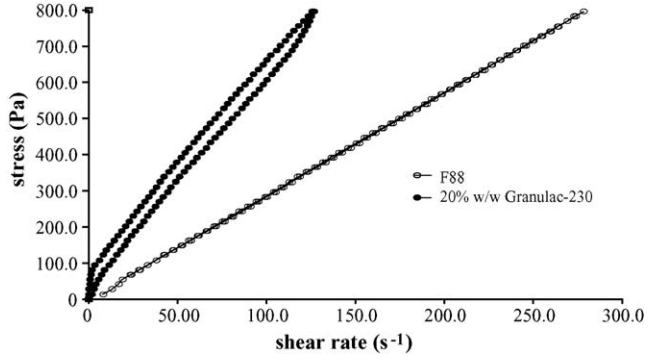

Fig. 5. Comparison between 20% (w/w) Granulac-230/poloxamer F88 dispersion and poloxamer F88.

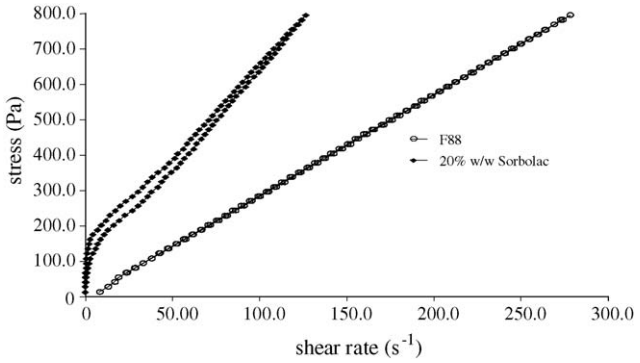

Fig. 6. Comparison between 20% (w/w) Sorbolac/poloxamer F88 dispersion and poloxamer F88.

10, 20 and 30 s^{-1} were 16.2, 9.2 and 7.3 Pa s for 20% (w/w) Sorbolac/F68 dispersions and 66.6, 33.3 and 24.6 Pa s, respectively, for the 30% (w/w) dispersions. This effect caused by increasing shear rate shows that it would be possible to increase the concentration of disperse phase, in particular for smaller particle size fractions, by increased controlled agitation in the machine hopper.

Detailed analysis of the rheograms using empirical models indicated that the Herschel Bulkley model which accounts for a non-linear flow curve above the yield stress, provided the best-fit over the widest range of disperse phase concentration for both Granulac-230 and Sorbolac dispersions. The Herschel Bulkley model offered the best-fit for Granulac-230 dispersions in the concentration range (10–32.5%, w/w), whereas, the Casson model gave comparable fit between 25 and 32% (w/w) and Sisko was comparable above 32.5% (w/w). Likewise for Sorbolac dispersions, Herschel Bulkley yet again conferred the best-fit over an extensive concentration range 10–27.5% (w/w), with the Casson model comparable from 20 to 25% (w/w) and Sisko comparable at ≥27.5% (w/w). The Herschel Bulkley model was consequently used to analyse the rheograms in detail and the rheological parameters attained, i.e. rate index, thixotropy and yield stress are presented in Tables 6–8.

For lactose/F68 dispersions, yield values of 2.6 and 6.2 Pa were seen at concentrations as low as 10% (w/w) for both Granulac-230 and Sorbolac dispersions, respectively. The concentration at which the yield value is detected, depends on the degree of interaction between the particles and additionally between the disperse phase and dispersion medium. Furthermore, the yield value increases with increase in lactose concentration to 87.2 Pa for 30% (w/w) Granulac-230 and 127.5 Pa for 25% (w/w) Sorbolac dispersions. The higher the proportion of lactose, the greater the strength of aggregation and this consequently resulted in an increase in yield stress. Nevertheless, these increases in yield stress with disperse phase concentration did not adversely affect capsule filling over the range 10–35% (w/w) and 10–27.5% (w/w) for Granulac-230 and Sorbolac, respectively. Analogous results for yield value were obtained for lactose/poloxamer F88 dispersions (Table 7), for example for 10% (w/w) Granulac-230 and Sorbolac dispersions yield values were 3.7 and 6.5 Pa, respectively. The yield values increased to 90.4 Pa for 30% (w/w) Granulac-230 and 132.3 Pa for 25% (w/w) Sorbolac dispersions. The yield value is present because

Table 6
Comparison of rheological data for lactose/poloxamer F68 formulations

Lactose concentration (%, w/w)	Mean rate index		Mean thixotropy (Pa s^{-1})		Mean yield stress (Pa)	
	Granulac	Sorbolac	Granulac	Sorbolac	Granulac	Sorbolac
10	0.95	0.940	6202	5738	2.6	6.2
12.5	0.95	0.93	7937	6429	5.0	18.4
15	0.92	0.91	10770	7484	13.5	29.9
17.5	0.89	0.87	10840	7924	25.8	46.5
20	0.85	0.83	11140	7727	29.7	72.3
22.5	0.76	0.76	7254	7413	46.9	100
25	0.73	0.66	6793	6390	59.8	127.5
27.5	0.69		6683		72.4	
30	0.47		5333		87.2	

Table 7
Comparison of poloxamer F88/Granulac-230 and poloxamer F88/Sorbolac dispersions

Lactose concentration (%, w/w)	Mean rate index		Mean thixotropy (Pa s^{-1})		Mean yield stress (Pa)	
	Granulac	Sorbolac	Granulac	Sorbolac	Granulac	Sorbolac
10	0.95	0.94	3118	745.8	3.7	6.5
12.5	0.95	0.94	4267	3454	11.9	33.6
15	0.93	0.92	4495	4220	24.3	41.5
17.5	0.91	0.89	4963	3761	30.6	54.8
20	0.86	0.84	6277	3680	45.8	89.5
22.5	0.83	0.81	4416	3522	51.8	119.3
25	0.79	0.71	3957	2336	62.9	132.3
27.5	0.70		3155		76.1	
30	0.60		2763		90.4	

Table 8
Comparison of Granulac-230/poloxamer F68 and Granulac-230/poloxamer F88 dispersions

Granulac concentration (%, w/w)	Mean rate index		Mean thixotropy (Pa s^{-1})		Mean yield stress (Pa)	
	F68	F88	F68	F88	F68	F88
10	0.95	0.95	6202	3118	2.6	3.7
12.5	0.95	0.95	7937	4267	5.0	11.9
15	0.92	0.93	10770	4495	13.5	24.3
17.5	0.90	0.91	10840	4963	25.8	30.6
20	0.85	0.86	11150	6277	30.3	45.8
22.5	0.76	0.83	7254	4416	46.9	51.8
25	0.74	0.79	6793	3957	59.8	62.9
27.5	0.69	0.70	6683	3155	72.4	76.1
30	0.47	0.60	5333	2763	86.9	90.4

of the presence of a particulate structure throughout the system and is the critical stress that must be exceeded before the material starts flowing. The results in Tables 6 and 7 therefore indicate that lactose/poloxamer dispersions produce structured systems, however, the pressure exerted by the pumping mechanism of the Hibar filling machine was sufficient to overcome the yield value.

The shear thinning behaviour of the dispersions was confirmed by rate index values less than 1 presented in Tables 6–8. For lactose/poloxamer F68 dispersions (Table 6), the rate index decreased from 0.95 to 0.47 for an increase in Granulac-230 concentration from 10 to 30% (w/w) and from 0.94 to 0.66 for 10 and 25% (w/w) Sorbolac dispersions, respectively. Similarly, as the Granulac-230 concentration in poloxamer F88 dispersions was increased from 10 to 30% (w/w) (Table 7), the rate index values decreased from 0.95 to 0.60 and correspondingly for Sorbolac/poloxamer F88 dispersions, from 0.94 to 0.71 with an increase in Sorbolac concentration from 10 to 25% (w/w). The lower the rate index value, the greater the shear thinning behaviour and the results therefore confirm that the shear thinning behaviour increased with increase in lactose concentration as indicated from the η_a values calculated at the specific shear rates 10, 20 and 30 s^{-1} reported earlier in this section.

The formulation was subjected to a uniformly increasing shear stress from 0 to 795 Pa for 1 min and then decreased to zero over the same time period. The area of the loop thus obtained provides a measure of the rate of structural breakdown and recovery for a given time ramp and was therefore used for the characterization of thixotropy. The results in Table 6 show an increase in thixotropy with Granulac-230 concentration from 6202 to 11,140 Pa s^{-1} for 10 and 20% (w/w) dispersions, respectively. However, the loop area decreased with an additional increase in lactose concentration to 7254 Pa s^{-1} for 22.5% and 5333 Pa s^{-1} for 30% (w/w) lactose. Correspondingly, for Sorbolac/poloxamer F68 dispersions, thixotropy was 5738 Pa s^{-1} at 10% (w/w), reaching a maximum of 7924 Pa s^{-1} at 17.5% (w/w) and decreasing to 6390 Pa s^{-1} for 25% (w/w) lactose. Similar results for thixotropy loop areas were observed for lactose poloxamer/F88 formulations (Table 7). This effect of disperse phase concentration on thixotropy has not been previously reported in the literature and further investigation is required to explain the anomalous behaviour.

Thus, the rheological investigations indicate that although the qualitative effect of two size fractions of lactose on rheology is quite similar, the degree of thixotropic shear thinning behaviour exhibited by each system is different. At any given concentration of disperse phase, Sorbolac/poloxamer dispersions exhibited higher values of yield stress compared to Granulac-230/poloxamer systems, whereas, at an equivalent concentration of disperse phase, the degree of thixotropy was greater for Granulac-230 dispersions. The driving force to rebuild the floc is Brownian motion and since this increases with decrease in particle size, dispersions with larger particles recover their structure more slowly than systems of small particles (Barnes, 2000). Also, at an equivalent concentration of disperse phase, Granulac-230/poloxamer F88 dispersions exhibited a higher value of yield stress and lower loop area but similar rate indices compared to Granulac-230/poloxamer F68 systems (Table 8). Interpreting rheological data in relation to capsule filling signifies that controlled stirring of the molten formulation in the hopper would cause shear thinning of the dispersions and could increase the limiting concentration of disperse phase for satisfactory filling.

3.5. Effect of dispersion rheology on capsule filling

The rheological properties of the dispersion at the capsule filling temperature control the filling characteristics and dosage uniformity. Capsule filling studies of lactose/poloxamer dispersions in Sections 3.1 and 3.2 revealed that there was a critical concentration of disperse phase beyond which the formulation could not be filled into capsules. The critical concentration depended on the particle size distribution of disperse phase and poloxamer molecular weight. Detailed analysis of the rheograms in Section 3.4 shows that disperse phase concentration had a pronounced effect on rate index, thixotropy and yield stress, whereas, particle size and poloxamer molecular weight affected yield stress and thixotropy but not rate index. The analysis therefore provided a useful means to characterize the dispersions, however, changes in rheological parameters could not be directly related to changes in capsule filling performance above the critical disperse phase concentration for the formulations analysed in this work.

For dispersions that could not be filled into capsules, inspection of the machine revealed that the formulation was not drawn from the hopper into the pump. To obtain a better understanding of the rheological behaviour of formulations during capsule

Table 9
Apparent viscosity (η_a) calculated at a shear rate of $12\,s^{-1}$ and 70 °C for Granulac-230/F68 formulation

Disperse phase (%, w/w)	Volume fraction	Mean fill weight (g)	% cv	η_a at $12\,s^{-1}$ and 70 °C (Pa s)
10	0.071	0.439	0.44	2.5
15	0.109	0.447	0.17	4.2
20	0.147	0.443	0.27	7.3
25	0.187	0.442	0.31	11.1
30	0.228	0.439	1.29	19.7
35	0.271	0.405	3.36	35.5
37.5	0.293	–	–	54.0

filling, the apparent viscosity was calculated at a shear rate of $12\,s^{-1}$, the shear rate for transfer from hopper to pump estimated from Eq. (1). Estimated values of shear rate for (a) liquid transfer from hopper to pump, and (b) pump to capsule through the nozzle, were 12 and $340\,s^{-1}$, respectively. The shear rates were calculated using Eq. (1) (Cogswell, 1981), for hopper orifice diameter and nozzle diameter of 9.1 and 3 mm, respectively, with a volume flow rate of $0.9 \times 10^{-6}\,m^3\,s^{-1}$ estimated from the average time to fill a capsule of known volume.

$$\gamma = \frac{4Q}{\pi r^3} \quad (1)$$

where γ is the shear rate, Q the volume flow rate, and r is the radius of the nozzle, or hopper orifice.

The apparent viscosity of lactose/poloxamer F68 formulations calculated at a shear rate of $12\,s^{-1}$ (Tables 9 and 10) increased as concentration of lactose and interparticulate interactions increased. However, it was observed that particle size distribution had negligible effect on η_a at $12\,s^{-1}$ when the volume fraction of Granulac-230 was 0.025–0.1, Fig. 7. It is envisaged that in dilute suspension, the lactose particles are sufficiently separated so that there is no significant interaction, and as a result, changes in particle size distribution had no significant effect on the rheological behaviour of dilute suspensions and the viscosity increase was a function of concentration in the system. However, the difference between the apparent viscosity values for the different particle size dispersions was more pronounced as the concentration of disperse phase was increased, as shown (Fig. 7) by the effect of increase in volume fraction on η_a for both Granulac-230 and Sorbolac dispersions. As the concentration of disperse phase increased, the resistance to flow increased and there was an abrupt increase in apparent viscosity

Table 10
Apparent viscosity (η_a) calculated at a shear rate of $12\,s^{-1}$ and 70 °C for Sorbolac/F68 formulation

Disperse phase (%, w/w)	Volume fraction	Mean fill weight (g)	% cv	η_a at $12\,s^{-1}$ and 70 °C (Pa s)
10	0.071	0.453	0.62	3.17
15	0.109	0.451	0.53	6.41
20	0.147	0.450	0.71	13.2
25	0.187	0.444	1.37	24.8
27.5	0.208	0.431	2.67	35
30	0.228	–	–	56.4

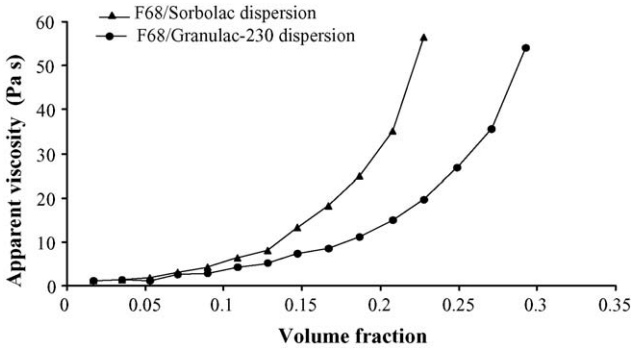

Fig. 7. Effect of disperse phase volume fraction and particle size on apparent viscosity at shear rate $12\,s^{-1}$ for lactose/poloxamer F68 dispersions at 70 °C.

between 0.228–0.271 phase volume for the Granulac-230/F68 dispersion and 0.147–0.187 for the Sorbolac/F68 formulation. As concentration levels corresponding to dense packing of solid particles are approached, there is no longer sufficient fluid in the system to lubricate the relative motion of particles and viscosity rises to infinity (Metzner, 1985). The results for η_a at $12\,s^{-1}$ in Tables 9 and 10 and Fig. 7 show that the magnitude of change in η_a becomes more pronounced between 25 and 30% (w/w) Granulac-230 and 20–25% (w/w) Sorbolac in F68. Further increase in lactose concentration in these systems cause greater changes in η_a values until the greatest increase occurs between 35 and 37.5% (w/w) Granulac-230 and 27.5–30% (w/w) Sorbolac. The results for changes in η_a with increase in lactose concentration, correlate with the capsule filling data which is reported in Sections 3.1 and 3.2, where at 37.5 and 30% (w/w) for Granulac-230 and Sorbolac dispersions, respectively, capsule filling was unsatisfactory.

Similar results were observed (Zettlemoyer and Lower, 1955) for dilute calcium carbonate dispersions in polybutene oil when viscosity was found to be directly proportional to concentration up to a volume fraction of 0.04 and above this concentration, viscosity increased markedly. An investigation of particle concentration on the rheology of titanium dioxide suspensions (Zupančič et al., 1997) showed a Newtonian plateau in a very low shear stress region, shear thinning in an intermediate shear stress region and shear thickening at higher shear stresses at the highest solid volume fraction. At a concentration of disperse phase when the distance between the particle surfaces approaches zero, surface characteristics play a significant role and this is evident by an abrupt change in slope on the viscosity versus volume fraction curve (Probstein et al., 1994). When the particle concentration approaches the maximum packing fraction the amount of dispersion medium is just enough to fill the voids between the particles and the relative viscosity increases abruptly. The results for concentrated dispersions of lactose/poloxamer F68 show similar effects of particle concentration on apparent viscosity and these data provide useful information in predicting limitations in capsule filling of particulate dispersions in polymer melts.

Similar findings have also been reported (Rowley et al., 1998) for PEG 6000/lactose dispersions, liquid filled into hard gelatin capsules. PEG 6000 had a viscosity of 1 Pa s at 70 °C and the

Table 11
Apparent viscosity (η_a) calculated at a shear rate of 12 s^{-1} and 70 °C for Granulac-230/F88 formulation

Disperse phase (%, w/w)	Volume fraction	Mean fill weight (g)	% cv	η_a at 12 s^{-1} and 70 °C (Pa s)
10	0.073	0.453	0.66	3.96
15	0.111	0.470	0.38	7.13
20	0.151	0.468	0.54	12.0
25	0.192	0.456	1.73	16.9
30	0.233	0.444	1.99	29.3
32.5	0.254	0.410	3.84	36.9
35	0.276	–	–	58.50

Table 12
Apparent viscosity (η_a) calculated at a shear rate of 12 s^{-1} and 70 °C for Sorbolac/F88 formulation

Disperse phase (%, w/w)	Volume fraction	Mean fill weight (g)	% cv	η_a at 12 s^{-1} and 70 °C (Pa s)
10	0.073	0.450	0.35	5.5
15	0.111	0.459	0.61	8.8
20	0.151	0.452	0.23	18.7
25	0.192	0.433	2.2	31.3
27.5	0.212	0.430	7.6	47.9

particle size distribution of lactose was 10% <3.7 μm and 90% <37 μm with a median volume diameter of 17 μm. The abrupt increase in apparent viscosity for this system occurred when the disperse phase concentration was 37.5% (w/w). In comparison, poloxamer F68 had a viscosity of 0.94 Pa s at 70 °C and for Sorbolac/poloxamer F68 dispersions used in this research, the abrupt increase in apparent viscosity occurred at lower concentration of disperse phase (>20%, w/w). Sorbolac has a slightly smaller particle size distribution 10% <2.4 μm and 90% <31.3 μm and a mean of 15.3 μm. The differences in the limiting concentration may be attributed to changes in the particle size distribution of lactose and as the concentration of disperse phase is increased, even slight changes in particle size distribution could have a significant effect on apparent viscosity.

Tables 11 and 12 and Fig. 8 present apparent viscosity data for lactose/poloxamer F88 dispersions calculated at a shear rate of 12 s^{-1}. There is little difference in apparent viscosity values

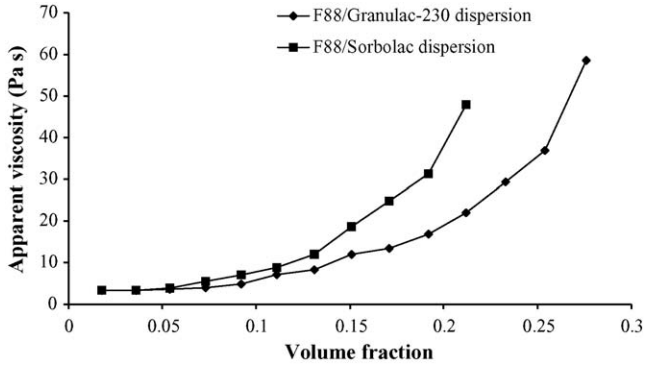

Fig. 8. Effect of disperse phase volume fraction and particle size on apparent viscosity at shear rate 12 s^{-1} for lactose/poloxamer F88 dispersions at 70 °C.

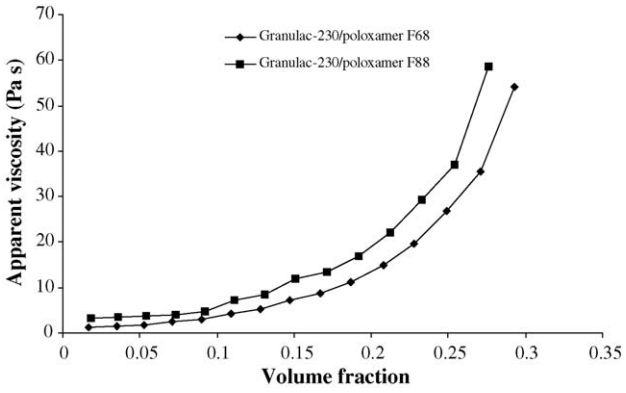

Fig. 9. Effect of disperse phase volume fraction and poloxamer viscosity on apparent viscosity at shear rate 12 s^{-1} for Granulac-230/poloxamer dispersions at 70 °C.

between lactose dispersions at disperse phase concentrations up to 7.5% (w/w) (volume fraction 0.054), Fig. 8. However, at higher concentrations there is a marked difference, with a higher apparent viscosity for dispersions containing Sorbolac compared to Granulac-230. The results indicate a marked effect of lactose particle size distribution on apparent viscosity above disperse phase volume of 0.15 and there is an abrupt increase in apparent viscosity at volume fraction 0.276 for Granulac-230/F88 dispersions and 0.212 for Sorbolac/F88 dispersions, attributable to the wider size distribution of Granulac-230. These differences correlate with capsule filling results reported in Sections 3.3 and 3.4 and confirm that the critical concentration of disperse phase that could be incorporated with satisfactory capsule filling, depends on the particle size distribution of disperse phase. The abrupt increase in apparent viscosity occurred at a lower concentration as the particle size distribution decreased.

Fig. 9 shows the effect of poloxamer molecular weight on the critical value of disperse phase volume fraction for Granulac-230/poloxamer dispersions. The abrupt rise in η_a occurred at a lower concentration of disperse phase as the poloxamer molecular weight increased from 8350 (F68) to 11,800 (F88). Capsule filling studies in Sections 3.1 and 3.3 revealed that F68/Granulac-230 dispersions could be filled satisfactorily with disperse phase volume fraction up to 0.271, whereas, satisfactory filling of F88/Granulac-230 dispersions could only be achieved up to 0.254. Beyond these concentrations there was an abrupt increase in apparent viscosity, which correlated with unsatisfactory capsule filling.

Formulations, which could not be filled into capsules had an apparent viscosity in the range of 54–58 Pa s at 12 s^{-1} with the exception of Sorbolac/F88 dispersions (47.9 Pa s), and examination of the machine showed that in all cases the formulation was not drawn from the hopper into the pump. As the apparent viscosity of the formulation increases, the pressure attainable by the pump may be insufficient to draw the formulation from the hopper into the pump chamber and as a result the formulation does not fill into capsules. Thus for the pressure used by the Hibar machine (60 psi), formulations with η_a in the range of 54–58 Pa s at 12 s^{-1} cannot be filled into capsules on the Hibar machine. However, for other manufacturing machines,

it may be possible to increase the pressure and hence fill formulations with higher apparent viscosity. Lactose/poloxamer dispersions exhibit thixotropic shear thinning behaviour and this would imply that formulations above the critical concentration could be filled into capsules, provided that a suitable mixer is placed in the hopper to decrease the apparent viscosity of the formulation. If this caused sufficient shear thinning to allow the formulation to be drawn into the hopper at a shear rate of $12\,s^{-1}$, then it is envisaged the extrusion of the formulation from pump to capsule at $340\,s^{-1}$ would proceed satisfactorily.

Further research should investigate the effect of mixer and hopper design on shear thinning behaviour and aeration of the formulation in relation to improvement of dispersion stability and pump filling stage of the capsule filling process. One of the major problems encountered during filling of viscous formulations was bridging of formulation between capsules. Increasing the temperature towards the maximum recommended for capsule filling may minimize this problem by decreasing the apparent viscosity of the formulation, however, the problem of sedimentation of drug particles as well as the solubility of the dispersed drug in the molten base may increase. It has been reported (Walker et al., 1980) that the dispenser of the capsule filling machine can be equipped with a device to reduce bridging by sucking back the formulation slightly on closure of the valve, alternatively, the forward speed control on top of the pump can be suitably adjusted, depending on the type of the formulation. Similarly, with highly viscous products, difficulties are encountered with transfer from hopper to pump and this may be due to backward speed of the pump piston being too high for the product to flow and fill the pump. In other words, the piston returns to the position to start its forward stroke before the formulation has fully filled in the pump and this certainly leads to variation in fill weights.

4. Conclusion

Capsule filling studies revealed that there was a limiting concentration of disperse phase beyond which the formulation does not fill satisfactorily into capsules. The limiting concentration of disperse phase decreased as the particle size distribution of the disperse phase decreased or the poloxamer molecular weight increased. Granulac-230, mean size 22.6 μm was filled satisfactorily in poloxamer F68 at 70 °C up to a concentration of 35% (w/w), whereas, Sorbolac mean size 15.3 μm was filled up to 27.5% (w/w). As the molecular weight of the poloxamer was increased from 8350 (F68) to 11,800 (F88) there was a decrease in the maximum concentration of disperse phase that could be filled satisfactorily into capsules. In general, it was observed that as the concentration of disperse phase increased, the mean fill weight decreased due to the increase in apparent viscosity and the bridging nature of the formulation. It was observed that there was a good correlation between satisfactory filling of molten dispersions into capsules and apparent viscosity of the formulation at $12\,s^{-1}$. Above the critical concentration, there was a pronounced increase in apparent viscosity and unsatisfactory filling occurred. Thus, the rheological investigations provided useful information in relation to the limitations of the capsule filling process and η_a values in the region of 50 Pa s at a shear rate of $12\,s^{-1}$ were associated with failure of the dispersion to flow from hopper into the pump. Analysis of the rheological data using the Herschel Bulkley model provided detailed characterization of all dispersion in terms of yield value, rate index and thixotropy, although these parameters could not be correlated with changes in filling properties above the critical disperse phase concentration. Lactose/poloxamer dispersions exhibit thixotropic shear thinning behaviour therefore the capacity of disperse phase could be increased by either introducing a mixer in the hopper to decrease the apparent viscosity of the formulation, or by increasing the pressure of the pump. The use of alpha lactose monohydrate as a model disperse phase with negligible solubility and thermal stability in the molten polymer has provided useful data for liquid-filling of capsules and this could be used to formulate a wide range of drugs with similar thermal and solubility properties.

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