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RESEARCH PAPER

Rheology and Filling Characteristics of Particulate Dispersions in Polymer Melt Formulations for Liquid Fill Hard Gelatin Capsules

G. Rowley,[1] A. R. Hawley,[1] C. L. Dobson,[1] and S. Chatham[2]

[1]*School of Health Sciences, University of Sunderland, Tyne & Wear, UK*
[2]*Lilly Research Centre Ltd., Windlesham, Surrey, UK*

ABSTRACT

The rheology and capsule filling properties of molten excipients, Dynafill, Dynasan-114, Lutrol-F68, and polyethylene glycols (PEG) 6000, 8000, 10,000, and 20,000 have been investigated. Lactose (α-monohydrate) was selected as a model particulate solid with low solubility in PEG in order to investigate the effects of disperse phase particle size, concentration, and PEG molecular weight on rheology and capsule filling properties of these systems. All excipients behaved as Newtonian fluids between 65 and 90°C, which was chosen as a possible temperature range for liquid filling of hard gelatin capsules. The excipients, apart from Dynasan-114 and PEG 20,000, showed satisfactory capsule filling properties at 70°C using a semi-automatic filling machine. Dynasan-114 (viscosity = 0.012 Pa·s at 70°C) leaked from the seals between the hopper and pump of the filling machine, whereas PEG 20,000 (viscosity = 24 Pa·s at 70°C) showed bridging of the molten polymer between successive capsule bodies during the filling process. The effect of disperse phase (lactose) particle size and concentration, and continuous phase (PEG) molecular weight on the apparent viscosity and filling properties of the non-Newtonian dispersions were investigated at 70°C. Satisfactory filling of the dispersions was achieved at 70°C up to a limiting concentration of disperse phase which was dependent upon disperse phase particle size and continuous phase molecular weight, and corresponded to a pronounced increase in apparent viscosity of the dispersion.

INTRODUCTION

Formulations for liquid fill hard gelatin capsules may be classified according to rheological properties during the filling stage. Liquid fill formulations can be (*a*) mobile Newtonian liquids, (*b*) thixotropic gels, both filled at ambient temperature (1), and (*c*) thermosoftened systems which are either Newtonian or non-Newtonian at elevated filling temperatures, e.g., 70°C, but solid at ambient temperature (2). Thus, fill weights and weight variation depend on the formulation rheology at the filling temperature.

Machinery is available to fill hard gelatin capsules at 60,000 capsules/hr with a low weight variation about the mean; a coefficient of variation <1.0% can be achieved for the three types of liquid fill already mentioned. In general, filling problems can be associated with formulation viscosity, and an approximate range of 0.01–25 Pa·s has been proposed for satisfactory filling. Formulation viscosity above the lower limit leads to (*a*) minimal losses through splashing during filling and (*b*) reduced chance of leakage from the two-piece shell, although leakage problems may be overcome by sealing the capsule with a gelatin band. Sealing equipment can be linked to the filling machine and rates of sealing match those of capsule filling. The upper limit of viscosity of the formulation is imposed by the limitations of the pump on currently available filling machines.

In general, if the active substance dissolves or melts in the excipient with little change in the viscosity of the formulation, then satisfactory filling is possible. However, if drug particles are insoluble or do not melt in the excipient, then the rheology of the disperse system becomes more complex and filling may be more difficult. The literature is lacking in detailed studies relating to the effects of particulate disperse phase on liquid filling of hard gelatin capsules.

In this work, the results of a practical investigation are presented to show the effects of excipient and formulation rheology, and disperse phase particle size and concentration on the filling properties of thermosoftened formulations.

MATERIALS AND METHODS

Materials

Polyethylene glycols MW 6000, 8000, 10,000, 20,000 (Hoechst); Dynafill, Dynasan-114 (Huls, UK); and Lutrol-F68 (BASF, UK) were used. α-Lactose monohydrate size fractions were (*a*) lactose$_1$ median volume diameter 169 μm (10% < 76 μm, 90% < 319 μm) and (*b*) lactose$_s$ median volume diameter 17 μm (10% < 3.7 μm, 90% < 37 μm), determined by laser diffraction technique using the Mastersizer (Malvern). Acetohexamide (Lilly), ibuprofen (Boots), indomethacin, prednisolone, propantheline bromide, sulfathiazole (all Sigma, Dorset, UK) were also used.

Methods

Particulate Disperse Phase Solubility in PEG 6000

The approximate solubilities of selected active substances and α-lactose monohydrate in PEG 6000 were determined at 70°C, which was chosen as a typical capsule filling temperature. A known mass of PEG 6000 was maintained at 70°C and solute particles added in small increments until saturation was observed over a period of 3 hr. The percentages w/w solute in PEG 6000 were as follows: propantheline bromide 0.6, prednisolone 1.0, sulfathiozole 1.7, α-lactose monohydrate 3.0, acetohexamide 5.2, and indomethacin 7.7. Lactose was thus chosen as a model for the disperse phase to represent active materials with low solubility in PEGS at a typical capsule filling temperature.

Capsule Filling

The excipients and dispersions were filled into hard gelatin capsules using a semiautomatic filling machine (Hibar, Canada) with hopper and nozzle temperature at 70°C (Fig. 1).

Rheology

Rheograms were determined for the unformulated excipients and disperse systems using a rotational viscometer (Haake RV3 and VT500) fitted with SV1 or MV2 concentric cylinder sensors.

RESULTS AND DISCUSSION

Rheology and Filling of Unformulated Excipients

Polyethylene glycols have been used extensively in research into solid dispersion formulations (3), whereas Dynafill, Dynasan-114, and Lutrol-F68 have been investigated previously as possible excipients for thermosoftened liquid fill formulations (2). Dynafill and Lutrol-F68 are poly(ethyleneoxide) poly(propyleneoxide) block copolymers with and without palmitic acid end groups, respectively, and Dynasan-114 is a myristic acid triglyceride. All of these materials melt below 65°C as indi-

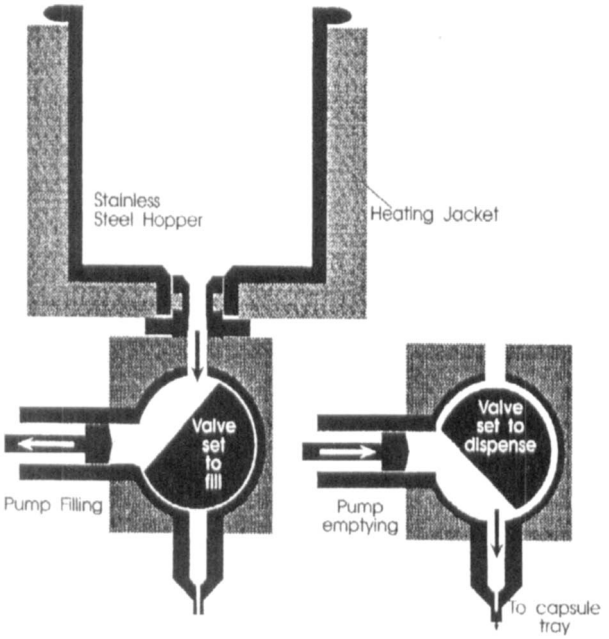

Figure 1. Hopper and filling valve on semiautomatic capsule filling machine.

cated in Table 1 and are thus potential excipients for liquid filling of capsules. The excipients behave as Newtonian fluids in the range of 65–90°C, which were chosen as possible liquid-filling temperatures, and the results for viscosity at 70°C and melting point values are presented in Table 1 for all excipients. However, because Dynafill, Dynasan-114, and Lutrol-F68, and higher molecular weight PEGS had not previously been used in liquid filling, a more detailed investigation was undertaken.

The results in Figs. 2–6 demonstrate Newtonian behavior for these excipients from temperatures just above the highest melting temperature up to 90°C. The upper temperature has been proposed as the maximum safe

Table 1

Viscosity and Melting Point of Various Excipients

Excipient	Viscosity at 70°C Pa·s	Melting Point °C
Dynafill	1.6	55
Dynasan-114	0.012	56
Lutrol-F68	1.2	53
PEG 6000	1.0	63
PEG 8000	1.9	63
PEG 10,000	5.5	63
PEG 20,000	24	64

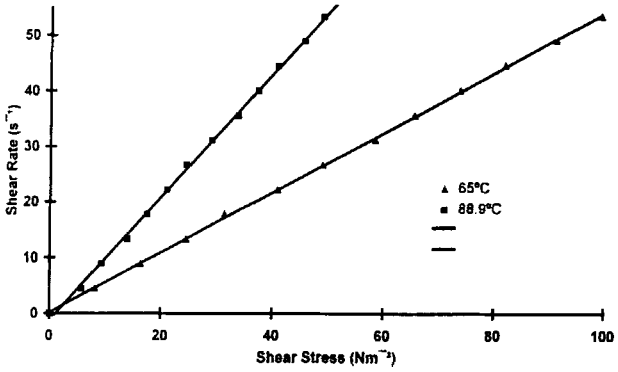

Figure 2. Rheograms for Dynafill at different temperatures.

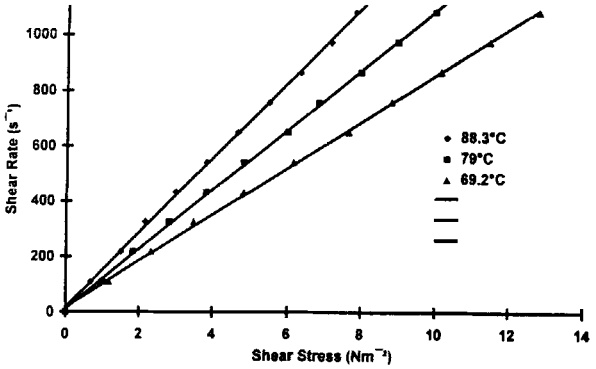

Figure 3. Rheograms for Dynasan-114 at different temperatures.

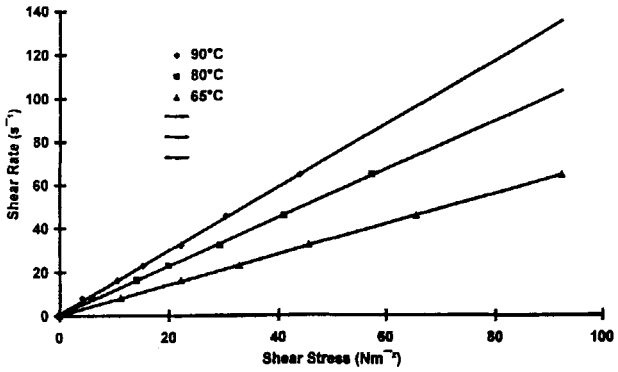

Figure 4. Rheograms for Luterol-F68 at different temperatures.

filling temperature for hard gelatin capsules, in order to minimize moisture loss from the shell. Small batches of approximately 100 capsules have been filled at 90°C in these laboratories, without adversely affecting the integrity of the capsule shell, and 80°C has been used for fill-

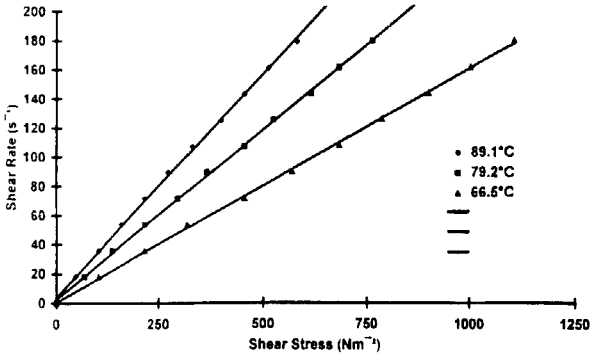

Figure 5. Rheograms for PEG 10,000 at different temperatures.

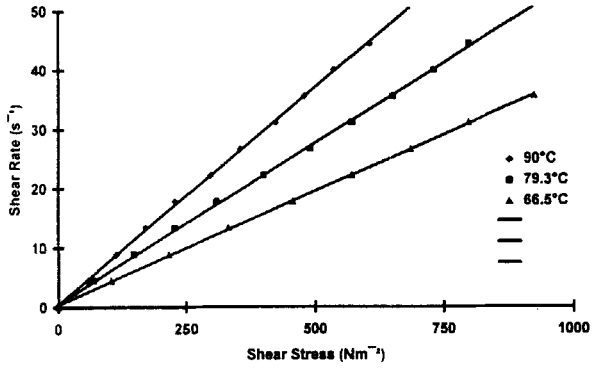

Figure 6. Rheograms for PEG 20,000 at different temperatures.

ing molten ibuprofen formulations (4). The results in Table 1 show a range of values for viscosity at 70°C from 0.012 Pa·s for Dynasan-114 to 24.0 Pa·s for PEG 20,000; however, the differences in viscosity at 70°C for the other excipients were much smaller, ranging from 1.0 for PEG 6000 to 5.5 Pa·s for PEG 10,000. Thus, it could be predicted that unformulated excipients in the latter group would have satisfactory filling properties. This was confirmed by analysis of the fill weight variation of the contents of no. 1 capsules, expressed as coefficient of variation (CV) in Table 2. PEGS 6000–10,000 had CV values less than 1.5%, whereas PEG 20,000 with a much higher viscosity at 70°C, had a CV value of 3.6%.

This increased variation for PEG 20,000 was attributed to the bridging of molten polymer between successive capsule bodies as shown diagramatically in Fig. 7. Dynasan-114 had a CV value for fill weight of 0.4%; however, two potential problems were observed for this low-viscosity excipient. First, slight seepage of the molten excipient occurred from the seals of the filler at the connection between hopper and pump. Second, there was evidence of splashing of the excipient from the capsule during delivery from the nozzle. From the results of the rheological and filling investigations of the unformulated excipients, it can be concluded that Dynafill, Lutrol-F68, and PEGs 6000, 8000, and 10,000 would be suitable materials for liquid filling of hard gelatin capsules. However, the effect of active ingredient on the rheology of liquid fill formulations requires detailed investigation.

Table 2

Analysis of Fill Weight Variation

Excipient	Mean Fill Weight (mg)	CV %	Sample Size
Dynafill	499	0.2	70
Dynasan-114	413	0.4	70
Lutrol-F68	504	0.5	66
PEG 6000	529	1.4	60
PEG 8000	537	1.3	60
PEG 10,000	521	0.3	70
PEG 20,000	503	3.6	48

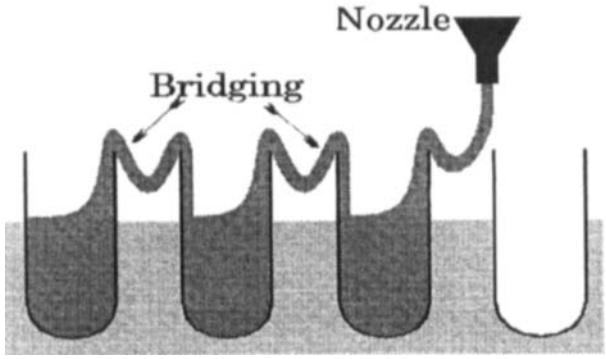

Figure 7. Bridging of molten PEG 20,000 between capsules during filling.

Rheology and Filling of Formulated Excipients

The incorporation of particulate drug into the molten excipient may result in drug dissolution, melting, or dispersion, and the rheology of the resulting formulation at the filling temperature will control the filling characteristics. Ibuprofen (melting point 75°C) was found to be miscible in all proportions with molten Dyanafill, Lutrol-

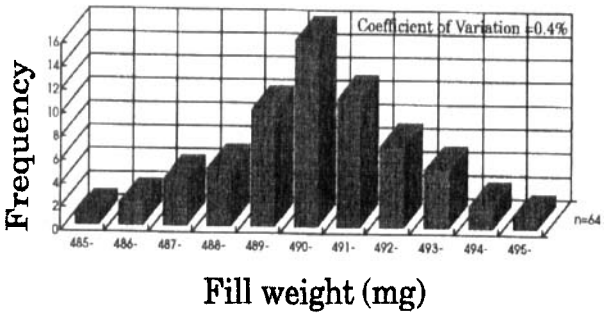

Figure 8. Capsule fill weight distribution of ibuprofen (50% w/w) Luterol-F68 (50% w/w) formulation.

F68, and PEGs 6000-10,000. In each case, the molten formulation was Newtonian at 70°C and the viscosity of formulations was similar to the values for unformulated excipient given in Table 1. Ibuprofen formulations with Dynafill, Lutrol F-68, and PEG 10,000 all had good filling properties in capsule size 1 with CV values for weight <0.5% in all cases. Figure 8 shows an example of this for a 50% w/w ibuprofen in Lutrol-F68 formulation filled at 70°C into size 1 capsules. The results showed a normal distribution of fill weights and CV value of 0.4%. Thus, active materials which have little effect on the rheology of the excipient should fill satisfactorily into hard gelatin capsules.

α-Lactose monohydrate was utilized as a model for an active substance which does not dissolve or melt, but forms a dispersion in the molten excipient. The effects of particle size, concentration of disperse phase, and viscosity of excipient were investigated and the excipients PEG 6000, 8000, and 10,000 were selected for this purpose. Size 3 capsules were used for the investigation of filling of lactose–PEG dispersions.

The rheograms of α-lactose monohydrate dispersed in PEG 6000 at 70°C show essentially Newtonian behavior and negligible shear thinning for lactose$_l$ up to 20% w/w lactose$_l$ in polymer, Fig. 9. Higher concentrations of this size fraction and all concentrations (from 6 to 45% w/w) of lactose$_s$ dispersions in PEG 6000 exhibited pseudoplastic (shear thinning) behavior at 70°C, as shown in Fig. 10. Similar effects on rheological behavior were observed for each lactose size fraction when dispersed in PEGs 8000 and 10,000.

The apparent viscosity of molten dispersions at 70°C was calculated at a shear rate of 12.5 sec^{-1} in order to facilitate the comparison of different formulations. The effects of particle size and concentration of disperse phase, and viscosity of continuous phase on the apparent viscosity of molten dispersions at 70°C is shown in

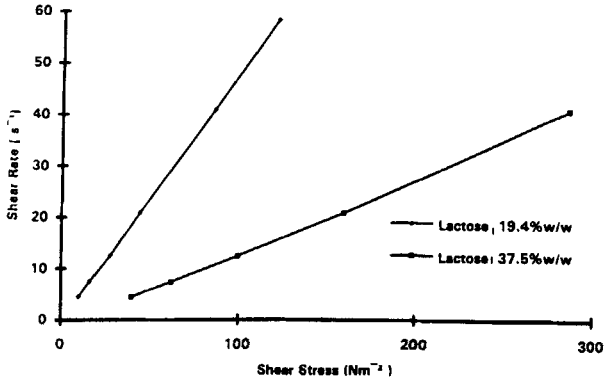

Figure 9. Rheograms of lactose$_l$ in PEG 6000 at 70°C

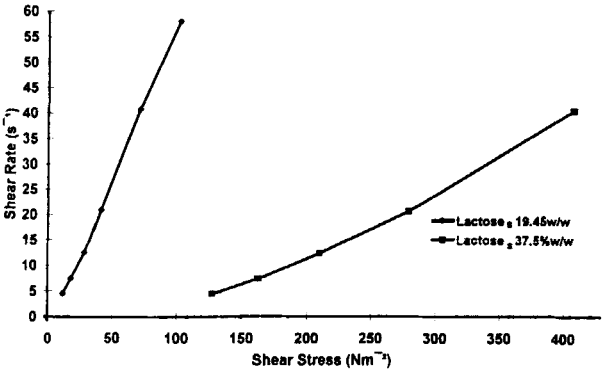

Figure 10. Rheograms of lactose$_s$ in PEG 6000 at 70°C.

Figs. 11 and 12. The effect of particle size on apparent viscosity is negligible up to approximately 35% w/w disperse phase, however, a considerable increase in apparent viscosity of the lactose$_s$–PEG 6000 (Fig. 11) occurs above 35% w/w disperse phase, resulting in a

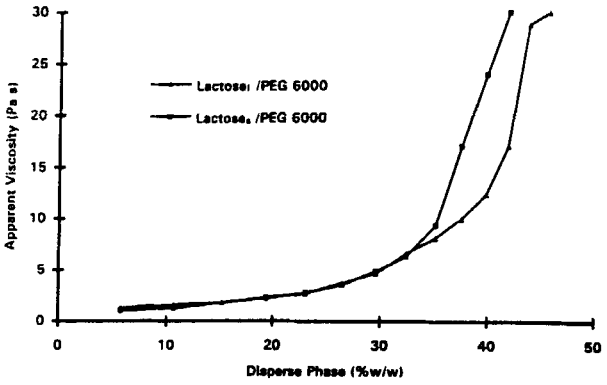

Figure 11. The effect on apparent viscosity of disperse phase concentration in PEG 6000 at 70°C.

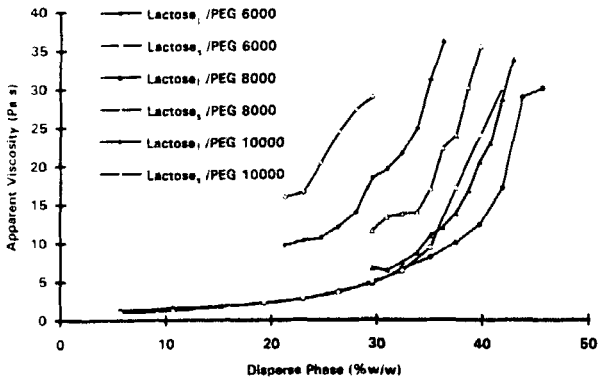

Figure 12. The effect on apparent viscosity at 70°C of disperse phase concentration and polymer molecular weight.

marked difference in apparent viscosity between the dispersions of each lactose size fraction at high disperse phase concentrations. These differences correlate with capsule fill weight variation shown in Table 3 and are discussed later.

Figure 12 shows the effect of PEG molecular weight as well as disperse phase particle size and concentration on apparent viscosity calculated at 12.5 sec^{-1} shear rate. The increase in apparent viscosity with disperse phase concentration for $lactose_l$ and $lactose_s$ in PEGs 8000 and 10,000 was similar in magnitude to that observed in Fig. 11 for $lactose_l$–PEG 6000 dispersions. However, these considerable increases in apparent viscosity occurred at lower disperse phase concentrations as particle size decreased and PEG molecular weight increased. These results will be discussed in relation to capsule fill weight variation.

Tables 3 and 4 show the capsule filling statistics for lactose dispersions in PEG 6000 and 8000, respectively, and it is clear from these results that both disperse phase particle size and continuous phase molecular weight affect the filling process. $Lactose_l$ dispersions from 16.7 to 50% w/w in PEG 6000 filled satisfactorily at 70°C with CV values of 3.3% or less. These filling statistics can be set in context by comparison with estimated CV values required for compliance with pharmacopeial weight uniformity tests. For example, the European Pharmacopoeial requirements for mean capsule content of 300 mg from a sample of 20 capsules is as follows: not less than 18 values should be within 277.5 and 322.5 mg and all 20 values should be within 255.0 and 345.0 mg.

From this it can be shown that a sample of 20 values comprising 2 values within outer limits (i.e., 255.5 and 344.5 mg) and 18 values within the inner limits (i.e., 9 of 277 mg and 9 of 322 mg) would comply with the EP requirements and have a coefficient of variation of 8.7%.

In a sample of 20 values, where all values lie within the inner limits and are normally distributed with a mean of 300 mg, and outer values are 279 and 321 mg, then the CV value is 3.5%. The capsule filling processes

Table 3

Capsule Filling Statistics for PEG 6000 Dispersions; Mean, m *(g) and Coefficient of Variation, CV (%)*

Disperse phase % w/w		16.7	28.6	37.5	44.4	47.3	50
$Lactose_l$							
m	315	325	317	319	303	293	
CV	3.1	1.6	0.8	1.3	2.9	3.3	
$Lactose_s$							
m	331	323	304	[a]			
CV	1.3	1.9	4.6	[a]			

[a]Formulation could not be filled.

Table 4

Capsule Filling Statistics for PEG 8000 Dispersions; Mean, m *(mg) and Coefficient of Variation, CV (%)*

Disperse phase % w/w	9.1	13.0	16.7	28.6	37.5	44.4	50
$Lactose_l$							
m	[a]	[a]	316	321	317	311	223
CV	[a]	[a]	0.9	0.8	2.2	6.0	44.0
$Lactose_s$							
m	302	313	[b]				
CV	5.4	8	[b]				

[a]Formulations not done.
[b]Formulation could not be filled.

should aim for CV values less than 3.5%, although as shown above, it is possible to comply with the EP specification with values between 3.5 and 8.7%. In this work, batches with CV values less than 3.5% will be regarded as satisfactory.

Whereas lactose$_l$ in PEG 6000 complied with this requirement (i.e., CV less than 3.5%) at disperse phase concentrations up to 50% w/w, the smaller particle size lactose$_s$–PEG 6000 dispersion showed satisfactory filling up to 28.6% w/w disperse phase. However, for 37.5% w/w lactose$_s$–PEG 6000 capsules the CV value increased to 4.6% and formulations with disperse phase concentrations greater than 37.5% w/w could not be pumped satisfactorily by the filler. Inspection of Fig. 11 shows that there is a considerable increase in apparent viscosity at dispersed lactose$_s$ concentrations greater than 35% w/w.

Table 4 shows that it is possible to satisfactorily fill lactose$_l$–PEG 8000 formulations up to 37.5% w/w lactose, whereas formulations of lactose$_s$ in the same polymer gave a CV of 5.4% and unsatisfactory filling at 9.1% w/w disperse phase. Formulations of 4.8% w/w lactose–PEG 10,000 gave unsatisfactory filling with CV values of 7.6 and 16.6% for lactose$_l$ and lactose$_s$, respectively.

Figure 12 shows similar changes in viscosity with increased disperse phase concentration for lactose$_s$–PEG 6000 and lactose$_l$–PEG 8000 formulations. These similarities in rheology correlate with the behavior of these formulations during liquid filling, i.e., 37.5% w/w disperse phase is the approximate upper limit for satisfactory filling. The maximum disperse phase concentration for satisfactory filling decreases markedly as the polymer molecular weight increases from 6000 to 10,000. Lactose$_l$–PEG 6000 can be filled with disperse phase concentrations up to 50% w/w, whereas dispersions of the same lactose size fraction with PEG 10,000 cannot be filled at 5% w/w disperse phase. Figure 12 shows that the pronounced increase in apparent viscosity occurs at lower disperse phase concentrations as the molecular weight of PEG increases.

CONCLUSIONS

The disperse phase capacity in molten vehicles is dependent upon the rheology of the formulation during the filling stage. The capacity corresponds to the concentration at which a pronounced increase in apparent viscosity occurs. Satisfactory liquid filling into capsules is dependent upon the viscosity of the molten continuous phase and the particle size of the disperse phase. It has been shown in this work that for a molten continuous phase with viscosity of 1 Pa·s at 70°C, the capacity of disperse phase is 50% w/w for the larger particle size fraction. This capacity is reduced by an increase in continuous phase viscosity and decrease in disperse phase particle size.

Detailed investigations of the effects of particle size distribution and particle agglomeration on the rheology and liquid filling properties of these systems is underway in order to predict disperse phase capacities in relation to capsule filling.

ACKNOWLEDGMENT

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