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The Effect of Poloxamer Viscosity on Liquid-Filling of Solid Dispersions in Hard Gelatin Capsules

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ABSTRACT Preliminary studies were undertaken on poloxamers to investigate their suitability for liquid-fill formulations for hard gelatin capsules. Poloxamers with viscosity in the range (0.32–2.8 Pa s) and melting point 48–58°C were used as the continuous phase, with α-lactose monohydrate of negligible solubility in the molten poloxamers, as a model insoluble disperse phase. Physicochemical characterization by rheology, melt solidification and moisture uptake indicated that poloxamers were suitable excipients for liquid-filling in hard gelatin capsules. 10% w/w lactose/poloxamer dispersions were thixotropic and shear thinning and exhibited good capsule-filling properties, disperse-phase uniformity and satisfactory apparent viscosity at 70°C.

KEYWORDS Thermosoftened system, Liquid-fill formulations, Rheology, Capsule filling, Poloxamers, Solid dispersion

INTRODUCTION

Liquid-fill formulations for hard gelatin capsules are often semisolid matrices and possibly thixotropic or thermosoftened formulations. In thermosoftened systems, the formulation is liquefied by heat to permit filling into the capsules, followed by rapid solidification on cooling to ambient temperature. The active ingredient will either dissolve, melt or form a particulate dispersion in the molten excipient at the capsule-filling temperature and the rheology of the resulting formulation will dictate the filling characteristics and dosage uniformity. The essential requirements, excluding those common to all pharmaceutical excipients, for formulating a thermosoftened system are principally related to thermal stability, rheology and effects on capsule integrity. The maximum safe temperature reported for satisfactory small-scale filling is 90°C, nevertheless in higoh-speed manufacture it is customary to fill at temperatures less than 70°C.

Several excipients have potential for use in thermosoftened formulations and among them, polyethylene glycol (Bowtle et al., 1988; Craig and Newton, 1992) and Gelucires® (Howard and Gould, 1987; Vial-Bernasconi et al., 1995) have been widely used. The majority of published work to date on thermosoftened formulations involved methods to enhance the dissolution properties of poorly water-soluble drugs using solid-dispersion technology (Khoo et al., 2000; Jung

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et al., 1999; Okonogi et al., 1997) or to develop sustained-release formulations (Esquisabel et al., 1996). Solid dispersions of griseofulvin with PEG produced improved drug dissolution (Chiou and Riegelman, 1969) and would have had the potential for liquid-filling into hard gelatin capsules due to the low melting temperature (< 65°C) of the PEGs. Drug/poloxamer thermosoftened systems have been researched (Utting et al., 1996 and Hawley, 1993), but in those cases the formulation formed a homogeneous one-phase system at the capsule-filling temperature, thereby eliminating any disperse-phase related filling problems.

Alternatively, if the drug forms a dispersion in the molten excipient, then the viscosity of the system will be affected and will be dependent on the concentration and particle-size distribution of the drug and also the molecular weight of the dispersion medium. For thermosoftened systems, good dispersion stability and apparent viscosity of the formulation play a significant role in achieving satisfactory capsule-filling properties and good drug content uniformity. So far, a detailed study investigating the consequence of disperse phase particle properties on dispersion stability, capsule filling and rheology has not been undertaken for thermosoftened systems, although investigations for thixotropic gels formulated for room temperature filling have been investigated (Saeed et al., 1999).

Poloxamers have the desired physicochemical characteristics essential for thermosoftened formulations but have not been investigated in detail and were accordingly considered as excipients for this research. α-lactose monohydrate remains essentially unaltered when heated up to 70°C, and this was an important consideration when selecting a model disperse phase for use in polymer melt formulations for liquid-filling into hard gelatin capsules. Even so, prior to final selection, the solubility of lactose in molten poloxamer at 70°C was investigated and found to be negligible. Lactose was thus chosen as a model for a drug that forms a dispersion in the molten base, in order to investigate the effect of disperse and continuous phase on dispersion stability, rheology, and capsule-filling properties.

MATERIALS AND METHODS

Materials

The physicochemical properties of the selected poloxamers (Synperonics PE/F38, PE/F87, PE/F68, PE/F88, ICI, 1994) are listed in Table 1, which indicates that all the polymers melt below 60°C and have viscosity in the range of 0.32–2.8 Pa s at 70°C.

TABLE 1 Physical Properties of Selected Poloxamers

Poloxamer	Approx. 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	11,800	28.0	58	2.80

α-lactose monohydrate Granulac-230 (Meggle GMBH) (mean particle size 23 μm; 10% < 2.9 μm, 90% < 49μm) investigated 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.

Preparation of 10% w/w Granulac-230/Poloxamer Dispersions

The poloxamers were melted in a constant temperature water bath at 70°C. Granulac-230 was added and mixed for 60 minutes under a vacuum using a paddle mixer (Ika-Werk RW 20 DZM) at 100 rpm in order to minimize aeration of dispersions (Kattige and Rowley, 1999).

Particle Size Analysis of Disperse Phase

Lactose/poloxamer solid dispersions were mixed with butan-1-ol to dissolve the poloxamer and leave the insoluble lactose in dispersion for particle size analysis using laser light scattering (Malvern Mastersizer 1000).

Moisture Uptake

The relative humidity was controlled using the saturated salt solution technique in glass containers with rubber seals (kilner jars), validated using a humidity/temperature probe (Testoterm 6000). Previous work (Mackin, 1995) reported that the lid-sealing system was satisfactory to maintain the required relative humidity. The jars containing the saturated salt solutions of magnesium chloride, sodium nitrite and sodium chloride were equilibrated for 1 week inside a

temperature cabinet at 25°C to provide relative humidities of 33%, 64%, and 75% respectively. Samples (0.5g ± 0.01mg) of each poloxamer were weighed in triplicate and placed inside open glass bottles in the kilner jars at each relative humidity at 25°C for 1 week to attain equilibrium. The samples were reweighed in order to calculate the equilibrium moisture content of the poloxamers at each relative humidity.

Analysis of Lactose and Disperse Phase Content Uniformity

The lactose content in poloxamer dispersions was ascertained by an enzymatic method (Boehringer-Manheim, 1999). β-galactosidic bonds in lactose was hydrolysed by β-galactosidase enzyme to form nicotinamide adenine dinucleotide, which is stoichiometric to the amount of lactose and measured spectrophotometrically at 340 nm. Preliminary studies indicated that poloxamer did not interfere with the analysis technique for lactose. Lactose content uniformity was established for 10 capsules from each batch prepared as described previously, by dissolving the contents of the capsule in distilled water at room temperature followed by enzymatic analysis.

Hot-stage Microscopy

Lactose/poloxamer dispersions were formulated as described previously and investigated qualitatively at 70°C using an optical microscope (Vickers model M170229) fitted with a hot-stage (Mettler FP 52) and temperature controller (Mettler FP5).

Cooling Characteristics

Cooling curves were obtained by using a K-type thermocouple attached to a digital thermometer (Coomark 9001) and inserted through a small hole made in the capsule wall. The temperature versus time was recorded every 10 seconds from the maximum temperature of the molten formulation (70°C) until it cooled to room temperature.

Rheology

Rheograms were determined at 70°C for poloxamers and disperse systems using a rotational viscometer (Haake VT 500) fitted with SV1 concentric cylinder sensors. The molten sample was equilibrated in the rheometer cylinder for 15 minutes at 70°C. Consequently, the shear rate was uniformly increased from 0–500 s^{-1} over 1 minute and then decreased to 0 s^{-1} for the same time period. The effect of temperature cycling on viscosity was investigated by heating the sample to 70°C, followed by cooling to room temperature and subsequently reheating to 70°C before viscosity determination. Furthermore, the consequence of storage time during capsule-filling was analysed by measuring the viscosity following storage of the poloxamer at the filling temperature (70°C) for 6 hours. Viscosity values were calculated from the slope of shear stress/shear rate data for three samples of each poloxamer dispersion.

Capsule Filling

The molten poloxamers and dispersions were filled into size 1 hard gelatin capsules using the Hibar capsule filler (Hi Tech Machinery, UK) and tested for weight uniformity by a modified BP method. The individual fill weight of 20 capsules per batch was determined by weighing each capsule before and after the filling process. The temperature of the hopper and pump was maintained at 70°C ± 0.1°C and the fill volume was set micromeretically to 0.2 ml for all poloxamers and their dispersions with lactose. The first 4 capsules were discarded to allow for removal of air from the pump/nozzle at the start of the experimental run. Capsules were filled semiautomatically in sets of 24 to produce a batch size of approximately 90 capsules from 150g of molten poloxamer or poloxamer/lactose dispersion. Removing and replacing the cap from the capsule body during the process was done manually.

RESULTS AND DISCUSSION

Rheology and Filling Characteristics of Molten Polymers

Rheological properties of the formulation at the filling temperature are vital in achieving suitable filling characteristics and dosage uniformity. Rheograms for all the molten poloxamers were linear at 70°C indicating Newtonian behavior. The correlation between poloxamer molecular weight and viscosity presented

in Table 1 denote that poloxamer F38 with a molecular weight of 4800 had a viscosity of 0.32 Pa s at 70°C. However, above molecular weight 7700 the viscosity increased sharply and was 2.8 Pa s for poloxamer F88.

Previous work (Hawley et al., 1992) signified that good uniformity of fill weights could be achieved with products having viscosity ranging from 0.1–25 Pa s whilst using a semiautomatic Hibar capsule-filler, as employed in this research. Nevertheless, it should be noted that the upper limit of viscosity for satisfactory capsule filling would depend on the type of capsule-filling machine utilized. The viscosity of the molten poloxamers used in this research is well within the range considered suitable for satisfactory capsule filling. Nonetheless, it was envisaged that the formation of a particulate dispersion due to addition of the lactose disperse phase, would augment the viscosity. Consequently, poloxamers with viscosity less than 3 Pa s at the capsule-filling temperature of 70°C were selected for this work.

In addition, the same sample of molten poloxamer was subjected to repeated shearing and temperature cycling (5 times) in order to investigate possible changes in viscosity that may occur during pharmaceutical processing. Preliminary results indicated that the poloxamers did not change in viscosity on repeated shearing or temperature cycling, and therefore should withstand typical liquid-filling processes for hard gelatin capsules.

Furthermore, filling of capsules by the thermosoftened technique may necessitate the maintenance of the molten excipient in the region of the filling temperature for several hours during manufacture and therefore it was crucial to investigate the rheological stability of molten poloxamers at 70°C. Table 2 depicts the results of the effect of heating period on the stability of molten poloxamers at 70°C. The value of viscosity for each poloxamer remained almost constant for 6 hours and there was no significant difference between viscosity values for 0-hour and 6-hour data when analysed using t test at a confidence level of 0.05. Each polymer showed excellent capsule-filling properties with a coefficient of variation (cv) less than 2.0%, as shown in Table 3. These results denote that poloxamers F38, F87, F68, and F88 have the appropriate rheological characteristics for liquid-filling into hard gelatin capsules by the thermosoftened technique.

Moisture Content Studies

The physical properties of hard gelatin capsules are strongly dependent upon moisture content, the optimum being in the 13–16% w/w range. Potential problems during filling and handling operations have been reported due to transfer of moisture between the gelatin capsules and their contents (Jones, 2004). When the moisture content falls below 10% w/w, the capsules become brittle and will easily split on handling and on rising above 18% w/w, the capsules soften, become sticky, and adhere to each other. The change in moisture content of the capsule is also reflected by changes in its physical dimensions (Jones, 2004). In addition, a capsule will have its optimum performance on high-speed filling machines if it is handled in an atmosphere with relative humidity between 30% and 50% (Bell, 1973). Consequently, it is essential to assess the moisture sorption/desorption characteristics of the excipient and actives to be filled in hard gelatin capsules.

Comparison of the mean % w/w moisture uptake values of selected poloxamers in this research is illustrated in Fig. 1 with values in the range 0.15–1.32% w/w, at relative humidity 33%, 64% and 75% respectively. Furthermore, all the poloxamers showed less than 1.4% moisture uptake at the highest relative humidity of 75%. If the relative humidity in the capsule filling area is less than 65%, then moisture uptake for the poloxamers will be $< 0.75\%$ w/w, thus providing strong evidence for the maintenance of capsule-shell integrity when filled with these poloxamers.

TABLE 2 **Effect of Heating Period on the Stability of Poloxamers Maintained at 70°C**

	Viscosity Pa s (% cv)			
	F38	F87	F68	F88
0 hours	0.332 (0.86)	0.655 (1.58)	0.949 (1.21)	2.817 (1.05)
2 hours	0.331 (0.70)	0.652 (2.00)	0.942 (1.79)	2.816 (1.3)
4 hours	0.328 (1.58)	0.656 (1.3)	0.943 (1.68)	2.800 (1.18)
6 hours	0.331 (1.05)	0.656 (1.36)	0.937 (1.96)	2.810 (1.46)

TABLE 3 Comparison of Capsule Fill Weight and Coefficient of Variation(cv) Values for Different Poloxamers at 70°C

Poloxamer	Mean fill weight (g)	cv (%)
F38	0.436	1.63
F87	0.437	0.81
F68	0.448	0.53
F88	0.447	0.30

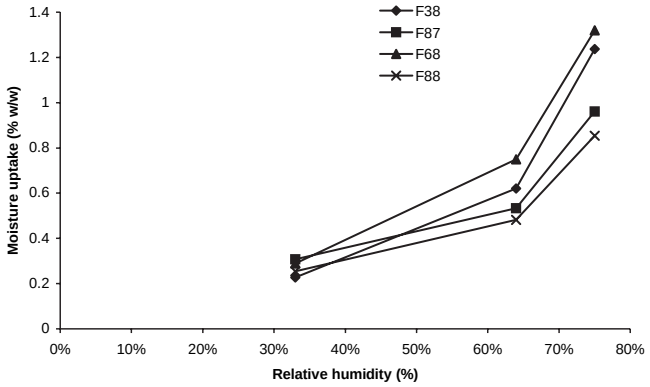

FIGURE 1 Moisture Uptake Data for Poloxamers at 25°C.

Granulac-230/Poloxamer Dispersions

Aeration of liquids during processing presents serious problems, particularly with disperse systems (Lin, 1962). High shear mixing of viscous solutions results in the formation of aerated systems, and as the viscosity of the suspension increases it becomes increasingly difficult to remove the entrapped air. Preliminary investigation of lactose/poloxamer dispersions indicated that significant aeration of the molten formulation occurred during incorporation of the disperse phase as evidenced by microscopy, especially for the two poloxamers of higher viscosity, F68 and F88. In order to overcome the problems associated with aeration, lactose/poloxamer dispersions were produced after mixing at 100rpm for 60 minutes under vacuum, and these dispersions were tested for particle size analysis, disperse phase content uniformity, weight uniformity and rheological reproducibility.

Particle Size Analysis of Disperse Phase

Lactose/poloxamer dispersion prepared using a paddle mixer at 100 rpm for 1 hour under vacuum may cause changes in particle size distribution of the disperse phase and therefore the size distribution of lactose was determined before and after mixing in the polymer melt.

TABLE 4 Comparison of Lactose Particle Size Distribution Before and After Mixing With the Polymer Melt

	Granulac-230 (μm)	Granulac-230 in thesolid dispersion (μm)
Mean	22.6	21.8
Median	16.2	15.5
10%<	2.90	3.90
90%<	47.6	45.1

The results presented in Table 4 indicated that the mean sphere diameters before and after mixing were 22.6 μm and 21.8 μm respectively. 10% of the particles were less than 2.9 μm and 90% were less than 47.6 μm in the original sample, whereas after mixing, 10% were less than 3.9 μm and 90% were less than 45.1 μm. There is little evidence for fracture of particles, and the size analysis data for original and mixed samples were not significantly different when analysed using t test at a confidence level of 0.05.

Disperse Phase Content Uniformity

The dispersions were assessed qualitatively by hot-stage microscopy, in order to observe the presence of any undispersed agglomerates. Samples from the formulations were taken every 10 minutes during the mixing process and examined microscopically to assess the state of dispersion. In all cases, de-aeration was accomplished within 60 minutes mixing as described previously. After mixing for 1 hour, the molten dispersion was poured into the hopper of the capsule-filling machine and was not agitated during capsule filling. Homogeneity of the dispersion will therefore depend not only on the efficiency of the initial mixing process, but also on the degree of sedimentation which may occur when the formulation is stored undisturbed in the hopper. The formulation was then filled into size 1 hard gelatin capsules and tested for lactose content uniformity by randomly selecting 10 capsules from the batch for lactose analysis and 20 capsules for weight uniformity. The nominal composition of the formulation in each capsule was 10% w/w lactose, 90% w/w poloxamer and the fill weight of each of the 10 capsules was recorded. The results for lactose content uniformity and weight

uniformity presented in Table 5 indicate that the mean fill weight range for the four poloxamer dispersions containing 10% w/w lactose was 0.450–0.460g with a cv in the range 1.04–1.29%. Individual capsule fill weights for all four dispersions were within ± 7.5% of the mean. The BP (1998) states that not more than 2 capsules are allowed to deviate from the mean by 7.5% where the capsule contents weighed more than 300 mg, and none are allowed to deviate by more than twice that percentage. The mean fill weight of all the formulations was therefore within BP specifications and cv less than 1.5%. The BP weight uniformity results and the low cv values verify that 10% w/w lactose dispersions in poloxamers are suitable for satisfactory liquid-filling in capsules.

The BP requirements for uniformity of content state that if not more than 1 of the individual values from a sample of 30 capsules obtained was outside the range 85–115% of the mean value and none were outside the limits 75–125% of the mean, the batch is satisfactory. All the formulations tested were within the BP specifications for drug content uniformity and in addition the coefficient of variation of all the formulations was less than 1.6% in each case (Table 5). The cv for F38 formulation was slightly higher than for other formulations and although assessment of this dispersion using hot-stage microscopy revealed that a longer mixing time was required for dispersing lactose in poloxamer F38 melt, the results in Table 5 show that this dispersion could be filled satisfactorily with a low cv for content uniformity, thus providing evidence for uniform distribution of lactose in the dispersion.

Mixing using a paddle mixer at 100 rpm for 1 hour under vacuum is therefore a suitable method for dispersing the lactose in the polymer melt and could be used for dispersion of other hydrophilic particles of similar size distribution in these excipients. Moreover, mixing under vacuum minimized air entrapment in the molten matrix, resulting in uniform capsule fill weights. Also, additional evidence for de-aeration of the formulation was confirmed by hot-stage microscopy. This investigation therefore proves that 10% w/w lactose dispersions in the selected poloxamers can be filled satisfactorily at 70°C, with a coefficient of variation values less than 1.5%.

Dispersion Stability

Dispersion stability is related to the drug particle size, viscosity of the excipient and the relative densities of the disperse phase and the dispersion medium at the capsule-filling temperature and during cooling. Significant sedimentation could seriously affect the drug content uniformity of capsules and therefore dispersion stability was investigated using the lowest viscosity poloxamer, F38 (0.32 Pa s). 10% w/w lactose/poloxamer F38 formulation was poured into the hopper of the capsule-filling machine and allowed to stand undisturbed in the hopper for 6 hours. Capsules were filled every 2 hours and tested for uniformity of weight and lactose content. The results presented in Table 6 demonstrate that the mean fill weight at the start of the experimental run was 0.438g and remained consistent for 6 hours with values of 0.449g, 0.451g, and 0.450g at 2, 4, and 6 hours respectively. Statistical analysis of mean fill weights obtained at different time intervals were not significantly different when compared by t test for unpaired values at a confidence level of 0.05. There appears to be no correlation between mean fill weight, coefficient of variation, and storage time in the hopper. The coefficient of variation was satisfactory and less than 1% in all the cases.

The results for mean lactose content and coefficient of variation in Table 6 show that the dispersion is stable with no significant effect of storage time on sedimentation of lactose particles. The lactose content in

TABLE 5 **Analysis of Mean Fill Weight, Lactose Content and Coefficient of Variation for 10% w/w Granulac-230/Poloxamer Dispersions**

10%w/w Granulac-230 and 90%w/w poloxamer	Content uniformity		Weight uniformity	
	Mean lactose content(mg)	% cv	Mean fill weight (g)	% cv
F38	45.1	1.55	0.451	1.13
F87	44.8	0.60	0.450	1.29
F68	43.8	1.12	0.451	1.04
F88	44.8	1.18	0.460	1.17

TABLE 6 Effect of Storage Time on Dispersion Stability for 10% w/w Granulac-230 Dispersed in F38 at 70°C

	Weight uniformity		Content uniformity	
Time (hours)	Mean fill weight (g)	% cv	Mean lactose content (mg)	% cv
0	0.438	0.35	43.7	0.30
2	0.449	0.94	44.9	1.38
4	0.451	0.11	44.6	2.18
6	0.450	0.18	44.2	1.40

the capsule at the start of the experimental run was 43.7 mg and was subsequently consistent with time, giving values of 44.9, 44.6 and 44.2mg at 2, 4 and 6 hours respectively. As there was no significant sedimentation for a period of 6 hours for the lowest viscosity poloxamer (F38), it can be assumed that there will not be any significant sedimentation for the higher viscosity poloxamers containing the same concentration of lactose.

Rheology of 10%w/w Granulac-230/ Poloxamer Dispersions

If the drug is soluble in the excipient, it is likely to have a negligible effect on the viscosity of the formulation except at extremely high concentrations. However, addition of insoluble powders, e.g. α lactose monohydrate, that form a suspension in the molten excipient will affect the viscosity of the system and will be dependent on (a) concentration and particle size distribution of the disperse phase and (b) molecular weight of the dispersion medium.

Table 7 denotes the apparent viscosity of the dispersion calculated at a shear rate of 150 s^{-1} and the relative increase in viscosity on addition of lactose to selected poloxamers. Addition of 10% w/w lactose increased the viscosity of all the poloxamers significantly, and conferred thixotropic behavior to the system as illustrated by the rheograms in Fig. 2. The relative increase in apparent viscosity was 2.38, 1.86, 1.79, and 1.14 for poloxamer F38, F87, F68 and F88 respectively. This signifies that for the same concentration of disperse phase, the relative increase in viscosity decreased with increase in poloxamer viscosity from the F38 to F88 dispersion. The shear thinning effect of these dispersions between shear rates of 50–150 s^{-1} is presented in Table 8. The percentage decrease in apparent viscosity (Table 9) for 10% w/w lactose/F38 dispersion was 7.5% and 11% at a shear rate of 100 s^{-1} and 150 s^{-1} respectively, compared with 4.7% and 6.3% for 10% w/w lactose/poloxamer F87 dispersion. A similar trend was observed for 10% w/w lactose F68 and F88 dispersions. The results in Table 9 clearly indicate the increasing shear thinning behavior with decrease in apparent viscosity of the formulation from F88 to F38 dispersions. In conclusion, the results indicate that for a particular concentration of disperse phase the relative increase in viscosity and shear thinning behavior decreases when the viscosity and PEO chain length of the poloxamer increases. These rheological properties of 10% w/w lactose dispersions in poloxamers with MW from 4800–11800 were therefore suitable for satisfactory liquid-filling of hard gelatin capsules.

Cooling Characteristics

Addition of the drug to the polymer melt may perhaps influence the recrystallization temperature of the polymer by nucleating and inducing crystallization of the polymer or through enhancing the degree of supercooling by retarding crystallization of the polymer. This phenomenon occurs when the drug is soluble in the base or when present in a high concentration (Chatham, 1987).

TABLE 7 Apparent Viscosity (η_a) and Relative Increase in Viscosity of 10%w/w Granulac-230/Poloxamer Dispersion at Shear Rate 150 s^{-1} Compared to That of the Individual Poloxamer

10% w/w Granulac-230/poloxamer dispersions	Molecular weight of PEO segment	η_a (Pa s) at 70°C and 150 s^{-1} shear rate	Relative increase in viscosity
F38	3882	0.76	2.38
F87	5282	1.21	1.86
F68	6532	1.68	1.79
F88	9382	3.21	1.14

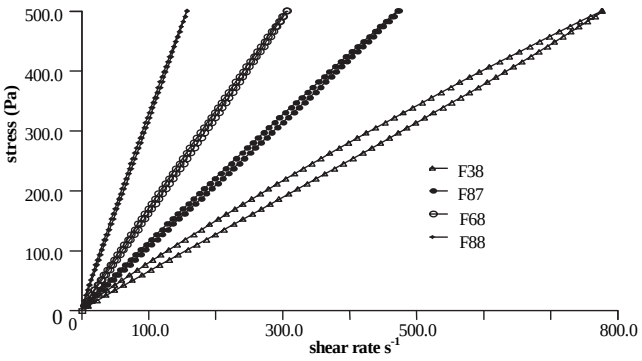

FIGURE 2 **Rheological Behavior of 10% w/w Granulac-230/ Poloxamer Dispersions at 70°C.**

Cooling profiles of molten poloxamers and lactose/ poloxamer dispersions from 70°C to room temperature occurred over 13–15 minutes as indicated in Figs. 3 and 4 respectively. The cooling curves consisted of 4 stages, (a) rapid temperature reduction lasting approximately 40–100 seconds, (b) a temperature minimum, (c) a small rise in temperature due to the exothermic heat of crystallization of the polymer and (d) a plateau temperature followed by a final temperature reduction as the solidified dispersion cooled to ambient temperature. The results for the cooling profile of molten poloxamers and 10% w/w lactose/poloxamer dispersions are depicted in Table 10 for stages c and d of the curves. The temperature minima were 33.5, 38, 36.6, and 38.4°C for poloxamers F38, F87, F68, and F88 respectively, whereas 10% w/w lactose/poloxamer formulations demonstrated higher values of 37.2, 39.6, 41.3, and 43.9°C for F38, F87, F68, and F88 respectively. These results indicate slight supercooling for both the molten poloxamers and lactose/poloxamer dispersions after the formulation was filled into capsules. T test analysis of the results for temperature minimum of poloxamers F38, F87, F68, and F88 were statistically different from that of 10% w/w lactose/poloxamer dispersions when compared by unpaired values at a confidence level of 0.05, thus providing evidence to show that the addition of lactose decreased the degree of supercooling. The presence of lactose crystals in the cooling polymer resulted in a higher solidification temperature than that for the polymer alone, as revealed by the comparison of cooling curve plateau temperatures in Table 10, and this was attributed to lactose particles inducing the nucleation for the recrystallization of the polymer.

In summary, although supercooling occurred for the poloxamer melt and to a lesser extent for the lactose/poloxamer dispersion, the recrystallization temperature was high enough in both cases to prevent leakage of the formulation after filling into capsules. The formulations solidified rapidly after filling into capsules as indicated by the completion of the plateau stage of the cooling curves in Fig. 4. The results signified that solidification of the lactose dispersions in F87, F68, and F88 was complete in approximately 2–3 minutes, whereas for F38 solidification took approximately 3–4

TABLE 8 **Apparent Viscosity (η_a) of 10%w/w Granulac-230/Poloxamer Dispersions at 70°C and at Different Shear Rates**

10%w/w Granulac-230/poloxamer dispersions	η_a (Pa s) at shear rate 50 s^{-1}	η_a (Pa s) at shear rate 100 s^{-1}	η_a (Pa s) at shear rate 150 s^{-1}
F38	0.86	0.79	0.76
F87	1.29	1.23	1.21
F68	1.79	1.71	1.68
F88	3.42	3.27	3.21

TABLE 9 **Comparison of the Shear Thinning Behavior of 10%w/w Granulac-230/Poloxamer Dispersions at 70°C**

10%w/w Granulac-230/poloxamer dispersions	η_a (Pa s) at shear rate 50 s^{-1}	% decrease at 100 s^{-1} from 50 s^{-1}	% decrease at 150 s^{-1} from 50 s^{-1}
F38	0.9	7.5	11
F87	1.3	4.7	6.3
F68	1.8	4.3	6.0
F88	3.4	4.3	6.0

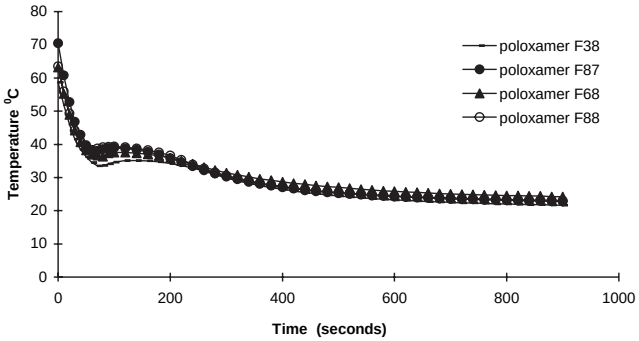

FIGURE 3 **Cooling Curves of Poloxamers.**

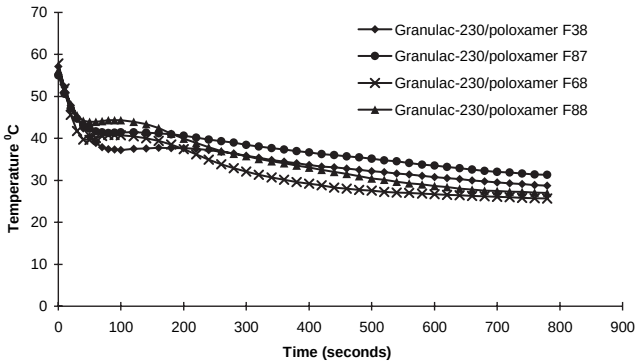

FIGURE 4 **Cooling Curves of 10%w/w Lactose Dispersions Formulated with Different Poloxamers.**

TABLE 10 **Cooling Characteristics of Molten Poloxamers and 10% w/w Lactose Poloxamer Dispersions, Shown as Temperature Minimum (T_{min}) and Temperature of the Plateau (T_{plat})**

	10%w/w lactose/ poloxamer dispersion		Molten poloxamer	
Poloxamer	T_{min} °C	T_{plat} °C	T_{min} °C	T_{plat} °C
F38	37.2	37.3–37.8	33.5	33.7–35.1
F87	39.6	40.1–40.7	38.0	38.5–38.9
F68	41.3	41.3–41.4	36.6	37.1–37.5
F88	43.9	44.0–44.3	38.4	38.7–39.3

minutes. Overall, it can be concluded that the lactose polymer dispersions are satisfactory for liquid-filling into capsules due to the lack of supercooling and rapid solidification times in the capsule.

CONCLUSION

The study indicates that poloxamers F38, F87, F68, and F88 are suitable materials for liquid-filling of hard gelatin capsules by the thermosoftened technique. Preliminary rheological investigations of poloxamers using a rotational viscometer at 70°C, revealed that they exhibited Newtonian behavior. In addition, the poloxamers were stable to heat when maintained at 70°C for 6 hours and did not change in viscosity on repeated shearing or temperature cycling. The poloxamers showed excellent capsule-filling properties with coefficient of variation values of the mean fill weight, less than 2%. The poloxamers and lactose/poloxamer dispersions solidified completely within 3–5 minutes in the gelatin capsule after filling at 70°C. Rapid solidification of a molten formulation after filling into capsules is desirable in order to minimize leakage of contents and settling of drug particles and to preserve the uniformity of the dispersion in the solidified poloxamers. All the poloxamers showed less than 1.4% moisture uptake at the highest relative humidity of 75% and therefore should not affect the mechanical properties and dimensions of the gelatin capsule. The results of the investigation showed that the selected poloxamers have suitable physical characteristics for filling into hard gelatin capsules. In addition, mixing under vacuum was instrumental in reducing the preparation time of the formulation and achieved a deaerated mix, with satisfactory capsule-filling statistics. 10%w/w formulations of lactose in different poloxamers were thixotropic and shear thinning with good filling properties and satisfactory disperse phase viscosity.

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