

## IMPORTANCE OF PREPARATION CONDITIONS ON SOME PROPERTIES OF POLYETHYLENE GLYCOL 6000 (PEG 6000) SOLID DISPERSIONS

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The influence of solidification temperature ( $T_c$ ) on the dissolution rates of solid dispersions is alleged to be critical since rapid cooling to low temperatures favours the generation of many nucleation sites, a small crystallite size and rapid dissolution rates (Collett et al 1976). The influence of fusion temperature ( $T_f$ ) on dispersion properties has not been quantified and we have therefore investigated the influence of  $T_c$  and  $T_f$  on PEG6000 dispersions containing 5% of indomethacin(I) or phenylbutazone (II).

Dissolution rates from constant area discs (Ford & Rubinstein 1978) were determined using a Copley Series 8000 Dissolution Tester, monitoring I and II at 266 and 264mm respectively. Dispersions were prepared by initial fusion at 160°C for 15 mins, solidification at ambient ( $\sim 20^\circ\text{C}$ ) for 24 hrs and subsequent reheating at  $T_f$  of 80, 100 or 120°C for 15 mins followed by crystallisation at a  $T_c$  of 4 or 37°C for 1 hr in the disc holders. For microscopy, PEG6000 and the dispersions were studied under identical preparation conditions but by weighing 2mg samples onto microscope slides, covered by cover-slips. Photomicrographs of the structures were taken using a Pentax KM camera attached to a Nikon Labophot Microscope fitted with crossed Nicol prisms.

Each system crystallised typically as spherulites which were smaller and more numerous at  $T_c = 4^\circ\text{C}$  where the minimum spherulite radius was  $< 16\mu\text{m}$  independent of  $T_f$ . For PEG6000 the maximum radii were  $\sim 0.8$ ,  $\sim 1.1$  and  $\sim 1.15\text{mm}$  at  $T_f$  of 80, 100 and 120°C and a  $T_c$  of 4°C. Similarly in the dispersions the maximum radii were  $\sim 0.5$ , 0.87 and 1.16mm for I at  $T_f$  of 80, 100 and 120°C but for II were 1.05mm irrespective of  $T_f$ . However at the  $T_c$  of 37°C PEG6000 showed maxima of  $\sim 1.9$ , 2.2 and 2.75mm for  $T_f$  of 80, 100 and 120°C and the minimum at each  $T_f$  was  $> 0.25\text{mm}$ . At  $T_c = 37^\circ\text{C}$  the minima were  $\sim 1.0$  and  $\sim 0.65\text{mm}$  for dispersions containing I and II respectively, independent of  $T_f$  and the maximum for each system was 4.5mm. These results are consistent with the findings of Vidotto et al (1969) that the number of nucleation sites in PEG decreased as  $T_f$  increased.

Table 1: Influence of  $T_f$  and  $T_c$  on the dissolution rates ( $\text{mg min}^{-1}$ ) of PEG6000 dispersions containing 5% I or II, mean of 4-6 results.

Dispersion	$T_c$ ( $^\circ\text{C}$ )	$T_f$			
		80°C	100°C	120°C	
5% I	4	3.95	3.34	3.04	The difference in spherulite size might be expected to modify dissolution but Table 1 indicates that although smaller spherulites of I dispersions were obtained at $T_c = 4^\circ\text{C}$
"	37	3.37	3.26	3.14	
5% II	4	0.53	0.57	0.51	
"	37	1.17	1.15	1.12	

only at  $T_f = 80^\circ\text{C}$  were significant differences obtained from dispersions solidified at  $T_c = 4$  or  $37^\circ\text{C}$ . In contrast dispersions of II displayed higher releases at  $T_c = 37^\circ\text{C}$  than  $4^\circ\text{C}$ . All the dissolution profiles were linear except for 5% II at  $T_c = 4^\circ\text{C}$  which were biphasic after an initial 2 min period which was used to calculate rates.

These preliminary results indicate that dissolution rates from solid dispersions cannot be anticipated merely from a knowledge of  $T_f$  and  $T_c$  and that both the temperatures of crystallisation and fusion should be tightly controlled to standardise dissolution from solid dispersions.

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