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An investigation into the production of paracetamol solid dispersions in PEG 4000 using hot stage differential interference contrast microscopy

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Abstract

The melting and crystallisation behaviour of paracetamol dispersions in polyethylene glycol (PEG) 4000 has been studied using differential interference contrast microscopy fitted with a hot stage. The effects of thermally cycling physical mixes of the two components have been studied with particular reference to the effects of the presence of molten PEG 4000 on the melting behaviour of the model drug. The effects of the drug particle size, the maximum temperature of heating and the holding time at the maximum temperature on the solid dispersion structure have been investigated, with profound changes in structure being observed depending on the manufacturing protocol used. In particular, higher maximum temperatures and holding times with lower drug particle sizes promoted greater dissolution of the drug into the molten PEG. In the majority of systems observed, the remaining paracetamol particles simply persisted as the system was cooled. However, for certain systems, involving high drug loadings and extended holding times and temperatures in the liquid state, the drug recrystallised over a 24-h period to form a fine dispersion within the carrier. The study has therefore demonstrated the usefulness of hot stage microscopy as a method of directly observing the processes involved during the manufacture of solid dispersions and has also indicated that changing the manufacturing protocol may have a profound effect on the structure of the dispersion. © 1997 Elsevier Science B.V.

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1. Introduction

The use of solid dispersions as a potential means of improving the dissolution behaviour of poorly soluble drugs has been well documented

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(e.g. Chiou and Riegelman, 1971; Corrigan, 1985; Ford, 1986; Craig, 1990). However, the practical applicability of this approach has remained somewhat limited, which may be ascribed to a number of factors. The mechanism by which drug dissolution enhancement takes place is still not fully understood, while problems such as physical instability have been frequently reported. There is also a need to develop rational manufacturing strategies; solid dispersions are usually prepared by heating a physical mixture of the drug and water soluble polymer to the liquid state, followed by cooling to room temperature. However, Chatham (1985) clearly demonstrated that the heating and cooling protocol used may be of importance in determining dissolution behaviour and possibly stability. There is therefore a need to extend the knowledge base regarding the relationship between the manufacturing protocol and the subsequent product performance. In particular, little is known regarding the effects of factors such as the initial particle size of the drug, the maximum temperature used and the holding time at that temperature.

One of the major difficulties associated with investigations into solid dispersions is that it has proved difficult to reliably characterise the solid state structure of the binary systems. Techniques such as differential scanning calorimetry (DSC), hot stage microscopy (HSM) and X-ray diffraction have been extensively used, although each method carries concomitant disadvantages and assumptions associated with its use. For example, a recent publication (Lloyd et al., in press) has discussed the use of DSC in the study of binary systems, demonstrating the ease with which misinterpretation of the data obtained may occur. In addition, there is a lack of knowledge regarding the physical changes that take place in both the drug and carrier during the manufacturing process itself. In this investigation, we report on the use of differential interference contrast (DIC) microscopy fitted with a hot stage as a means of studying the processes associated with the manufacture of solid dispersions using a model drug, paracetamol. In particular, the effects of the manufacturing conditions on the structure of the dispersions will be discussed.

2. Materials and methods

2.1. Materials

Polyethylene glycol (PEG) 4000 (Hoechst, Hounslow, England) was ground, sieved and the < 250 μm size fraction used. Paracetamol (Sterling Organics, Dudley) was sieved and three size fractions used as stated (< 50, 150–200 and 300–350 μm). Physical mixtures containing 5, 10, 15, 20, 25 and 30% w/w paracetamol were prepared using a Turbula T2C Mixer (Bachofen, Basle, Switzerland).

2.2. DIC hot stage microscopy

Differential interference contrast microscopy works on the principle of illuminating the sample using plane polarised light which is separated into two beams by a Wollaston prism. One passes through a feature in the sample, the other to one side. The beams are recombined by a second Wollaston prism above the objective lens. When this occurs, phase change introduced into the object beam by the sample is converted into an amplitude of colour difference. Therefore, it is possible to view samples in a variety of colours, while images are more three dimensional in appearance when compared to those produced by conventional light microscopes. The angle at which the second prism is set relative to the first can be manually adjusted, allowing the background to be altered through the primary colours of the visible spectrum. The colours of sample materials will then be set relative to the background dependent on the beam phase changes introduced (Bradbury, 1984).

2.3. Solid dispersion production simulation

Samples were analysed using a Mettler FP52 Hot Stage (Mettler, Zurich, Switzerland) connected to an FP5 Temperature Controller and viewed using an Olympus BX50 DIC Microscope (Microscope Service and Sales, Egham). The DIC microscope employed in conjunction with the hot stage was fitted with a long working distance $\times$ 10 magnification objective lens. The microscope

Table 1
HSM data for paracetamol (<50 μm)–PEG 4000 physical mixtures thermally cycled using a scanning speed of 2°C min^{-1}

Drug content (%w/w)	Mean PEG 4000 melting range (°C)	Mean PEG 4000 recrystallisation onset temperature (°C)	Mean PEG 4000 remelting range (°C)	Mean paracetamol remelting range (°C)
0	54.6–58.9 (±0.1/0.2)	44.6 (±0.1)	54.4–58.7 (±0.2/0.2)	—
5	54.0–58.3 (±0.1/0.2)	43.8 (±0.1)	52.8–56.2 (±0.1/0.2)	56.2–69.5 (±0.2/0.2)
10	53.7–57.9 (±0.1/0.2)	42.6 (±0.1)	52.3–55.7 (±0.2/0.2)	55.7–83.8 (±0.2/0.3)
15	53.3–57.7 (±0.1/0.2)	41.7 (±0.2)	51.9–55.2 (±0.2/0.3)	55.2–94.1 (±0.3/0.3)
20	53.0–57.6 (±0.2/0.2)	40.6 (±0.2)	51.6–54.9 (±0.3/0.3)5	54.9–103.2 (±0.3/0.3)
100	—	—	—	166.8–170.6 (±0.2/0.3)

had been set up to deliver Kohler illumination, as described by Bradbury (1984) and the prism alignment was arranged so that the background colour was blue. Photographs were taken at intervals on Kodacolor Gold 200 ASA using a Nikon F-601M 35 mm Camera. Melting temperature ranges were recorded as those between the first visible sign of any melting behaviour and the point at which the last crystal disappeared.

Solid dispersion production was mimicked on microscope slides using the hot stage. Approximately 100 mg of paracetamol (<50 μm)–PEG 4000 physical mixtures were accurately weighed onto microscope slides and covered. The samples were placed in the hot stage and heated to 70°C at a controlled rate of 2°C min^{-1}. Once at 70°C, the systems were immediately cooled back down to room temperature, again at 2°C min^{-1}. They were allowed to equilibrate for 1 h before complete remelting of both carrier and drug was performed, also at 2°C min^{-1}. Recrystallisation onset temperatures (temperatures at which crystals appeared against the blue background) were recorded, in addition to melting and remelting ranges of the dispersion components.

2.4. In-process sampling

The solid dispersion in-process sampling technique developed for this investigation was operated in the following way. Into stainless steel dispersion cylinders were weighed 3 g quantities of paracetamol–PEG 4000 physical mixtures. The cylinders were loaded into an LTE G150 programmable oven (LTE, Oldham) and heated to one of the standardised fusion temperatures, at a constant rate of 2°C min^{-1}, before being held for one of the set fusion times. Once the molten dispersions had been held for the stated times, samples of approximately 100 mg were removed via glass rods and transferred onto microscope slides, covered and placed onto the hot stage. All equipment was held at the relevant fusion temperatures in order to avoid premature recrystallisation. The samples were subsequently cooled to room temperature at 2°C min^{-1}. After cooling, samples were stored for 24 h before remelting. The calibration of the hot stage was checked using crystals of benzoic acid standard (Mettler Melting Point Standard 18555, melting point 122.1°C). All HSM experiments, including the calibration checks, were conducted four times.

3. Results and discussion

3.1. Thermal cycling of paracetamol (<50 μm)–PEG 4000 physical mixtures

Table 1 shows the melting and crystallisation data for PEG 4000 alone and for dispersions containing (<50 μm) paracetamol following thermal cycling. The recrystallisation and remelt temperatures of the PEG 4000 decreased in com-

parison with the initial melting temperature on increased addition of paracetamol. The paracetamol particles began to dissolve into the PEG 4000 as soon as the carrier went into the liquid state, the last paracetamol crystals disappearing well before the melting point of the pure drug was reached. These findings are similar to those made by Francés et al. (1991) upon analysis of ciprofloxacin–PEG 4000 physical mixture systems and are also similar to the effects observed by Dordunoo et al. (1991) for triamterene and temazepam–PEG physical mixtures. The results support the suggestion by Lloyd et al. (in press) that, at low drug loadings, no detectable paracetamol melting endotherms are observed using DSC, because there is insufficient solid drug melting at any single temperature to result in detectable endotherms on the thermoanalytical curves. Indeed, in comparison to the DSC data generated for equivalent systems, it is clear that HSM is far more sensitive to the presence of small quantities of solid drug. It is also interesting to note that the onset melting temperatures of the PEG 4000 decreased in the presence of paracetamol. It is well known that other constituents and impurities can lower the melting points of materials, although the reasons for these effects remain poorly understood. This finding is complementary to similar observations made during the DSC studies (Lloyd et al., in press).

Photomicrographs were obtained for the various stages of the melting, recrystallisation and remelting process. Fig. 1 shows the recrystallisation of the 5% paracetamol systems after heating to 70°C and cooling, indicating the presence of small (< 10 μm) paracetamol crystals which have persisted in the PEG melt and the formation of PEG spherulites. It is interesting to note that the drug crystals do not appear to nucleate the PEG spherulites, nor is there any evidence of eutectic formation, as was also suggested as a result of DSC studies (Lloyd et al., in press). On the contrary, the two components appeared to behave completely independently, hence the dispersions formed on the slides are probably not eutectics but monotectics, whereby the eutectic point is effectively equivalent to the melting point of the PEG.

3.2. In-process sampling of paracetamol–PEG 4000 solid dispersion systems

The in-process sampling analysis of a wide range of paracetamol–PEG 4000 solid dispersions, with remelting analysis conducted at 2°C min^{-1} after the 24-h equilibration period, showed that the presence of paracetamol particles of a detectable size was highly dependent on the method of manufacture. Table 2 gives an overall summary of the results, showing that, under certain manufacturing conditions, no drug particles could be detected, indicating that either the particles have dissolved in the solid PEG to form a solid solution or are present at a particle size lower than that detectable by the microscope. Initial drug particle size is clearly an important factor, with smaller sizes promoting greater disappearance of the drug particles, as did higher fusion temperatures and longer holding times. Many workers (e.g. Dordunoo et al., 1991) have used much higher fusion temperatures to allow complete drug dissolution into the molten carrier, whilst others have employed very long fusion times (e.g. Hargreaves, 1982) to enable this process to go to completion. However, in many cases the manufacturing conditions are not stated at all; the results presented here indicate that these conditions may have a profound influence on the structure of the solid dispersion.

Representative quantitative data is given for three of the solid dispersion systems, showing the melting behaviour of the PEG on reheating (Table 3). For systems containing paracetamol (< 50 μm) produced using a fusion temperature of 70°C and a fusion time of 10 min, all the solid drug had dissolved into the molten carrier during production for the 5% samples which did not appear to recrystallise on cooling, but drug particles remained in all other systems which subsequently dissolved upon remelting. Table 3 shows the equivalent data for the paracetamol (300–350 μm)–PEG 4000 solid dispersions produced using a fusion temperature of 70°C for a fusion time of 10 min; a much wider range of paracetamol melting was observed for these systems. Examination of the photomicrographs (Fig. 2) shows that the paracetamol particles appear to remain largely intact during the thermal cycling.

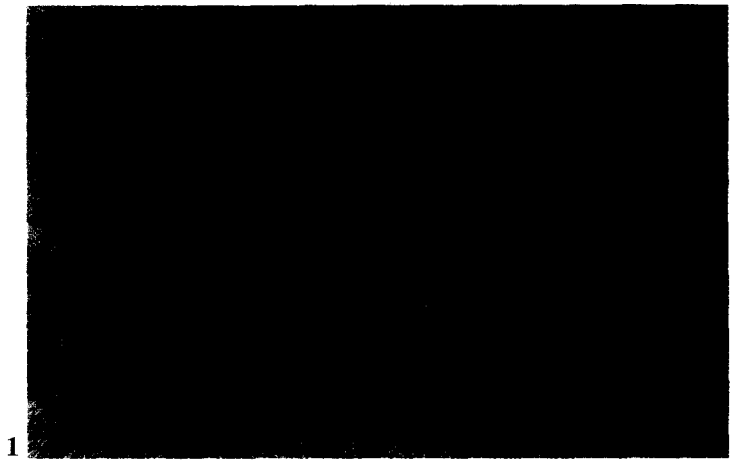

Fig. 1. HSM photomicrograph taken during recrystallisation of 5% w/w paracetamol physical mixtures thermally cycled at 2°C min^{-1} at 41.5°C. Bar represents 100 μm.

Fig. 2. HSM photomicrograph taken during recrystallisation of 20% w/w paracetamol physical mixtures (300–350 μm, 70°C for 10 min) at 37°C. Bar represents 100 μm.

Fig. 3. HSM photomicrograph taken during recrystallisation of 25% w/w paracetamol physical mixtures (< 50 μm, 100°C for 60 min) at 25°C. Bar represents 100 μm.

Table 2
HSM data summery for in-process sampling analysis of paracetamol–PEG 4000 solid dispersions, indicating the presence of paracetamol particles (+) upon remelting at 2°C min^{-1}

Drug (%w/w)	LLL	LLH	LML	LMM	LMH	LHL	LHH
5	–	–	–	–	–	–	–
10	+	–	+	–	–	–	–
15	+	+	+	+	+	+	–
20	+	+	+	+	+	+	+
25	+	+	+	+	+	+	+
30	+	+	+	+	+	+	+
	MLL	MLH	MML	MMM	MMH	MHL	MHH
5	+	–	+	–	–	–	–
10	+	+	+	+	+	+	–
15	+	+	+	+	+	+	+
20	+	+	+	+	+	+	+
25	+	+	+	+	+	+	+
30	+	+	+	+	+	+	+
	HLL	HLH	HML	HMM	HMH	HHL	HHH
5	+	+	+	+	+	+	–
10	+	+	+	+	+	+	+
15	+	+	+	+	+	+	+
20	+	+	+	+	+	+	+
25	+	+	+	+	+	+	+
30	+	+	+	+	+	+	+

Dispersion key: First letter, particle size (L, <50 μm; M, 150–200 μm; H, 300–350 μm). Second letter, maximum temperature (L, 70°C; M, 85°C; H, 100°C). Third letter, holding time at the maximum temperature (L, 10 min; M, 30 min; H, 60 min).

In general, there was no evidence for extensive recrystallisation of the drug from the melt; instead, the remaining drug appeared to persist into the solid state on cooling. There was one notable exception to this observation. For systems prepared using the 50-μm size fraction at a maximum temperature of 100°C for 1 h (i.e. the smallest particle size and the longest time and highest temperature in the melt), samples containing 20% drug or greater showed recrystallisation in addition to the persisting particles during the post-production equilibration period of 24 h (Fig. 3, Table 3), after the PEG had solidified. These samples may have shown different behaviour to the other systems under study due to the elevated temperatures and holding times, combined with the smaller particle size. This may be expected to lead to greater dissolution of the paracetamol particles into the molten PEG. On cooling, the PEG solutions become supersaturated as the solubility of the drug is exceeded, leading to recrystallisation of the drug particles over a period of time; the size of these particles could be estimated from the photomicrograph as being $< \sim 10$ μm. The fact that the PEG had already recrystallised suggests that the observed particles are outside the focal plane of the PEG spherulites, i.e. the particles remained physically separate from the solid polymer throughout the crystallisation process. Clearly, this recrystallisation process may have implications not only for the understanding of the solid state structure of these systems but may also have repercussions in terms of the physical stability of the dispersions.

4. Conclusions

The study has raised several points regarding both the nature of the solid dispersions under study and the use of HSM as a tool with which to study these systems. The investigation has confirmed the suggestion (Lloyd et al., in press) that the drug dissolves into the molten PEG over a

Table 3
HSM data for in-process sampling of paracetamol–PEG 4000 solid dispersions, showing the paracetamol remelting range (°C) after 24 h for a series of preparation conditions

Drug load (%w/w)	LLL	HLL	LHH
5	—	56.3–85.3 (±0.2/0.2)	—
10	55.2–62.8 (±0.2/0.2)	56.1–102.7 (±0.2/0.2)	—
15	54.2–74.8 (±0.2/0.2)	54.5–111.5 (±0.2/0.2)	—
20	53.7–88.6 (±0.2/0.3)	53.5–131.1 (±0.2/0.3)	53.2–67.6 (±0.2/0.2)
25	53.5–106.4 (±0.3/0.3)	52.6–134.7 (±0.2/0.3)	53.1–93.6 (±0.3/0.3)
30	52.8–119.4 (±0.3/0.3)	52.1–136.4 (±0.2/0.3)	52.6–110.9 (±0.3/0.3)

Dispersion key: First letter, particle size (L, 50 μm; H, 300–350 μm). second letter, maximum temperature (L, 70°C; H, 100°C). Third letter, holding time at the maximum temperature (L, 10 min; H, 60 min).

range of temperatures, thereby explaining why the drug peak is often absent during DSC studies of equivalent systems. The absence of the drug melting peak has arguably led to misinterpretation of DSC data, hence this study indicates that there are many advantages to using HSM as a supplement to DSC investigations. Indeed, comparison with DSC indicates that HSM is considerably more sensitive to the presence of the higher melting component in binary systems, an observation which has implications for approaches such as excipient compatibility studies. In addition, HSM has been shown to be capable of differentiating between persisting and recrystallised particles in binary systems. It is also important to note that no evidence of co-recrystallisation behaviour was observed, with drug and carrier appearing to behave independently of each other during recrystallisation and remelting. The conditions used to manufacture the dispersions clearly has a profound effect on the subsequent structure, with higher holding temperatures and times, as well as lower particle sizes, leading to more extensive drug dissolution in the molten PEG. It is debatable from these studies alone whether these mixed systems form true solid solutions on cooling, as it is not possible to detect submicron particles using the technique in this way. However, it is clear that the particle size of the drug will vary considerably, depending on the thermal cycling and initial particle size. The link between the structure of solid dispersions and their subsequent dissolution behaviour has not yet been fully clarified, arguably because it has proved difficult to reliably characterise the former. However, Sjökvist Saers and Craig (1992) have suggested that under certain circumstances the drug particle size may dictate the dissolution rate, hence the data presented here is of some interest. Similarly, the time-dependent recrystallisation noted here may be of relevance to the changes in dissolution rate frequently noted on storing these systems.

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