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Interactions during aqueous film coating of ibuprofen with Aquacoat ECD

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Abstract

During the development of a coated ibuprofen formulation a sticking tendency occurred when applying Aquacoat ECD. This interaction indicated the formation of a eutectic mixture. The compatibility of the components of Aquacoat ECD with ibuprofen was investigated by differential scanning calorimetry. Cetyl alcohol, a stabilizing excipient in Aquacoat, was found to form a eutectic system with ibuprofen. It was characterized by the construction of a phase diagram with 33 mol% ibuprofen and an onset temperature of 40.5°C. Wide-angle X-ray diffraction was used to identify the polymorphic forms of cetyl alcohol. The results confirmed the amorphous state in the aqueous dispersion in contrast to the β_0- and γ_4-polymorphs of solid cetyl alcohol.

Keywords: Ibuprofen; Cetyl alcohol; Phase diagram; Eutectic; Polymorphism

1. Introduction

Ibuprofen is a common non-steroidal anti-inflammatory drug. However, its effectiveness is often accompanied by a high incidence of adverse reactions, especially gastro-intestinal problems, and its bitter, irritating taste. To reduce these side effects, most of the formulations are film coated.

Choosing the suitable polymer for ibuprofen, not only the interactions between drug and polymer must be taken into account, but also those between excipients and drug. Plasticizers, surfactants, stabilizers, even in negligible amounts, may lead to problems when incompatible with the drug. Racemic ibuprofen is known to form eutectic mixtures with a wide range of additives including polyethylene glycol (Mura et al., 1987; Shehab and Richards, 1996), stearates (Gordon et al., 1984), polyvinylpyrrolidone (Najib et al., 1986), ethenzamide (Aoki et al., 1997), cetostearyl alcohol (Wong et al., 1992) and even its enantiomers (Dwivedi et al., 1992).

The aim of the present paper is to outline the difficulties that will arise by coating ibuprofen

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with Aquacoat ECD. This pseudolatex contains ethylcellulose as a film-forming polymer, and cetyl alcohol and sodium lauryl sulfate as stabilizing agents.

During the process, a sticking tendency could be observed at a core bed temperature of about 40°C. A similar case has been reported in the literature (Paeratakul, 1993). Investigations of the thermal behaviour of ibuprofen and its interactions with the components of Aquacoat were done to examine these effects. Furthermore, the physical state of cetyl alcohol, being dispersed in Aquacoat, was examined.

2. Materials and methods

Ibuprofen (batch no. 460490) was generously supplied by Knoll Pharmaceuticals (Nottingham, UK). Cetyl alcohol (lot no. MA96198012) and sodium lauryl sulfate (lot no. 7-04191), which are used in Aquacoat ECD, and the aqueous dispersion Aquacoat ECD (lot no. J7471) were kindly provided by FMC (Philadelphia, PA, USA). Ethocel 10 Standard Premium quality (lot no. MG05013T01), the same type of ethylcellulose used in Aquacoat (Wheatley and Steuernagel, 1997), was received from Dow Corning (Michigan, USA).

2.1. Differential scanning calorimetry measurements

Differential scanning calorimetry (DSC) measurements were performed using a Mettler TA 8000 System comprising a TAS 811 system and a DSC 820 measuring cell (Mettler Toledo, Gießen, Germany). The system was calibrated from 30 to 420°C with respect to temperature, heat flow and tau lag according to the manual's specifications using gallium, indium, stannum and zinc as reference materials.

The experiments (6–8 mg per run) were performed in perforated 40 μl aluminium standard pans. The mixtures of ibuprofen and cetyl alcohol were prepared by weighing each component according to the molecular weight fraction ranging from 10 to 90 mol% ibuprofen. The compounds were ground for 10 min using a pestle and mortar. The powders obtained were slightly compacted in the aluminium pan by a steel plunger to achieve a uniform powder bed in contact with the pan bottom. The heating sequences were carried out within a temperature range from 25 to 90°C, at a heating rate of 2°C/min, purging continuously with 20 ml nitrogen per minute. Triplicate measurements were performed on each sample to check for reproducibility.

2.2. Wide-angle X-ray diffraction

The X-ray source was a Philips PW 1710 generator (40 kV, 25 mA) with a tube PW 2213/20 (wavelength 0.154 nm, copper as anode material, Ni filter). A goniometer PW 1050/25 (Philips, NL-Eindhoven) was mounted on the tube. A scintillation counter type A (Siemens, D-Karlsruhe) was used as detector. Powdered samples were measured in aluminium holders at ambient temperature (22–25°C). Data analysis was performed with APD–software (Philips, NL-Eindhoven) and plotted as counts versus the diffraction angle 2ϑ. According to Bragg's equation $n\lambda = 2d \sin \vartheta$, with a wavelength of $\lambda = 0.154$ nm and the diffraction order $n = 1, 2, \ldots$, the interlayer spacing d of the crystalline material could be calculated from the maxima of the interferences.

3. Results and discussion

During the coating process, only the surface of the ibuprofen crystals interacts with Aquacoat, whereas the core does not contribute to this reaction. The mean particle diameter of ibuprofen is 53 μm. The large surface of the powder bed is responsible for the interaction between ibuprofen and the components of Aquacoat ECD.

In DSC, ibuprofen shows a single, sharp endothermic peak at 75.3°C. By adding dried Aquacoat dispersion, a decrease of the melting point combined with a broadening of the base line was observed (Fig. 1). The enlargement of curve (d) reveals an endothermic peak, indicating the for-

mation of a eutectic mixture. The sticking tendency during the coating process at about 40°C can be attributed to the thermodynamic behaviour, reflected in curve (d). This melting will cause problems, for the final glass transition temperature at about 40°C has to be reached.

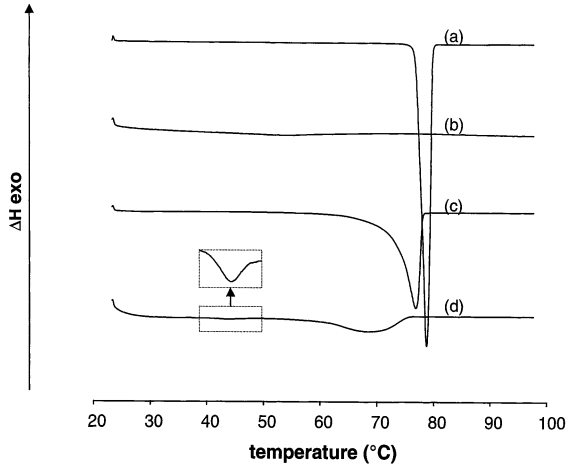

Fig. 1. DSC tracings of (a) ibuprofen, (b) dried Aquacoat dispersion, (c) Aquacoat–ibuprofen (1:6), and (d) Aquacoat–ibuprofen (1:2). The addition of Aquacoat lowers the melting point and broadens the base line. Enlarging curve (d) reveals an endothermic peak, demonstrating the formation of a eutectic mixture.

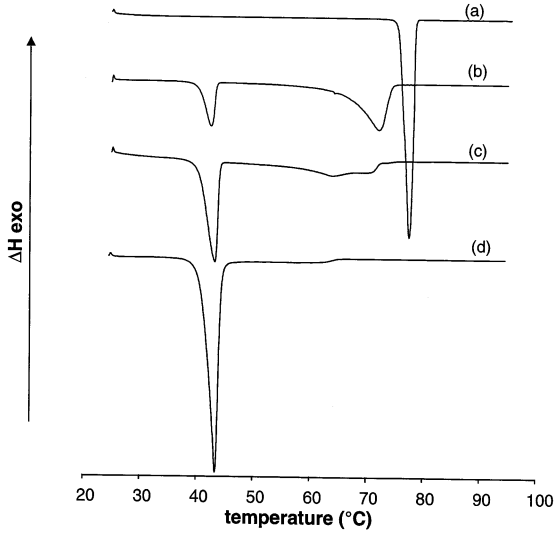

Fig. 2. DSC thermograms of ibuprofen–cetyl alcohol mixtures: (a) ibuprofen, (b) 90 mol% ibuprofen, (c) 75 mol% ibuprofen, and (d) 50 mol% ibuprofen, indicating the existence of a eutectic mixture.

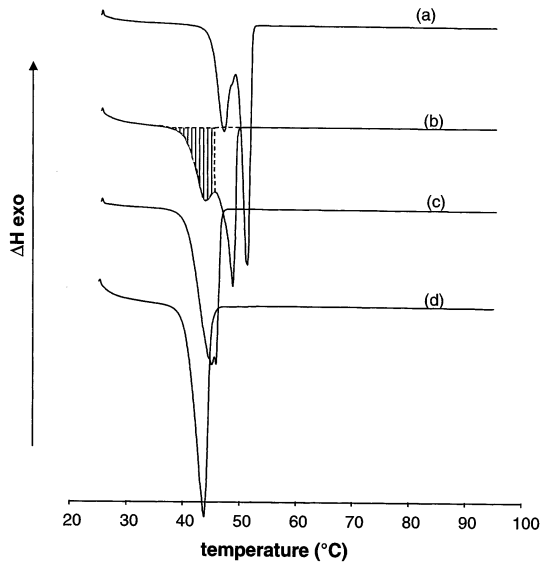

Fig. 3. DSC thermograms of ibuprofen–cetyl alcohol mixtures: (a) cetyl alcohol, (b) 10 mol% ibuprofen, (c) 25 mol% ibuprofen, and (d) 33 mol% ibuprofen. The polymorphic transition of cetyl alcohol is responsible for the partially overlapping peaks at 10 and 25 mol% ibuprofen.

Aquacoat ECD is an aqueous pseudolatex with 30% solids content. According to the product specifications, it consists of 27% ethylcellulose, 1.6% sodium lauryl sulfate and 2.5% cetyl alcohol. To determine the component being responsible for the sticking tendency, binary mixtures of ibuprofen with ethylcellulose, sodium lauryl sulfate and cetyl alcohol were analysed. Only cetyl alcohol lowered the melting point significantly to 40.5°C, confirming the interaction.

Fig. 2 represents the DSC curves of mixtures containing 50–100 mol% of ibuprofen. The first peak of each composition corresponds to the eutectic, whereas the second represents the main component ibuprofen. Fig. 3 shows the mixtures with a higher percentage of cetyl alcohol. The DSC tracing of cetyl alcohol reveals a characteristic double peak. The first peak, which corresponds to the melting at 44.7°C, can be assigned to the β_0 modification. The monoclinic γ_4-polymorph can be determined by the small endothermic peak, subsequent to the β_0 form. These modifications

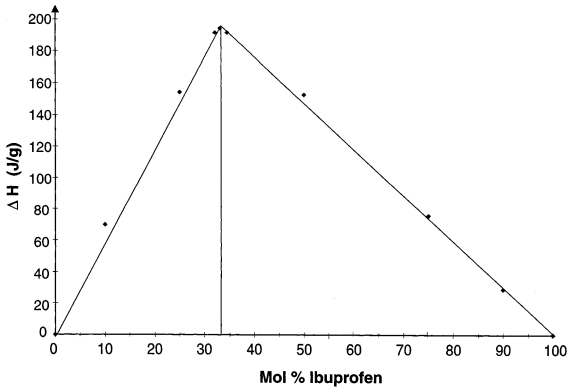

Fig. 4. Phase diagram of an ibuprofen–cetyl alcohol binary mixture constructed according to Tammann (1924).

are transformed to the α-polymorph at higher temperatures. This phase transition is shown by the second peak of cetyl alcohol. Junginger et al. (1979) described the polymorphism of stearyl alcohol and cetostearyl alcohol, respectively.

The enthalpies of the eutectic peaks (ΔH) were determined by integration. These values were used to construct a Tammann diagram (Tammann, 1924). An overlapped area of the eutectic mixture and cetyl alcohol is shown for 10 and 25 mol% ibuprofen, respectively (Fig. 3). Their melting temperatures are close together and could not be treated in the normal way. Therefore, only the partial integral of the first shoulder, which represents the eutectic part, was evaluated. According to the Tammann diagram, eutectic formation occurs at 33 mol% ibuprofen (Fig. 4). The eutectic concentration was confirmed by three mixtures close to the eutectic point.

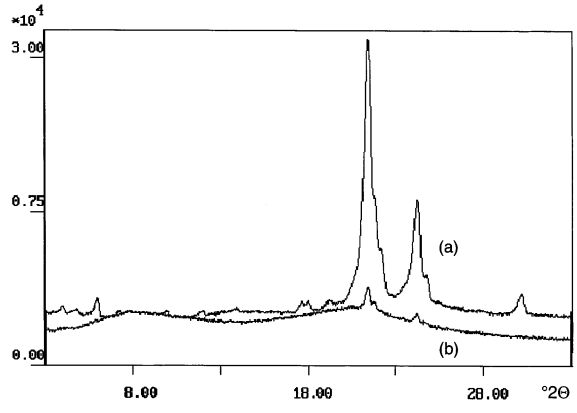

Fig. 5. WAXD diffractogram of (a) powdered cetyl alcohol and (b) dried Aquacoat dispersion spiked with 8% cetyl alcohol.

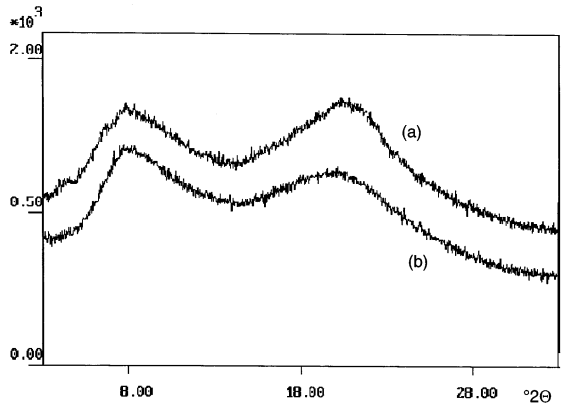

Fig. 6. WAXD diffractogram of (a) Ethocel and(b) dried Aquacoat dispersion; extended ordinate in comparison with Fig. 5.

In addition, it was of interest to prove the physical state of cetyl alcohol in the aqueous dispersion in comparison with the dry state. Powdered cetyl alcohol is crystalline as demonstrated by the sharp and intense diffraction peaks at $2\vartheta = 21.4$ and 24.2° (Fig. 5). They can be assigned to the 200 and 110 levels, as their positions are identical with the orthorhombic subcell of paraffins (Kohlhaas and Soremba, 1939). The interferences in the small-angle area could be detected for the second up to the sixth diffraction order of the β_0 and γ_4 modification, respectively (Precht, 1974). For the first diffraction order, the Bragg spacings were calculated.

A dried Aquacoat dispersion contains 8% cetyl alcohol, which should be visible in the X-ray diffraction pattern. However, only two diffuse halos can be seen that correspond to ethylcellulose (Fig. 6). On adding another 8% of cetyl alcohol to the dried dispersion, the crystalline structure can be identified (Fig. 5). It can be assumed that the crystalline structure of the stabilizers disappears during the manufacturing process of Aquacoat. Both cetyl alcohol and sodium lauryl sulfate, respectively, are molecularly dis-

persed and therefore amorphous with respect to X-ray diffraction, even after drying.

4. Conclusion

Thermoanalytical and X-ray diffraction methods were used to identify the interaction between Aquacoat and ibuprofen. It was shown that cetyl alcohol, included in Aquacoat, is responsible for the melting point lowering of ibuprofen, and therefore for sticking tendencies during the film coating process of ibuprofen crystals. Crystalline cetyl alcohol and ibuprofen demonstrate a sharp eutectic peak at 40.5°C. Construction of a phase diagram of these two components revealed the existence of a stable invariant characterized by 33 mol% ibuprofen. X-ray investigations confirmed the amorphous state of cetyl alcohol in Aquacoat, in contrast to the β_0- and γ_4-polymorphs of solid cetyl alcohol.

As a result, excipients used in polymer dispersions may lead to unexpected interactions. Therefore, choosing the appropriate dispersion for the coating process is of prime importance.

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