Videomicroscopy Techniques for Agglomeration Studies

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INTRODUCTION

Maintaining a smooth, uniform dispersion of drug in semisolid dosage forms is critical to the bioavailability and physical stability of a product. The theory of suspension stabilization and methods for studying the physical stability of these systems are discussed in a number of pharmaceutical texts (1–4). A number of these methods are based on indirect, automated particle size analysis techniques such as light imaging and electrical sensing. While these methods are rapid and easily performed, commonly cited deficiencies relate to particle shape insensitivities, agglomerate destruction by sample preparation, matrix interference, and the inability to distinguish between particles of different components. Photomicroscopy is a direct method of studying particle size changes and crystal growth. However, matrix interference can still present a problem with multicomponent systems and a means of distinguishing the particle of interest is necessary. A videomicroscopy technique is presented here which allows rapid, direct study of agglomerates, without interference from the matrix, and which distinguishes the particles by their melting points.

MATERIALS AND METHODS

Samples

A drug, insoluble over the temperature range studied and having a melting point above 150°C, was dispersed in a model cream to demonstrate the technique. A previous study described the structure of the cream as a glyceryl monostearate/stearamidoethyl diethylamine emulsifier network system with cetyl palmitate globules embedded in the network as distinct entities (5). To illustrate an application of the technique, samples of the cream with dispersed drug were passed through a variable speed rotor/stator mixing device with a 4-mm gap to evaluate shear-induced agglomeration. A dispersion of this drug in a model ointment was used to demonstrate the utility of the technique in distinguishing particulates of multicomponent systems and in assessing the impact of varying cooling rates on particle morphology. The model ointment containing petrolatum, mineral oil, microcrystalline wax, and a paraben preservative was previously characterized structurally (6).

Equipment

Polarized light microscopy was performed using a Zeiss Universal microscope equipped with a 20× long working distance pol objective. The final magnification was 193×. Samples were melted using a Mettler FP 82 hot stage at a heating rate of 5°/min over the range of 25°C to slightly above the melting point of the highest-melting vehicle component. The melting transition was videotaped through the microscope using a Panasonic WV-D5000 CCD color videocamera and recorded in real time with a Panasonic AG-6050 time lapse VHS recorder. The video signal was displayed with a Panasonic CT-1330 13-in. color video monitor. A Leightronix CG-1000 temperature-monitoring character generator was interfaced between the hot stage and the video monitor to provide on-screen display of the temperature as melting progressed. A Polaroid FreezeFrame video image recorder was used to obtain videomicrographs at selected temperatures.

Methods

The technique can be summarized as follows.

(1) Videotape the melting transition of a sample in a hot stage using polarized light.
(2) Freeze-frame photography obtains photos at the melting point of each component and just prior to flow.
(3) The series of photos corresponds to selective melting away of the matrix component.
(4) The final photo is a clear view of only the drug dispersion in the same arrangement as the unmelted sample.

RESULTS AND DISCUSSION

Figure 1 shows a series of videomicrographs which demonstrate the technique. The 25°C photo shows drug dispersed in a cream matrix. However, an accurate assessment of the drug dispersion is not possible since the drug particles and the emulsion droplets are of similar size. The photos at higher temperatures increase the differentiation between drug and matrix by melting away the cetyl palmitate and glyceryl monostearate components at 50 and 53.4°C, respectively. The final photo yields an unobscured view of uniformly dispersed drug in the molten cream matrix, which becomes part of the isotropic background.

The videomicroscopy technique lends itself well to assessing the impact of process parameters on agglomeration characteristics. The following examples demonstrate its utility with respect to shearing stresses and cooling rates.

Shear-Induced Instability

Using the technique described above, samples of the model cream were determined to have a uniform drug dispersion and uniformity of the lot was confirmed by sampling

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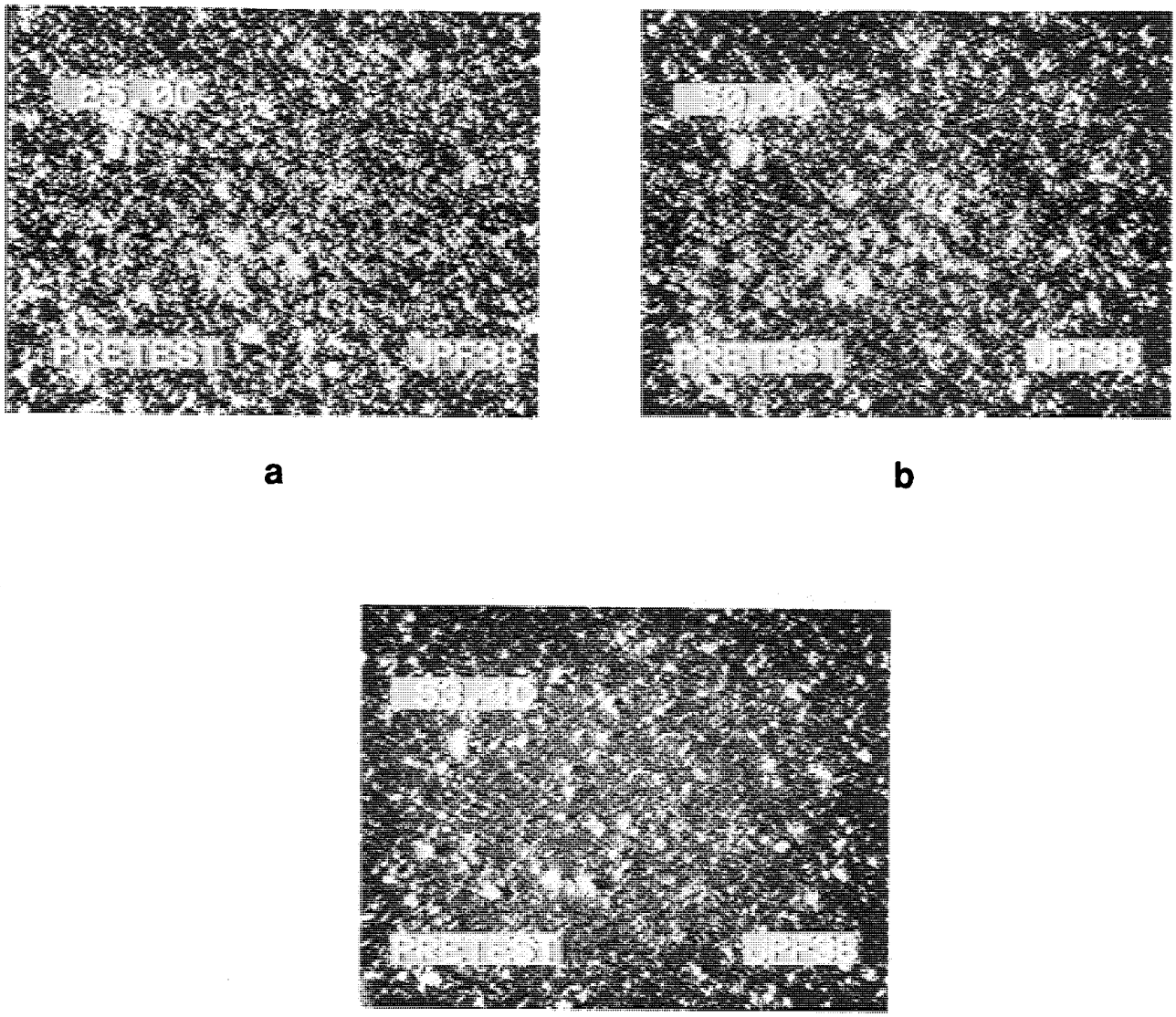

Fig. 1. Melting transition of the model cream. (a) Drug plus cream matrix; (b) drug plus cream matrix with isotropic molten cetyl palmitate; (c) drug in isotropic molten cream matrix.

at strategic locations in the manufacturing vessel. To examine the impact of shearing stresses, the model cream was warmed to 40°C to increase fluidity, then subjected to varying shear stresses in a rotor/stator mixing device and sampled at the designated intervals. As Fig. 2 indicates, agglomeration progresses as the rate and duration of shear increases. A single-pass or 15-min recirculation through the rotor/stator at low speed produces only slight agglomeration in comparison to the pretest sample. However, an additional 15 min at high speed yields a dramatic increase in the size of the agglomerates.

Cooling Effects on Particle Morphology

The model ointment was manufactured using two cooling methods which resulted in different morphologies for a precipitated species. The shock-cooled ointment yielded needles, but the slower cooling of the water jacketed mixer gave large platelets. Knowing the composition of the ointment and the component melting points, the precipitates were identified as parabens. Figure 3 illustrates the technique for distinguishing particulates in multiple-component systems. The 25°C sample contains the dispersed drug and the precipitated species in the ointment matrix. At 50°C the matrix is molten and becomes isotropic, leaving only the dispersed drug and precipitated species in the field. In the final photo, the precipitated species has melted away, resulting in a clear view of the drug dispersion.

A videomicroscopy technique has been developed which permits direct evaluation of dispersion characteristics without matrix interference. Any particle suspended in a semisolid matrix can be studied using this technique, pro-

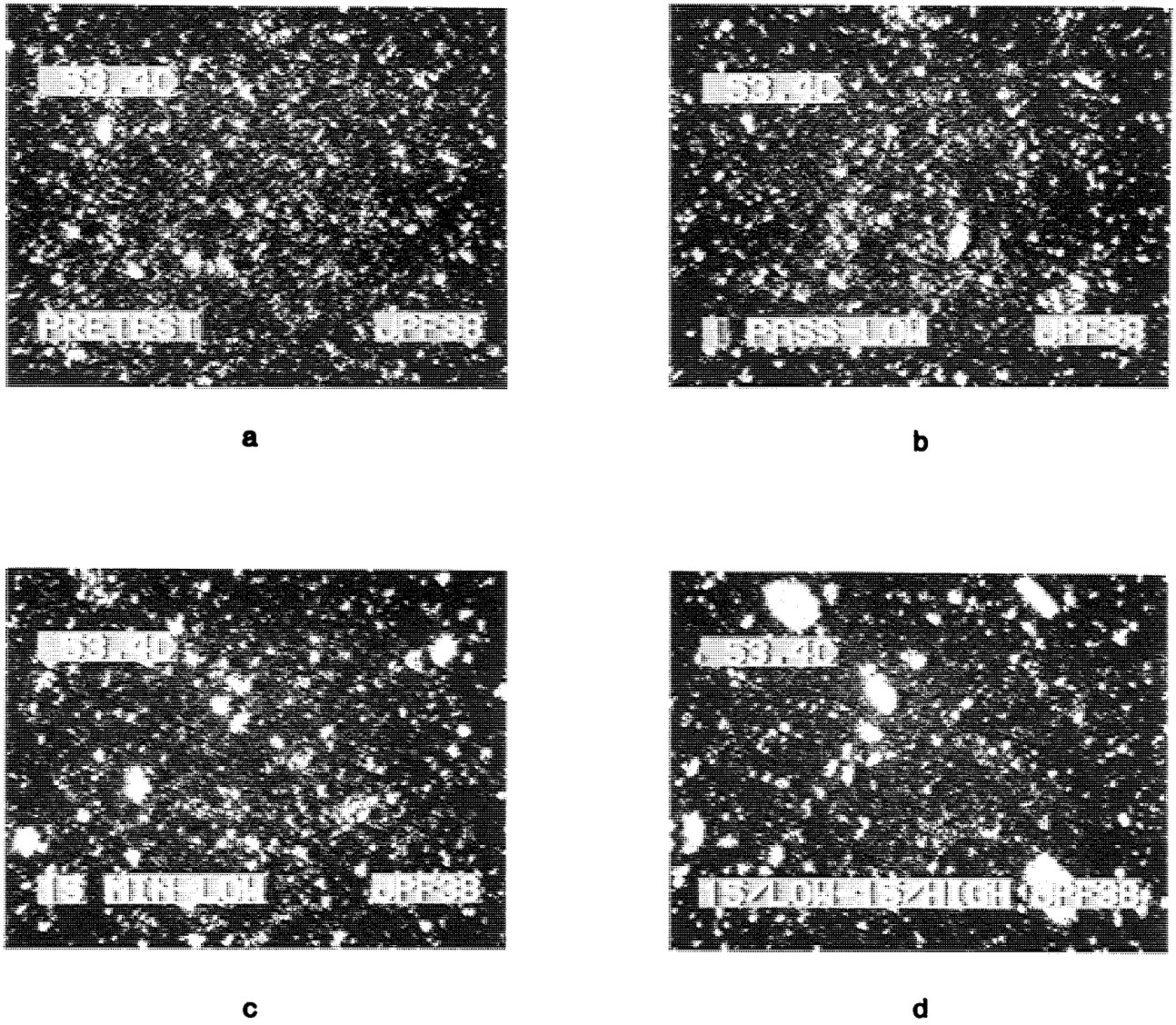

Fig. 2. Shear-induced agglomeration. Shear stress parameters as designated.

vided that it does not melt or become solubilized by the matrix over the temperature range examined. The technique can also be used to separate and identify particles in multiple component systems when the composition of the cream or ointment and associated melting points are known and if there is sufficient separation in the component melting points to avoid misinterpretation. Also, when using this technique for particle identification, melting points will deviate slightly from literature values due to impurities from the matrix. Applications have been demonstrated with respect to evaluating process variables. However, this videomicroscopy technique can also be a powerful tool in formulation optimization and in assessing long term physical stability.

The technique offers several advantages over hot-stage microscopy with 35-mm or Polaroid photography. While a simple hot stage can be used to melt away the matrix and distinguish particles by their melting points, obtaining a photographic record at the points of interest can be a laborious, time-consuming task. Polarized light provides the best contrast between the matrix and the suspended particles. However, as the temperature rises and the matrix melts, the light intensity progressively decreases, resulting in slower shutter speeds. At the melting point, the shutter speed required for proper illumination is frequently slower than the movement of the particles, resulting in a severely blurred image. During videotaping, the autoiris of the camera continuously adjusts for the changes in light intensity, thus allowing the details of the melting transition to be recorded. Freeze-frame photography then allows a sharp, properly exposed photograph to be obtained from any point in the melting transition. In addition, the videomicroscopy technique provides a permanent record of the entire melting transition rather than the single-point records obtained with conventional methods. This becomes particularly important when limited sample is available or minute variations in sample behavior are being monitored.

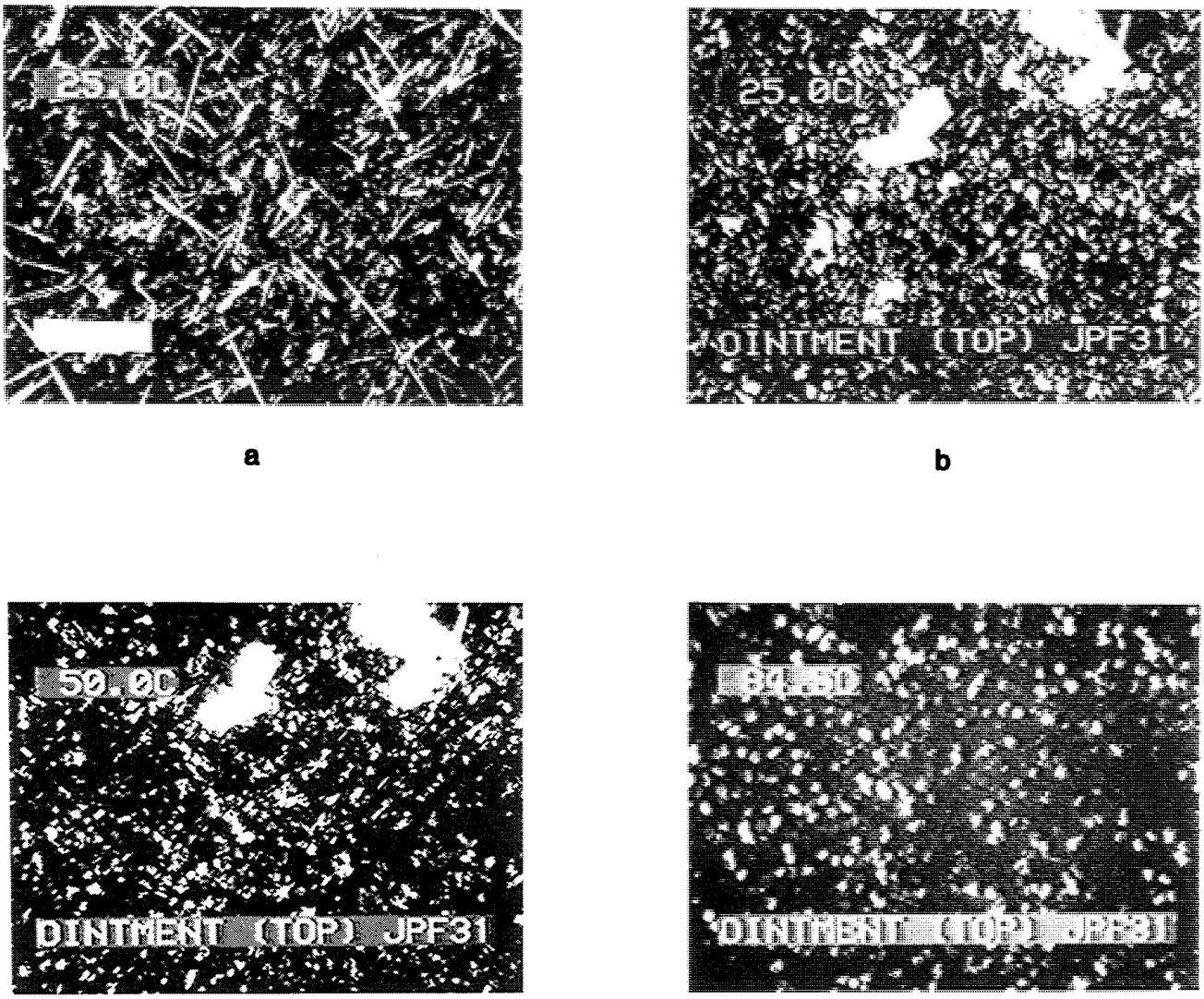

Fig. 3. Cooling effects on particle morphology. (a) Ointment containing drug and needles from the shock-cooled process; (b) ointment containing drug and platelets from the water-jacketed mixer process; (c) drug and platelets in isotropic molten ointment matrix; (d) drug dispersion in isotropic molten ointment matrix with the platelets melted.

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