microscope (Biopharma Technology Ltd., Winchester, U.K.), using the format depicted in Figure 1 with sample volume 2μl and sample thickness 70μm.

Figure 2 shows a sample of sodium chloride solution drying below and above its eutectic temperature, illustrating the fact that the eutectic temperature can be identified very clearly using FDM because of the marked visible change in sample appearance that occurs at T_{eu}. Figure 3 shows a sample of sucrose solution drying below, at the onset of, and above, its collapse temperature, demonstrating the effectiveness of FDM as a method of identifying the collapse event. Figure 4 illustrates the visual indication of skin formation that a sample may exhibit, even when cooled rapidly from the liquid state. Figure 5 depicts an FDM image taken around the collapse temperature of a minor component (glucose) in the presence of a more concentrated crystalline component (mannitol), highlighting separate areas of dense structure between apparent voids in the dried material. Figure 6 shows the affect of annealing a frozen sample on ice crystal growth, which can be assessed on a semiquantitative basis if a calibrated microscope lens is employed. Figure 7 shows how FDM can be set up to employ a polarized light source, while Figure 8 illustrates how this technique may be employed to qualitatively assess whether solute crystallization occurs during freezing and/or sublimation and whether this can be induced by warming of the sample. Zhai et al. also demonstrated that FDM can also be used to compare primary drying rates for different formulations or for a single formulation following the use of different freezing and drying conditions (24).

Differential Thermal Analysis

Differential thermal analysis (DTA) involves cooling or warming a sample and a reference (usually the same standard of water used to prepare the sample) under identical conditions (25–28), observing the differences in their temperatures (ΔT) and plotting this as a function of temperature or time. This enables detection of any measurable endothermic or exothermic transitions in the sample that do not occur in the reference material. A historical perspective of DTA is provided by Ozawa (29). DTA was the first method to be employed for the systematic investigation of the thermal characteristics of frozen solutions (30), where a series of transitions were reported prior to the melting event upon warming. In particular, an apparent heat capacity increase was noted prior to the main melting endotherm; this event was termed "antemelting." Limitations of DTA as a method arise from some of the practical aspects such as the placement of the temperature measuring devices (usually thermocouples) within the sample and reference holders, the thermal resistance that can restrict the flow of heat to and from the temperature measuring devices, and the relative lack of sensitivity to low energy or adiabatic events when compared with that in more advanced calorimetric methods (16). However, DTA can prove a simple yet effective technique when dealing with relatively simple solutions that undergo changes that are accompanied by a significant heat flow.

Differential Scanning Calorimetry and Modulated Differential Scanning Calorimetry

While DTA provides a measure of the difference in temperatures between a sample and a reference material, DSC provides an additional level of detail in