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RESEARCH PAPER

Characterization of Solid Dispersion Phase Transitions Using a New Optical Thermal Analyzer

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ABSTRACT

The phase transitions occurring during the heating of progesterone PEG6000, and progesterone–PEG6000 solid dispersions (3% and 20% w/w) were studied. Investigations were performed by differential scanning calorimetry (DSC) and optical thermal analysis (OTA). For complex systems, such as solid dispersions, the use of OTA allow a new interpretation of the DSC results. For instance, we have shown that peaks which were at first appearance identified as two superposed endothermic peaks, were in fact the result of a more complex set of reactions including a melting, a devitrification, and a second melting reaction.

INTRODUCTION

The solid dispersion technology is a well-known process used to increase the dissolution kinetics and the oral absorption of poorly water-soluble drugs (1–3). We have applied this technology to progesterone and prepared a number of solid dispersions by means of fusion–solidification and dissolution–evaporation technics (4,5). Because of progesterone polymorphism (6), the behavior of these products may differ according to their physical structure, more particularly, the dissolution rate of the drug and the stability of the solid dispersions (7,8). After fusion, the physical state of the solid dispersion strongly depends on the cooling rate value. Indeed, stable crystalline structures are obtained by slowly cooling (1°C/min) the melted samples, while metastable crystalline structures and/or vitreous states are reached for higher cooling rate values (>20°C/min) (9).

The physical structures of the solid dispersions are usually studied by x-ray diffraction and differential scanning calorimetry (DSC). However, in some cases, these technics are not sufficient to explain the complex phenomena observed, for instance, on a DSC trace. Recently, a new device (the optical thermal analyzer—OTA), devoted to the microscopic observations of phase transitions appearing in a freeze-drying process, has been developped by Normalab S.A. (10,11). Owing to the large temperature range scanned by this new instrument and the possibility of controlling both heating and cooling rates, we have used this technology to observe phase transitions occurring in progesterone–PEG6000 solid dispersions.

Four mixtures, 0%, 3%, 20%, and 100% w/w of progesterone in PEG6000, were investigated. These compositions were chosen because the 3% w/w solid dispersion is expected to be close to an eutectic transition, while the 20% w/w is expected to melt in a wide range of temperatures (12). The two limits (0% and 100%) were also investigated to enable recognition of each constituent on the solid dispersion photographs. In order to observe different types of phase changes (devitrification, crystallization, fusion, etc.), the samples were prepared using the highest cooling rate (i.e., 100°C/min) accessible with the OTA device.

MATERIALS AND METHODS

Materials

Pure crystallized progesterone (<200 μm, form I—Laboratoire Besins–Iscovesco, France) and PEG 6000 (Lutrol 6000, BASF) were used without further purification. Solid dispersions (3% and 20% w/w of progesterone in PEG6000) were prepared using the fusion method previously described (7,8).

Methods

Calorimetric studies were performed with a differential scanning calorimeter (DSC4, Perkin–Elmer). Calibration of the calorimeter is obtained from the measurement, at different heating rates, of the enthalpy and the temperature of fusion of different standards. In the following experiments, we defined the glass transition temperature as the onset one, the devitrification temperature at the minimum of the exothermic peak, and finally the melting temperature at the maximum of the endothermic peak.

The device used for the in situ observations of the phase transitions was developed by Normalab S.A. and is called the optical thermal analyzer (OTA). The synoptic diagram of the OTA device is displayed in Fig. 1.

This equipment has the following attributes: A volume of some microliters can be analyzed. The range of temperature scanned is 200°C to −150°C. Controlled cooling rates of 0.1°C/min to 100°C/min, and controlled heating rates of 0.1°C/min to 100°C/min can be used. The accuracy of the temperature measurement is ±0.4°C in the whole range of temperature scanned during the experiments. A vacuum of 10^{-3} Torr can be obtained inside the sample cell if freeze-drying experiments are performed. The observations can be made with the reflection and/or the transmission mode with any commercial microscopic instrument. In our case, a Nikon (Optiphot) microscope equipped with ×5, ×10, and ×20 lenses is used. The recordings of the observations are made during the experiments with a video tape recorder via a camera (Sony XC-999). Finally, the measurements (sizes, distances, numbers) are made with an image processor (Argus 10, Hamamatsu).

Two chains of programs were written. The first computes the sequences of the thermal cycles and commands the different instruments of measurements. The second analyzes the results (recording) and allows the determination of liquid/solid, solid/gas, and eventually solid/liquid transformation kinetics at each stage of the process.

All the samples studied have undergone the thermal cycle displayed in Fig. 2.

RESULTS AND DISCUSSION

Figure 3 displays the enthalpic curve obtained on pure progesterone. At low temperature (T_g = 12°C), a glass transition endothermic phenomenon is observed (Fig. 3, expanded view). Then, an exothermic reaction of devitrification (or crystallization) appears at T = 56°C with an enthalpy of ΔH_c = −40 J/g. Finally, the fusion of the crystalline part of the material appears at T = 124°C with an enthalpy of ΔH_f = 85 J/g.

These data show that the devitrification process leads to the appearance of the progesterone metastable form II (6).

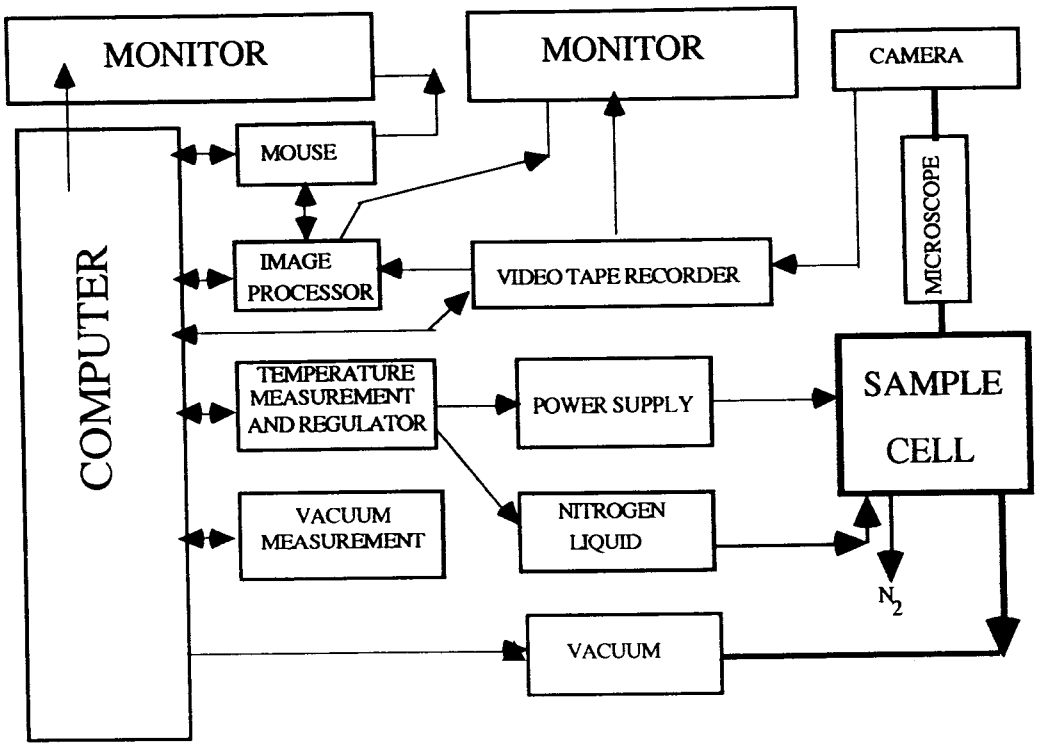

Figure 1. Synoptic diagram of the optical thermal analyzer developed by Normalab S.A.

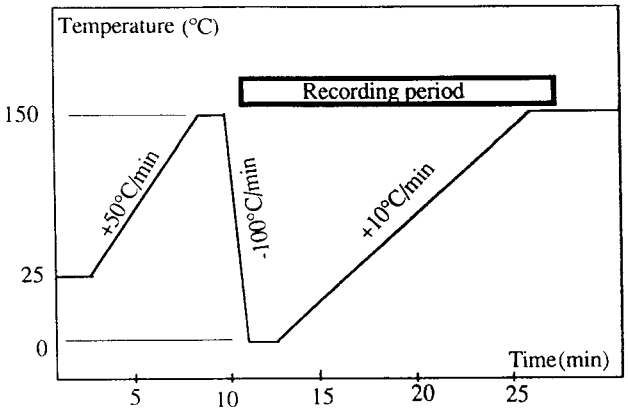

Figure 2. Thermal cycles performed on the different samples by DSC and OTA.

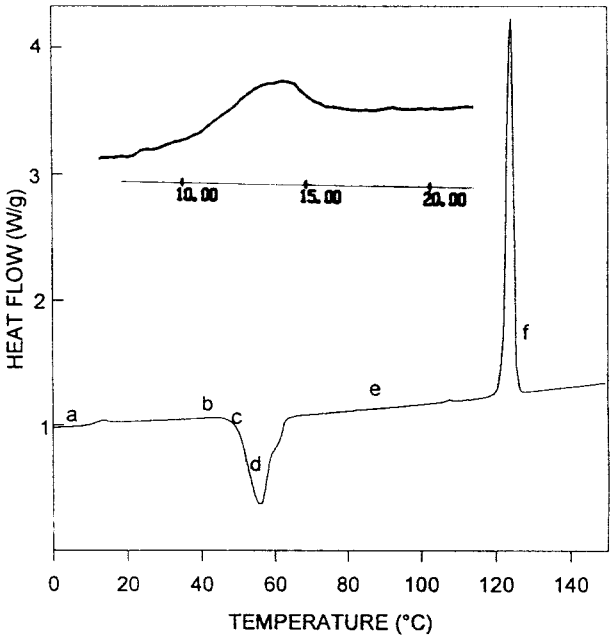

Figure 3. Enthalpic curve obtained on pure progesterone, after quenching at -100°C/min from the liquid state.

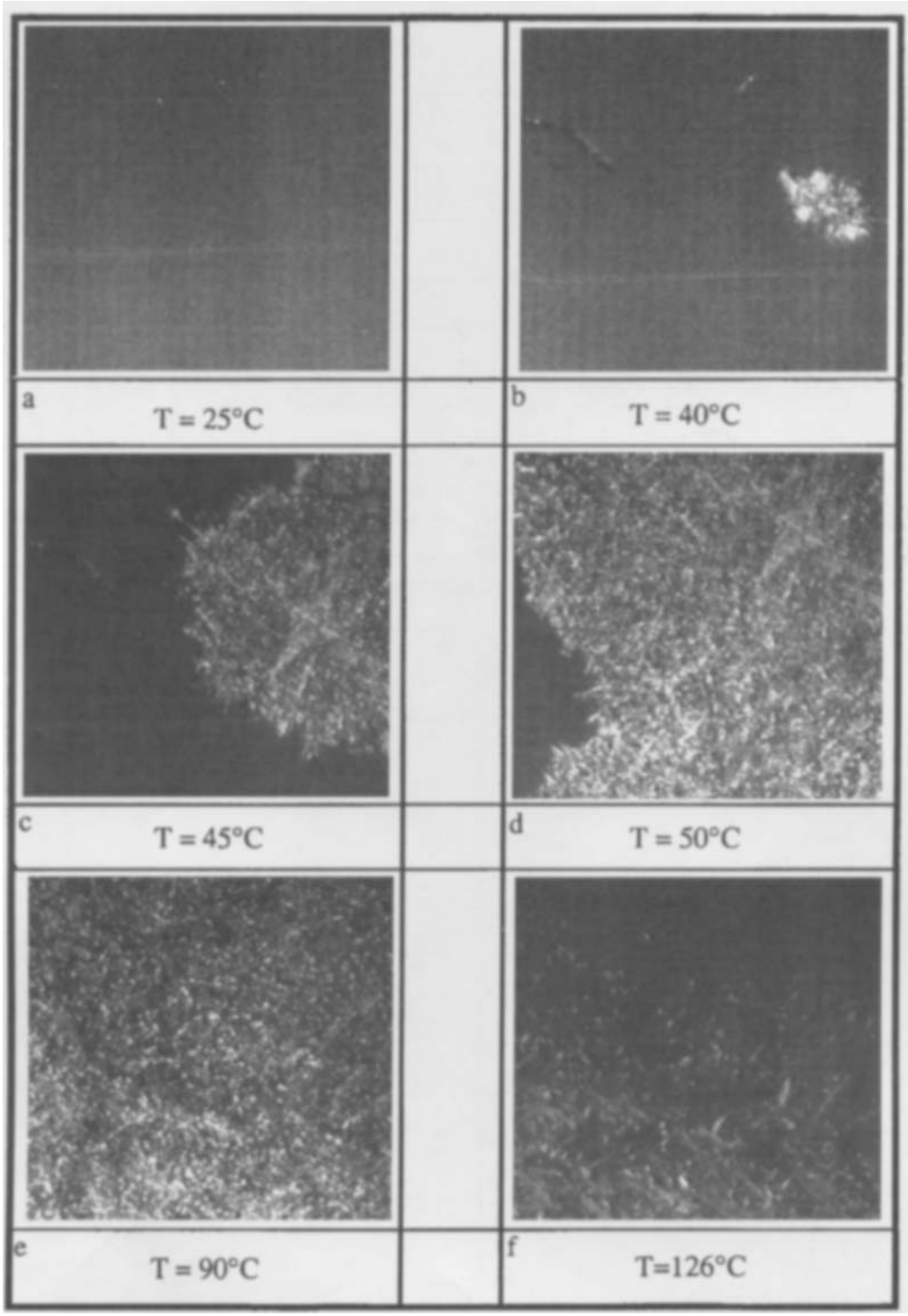

Figure 4. Photographs of quenched progesterone, obtained from OTA during the heating period.

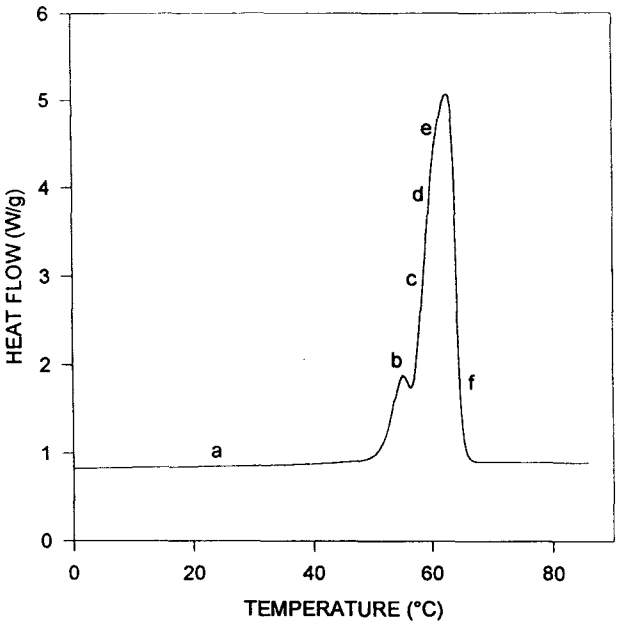

Figure 5. Enthalpic curve obtained on pure PEG 6000, after quenching at −100°C/min from the liquid state.

The OTA photographs presented in Fig. 4 show that no crystalline phase is detected for $T < T_g$ [Fig. 4(a)]. Thus, the sample can be considered as wholly vitreous in this temperature range. For $T > T_g$ and up to $T \approx 90°C$ [Figs. 4(b), 4(c), 4(d), and 4(e)], the devitrification process follows the well-known germination-growth model. At the end of this stage, the sample can be considered as wholly crystallized. Finally, for $T = 126°C$, [Fig. 4(f)] the fusion of the full-grown crystallites is observed.

The enthalpic curve obtained on pure PEG 6000 (Fig. 5) exhibits two successive endothermic peaks. The first one, of low magnitude, occurs at $T = 55°C$; the second one, of high magnitude at $T = 62.5°C$. This type of enthalpic curve could be interpreted as the succession of two melting phenomena due to the existence of either two molecular mass distributions in the polymer or two crystalline species.

The OTA photograph presented in Fig. 6(a) shows that the sample is crystallized at $T = 25°C$. This crystalline phase is made of spherulites. When the temperature increases, at $T = 58°C$ [Fig. 6(b)], two phenomena occur simultaneously, the fusion of the spherulites and the formation of a new structure located at the spherulite interfaces. When the temperature reaches $T = 61°C$ [Fig. 6(c)], we observed that this interfacial structure grows while the fusion of the spherulite is going on. At $T = 62°C$ [Fig. 6(d)] all the spherulites are fully melted while the new interfacial structure remains observable. Finally, at $T = 63°C$ [Figs. 6(e), 6(f)], the interfacial structure melts. This last observation allows us to conclude that, in the temperature range $58°C < T < 63°C$, the interfacial structure is crystallized. This new crystalline phase comes from a devitrification process (at 58°C) of an initial interspherulitic vitreous phase. These data show that the classical interpretation of DSC data is erroneous. In fact, the DSC trace is the result of the convolution of, first, a large endothermic peak characteristic of the spherulitic phase melting, second, an exothermic reaction due to the devitrification of the vitreous interspherulitic phase, and third, an endothermic reaction due to the melting of this new crystalline phase (Fig. 7).

The enthalpic curve obtained at 3% w/w progesterone–PEG6000 solid dispersion is displayed in Fig. 8. Only one endothermic reaction is observed, at $T = 60°C$, as expected for this eutectic composition. Nethertheless, we can also notice the existence of some shoulders at the beginning of the peak.

The photographs obtained from OTA are displayed in Fig. 9. At $T = 25°C$ [Fig. 9(a)], we can notice the presence of spherulites, previously observed on pure PEG samples. Owing to the presence of progesterone in the mixture, their average radius is more regular and smaller. when the temperature reaches 45°C [Fig. 9(b)], we observe the beginning of the spherulite melting and simultaneously the emergence of a new structure at the spherulite interfaces. This new structure differs from the one observed for the pure PEG and looks like small particles. At higher temperature, $T = 58°C$ [Fig. 9(c)]. the melting of the spherulite is going on and the interfacial structure remains observable. At $T = 62°C$ [Fig. 9(d)], all the spherulitic phase is fully melted and the surrounding particles remain observable before melting progressively up to 90°C [Figs. 9 (e), 9(f)].

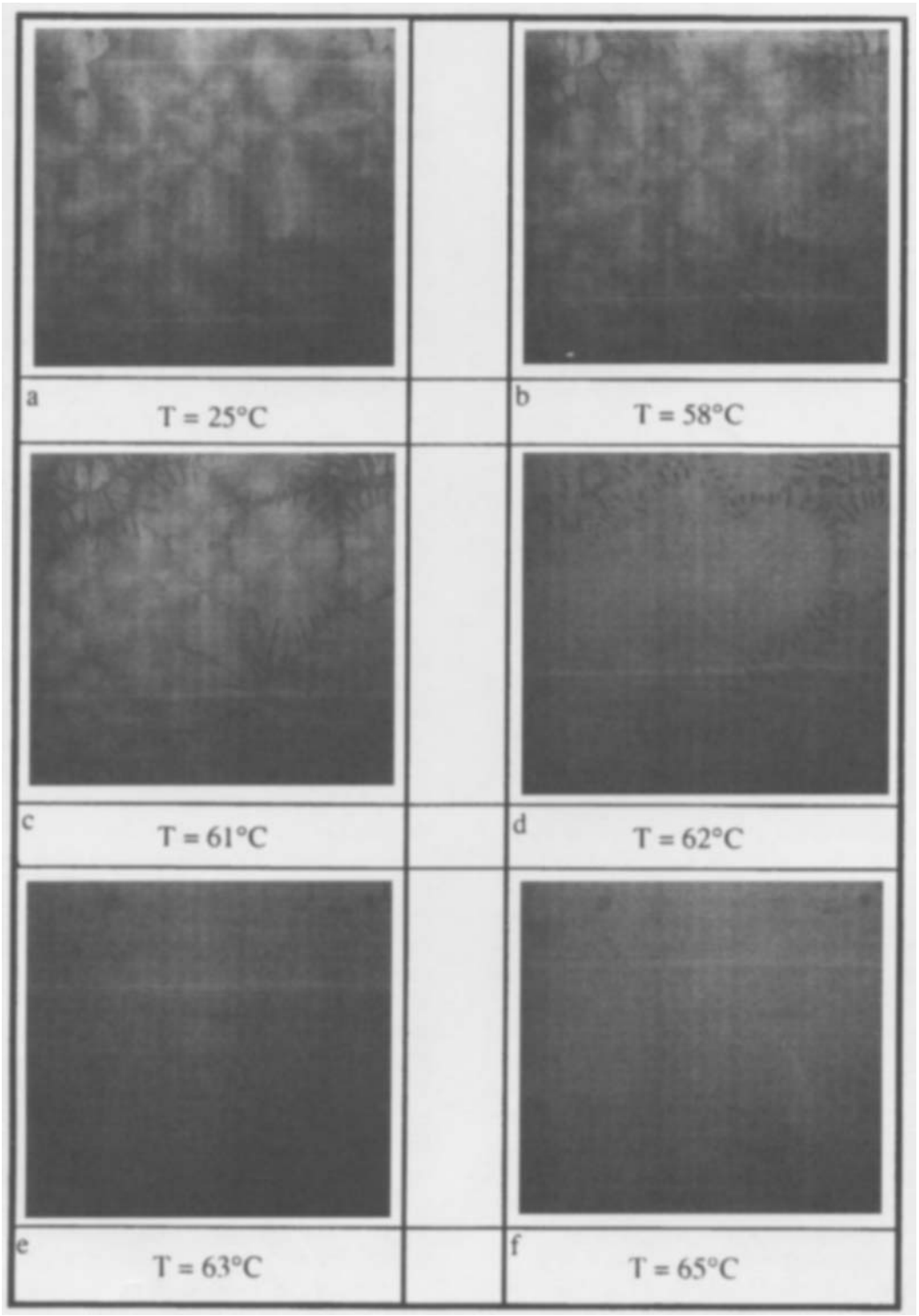

Figure 6. Photographs of quenched PEG 6000, obtained from OTA during the heating period.

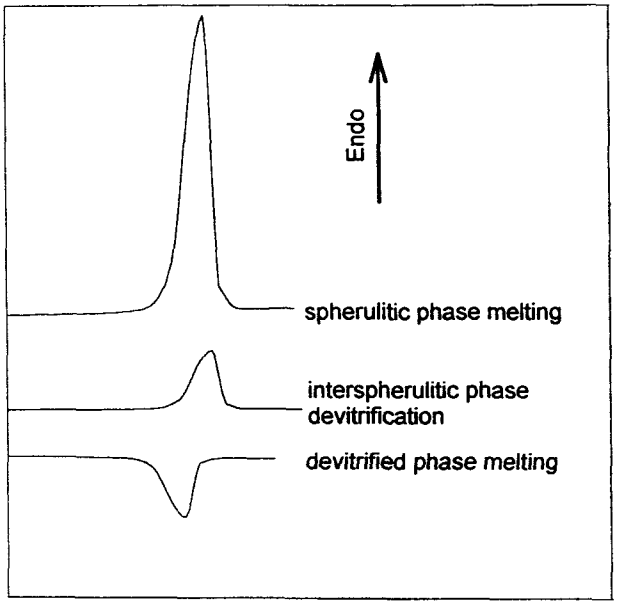

Figure 7. Schematic view of the convoluted thermal reactions leading to the enthapic curve presented in Fig. 5.

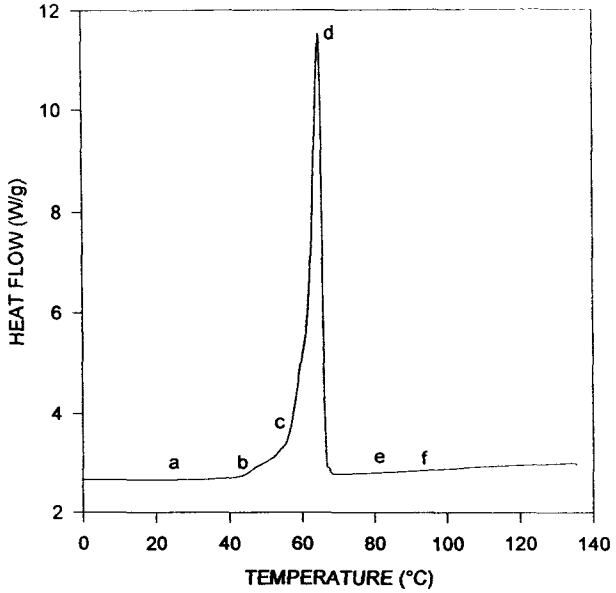

Figure 8. Enthalpic curve obtained on 3% w/w solid dispersion, after quenching at -100°C/min from the liquid state.

These results show that, as for pure PEG, a vitreous phase located at the spherulite interfaces can be observed at room temperature. However, in this case, this vitreous phase is mainly composed of a mixture of progesterone and PEG. Thus, we can conclude that, at room temperature, the 3% w/w solid dispersion composition consists of a mixture of pure crystallized PEG6000 and of a vitreous progesterone/PEG6000 mixture located in the interspherulitic space.

Figure 10 shows the DSC trace obtained at the 20% w/w progesterone–PEG6000 solid dispersion which exhibits a complex set of exothermic and endothermic peaks. Owing to the complexity of this enthalpic curve, it is difficult, without further information, to assign a reason for all these thermic phenomena. So, the analysis of the data requires the use of another experimental method of investigation.

The photographs obtained from OTA are displayed in Fig. 11. At T = 15°C [Fig. 11(a)], the typical spherulitic structure due to PEG is observed. At T = 20°C [Fig. 11(b)] a new structure appears and increases up to T = 46°C [Figs. 11(c), 11(d), 11(e)]. The emergence of this new structure corresponds to the exothermic phenomenon observed in Fig. 10. The comparison with the data obtained on pure progesterone samples leads to the conclusion that this new structure is due to the devitrification of the vitreous phase mainly composed of progesterone. This new structure grows and hides the PEG crystalline structure previously observed in the photographs. Nevertheless, from T = 46°C to T = 62°C [Figs. 11(e) and 11(f)], some parts of the photographs show the existence of a liquid phase, indicating that the fusion of the PEG is going on. This fusion is achieved at T = 65°C [Fig. 11(g)]. Finally, when the temperature increases up to 118°C [Figs. 11(h) to 11(l), we observe the melting of the devitrified phase. Thus, from the OTA data it appears that, at room temperature, the 20% w/w progesterone–PEG6000 solid dispersion is composed of two phases. One is crystallized and mainly composed of PEG; the second one is vitreous and mainly composed of progesterone.

CONCLUSION

In this work, phase transitions of progesterone, PEG6000, and (3% w/w and 20% w/w) solid disper-

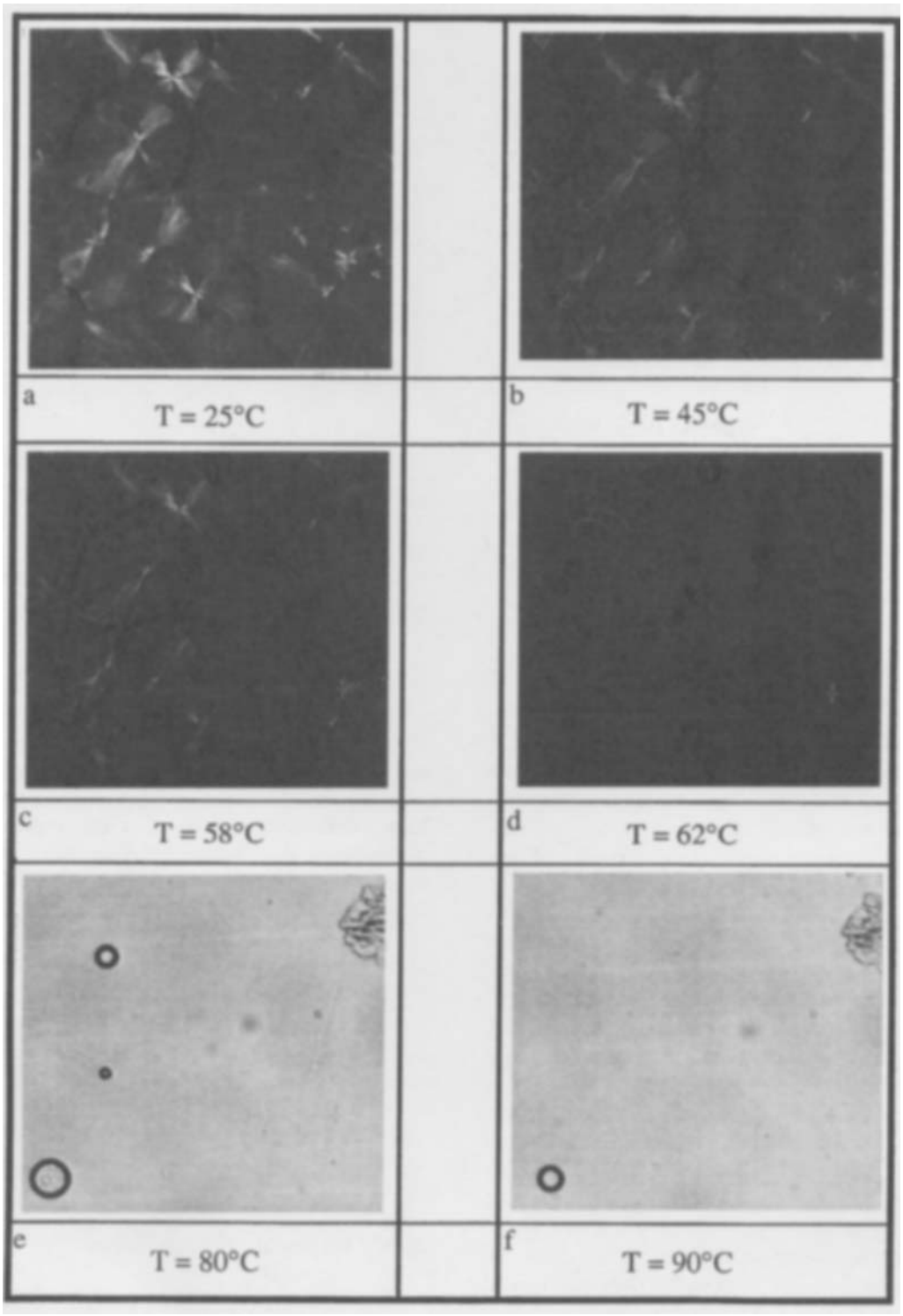

Figure 9. Photographs of 3% w/w quenched solid dispersion, obtained from OTA during the heating period.

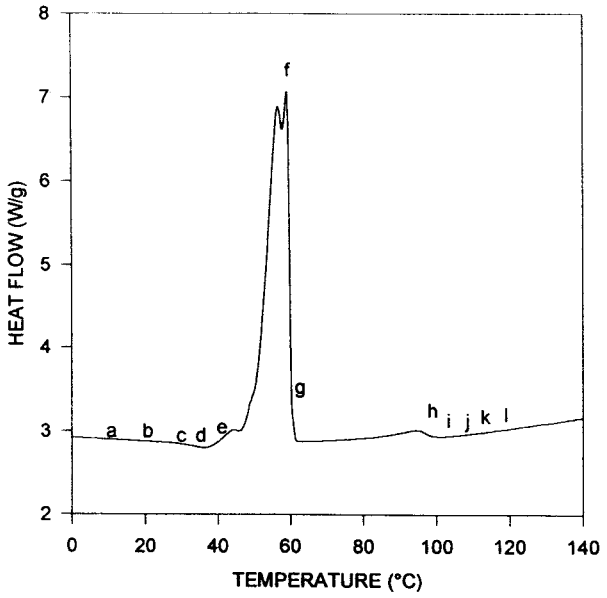

Figure 10. Enthalpic curve obtained on 20% w/w solid dispersion, after quenching at -100°C/min from the liquid state.

sions were studied. To obtain crystalline and/or vitreous systems at room temperature, we have intentionally quenched the samples from the melt and investigated them by differential scanning calorimetry (DSC) and optical thermal analysis (OTA). For complex systems like solid dispersions, we have shown that the OTA allowed a new interpretation of enthalpic curves and appears to be a powerful complementary tool to interpret the DSC data.

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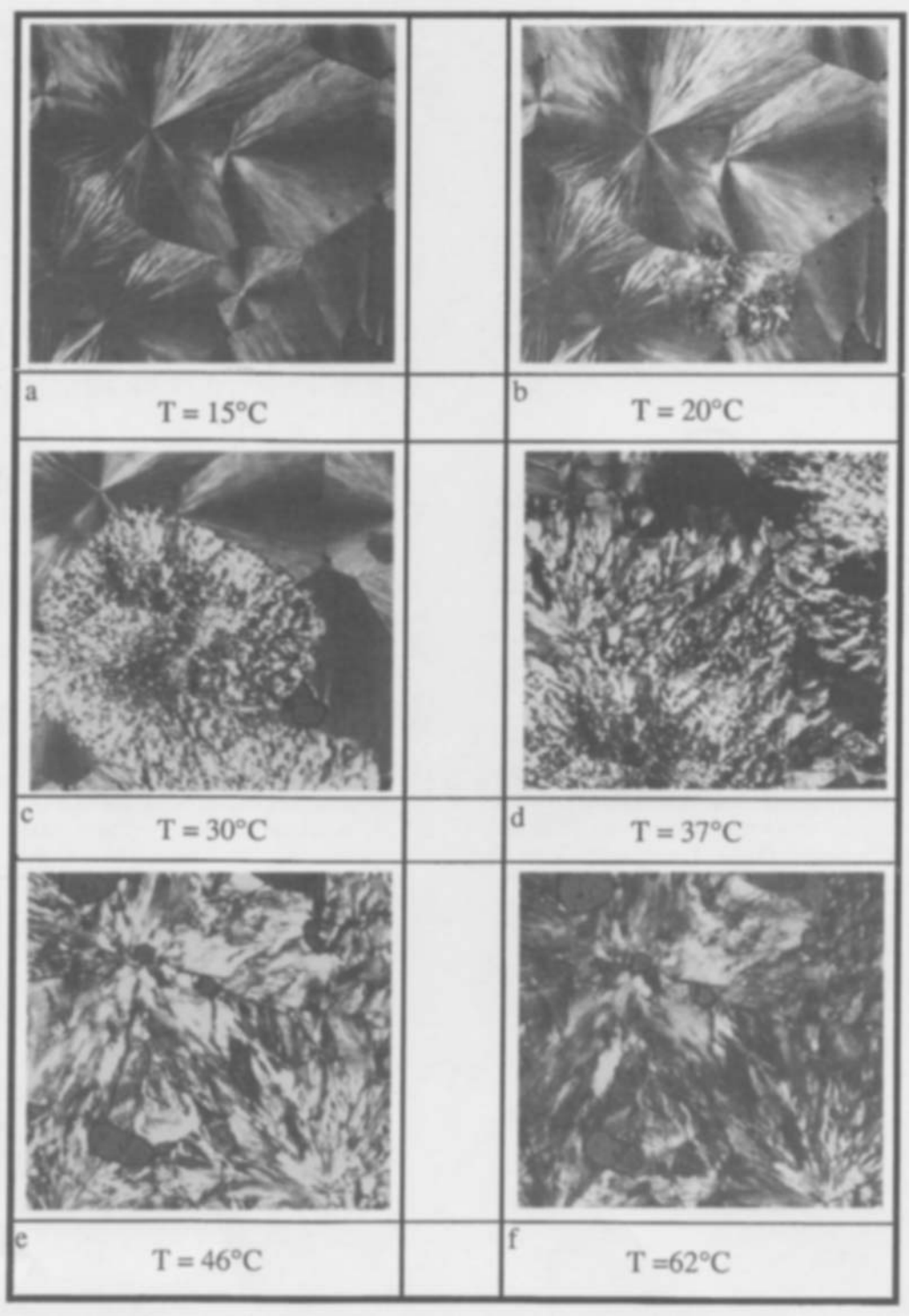

Figure 11. (a)–(f) Photographs of 20% w/w quenched solid dispersion obtained from OTA during the heating period from $T = 15°C$ to $T = 62°C$. (g)–(l) Photographies of 20% w/w quenched solid dispersion obtained from OTA during the heating period from $T = 65°C$ to $T = 118°C$.

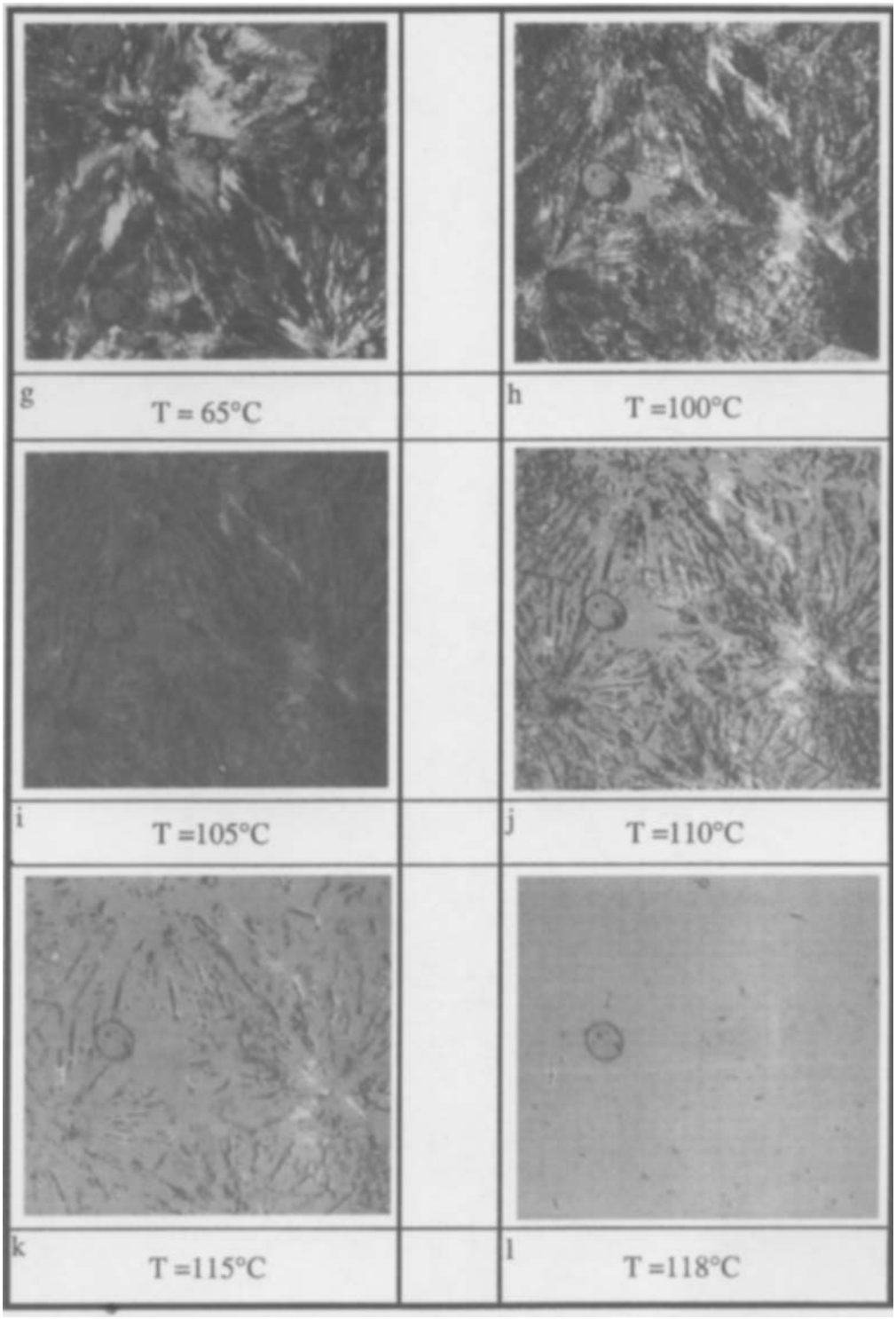

Figure 11. Continued