Solid-State Emulsions: The Effects of Process and Storage Conditions

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The effects of process and storage conditions of solid-state emulsions were studied. Oil-in-water emulsions may be prepared from solid state emulsions by adding an aqueous phase to the solid. Solid-state emulsions are prepared by processing an oil phase and an aqueous solution of matrix material via a solvent removal process. Sucrose, the carrier material utilized in this report, results in a metastable solid or glass, which can transform upon aging to a more stable thermodynamic state. Aging was determined by monitoring the crystallinity as a function of time, temperature, relative humidity, and grinding. The crystallinity of solid-state emulsions was determined with X-ray diffraction and differential scanning calorimetry. Results indicate that solid-state emulsions should be stored between 15 and 25% relative humidity at 25°C. Grinding has no apparent effect on the crystallinity of the sample, as detected by X-ray diffraction, although the microcrystallinity is increased. The utilization of silinized glassware enabled the sample-to-sample microcrystalline variability to be reduced.

KEY WORDS: self-emulsification; glass; solid transformation; self-emulsifiable solid; emulsifiable glass.

INTRODUCTION

Solid-state solutions or dispersions (more appropriately termed solid-state suspensions) are metastable solids formed by dissolving or suspending a compound of interest within a carrier using solvent removal or fusion techniques (1–3). The addition of an aqueous vehicle to a solid state solution or suspension produces a homogeneous aqueous solution. Numerous materials have been utilized to prepare solid dispersions or coprecipitates (1). Glass solutions or suspensions are a form of solid-state dispersions (3). Glasses, by definition, exhibit glass transition regions and are therefore metastable solids. Those materials reported to form glasses include sugars such as dextrose, galactose, and sucrose (2).

The utilization of glass systems as drug delivery vehicles is the subject of several reviews and articles (1,2,4–6). Because of the ability to increase the dissolution rates of poorly water soluble compounds (1,4,7), solid-state solutions or suspensions have been of interest (1). In cases where the dissolution rate of a drug is proportional to bioavailability, increased dissolution rates are known to result in increased gastrointestinal absorption (3,7), reduced presystemic metabolism, and, ultimately, a reduction of the dose administered. Other advantages, specific to the glass forming material and the drug, have also been claimed (8,9).

The failure of glass systems to be widely utilized relates to process limitations such as high temperature, cosolvent requirements (4) and aging, i.e., the transformation of a metastable state to a lower energy state (3,10). The physical characteristics of glasses dramatically change at the glass transition temperature. The best physical stability of glasses is achieved by maximizing the difference between the storage temperature and glass transition temperature. Residual solvent or atmospheric moisture has been shown to plasticize the glass, i.e., lower the glass transition temperature (11), thus decreasing the difference between the storage temperature and the glass transition. In some instances, the aging of glasses, especially those that are hygroscopic, may be accelerated as a result of storage at improper relative humidity (12).

The current system under investigation produces an oil-in-water (o/w) emulsion upon the addition of an aqueous phase to a solid (13). To be consistent with the nomenclature developed for solid-state solutions and suspensions, the systems discussed in this report are referred to as solid-state emulsions. The term solid-state emulsion refers to the fine dispersion of an immiscible oil phase within a solid phase. Since solid-state emulsions are not prepared by melt fusion techniques, the medicinal and other various components are not exposed to high temperatures. Due to the presence of an oil phase, medicinal agents can be dissolved in the oil phase and therefore the need for a cosolvent is eliminated. Although the preparation of solid-state emulsions does not require high temperatures or the use of cosolvents, the observation of a glass transition region within the sucrose-based solid-state emulsions (13), necessitates that the aging properties of this system be evaluated.

We therefore studied the aging of these solid-state emulsions under various process and storage conditions as a function of temperature, relative humidity, and time. Further, the following process conditions, as they relate to physical stability, include exposure to mildly elevated temperatures (less than 50°C), grinding, and the processing vessel surface.

MATERIALS AND METHODS

Sucrose (MCB, reagent grade) and heavy mineral oil (Fisher Scientific, USP/FCC) were used without further purification. Double-distilled water was used throughout the study. Relative humidities in each case were achieved through the use of various saturated salt solutions. Glassware was silinized using Sigmacote (Sigma Chemical Company, USA). As controls, physical mixtures of the appropriate composition of sucrose and mineral were prepared.

Production of Solid-State Emulsion. Solid-state emulsions were prepared by adding sucrose (2.5–3.5 parts by weight) and mineral oil (1 part by weight) to a round-bottom vacuum flask. Sufficient water to dissolve the sucrose was then added to the flask. The flask was fitted to a rotary evaporator and vacuum was applied (approximately 5 mm Hg). The mixture was slowly rotated until a brittle foam was produced. Solid-state emulsion systems with the following sucrose-to-mineral oil ratios were prepared: 2.5:1, 2.75:1, 3:1, and 3.5:1. The solid was stored in a desiccator at room temperature. The process was continued until the moisture content of the solid, as determined by Karl-Fisher titration, was 0.25% (w/w).

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X-Ray Powder Diffraction. Diffraction patterns were collected using monochromatized Cu radiation (Scintag USA). Samples were prepared by finely grinding the sample in an agate mortar and pestle and then packed into a plexiglass sample holder. The diffraction patterns were collected as a function of the angle at a rate of 3° (2θ) per min. As controls, physical mixtures of the appropriate composition of sucrose and mineral were prepared.

Differential Scanning Calorimetry. In all cases, a Perkin–Elmer DSC-7 was utilized for the collection of calorimetric data. The calorimeter was equipped with an intracooler (capable of achieving −60°C) and a glove box. The sample compartment was purged with a continuous flow of nitrogen (USP) at 20 psi, while the glove box was purged with nitrogen at 2 psi. The calorimeter was calibrated daily with indium. Samples were accurately weighed (3.00 to 10.00 mg), placed, and compressed into aluminum sample pans (Perkin–Elmer Corporation, USA), prior to being sealed. Calorimetric data were then collected at a rate of 10° per min.

RESULTS AND DISCUSSION

Several techniques are available for evaluating crystalline properties and recrystallization, e.g., X-ray diffraction and calorimetry. The recrystallization or aging of solid-state emulsions was monitored using X-ray diffraction (5,14) and differential scanning calorimetry (6,11,15) as a function of storage and handling conditions. The feasibility of utilizing X-ray diffraction as a technique to monitor the aging of glass solid emulsions was evaluated by collecting diffractograms

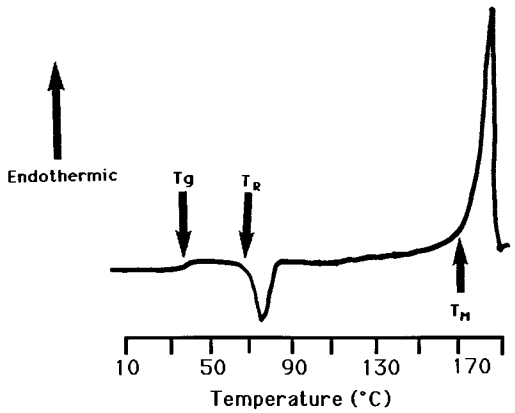

Fig. 2. DSC thermogram of a sucrose solid-state emulsion (sucrose:mineral oil, 3:1) collected at 10° per min. T_g, glass transition; T_R, temperature of recrystallization; T_M, temperature of crystalline melting.

for the various physical mixtures and corresponding solid-state emulsions (Figs. 1A and B, respectively). The physical mixture of sucrose and mineral oil had numerous sharp diffraction peaks that are indicative of long-range molecular order or crystallinity (Fig. 1A). In comparison, the representative solid-state emulsion of Fig. 1B, having the same composition as in Fig. 1A, lacks the characteristic crystalline

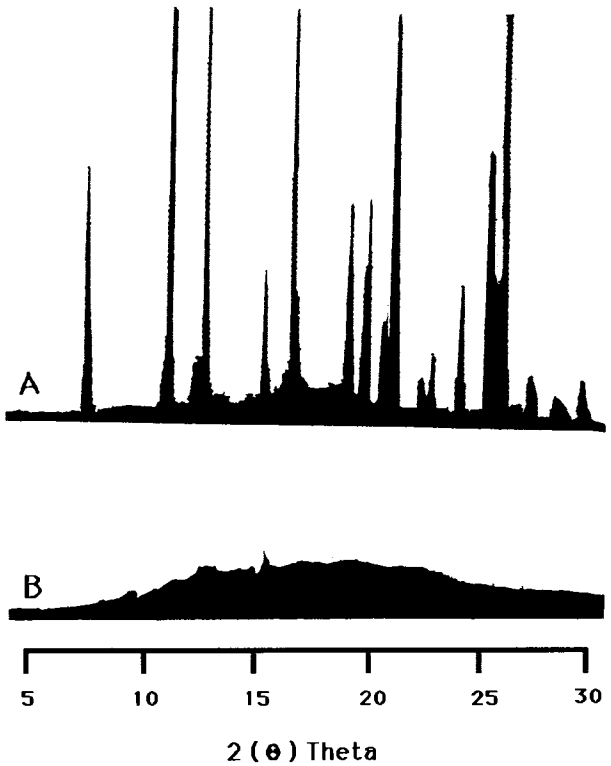

Fig. 1. X-ray diffractogram of (A) a physical mixture (sucrose: mineral oil, 3:1) of sucrose and oil and (B) a solid-state emulsion of mineral oil and sucrose at the same ratio.

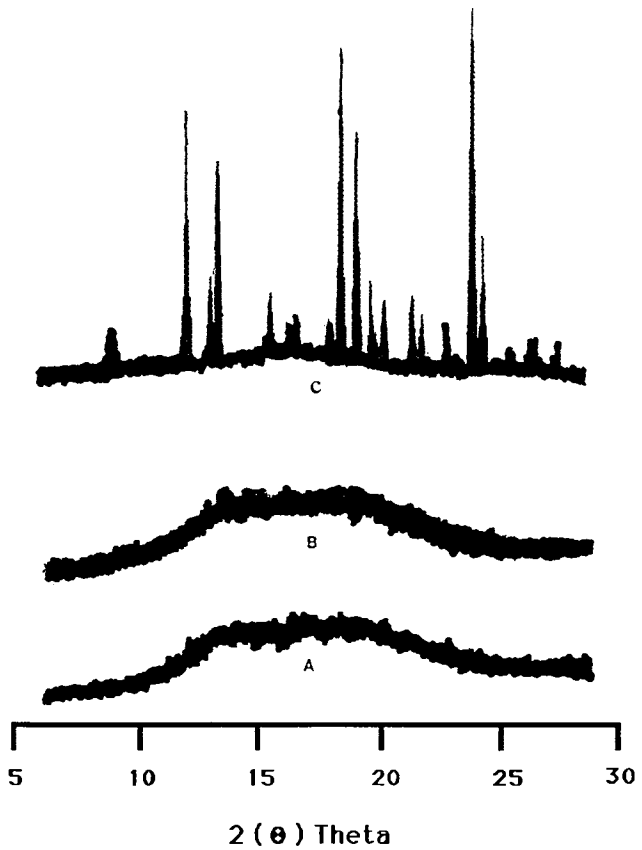

Fig. 3. X-ray diffractograms of a solid-state emulsion (sucrose:oil, 3:1) stored as a function of relative humidity at 25°C. Lower diffractogram, 1% RH; middle diffractogram, 35% RH; upper diffractogram, 87% RH.

diffraction peaks. The appearance of crystalline diffraction peaks within solid-state emulsions positively correlates to poor emulsification properties, e.g., no dispersion produced or a noticeably oily solid. X-ray diffraction is therefore an appropriate technique to monitor the aging of these systems.

A representative thermogram for a solid-state emulsion is shown in Fig. 2. Analysis of Fig. 2 indicates a glass transition at approximately 45°C, an exothermic recrystallization peak at approximately 71°C, and an endothermic crystalline melting peak at approximately 180°C. Because these samples appear amorphous to X-ray diffraction, the observed crystallinity by DSC is referred to as microcrystallinity. The microcrystallinity of the sample can be calculated according to the method utilized by Peppas and Merrill (16).

$$X\% = \frac{\Delta H_R + \Delta H'_m}{\Delta H_m} * 100$$

$X\%$ = percentage crystallinity of sample
ΔH_R = sample heat of recrystallization (exothermic)
$\Delta H'_m$ = sample heat of melting (endothermic)
ΔH_M = pure sucrose heat of melting

According to this method, the sum of the heat of recrystallization (ΔH_R) and the heat of melting ($\Delta H'_m$) is divided by the heat of melting for a pure sample (ΔH_m), e.g., sucrose. Although not addressed by Peppas and Merrill (16), an important assumption of this method is that the heat of recrystallization is equal in magnitude but opposite in sign to the heat of melting.

Moisture has been reported to lower the glass transition or act as a plasticizing agent for amorphous solids having glass transitions, i.e., glasses (11). The presence of moisture can therefore accelerate the aging process. Based on this understanding, the determination of appropriate storage conditions for solid-state emulsions was of interest. After 3 months of storage at 25°C, under known relative humidities, the X-ray diffraction patterns of solid-state emulsions were collected (Fig. 3). Based on the relative number of sharp diffraction peaks, a qualitative description of the fraction recrystallized may be achieved. Analysis of the results shown in Fig. 3 suggest that at 1% RH (25°C), there was essentially no aging after 3 months of storage. In contrast, the samples stored under 82% RH (25°C) had numerous crystalline diffraction peaks, indicating that significant recrystallization had taken place. As a result of utilizing multiple moisture storage conditions, it was determined that the maximal moisture content should be less than 35% (for 3 months' storage at 25°C).

Since microcrystallinity of an aging sample is likely to be a precursor to crystallization, detectable by X-ray diffraction, the microcrystallinity of these solid-state emulsions was determined. The percentage microcrystallinity was calculated for several storage temperatures (4, 15, 25, 45, and 75°C) and relative humidities (0, 15, and 30%) as a function

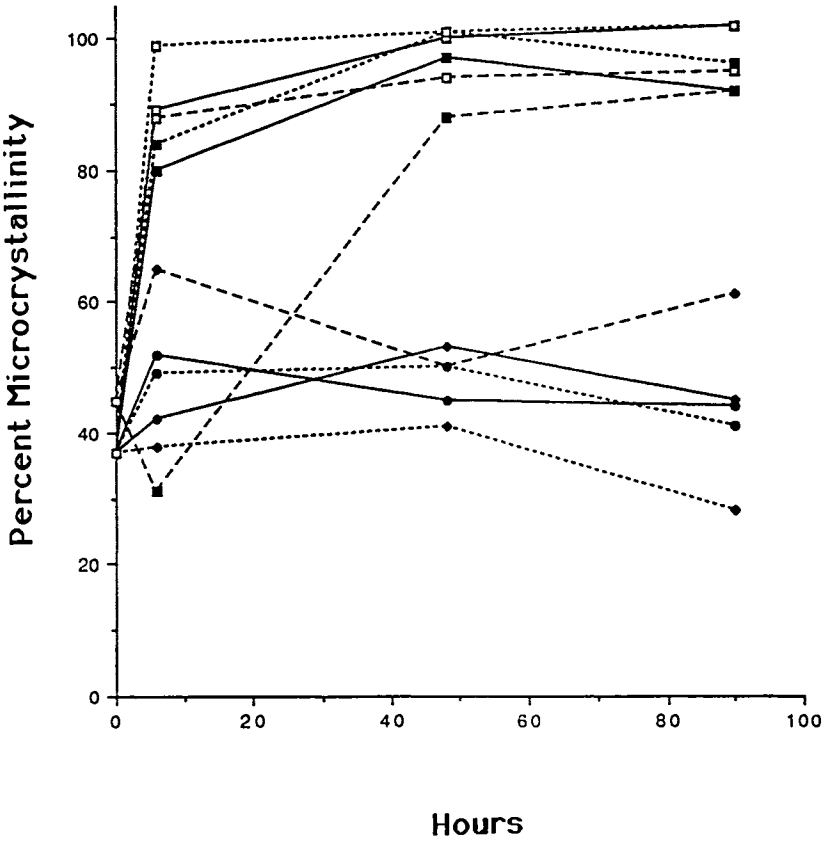

Fig. 4. Percentage microcrystallinity of a solid-state emulsion (sucrose:mineral oil, 3.5:1) as a function of time, relative humidity, and temperature. 0% RH, – – – –; 15% RH, ——; 39% RH, -----. 4°C, ●; 25°C, ◆; 45°C, ■; 75°C, □.

of time (Fig. 4). From the analysis of Fig. 4, two distinct regions became apparent.

According to Fig. 4, the microcrystallinity of samples at and above 45°C rapidly increased in the first 10 hr and reached microcrystallinity values ranging from 90 to 100%. While at temperatures below 45°C the microcrystallinity increased only slightly, if at all, and reached plateau values that ranged from 35 to 55%. The results shown in Fig. 4 suggest that the temperature of storage is probably more important than the relative humidity (when at or below 30% RH). For example, the high microcrystallinity of the samples stored under conditions of 0% RH and 75°C was very similar to the samples stored at 30% RH and 45°C. Due to sucrose-based solid-state emulsions with a glass transition temperature of 45°C, the abrupt change in aging is in agreement with established theory (17,18). When stored below the glass transition temperature, molecular rotation and translation are hindered, thus slowing or preventing recrystallization (19). At storage temperatures above the glass transition temperature, there is sufficient molecular reorientation to propagate recrystallization within the sample. It is important to note that the observed glass transition for these solid-state emulsion systems is approximately 25°C higher than that previously reported for amorphous sucrose (17). The incorporation of mineral oil within the glass appears to increase the glass transition temperature of sucrose.

The manipulation of glasses has the potential to accelerate recrystallization through the introduction of nucleation foci (19). For sucrose-based solid-state emulsions to be feasible as a drug delivery system, the glass must be able to withstand manipulations that may be encountered during the manufacturing process, such as grinding and sieving. X-ray diffractograms were therefore collected as a function of grinding procedures and are shown in Fig. 5. Analysis of Fig. 5 suggests that grinding did not significantly alter the crystallinity compared to controls (not shown). A few peaks may be noted in Fig. 5 but their presence is more likely due to extended exposure to elevated room humidities (~78–80% RH). Since Fig. 5 represents multiple grinding procedures of the same sample (~35 min per diffractogram), the sample was exposed to at least 3 hr of high-humidity conditions. Control samples (no grinding) exposed to the laboratory atmosphere had essentially the same small diffraction peaks. The observed randomness of the peaks is most likely due to preferential orientation of the sample.

Differential scanning calorimetry was further utilized to characterize the effect of grinding. The percentage crystallinity was determined, as before, for samples before and after grinding ($N = 3$) (Table I). Analysis of Table I indicates that the samples appeared to be about 36% (SD, ±7.5%) microcrystalline prior to any grinding. The microcrystallinity increased to 87% (±1.6%) after the samples were ground suggesting that grinding did introduce new nuclei for crystallization at 25°C. No noticeable changes in the self-emulsifying properties at the higher microcrystalline values were observed, however. Although microcrystallinity has no apparent deleterious effect on the observed self-emulsifying properties, it is anticipated that the growth of microcrystalline regions at some time will eventually result in crystalline regions that are detectable by X-ray diffraction, with a concomitant decrease in self-emulsification.

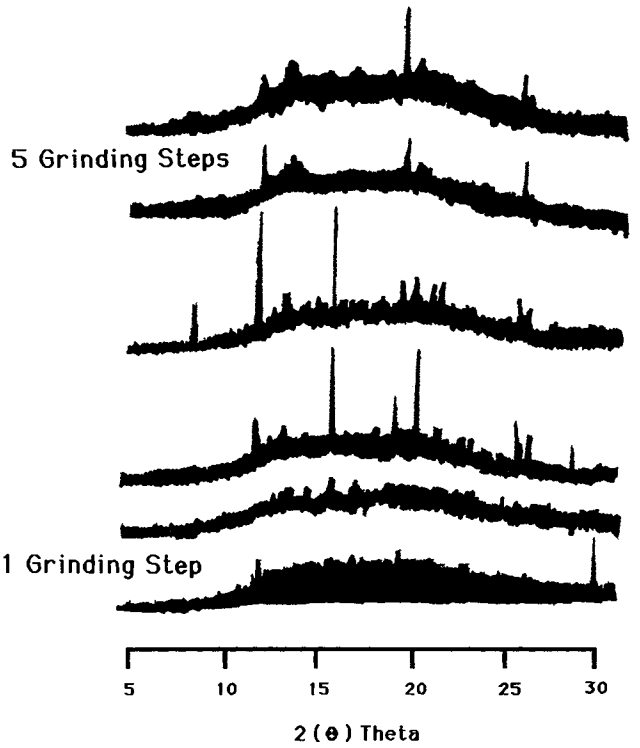

Fig. 5. X-ray diffractograms of a solid-state emulsion (sucrose: mineral oil; 3:1) as a function of the number of grinding procedures at 25°C (relative humidity was approximately 65%). Lower diffractogram, no grinding; upper diffractogram, five grinding procedures).

Based on theories describing the initiation of crystallization, the rotary evaporation vessel was coated with silicone, i.e., reducing the porosity and polarity of the surface (20). The microcrystallinity was determined as a function of the various processing conditions and summarized in Table II. Analysis of Table II indicates that after 1 and 3 hr of processing (without heat), the percentage microcrystallinity was essentially unchanged at 21–19%, respectively. However, after 4 hr of processing with heat (40°C), the microcrystallinity increased to approximately 50%. These results may be explained in light of the fact that crystalline sucrose is anhydrous and therefore the removal of water from a glass tends to induce a certain degree of crystallinity. Further analysis of Table II indicates that the sample-to-sample variability, based on microcrystallinity, improved as a function of processing time. A comparison of Tables I and II indicates

Table I. Microcrystallinity as a Function of Sample Grinding for a Solid-State Emulsion (Sucrose:Mineral Oil, 3:1) at 25°C

Condition	Micro-crystallinity (%)	Average (%)	SD (%)
Pregrinding	27.688		
	45.852	35.992	7.497
	34.435		
Postgrinding	88.723		
	88.336	87.393	1.615
	85.121		

Table II. Microcrystallinity as a Function of Sample Preparation Within Silicone-Coated Glassware for a Solid-State Emulsion (Sucrose:Mineral Oil, 3:1)

Condition	Microcrystallinity (%)	Average (%)	SD (%)
After 1 hr (− heat)	8.721		
	28.798	21.641	9.153
	27.403		
After 3 hrs (− heat)	10.919		
	21.461	18.974	5.834
	24.544		
After 4 hrs (+ heat)	46.768		
	52.222	49.543	2.222
	49.543		

that the use of silinized glassware slightly increased the percentage of microcrystallinity but dramatically reduced the sample-to-sample variability.

In summary, sucrose-based solid-state emulsions appear to age or revert to a more crystalline state as a function of time but have better properties than neat amorphous sucrose glasses. Through the control of the appropriate storage temperature and relative humidity conditions, the aging process can be made negligible. The sample-to-sample variance, as judged by microcrystallinity, can be made quite small through the utilization of silinized glassware. Studies are currently in progress to evaluate what effect the incorporation of a drug within the oil phase has on the physical stability of the solid and aqueous emulsion.

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REFERENCES

1. W. L. Chiou and S. Reigelman. Pharmaceutical applications of solid dispersion systems. *J. Pharm Sci.* **60**:1281–1302 (1971).
2. L. V. Allen, V. A. Yanchick, and D. D. Maness. Dissolution rates of corticosteroids utilizing sugar glass dispersions. *J. Pharm. Sci.* **66**:494–487 (1977).
3. W. L. Chiou and S. Riegelman. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.* **58**:1505–1509 (1969).
4. J. L. Ford. The current status of solid dispersions. *Pharm. Acta Helv.* **61**:69–88 (1986).
5. R. J. Timko and N. C. Lordi. Thermal characterization of citric acid solid dispersions with benzoic acid and phenobarbital. *J. Pharm. Sci.* **68**:601–605 (1979).
6. J. L. Ford. The use of thermal analysis in the study of solid dispersions. *Drug Dev. Ind. Pharm.* **13**:1741–1777 (1987).
7. E. I. Stupak and T. R. Bates. Enhanced absorption and dissolution of reserpine from reserpine-polyvinylpyrrolidone coprecipitates. *J. Pharm. Sci.* **61**:400–403 (1972).
8. A. Halpern and C. H. Bradney. U.S. Patent 2,698,822 (1955).
9. A. Thakkar, C. A. Hirsch, and J. G. Page. Solid dispersion approach for overcoming bioavailability problems due to polymorphism of nabilone, a cannabinoid derivative. *J. Pharm. Pharmacol.* **29**:783–784 (1977).
10. H. P. Merkle. Aging of coprecipitates: Self-association as observed by dynamic dialysis of supersaturated aqueous solutions of hydrocortisone. *Pharm. Acta Helv.* **57**:1601–1633 (1982).
11. R. J. Timko and N. G. Lordi. Thermal analysis studies of glass dispersion systems. *Drug Dev. Ind. Pharm.* **10**:425–451 (1984).
12. I. Sugimoto, A. Kuchiki, H. Nakagawa, K. Tohgo, S. Kondo, and K. Takahashi. Dissolution and absorption of nifedipine from nifedipine-coprecipitate. *Drug Dev. Ind. Pharm.* **6**:137–160 (1980).
13. S. L. Myers and M. L. Shively. Preparation and characterization of emulsifiable glasses: Oil-in-water and water-in-oil-in-water emulsions. *J. Colloid Interface Sci.* **149**:271–278 (1992).
14. M. Mathiouthi. Physical state of sucrose after lyophilization. II. *Ind. Aliment. Agr.* **92**:1279–1285 (1975).
15. A. Smith. Use of thermal analysis in predicting drug-excipient interactions. *Anal. Proc.* **19**:559–561 (1982).
16. N. A. Peppas and E. W. Merrill. Differential scanning calorimetry of crystallized PVA hydrogels. *J. Appl. Polym. Sci.* **20**:1457–1465 (1976).
17. J. T. Carstensen and K. Van Scoik. Amorphous-to-crystalline transformation of sucrose. *Pharm. Res.* **7**:1278–1281 (1990).
18. K. Van Scoik. *Nucleation and Crystallization Phenomena in Amorphous Sucrose Systems,* Ph.D. thesis, School of Pharmacy, University of Wisconsin, Madison, 1987, pp. 167–176.
19. D. R. Uhlmann and B. Chalmers. The energetics of nucleation. In *Nucleation Phenomena,* American Chemical Society, Washington, DC, 1966.
20. S. K. Heffels, L. J. Kuijvenhoven, and E. J. de Jong. In S. J. Jancis and E. J. de Jong (eds.), *Industrial Crystallization 84,* Elsevier Science, Amsterdam, 1984.