The accuracy and precision of the NMR procedure were studied by analyzing solutions of pure I · HCl in the range from about 80 to 100 mg in 3–4 ml of solution together with varying amounts of II internal standard. Five integrations were run on each of eight samples prepared by using the double-extraction procedure described (Table I). Since the sample taken was a pure chemical, the average value is close to 100% as expected. The standard deviation obtained for the eight known mixtures was 0.8%. The agreement between the NMR and NF procedures is excellent; both results show the measurements to be accurate. The relative proportions of I to II, as noted in Table I, have no significant bearing on the accuracy of the determination for the range of proportions shown.

The suitability of this procedure for the analysis of actual samples was established since 15 trials involving commercial I · HCl soft gelatin capsules and syrups were analyzed by NMR with no evidence of interference from excipients present. For comparison, 10 of these samples were also analyzed by the NF XIII procedure. The results (Table II) indicate good agreement between the NMR and official procedures, the average values being within at most 0.5% of each other. The reproducibility of the NMR measurement is 0.9% *SD*.

As previously demonstrated, the use of NMR for quantitative analysis offers a number of advantages, experienced in this case as well. Thus far, monograph specifications for the identification and purity of pharmaceutical substances drawn up by books of standards do not use NMR spectroscopy. There can be little doubt, however, that NMR has an important role to play in the area of good drug standards. This situation arises probably because many people are unaware of the full potential of the NMR technique and hesitate before allowing a relatively new, and apparently expensive, method to take its rightful place alongside the established methods such as IR, UV, and visible spectroscopy.

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[4] For Part XI of this series, see J. W. Turczan, *Anal. Chim. Acta*, **68**, 395(1974).

Quantitative Analytical Method for Determination of Drugs Dispersed in Polymers Using Differential Scanning Calorimetry

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Abstract □ A differential scanning calorimeter was used to determine quantitatively the concentration of dispersed progesterone and cholesterol in a silicone rubber matrix. With this technique, the heat of mixing and the solubility of the drug at the drug melting point also were obtained. In the progesterone study, four polymorphic forms in silicone rubber were observed.

Keyphrases □ Polymers, silicone rubber matrix—determination of dispersed progesterone and cholesterol, differential scanning calorimetry □ Progesterone—determination of concentration dispersed in silicone rubber matrix, four dispersed polymorphic forms observed, heat of mixing and solubility at drug melting point determined, differential scanning calorimetry □ Cholesterol—determination of concentration dispersed in silicone rubber matrix, differential scanning calorimetry □ Silicone rubber—determination of dispersed progesterone and cholesterol, differential scanning calorimetry □ Polydimethylsiloxane—determination of dispersed progesterone and cholesterol, differential scanning calorimetry □ Differential scanning calorimetry—analysis, progesterone and cholesterol dispersed in silicone rubber matrix

Differential scanning calorimetry has been employed for semiempirical determinations of purities of drug substances (1, 2) and for kinetic studies of polymorphic phase transitions (3). In the present study, the technique was used to determine quantitatively the concentration of solid drugs dispersed in a polymeric matrix. Polydimethylsiloxane (silicone rubber) was selected as the matrix material since it has been widely used as a rate-controlling membrane in sustained-release drug delivery devices (4–12). With these devices, it is important to know in which physical state the drug is present; in quantitative work, determination of the total amount of drug remaining in the matrix is a frequent analytical problem. Conventionally, radiolabeled drug can be used or the matrix can be extracted and the drug determined spectrophotometrically or by GLC. These techniques are often time consuming and yield no in-

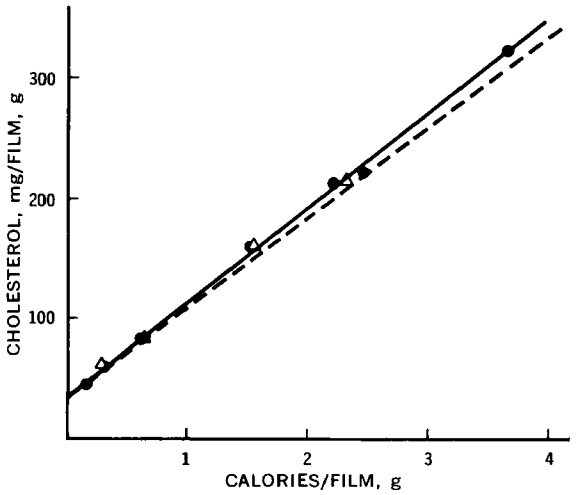

Figure 1—*Cholesterol concentration of the film samples as a function of the observed heat. Key: ●, observed heats at first melting; △, observed heats at second melting; —, average line through experimental data; and – – –, calculated line from drug solubility intercept and heat of melting of the pure drug.*

formation as to the physical state of the drug. Differential scanning calorimetry, on the other hand, is rapid and simple. In addition, it provides information about several useful thermodynamic properties of the drug polymer dispersion such as the heat of mixing of the drug in the polymer, the presence of various polymorphic forms of the drug in the polymer, the solubility of the drug in the polymer at the drug melting point, and the fraction of the drug present in the crystalline form.

EXPERIMENTAL

Materials—Cholesterol[1] and progesterone[2] were used without further purification. Polydimethylsiloxane[3] was the polymer used.

Sample Preparation—Polydimethylsiloxane was mixed with a known weight of steroid at room temperature. To obtain a workable viscosity of the mix, small quantities of silicone oil were added in quantities less than 3% of the total weight of the blend. Stannous octoate (≃0.04 wt%), a room temperature polymerization catalyst, was then added and the dispersion was cast as a film approximately 1 mm thick between two glass plates.

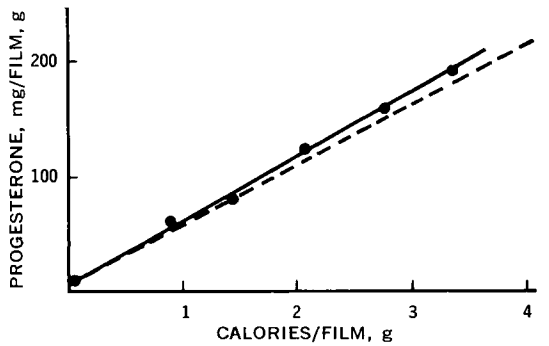

Figure 2—*Progesterone concentration of the film samples as a function of the observed heat. Key: ●, observed heat at first melting; —, average line through experimental data; and – – –, calculated line from drug solubility intercept and heat of melting of the pure drug.*

[1] Aldrich Chemical Co., Milwaukee, Wis.
[2] Calbiochem, Los Angeles, Calif.
[3] Medical grade Silastic 382, Dow Corning Co.

Table I—Observed Endothermic Heats on Silicone Rubber Samples Containing Dispersed Cholesterol

Concentration of Cholesterol in the Film, mg/g of Film	Observed Endotherm (First Heating), cal/g	Observed Endotherm (Second Heating), cal/g
7.96	Not observed	—
43.7	0.088	—
61.2	0.328	0.287
83.6	0.62	0.66
160.0	1.54	1.56
213.8	2.21	2.34
222.5	2.47	—
322.9	3.65	—

Differential Scanning Calorimetry Analysis—The pure steroids in about 2-mg samples and sections of the films in about 20-mg samples are analyzed in aluminum pans on a differential scanning calorimeter[4]. A scanning speed of 10°/min is used. Temperature is calibrated with an indium standard with the melting point at 430°K.

The heats of melting are calculated based on a gallium standard with heat of melting taken to be 19.15 cal/g. Upon heating of a film sample in the differential scanning calorimeter, one observes an endothermic peak at the melting temperature of the steroid. The endotherm observed at a scanning speed of 10°/min was found to be the same for an identical sample when the scan was made starting from room temperature or when the sample was held for several minutes a few degrees below the melting point of the steroid. Because of this and because of the presence of the drug in the homogeneous fine dispersions, it was assumed that the polymer was continuously in equilibrium with the excess steroid at this scanning speed of 10°/min. Thus, at each temperature, the equilibrium amount of drug is dissolved in the matrix. At the melting temperature, the observed endotherm then corresponds to the melting of the residual undissolved drug. After melting, the samples are cooled to room temperature and then reheated at 10°/min.

RESULTS AND DISCUSSION

Cholesterol Samples—For pure cholesterol, the heat of melting was found to be 13.4 cal/g at 404°K. The melting of cholesterol in the film samples was observed at the same temperature, and the endothermic heats for films containing different concentrations of cholesterol are shown in Fig. 1 and listed in Table I.

After one heating cycle, the samples were cooled to room temperature for about 5 min and then slowly reheated. Upon reheating, melting occurred at the same temperature and the observed

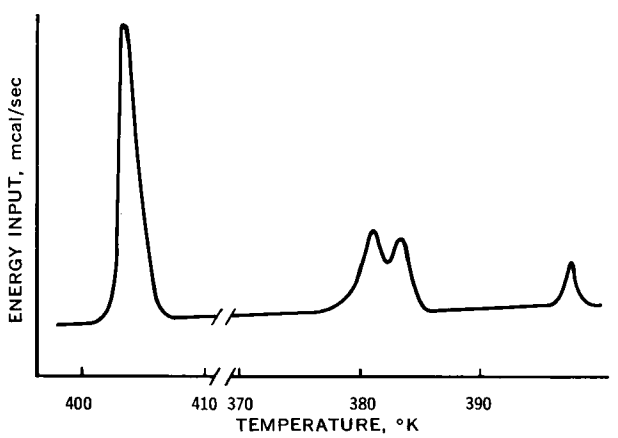

Figure 3—*Differential scanning calorimeter thermogram on the first and second heating of a progesterone sample in polydimethylsiloxane.*

[4] Perkin-Elmer DSC-1B.

Table II—Observed Endothermic Heats on Silicone Rubber Samples Containing Dispersed Progesterone

Concentration of Progesterone in the Film, mg/g of Film	Observed Endotherm (First Heating), cal/g
9.36	0.056
62.61	0.907
80.95	1.44
125.2	2.08
160.0	2.77
191.8	3.36

heats were essentially identical, indicating that the drug was in the same crystal form. By using these calibration data, the concentration of cholesterol in any other sample of silicone rubber can be determined to within ±10 mg/g of polymer by simply measuring the endothermic heat. The intercept of the line in Fig. 1 at 35 mg cholesterol/g of film is the solubility of the drug at the melting temperature. It follows that concentrations below 35 mg/g of film cannot be detected with differential scanning calorimetry.

From the solubility of cholesterol of 35 mg/g in polydimethylsiloxane and from the heat of melting of pure cholesterol, the expected endothermic heat for each film sample can be calculated from the composition when other caloric processes have negligible heats (Fig. 1). The expected values (Fig. 1) fall outside the limit of experimental error, indicating that an exothermic mixing process is also occurring at melting. The heat of mixing is calculated from Eq. 1:

$$q_o = (m_t - m_s)q_m - (m_t - m_s)q_d \qquad \text{(Eq. 1)}$$

where q_o is the observed heat per unit film weight, q_m is the heat of melting of the drug, q_d is the heat of mixing, m_t is the total mass of drug per unit film weight, and m_s is the dissolved mass of drug per unit film weight. The heat of mixing is found to be 0.6 cal/g by taking the q_o as the average observed heat from Fig. 1.

Progesterone Samples—The heat of fusion of pure (α) progesterone was found to be 19.1 cal/g at the melting temperature of 402°K. From the literature, two crystal forms are known: the α-form melting at 402°K and the β-form melting at 395°K. Melting and cooling of normal α-progesterone produce progesterone which, on reheating, melts at 395°K, indicating that the drug has crystallized from the melt in the β-form.

The polydimethylsiloxane samples containing the dispersed progesterone showed endothermic peaks at 402°K at the first heating. These heats (Table II) are plotted in Fig. 2 against the concentration of progesterone in the film. As before, the intercept gives the solubility of the drug in the matrix at the melting point. The solubility is found to be 6 mg/g film. The calculated values (Fig. 2) represent the expected heat calculated from Eq. 1, neglecting q_d, the heat of mixing. The difference between the lines gives the heat of mixing calculated from Eq. 1 and is found to be 1.3 cal/g.

After heating to about 410°K, the film samples were cooled to room temperature for 5 min and then reheated. Upon reheating, a complete new picture was obtained (Fig. 3). The α-progesterone peak previously found completely disappeared and was replaced by three new peaks due to different polymorphs of progesterone. Two peaks were close together, one at about 378°K and the second one at 381°K, while the third at 396°K was presumably due to the β-form. That all three peaks were due to progesterone was shown by varying the mode of cooling which changed the relative magnitude of the peak areas.

SUMMARY

From the differential scanning calorimetry study of dispersed drugs in polymer matrixes, one can obtain the total concentration of drug in the polymer, the solubility of the drug in the polymer at the melting point of the drug, and the heat of mixing of the drug in the polymer. At the same time, different polymorphic forms of the drug present in the polymer can be detected.

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