Testing of Heat Sealing by Thermal Analysis

Keyphrases ☐ Seals, heat—unit-dose packages, examined by calorimetry, IR spectroscopy, and thermomechanical analysis ☐ Containers, pharmaceutical—unit-dose packages, heat seals examined by calorimetry, IR spectroscopy, and thermomechanical analysis ☐ Packages, unit dose—heat seals examined by calorimetry, IR spectroscopy, and thermomechanical analysis

To the Editor:

The compendia seek to provide comprehensive standards for pharmaceutical containers. A moisture *permeation* standard for multiple-dose prescription containers has been presented (1, 2). Devising comparable standards for unit-dose packages is more difficult; not only must the moisture permeability characteristics of the component film and laminate be measured, but separate verification is required to determine the efficacy of the heat seal that must be formed for complete closure. This communication deals with the latter problem.

When laminates or films are suited for testing under reduced pressure, the efficacy of the heat seal is determined by vacuum testing. This procedure gives only "pass–fail" information. A physical or chemical determination, applicable to single packages, is needed for more meaningful data.

The characterization of high polymers, including films and laminates, by thermal methods is well established (3), and the high temperature glass transition, T_g, of film samples has been studied by thermomechanical analysis (4) with the sample stretched between two hooks. Linear expansion determinations (5) have correlated with the degree of molecular ordering in polyurethane elastomers.

The possibility exists that the heat-sealing event may modify the polymer's crystallinity, thus changing the melting characteristics or rheological behavior. Physical or chemical measurements can give evidence of the thermal history of the polymers. With this in mind, a few commercial unit-dose packages were examined by differential scanning calorimetry, multiple internal reflectance IR spectroscopy, and thermomechanical analysis. The manufacturers of the unit-dose packaged pharmaceutical products made available some samples that were visibly integral but deliberately designed to fail vacuum testing and some samples that passed vacuum testing. Initial results of this study are reported here.

High density polyethylene trays [0.55 mm (1 mil = 0.025 mm)], composed of a lid-stock of low density polyethylene-coated foil with paper overlay for labeling (0.15 mm), are used to package pilocarpine ophthalmic matrix[1]. Differential scanning calorimetry was performed on the following portions of the samples:

1. The low density polyethylene lid-stock, showing an endotherm from 105 to 110° and peaking at 107°.
2. The high density polyethylene tray, center section, showing an endotherm from 115 to 137° and peaking at 133°.
3. Samples cut from heat-sealed areas that: (*a*) passed vacuum testing or (*b*) failed vacuum testing.
4. Unsealed sandwiches prepared from untreated cuttings of the lid-stock and tray, incorporating both endotherms 1 and 2.

Comparisons of thermograms 3*a*, 3*b*, and 4 revealed no correlation in either the width or peak values of the endotherms or the individual heat of fusion values as represented by area *versus* sample weight. Therefore, no distinct correlation between the efficacy of the heat seal and differential scanning calorimetry was readily apparent. An initial X-ray diffraction crystallographic study[2] revealed no ready correlation between the efficacy of the seal and the fine structure of the diffractograms. Reflectance IR spectra obtained in our laboratory gave the expected functional group information but did not correlate with heat sealing.

In sharp contrast to this physical evidence, thermomechanical analysis gave substantial evidence of a correlation between the ability of the weighted probe to penetrate the sample and the efficacy of the heat seal of these high density polyethylene trays with the low density polyethylene-coated foil/paper lid-stock.

To make the thermomechanical measurement, a sample about 3–4 mm in diameter was cut from the tray, lid-stock, heat-sealed area or a sandwich of the tray and lid-stock was prepared. A 5-g weight was placed on top of the quartz probe shaft of the analyzer module[3]. The penetration of the quartz probe into the sample as the system was heated was detected by a moving-coil transducer located on the shaft between the sample and the weight pan, and this displacement *versus* temperature was displayed on the axis of the *x–y* recorder. Complete penetration of the high density polyethylene tray (0.55 mm) and the low density polyethylene foil/paper lid-stock (0.15 mm) made into an average 0.7-mm heat-sealed sandwich would be about 0.5 mm.

Full-scale vertical deflection of the primary pen was set to represent 1.0 mm. A secondary pen recorded the first derivative of the displacement. The results were as follows.

The penetration of the lid-stock alone corresponded exactly to the first endotherm of low density polyethylene of 100–115°, as determined in the differential scanning calorimetry mode.

Penetration of virgin high density polyethylene trays corresponded, at the onset of 135°, to the second endotherm determined in the differential scan-

[1] Ocusert Pilo-20 and 40, Alza Corp., Palo Alto, Calif.; W. J. Mader, Alza Corp., Palo Alto, Calif., personal communication.

[2] N. J. DeAngelis and G. J. Papariello, Wyeth Laboratories, Radnor, Pa., personal communication.

[3] Model 941 thermomechanical analysis accessory in conjunction with model 940 thermal analyzer, DuPont Instruments Division, Newark, Del.

ning calorimetry mode and was nearly complete on heating up to 180°. The softened polymer flowed up around the end of the penetration probe, engulfing the tip.

Thermograms of the tray and lid-stock sandwich were indicative of complete penetration of the high density polyethylene tray as well as the initial penetration of the lid-stock. The softened polymer, once again, flowed upward around the probe.

On well-sealed samples, only 1% of the material was penetrated in the region associated with the high density polyethylene endotherm. At 180°, penetration values were 0.005–0.016 mm (average of six measurements = 0.007 mm). No additional penetration was noted when the sample was heated to 300°. The polymer retained its shape with no evidence of flow.

On samples that failed the leak test, about 70% of the tray and lid-stock sandwich value was penetrated at 180°. Penetrations of 0.52–0.55 mm (average of six measurements = 0.53 mm) were noted at this temperature. Continued heating to 300° showed complete penetration.

Subsequent removal and physical examination of the high density polyethylene layer confirmed that the penetration was complete. Linear expansion caused the trays to be 5% thicker at 50° than at ambient temperatures at which caliper measurements were made.

During the sealing process, the polymer sandwich is subjected to a relatively high temperature under pressure for very short periods. To simulate the sealing process in our laboratories, centers were cut from the unsealed areas of the tray and lid-stock. The plastic top and backing were pressed together between two wooden slats with a screw clamp. Sections of plastic were heated below the melting point for 15 min at 65, 90, 95, 100, 110, 115, and 120°. Finally, at 120°, samples did not allow probe penetration, which was characteristic of a good seal and a more crystalline structure.

An unclamped center section of high density polyethylene alone was heated at only 110° for 15 min and became rigid and concave, giving a penetration curve characteristic of an essentially crystalline polymer. A sample heated beyond the melting point to 140° and then cooled contracted to a thick bar; this material was easily penetrated with a 5-g weight and was considered amorphous. Heating the sample of polyethylene below its melting point to 110 or 120° clearly allows a transition to a more crystalline form.

A sample of amorphous material was heated to 140° in the thermomechanical analysis system and held at that temperature under a 5-g weight. After 10 min, 75% of the sample's thickness had been penetrated; the entire sample was penetrated after 50 min. The crystalline sample was not penetrated in a similar experiment. A narrow probed, temperature-adjustable penetrometer probably could be designed for routine measurements after method development.

High density polyethylene is essentially crystalline when prepared: 95% crystalline by the Phillips process and 85% crystalline by the Zeigler process (6). When film is prepared and shaped, the polymer is heated under pressure to a white, essentially amorphous substance. The results of our testing indicate that the unheated centers and the improperly sealed sides of the unit-dose container are composed of this essentially amorphous material, which will flow (penetrate) at 140° at 5 g/3.14 mm^2. The well-sealed area of the container is composed of essentially crystalline polymer, which will not exhibit significant flow under a 5-g weight.

The flow index of polyethylene (7) is measured at 190° and 43.2 psi (30.5 g/3.14 mm^2). A crystalline portion of the tray was placed in the thermomechanical analysis test apparatus and heated to 190° under a 30-g weight, at which time the sample exhibited flow (penetration). After the sample was allowed to cool, a penetration test was performed using the 5-g weight. The sample then flowed at 140°, characteristic of the amorphous polymer. The degree of penetration is obviously a measure of the degree of crystallinity.

A correlation also was found between probe penetration and the efficacy of the heat seal of samples composed of 1.5-mil polyethylene/0.7-mil aluminum foil/0.67-mil polyethylene/1-mil transparent cellophane sealed to an identical strip[4]. The findings were complicated by inconsistent results caused by nonuniformity of the seal and the fact that there were three layers of plastic in the final product. Samples were taken from each of the four sides of the package. On the samples that failed the vacuum leak test, one end of the package tested as properly sealed, the sides tested the same, and the other end had such a poor seal that the sample separated during the test procedure. Therefore, at lower temperatures, one section of the sealing mechanism is less effective than the others. Even with these complications, differences were easily detected by thermomechanical analysis between acceptable and unacceptable containers.

The scope of applicability offered by thermomechanical analysis is uncertain with respect to pharmaceutical packaging, both in testing heat seals and characterizing batches of polymeric materials. The sealing process would have to cause changes in the polymers consistently. It is our experience that thermomechanical analysis is a more sensitive instrumental method for detecting transitions in polyethylene structure. Thermoplastic materials, which retain the ability to flow upon reheating, are used largely in unit-dose packaging and especially in the heat-sealing process; this area of promise for thermomechanical analyses needs to be surveyed. Experiments with polymers other than polyethylene and other strip packaging systems are in progress.

(1) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 647.

(2) "The National Formulary," 14th ed., Mack Publishing Co., Easton, Pa., 1975, p. 888.

(3) J. Mitchell, Jr., and J. Chiu, *Anal. Chem.*, **47**, 303R, 304R(1975).

(4) H. D. Burks, *J. Appl. Polym. Sci.*, **18**, 627(1974).

(5) G. W. Miller, *ibid.*, **15**, 39(1971).

[4] G. Irwin and J. J. Pierantozzi, Wyeth Laboratories, Radnor, Pa., personal communication.

(6) R. B. Seymour, "Modern Plastics Technology," Reston Publishing, Reston, Va., 1975, p. 167.
(7) *Ibid.*, p. 97.

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Kinetics of Butaperazine Adsorption onto Quartz Cells

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To the Editor:

Kinetics of adsorption of drugs onto plastic and filtering materials are well documented (1–7). However, kinetics of adsorption of drugs onto quartz cells appear to be rarely reported. During our study on the interaction between butaperazine, an antipsychotic agent, and a saliva-stimulating device[1], we found that the fluorescent intensity of the butaperazine solution in cyclohexane stored in quartz cells decreased with time. Additional studies were carried out to explore this interaction, and the results of these preliminary studies are reported here.

The stock solution (2 mg/ml) of butaperazine maleate[2] was prepared in 95% ethanol. This solution was diluted with cyclohexane[3] in 100-ml volumetric flasks to concentrations of 2.0 and 0.14 μg/ml. Then 1 ml of 1 *N* NaOH solution was added, and the flasks were shaken to convert butaperazine maleate to its free base in cyclohexane. The cyclohexane was transferred immediately and directly into three quartz cells, which were then covered with lids.

Fluorescent intensities were measured immediately and every 5 min thereafter for 30 min with a fluorometer[4] at the excitation wavelength of 312 nm and the fluorescent wavelength of 498 nm. The average results, expressed in terms of percent of the initial fluorescent intensity as a function of time, are shown in Fig. 1. In the study with the higher initial concentration, the fluorescent intensity decreased to a constant 88% after 10 min. The decrease in intensity with the lower initial concentration followed an apparent first-order process with a half-life of 16 min.

These concentration-dependent decrease phenomena are consistent with the saturable adsorption theory. This contention is also supported by the following desorption study. Two cells were filled with 2 μg/ml of the butaperazine solution. After 10 min of adsorption equilibration, the solution in the cell was discarded and the cell was filled with pure cyclohexane. The fluorescent intensity of the solution was then measured as a function of time. The average results are also shown in Fig. 1. The average recovery into the fresh cyclohexane at 30 min was about 33%.

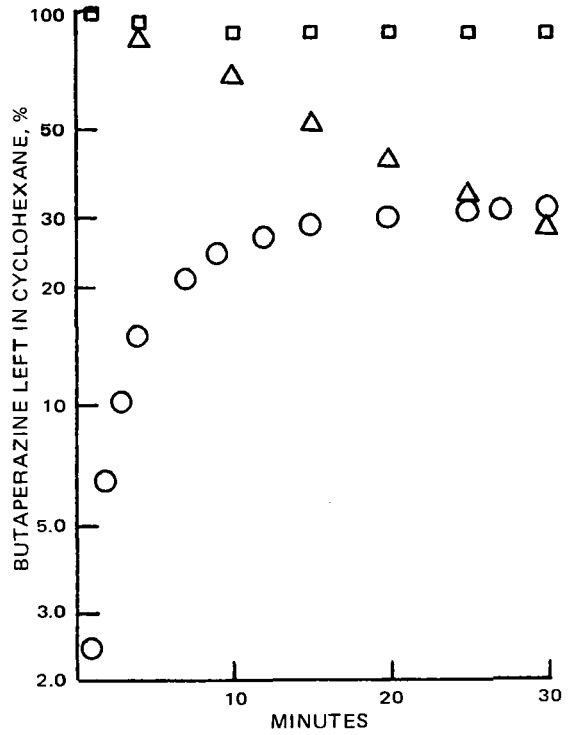

Figure 1—*Time course of the fluorescent intensity of cyclohexane solutions of butaperazine in the cell. Key:* □, *initial concentration of 2.0 μg/ml in the adsorption study;* △, *initial concentration of 0.14 μg/ml in the adsorption study; and* ○, *desorption study where the scale 100 is equivalent to 0.22 μg/ml when all adsorbed butaperazine was desorbed into cyclohexane.*

In all of these studies, the butaperazine solutions were protected from light irradiation whenever feasible. Adsorption of butaperazine onto the glassware was mentioned in one (8) of two recent papers (8, 9) describing similar fluorometric methods for the measurement of butaperazine concentrations in plasma. Moreover, in the present study, coating the cells with silicone[5] was ineffective in reducing the adsorption effect.

(1) A. H. Kapadia, W. L. Guess, and J. Autian, *J. Pharm. Sci.*, **53**, 720(1964).
(2) M. B. Rodell, R. Bodnar, W. L. Guess, and J. Autian, *ibid.*, **54**, 129(1965).
(3) S. Weisenfeld, S. Podolsky, L. Goldsmith, and L. Ziff, *Diabetes*, **17**, 766(1968).
(4) W. L. Chiou and L. D. Smith, *J. Pharm. Sci.*, **59**, 843(1970).
(5) K. Kakemi, H. Sezaki, E. Arakawa, L. Kirmura, and K. Ikeda, *Chem. Pharm. Bull.*, **19**, 2523(1971).
(6) P. Moorhatch and W. L. Chiou, *Amer. J. Hosp. Pharm.*, **31**, 72(1974).
(7) W. L. Chiou, *Can. J. Pharm. Sci.*, **10**, 112(1975).
(8) D. H. Manier, J. Sekerke, J. V. Dingelland, and M. K. El-Yousef, *Clin. Chim. Acta*, **57**, 225(1974).
(9) J. M. Davis, D. S. Janowsky, H. J. Sekerke, H. Manier, and M. K. El-Yousef, in "The Phenothiazines and Structurally Related Drugs," I. S. Forrest, C. J. Carr, and E. Usdin, Eds., Raven, New York, N.Y., 1974, p. 433.

[1] Parafilm, American Can Co., Neenah, Wis.
[2] A. H. Robins Co., Richmond, Va.
[3] Certified ACS grade, Fisher Scientific Co., Fair Lawn, N.J.
[4] Perkin-Elmer model 203 fluorescence spectrometer, Norwalk, Conn.
[5] Siliclad, Clay Adams, Division of Becton, Dickinson and Co., Parsippany, NJ 07054