Hermetic Packaging of Drugs: Optimized Sealing of Foil Pouches

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Abstract □ Factors affecting the sealing of foil packages were studied in three laboratories. The relationship of sealing temperature (with machine speed and pressure kept constant) to the incidence of defective packages was determined. The maximum acceptable limit for defective pouches was 1%. Three tests were employed to detect defects: vacuum–dye, seal strength, and pressurized ammonia vapor. Only the last was sensitive enough to determine the optimum sealing conditions. This test also was capable of detecting leakage sites. Replacement of the cellophane layer of the foil laminate with polyvinylidene chloride-coated polyester improved the barrier properties of the package.

Keyphrases □ Foil packages—heat seals, relationship of sealing temperature to incidence of defective packages, vacuum–dye, seal strength, and pressurized ammonia vapor tests for defects □ Seals, heat—foil packages, relationship of sealing temperature to incidence of defective packages, vacuum–dye, seal strength, and pressurized ammonia vapor tests for defects

The flexible pouch or foil package is assuming a major role in drug distribution, particularly in overseas markets, because of its ease of formation and strength. However, the lack of adequate methodology for evaluating package performance has become apparent. The technology used in testing packages generally is similar to that used for ampuls (1–3).

A typical foil package is a four-ply laminate. The outermost portion is generally cellophane, paper, or polyester. This portion is bonded to aluminum foil, usually with polyethylene or a similar adhesive material. The innermost film is a heat-sealable polymer, either colaminated or coextruded with the foil. The most commonly used heat-sealing polymer is polyethylene.

An important factor affecting the stability of drugs in foil packages is the effectiveness of the heat seal formed during commercial production. The need for an almost absolute barrier was shown previously with yeast products packaged in foil (4).

A fusion heat seal is formed by melting the thermoplastic polymer used as the inside sealing layer. Most polymers form seals at 90–200°. An optimum heat seal results from the correct interaction of three variables: (*a*) temperature of the sealer platens, (*b*) pressure applied to the seal area by the heated platens, and (*c*) dwell time (period for which the heated sealable surfaces are held under pressure to form an effective bond) (5).

The procedure most commonly used for assessing foil packages is the vacuum–dye test. Packages are submerged under vacuum in a dye solution, and discovery of the dye within the package is considered clear evidence of incomplete sealing. The advantages and disadvantages of this test were discussed previously (1–4). In particular, failure to standardize the test may lead to erroneous conclusions because of capillary resistance (2, 3).

Deficiencies in this test, particularly with respect to gas permeation, have been observed in this laboratory.

This article discusses the inadequacies of tests now employed for measuring package integrity, reports an improved test procedure, and demonstrates how the optimization of the sealing conditions for two foil laminates can be obtained.

EXPERIMENTAL

Materials—The following materials were used: nitrocellulose-coated cellophane–polyethylene–0.018-mm aluminum foil–0.043-mm polyethylene[1], polyvinylidene chloride-coated polyester[2]–polyethylene–0.018-mm aluminum foil–0.043-mm polyethylene[3], and nitrocellulose-coated cellophane–polyethylene–0.018-mm aluminum foil–0.030-mm polyethylene[4].

Vacuum–Dye Test—Foil packages were submerged in an aqueous solution of amaranth for 1 min at 38 cm (15 in.) of vacuum. After this treatment, packages were blotted dry. The package was considered a leaker if the contents or the inner lining revealed a red spot.

Seal Strength Test—The seal strength of end (shorter dimension) and side (longer dimension) foil packages was measured with a tensile tester[5]. Samples 1 cm wide were taken from the center end and center side positions.

Pressurized Ammonia Vapor Test—Approximately 200 packages were placed in a suitable pressure container evacuated for 5 min at 38 cm (15 in.) of vacuum. The vacuum was broken by the slow addition of 2 kg/cm^2 (2 atm) of ammonia vapor, and this pressure was maintained for 1 hr. Subsequently, the packages were rinsed with a 10% citric acid solution to remove residual surface ammonia and were then dried over an air current. A 1% phenolphthalein gel [water–ethanol (1:1) with 1% carboxypolymethylene[6]] was applied with slight pressure to the entire surface. The appearance of a pink color indicated that the foil package leaked.

Optimization Studies—Trials were conducted at three outside locations using sealing temperatures over approximately a 60° range (Table I).

About 50,000 placebo capsules (No. 0) were used per foil laminate per machine. Each run was performed at the operating pressure and dwell time (machine speed) normally used for that machine and foil laminate. All machines were of the rotary sealing type. The dwell time and pressure were kept constant, and the sealing temperature was varied to provide for a broad range of conditions. During the optimization trials, 100 and 25–50 packages were used for the pressurized ammonia and vacuum–dye tests, respectively, at 15-min intervals.

RESULTS AND DISCUSSION

Pressurized Ammonia Vapor Test—The number of defective

[1] Dow, Inc., Cleveland, Ohio
[2] Mylar, E. I. du Pont de Nemours and Co., Wilmington, Del.
[3] Standard Packaging, Clifton, N.J.
[4] *Champion Packaging*, Englewood Cliffs, N.J.
[5] Instron Universal testing instrument, Instron Corp., Canton, Mass.
[6] Carbopol 961, B. F. Goodrich, Cleveland, Ohio.

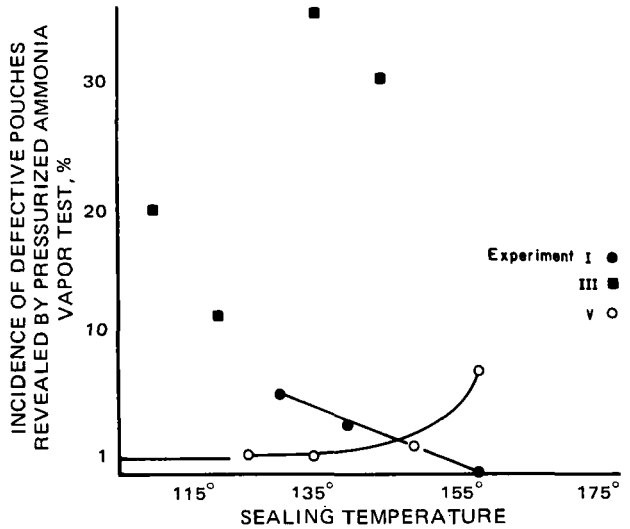

Figure 1—*Effect of sealing temperature on the incidence of defective pouches revealed by the pressurized ammonia vapor test.*

packages was plotted against the sealing temperature (Figs. 1 and 2). Arbitrarily, the maximum acceptable limit was set at 1%. In Experiment I, at 155–165°, this optimum point was achieved. Above 180°, under these experimental conditions, the exterior portion of the laminate started to "steam."

In Experiment III, the incidence of defective pouches was considerably over 1%. A clearly defined defect in the crimp area, as determined from the nature of the color reaction, was ascribed to excessive localized pressure arising from the design of the machine. With the pressurized ammonia vapor test, the use of an indicator dye revealed the site of permeation and subsequently provided insight into the reasons for the defect.

In Experiment V, the 1% limit was approached asymptotically. Hypothetically, the decreased thickness in the polyethylene heat sealing layer (Table I) was responsible for the inability of this foil laminate to achieve the 1% limit under these conditions.

The critical feature of Experiments II, IV, and VI was the replacement of cellophane with polyvinylidene chloride-coated polyester. The data (Fig. 2) show that this change afforded a significant improvement in the pouches.

Cellophane is a hydrophilic polymer that can become brittle when dried during sealing; in contrast, polyester is a thermoplastic and hydrophobic polymer which elongates under deforming stresses (6). In addition, the polyvinylidene chloride coating provides an excellent barrier to gases (6).

The effect of the polyvinylidene chloride-coated polyester was most evident in Experiment IV, where the incidence of defective pouches was reduced to zero. Apparently, the thermoplastic properties of polyester aid in reducing any damage to the laminate caused by the sealing dies.

That the pressurized ammonia vapor test is more sensitive than the vacuum–dye test is illustrated in Table II.

Seal Strength (Experiment I)—Samples taken from the shorter

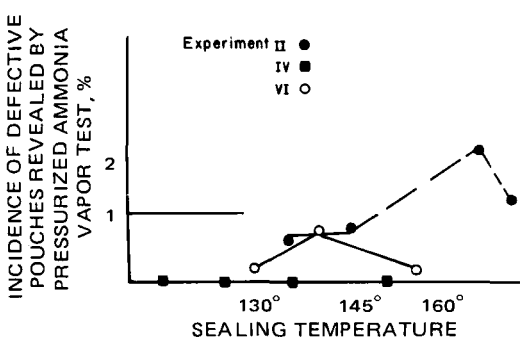

Figure 2—*Effect of sealing temperature on the incidence of defective pouches revealed by the pressurized ammonia vapor test.*

Table I—Conditions Used in the Optimization Studies

Experiment	Location	Foil Laminate	Machine Speed, rpm
I	A	Nitrocellulose-coated cellophane–polyethylene–0.018-mm aluminum foil–0.043-mm polyethylene	14
II	A	Polyvinylidene chloride-coated polyester–polyethylene–0.018-mm aluminum foil–0.043-mm polyethylene	14
III	B	Same as in Experiment I	45
IV	B	Same as in Experiment II	45
V	C	Nitrocellulose-coated cellophane–polyethylene–0.018-mm aluminum foil–0.030-mm polyethylene	14
VI	C	Same as in Experiment II	14

Table II—Comparison of the Pressurized Ammonia Vapor Test with the Vacuum–Dye Test

Experiment	Temperature	Incidence (%) of Leaking Pouches Revealed by: Pressurized Ammonia Vapor Test	Vacuum–Dye Test
I	135°	6.0	1.3
	145°	3.8	0.8
	165°	0.2	0.0
II	135°	0.6	0.3
	145°	0.8	0.0
	165°	2.0[a]	0.0
	175°	1.2[a]	0.0
III	115°	20.0	0.0
	125°	12.0	0.0
	140°	35.0	8.3
	150°	30.0	2.1
IV	115°	0.0	0.0
	125°	0.0	0.0
	140°	0.0	0.0
	150°	0.0	0.0
V	130°	1.5	0.5
	140°	1.5	1.0
	155°	2.0	0.0
	165°	8.5	1.6
VI	130°	0.2	0.0
	140°	0.8	0.0
	155°	0.2	0.0

[a] These defects were attributable to a specific machine error.

dimension showed that parting took place predominantly at the foil–cellophane laminate, with the polyethylene–polyethylene heat seal remaining intact. This finding suggests that the heat seal was stronger than the lamination and that the strength of the foil–cello-

Table III—Average Force Required to Separate Pouch at the Seal

Sealing Temperature	Force, kg
	End
135°	1.77 ± 0.10
145°	1.73 ± 0.18
165°	1.95 ± 0.24
175°	1.77 ± 0.20
	Side
135°	2.22 ± 0.20
145°	2.32 ± 0.15
165°	2.41 ± 0.10
175°	2.36 ± 0.22

phane bond was not affected by temperature.

Analysis of the data displayed in Table III by the Student–Newman–Keul's test (7) showed that none of the observed differences in separation force for both end and side samples was statistically significant.

Seal strength measurements of samples from the longer dimensions showed that parting took place at the polyethylene–polyethylene heat seal for all temperatures studied except 175°. At 175°, parting was at the foil–cellophane lamination. These data suggest that, except for the 175° treatment, the seal was less strong than the lamination. At 175°, the seal strength must surpass the lamination strength, causing parting at the latter site. This finding indicates that the seal strength increased as temperature increased. Miller (8) found a similar correlation.

The seal strength test was not pursued after Experiment I since a definitive discrimination among sealing temperatures was not shown.

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Comparison of Observed and Predicted First-Pass Metabolism of Imipramine in Humans

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Abstract □ The first-pass metabolism of imipramine was calculated based on the dose, hepatic blood flow, and total area under the plasma–time curve after oral administration of 0.71 ± 0.03 mg/kg of imipramine to four individuals suffering from mild depression. The predicted values of first-pass metabolism ranged from 37 to 68%, consistent with experimentally derived estimates.

Keyphrases □ Imipramine—comparison of observed and predicted first-pass metabolism □ Metabolism, first pass—imipramine, comparison of observed and predicted values □ Antidepressants—imipramine, comparison of observed and predicted first-pass metabolism

The bioavailability of imipramine following oral administration in humans was recently reported (1). A comparison of the total metabolites excreted following intravenous and oral administration shows that the absorption of impramine from the solution dosage form was complete. The low bioavailability of imipramine following oral administration was attributed to the first-pass metabolism, mainly to desipramine, as evidenced by the higher levels of this metabolite following administration of an oral dose compared to an equal intravenous dose.

DISCUSSION

The following equation was proposed by Gibaldi and coworkers (2, 3) to predict the degree to which a drug is subject to first-pass metabolism:

$$f = \frac{\text{flow rate}}{\text{flow rate} + \left(\text{dose} \Big/ \int_0^\infty C_0\, dt\right)} \qquad \text{(Eq. 1)}$$

where f is the fraction of orally administered dose that actually reaches the systemic circulation, the flow rate is the hepatic blood flow rate, and $\int_0^\infty C_0\, dt$ is the total area under the plasma concentration–time curve after oral administration. This equation is applicable, however, only if the absorption is complete, as was evidenced for imipramine (1). A correction factor is needed(2) if the dose administered orally is not completely absorbed.

Therefore, the percentage of drug metabolized during the first pass can be expressed as:

$$\%\ \text{first pass} = \frac{\left(\text{dose} \Big/ \int_0^\infty C_0\, dt\right) \times 100}{\text{flow rate} + \left(\text{dose} \Big/ \int_0^\infty C_0\, dt\right)} \qquad \text{(Eq. 2)}$$

EXPERIMENTAL

The area under the plasma concentration–time curve following oral administration was calculated from reported (1) values of apparent hepatic blood flow and apparent clearance (Table I). A mean blood flow of 1.53 liters/min (3) was used for calculations using Eq. 2.

RESULTS

As reported in Table I, the predicted first-pass metabolism, 58.25 ± 14.38, correlated very well with the experimentally determined value, 52.75 ± 21.36, obtained by comparison with the intravenous data. Therefore, the reliability of Eq. 1 for the prediction of first-pass metabolism following oral administration was confirmed.

The variability of blood flow rates does not seem to affect the first-pass metabolism estimates significantly. For example, the reported apparent hepatic blood flow rates were 1.3–3.5 liters/min (1), whereas a constant value of 1.53 liters/min was used for the calculation of first-pass metabolism in all individuals; both values resulted in fairly good agreement.