Measurement of Film-Coating Adhesiveness

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Abstract □ A modified balance was used to measure the adhesive force between the film coating and the tablet surface of 10 commercial film-coated tablets. The adhesiveness or force required to remove the film coating from a unit area of tablet surface ranged from 1.06 to 4.67 × 10^4 Nm^{-2}. Measurement of at least eight film coatings from the sides of four tablets was calculated to be required to obtain a result with 95% confidence. The method also was useful in studying the influence of solvents and humidity on bonding of the film coating to the tablet.

Keyphrases □ Adhesiveness—commercial film-coated tablets, measurement of force between film coating and tablet surface, effect of solvents and humidity on bonding of film to tablet surface □ Tablets—commercial film-coated preparations, measurement of adhesion of film coating to tablet surface, effect of solvents and humidity on bonding of film to tablet surface □ Film-coated tablets—measurement of adhesion of film coating to tablet surface, effect of solvents and humidity on bonding of film to tablet surface

Although film coating has been used in pharmacy for over 25 years, limited research has been conducted on the measurement of the adhesive force between the film coat and the tablet surface. The first method suggested for studying the adhesion of a film coating to a film-coated tablet was a peel test in which a section of the film coating was peeled from the tablet by a tensile tester (1, 2). To overcome the deficiencies of the peel test, an instrument was designed for removing the film normal to the interface between the film coating and the tablet surface (3, 4). Examination of the tablet and the film after removal showed that a rupture occurred at the boundary between the film surface and the tablet surface (5).

In the last 15 years, there has been an emphasis on quality assurance, increased testing, and stringent specifications for pharmaceuticals. Although coated tablets are evaluated in terms of exposure to moisture and chipping of the coating during handling, no test is used to express quantitatively the adhesiveness of a coating to a tablet. A method for measuring the adhesiveness would be useful in developmental work to evaluate tablet excipients (6), solvents (1), polymeric coating materials, humidity effects, formulations, and processes; it also would be useful in quality control to ensure uniformity of application.

This report demonstrates the feasibility of measuring the force required to remove a film coating from a film-coated tablet and explores the range of adhesiveness that has been acceptable on marketed film-coated tablets. The usefulness of the adhesive force measurement in determining solvent and humidity effects on adhesiveness also is demonstrated.

EXPERIMENTAL

Instrumentation—An analytical balance[1] was modified by replacing the left pan and pan support with a metal ring attached by a nylon cord. The coated tablet was attached to the metal ring by a hook with a 35-mm shaft, which was soldered at a right angle to an 18-mm circular stainless steel plate. A backing cut from a rubber stopper was carved on one side to fit any curvature of the tablet and was attached by double-sided adhesive tape[2] to the circular plate. Preliminary work showed that a backing was required to ensure even compressive force over the entire surface of the tablet when the adhesive tape was applied to the coated tablet. Another piece of double-sided adhesive tape was applied to the second surface of the backing.

The coated tablet was positioned carefully and pressed firmly onto the adhesive tape attaching it to the assembly (Fig. 1). The assembly holding the coated tablet was hooked onto the metal ring and nylon cord attached to the left arm, and the balance was balanced by counterweights. The tablet then was clamped on its edge into a fixed position during the measurement using two sets of screws attached to a heavy metal base. The weight applied to the right pan was increased until the film coating separated from the tablet.

In preparation for measurement, the coating on the edge of the tablet was removed with a razor blade to ensure that the force was used to remove only the film coating from the upper tablet surface and to eliminate any coating effect at the tablet edge.

The dimensions of each tablet and the film-coating thickness were measured by a micrometer[3]. For round, flat tablets, the surface area is πr^2. When the same relationship is used to estimate the surface area of tablets prepared with standard concave punches, an error of ~5% is introduced (4).

Humidity—Relative humidities (RH) of 0, 20, 45, 70, and 90% were obtained using various concentrations of sulfuric acid and water (7). Tablets of each commercial product were placed in aluminum cups and were kept at each of the five humidities for 2 weeks at room temperature. The adhesive force was measured immediately after removal from the humidity chamber.

Preparation of Film-Coated Tablets—Tablets with a hardness of 8 ± 1 kg were prepared in batches of 20,000 using a standard concave 11.11-mm punch and die set in a single-punch tablet machine[4]. Each tablet contained 10 mg of FD&C Red No. 3, 380 mg of dicalcium phosphate[5], 20 mg of cornstarch, 85 mg of microcrystalline cellulose[6], and 5 mg of magnesium stearate.

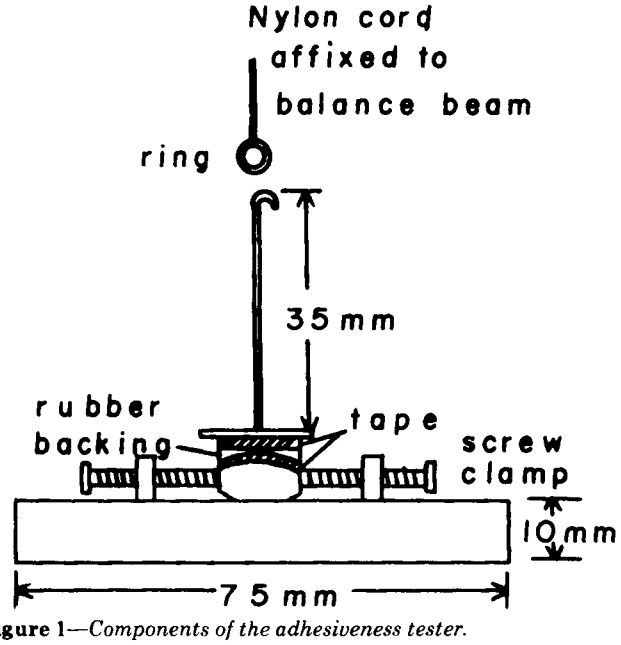

Figure 1—*Components of the adhesiveness tester.*

[1] Model 220, Voland & Sons, New Rochelle, N.Y.

[2] Tuck carpet bond.
[3] Screw gauge, Ames Co., Waltham, Mass.
[4] Stokes A-3.
[5] Encompress, Edward Mendell Co., Carmel, N.Y.
[6] Avicel PH 101, FMC Corp., Philadelphia, Pa.

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Table I—Average Adhesive Force (±*SD*), Adhesiveness, and Thickness

Product	Adhesive Force: Front[a] Surface, g	Adhesive Force: Back[a] Surface, g	Adhesive Force: Average[b], g	Adhesive Force: Average[b], N	Area, cm^2	Adhesiveness $\times 10^{-4}$, Nm^{-2}	Thickness[c], mm
A[d]	236 ± 21.3	235 ± 23.8	235 ± 18.2	2.31	1.31	1.76	0.108
B[e]	493 ± 52.7	492 ± 44.9	493 ± 44.0	4.83	1.30	3.72	0.085
C[f]	365 ± 56.0	356 ± 56.4	360 ± 44.6	3.53	1.31	2.69	0.100
D[g]	358 ± 60.0	357 ± 71.0	357 ± 49.6	3.51	1.28	2.74	0.100
E[h]	103 ± 16.4	112 ± 16.2	107 ± 16.5	1.05	0.99	1.06	0.062
F[i]	284 ± 24.6	292 ± 24.4	288 ± 22.3	2.82	1.41	2.00	0.108
G[j]	316 ± 29.5	296 ± 33.3	306 ± 27.7	3.00	1.51	1.99	0.245
H[k]	391 ± 36.0	386 ± 40.7	390 ± 28.6	3.81	1.89	2.02	0.138
I[l]	296 ± 31.3	275 ± 28.0	285 ± 29.0	2.80	0.60	4.67	0.097
J[m] (colored)	390 ± 32.1	—	—	3.82[a]	1.55	2.46	0.059
J[m] (white)	—	294 ± 45.5	—	2.88[a]	1.55	1.86	0.059

[a] Average of 10 measurements. [b] Average of measurements of 10 front and 10 back surfaces. [c] Average of four measurements. [d] Erythromycin stearate (250 mg), Lederle lot 437-113. [e] Bristamycin (250 mg), Bristol lot L3118. [f] SK-Erythromycin (250 mg), Smith Kline & French lot 142367. [g] Robimycin (250 mg), A. H. Robins lot 72-23-11. [h] Triaminic, Dorsey lot A53493. [i] Unipen (500 mg), Wyeth lot 1740664. [j] Stresstabs 600, Lederle lot 247-137. [k] Ethril (250 mg), Squibb lot 2G305. [l] Betaphen-VK (250 mg), Bristol lot B4544. [m] Cama Inlay, Dorsey lot M43438.

Approximately 2000 tablets were coated in a 20-cm coating pan that was rotating at 25 rpm. With the organic solvent systems, six applications of 25, 20, 15, 12, 8, and 5 ml of coating solution were applied, with drying between each application. The aqueous solution was applied in eight applications of 4 ml each. The coating solution contained 4.9% (w/v) hydroxypropylcellulose[7], 1.0% (w/v) propylene glycol 4000, and the solvent system to 100 ml. The solvent systems were methylene chloride–methanol (9:1), 95% ethanol, acetone–water (9:1), chloroform, and distilled water.

RESULTS AND DISCUSSION

Ten commercial film-coated tablets of various shapes and sizes were selected (Table I). With the modified balance, the intact film coating was pulled from these tablets without tearing or rending. Close examination showed that only traces of the substrate were pulled from the tablet surface with the film coating and that a rupture occurred at the interface between the film coating and the tablet as reported previously (5). The integrity of a removed film coating was not affected by the lettering indentations on the surfaces of Products D–G and J.

Adhesive force is the force required to pull a film coating from the tablet surface. Adhesiveness may be defined as the force required to remove the film coating from a unit area of the tablet surface.

The adhesive force was measured on both sides of 10 tablets of each product. For all tablets except Product J, there was no significant difference in the adhesive force measured on either tablet surface (Table I). Thus, there was no disturbance of the film coating on the opposite surface of the tablet when the adhesion of one side was measured (3).

Product J was a double-layered tablet with a white side and a colored side. Because the substrate was different on the two sides, the adhesive force would not necessarily be the same on each surface.

Since there was no difference in adhesive force on either side of the film-coated tablet, the adhesiveness was calculated using the average adhesive force of 20 film coatings. For the 10 products studied, adhesiveness ranged from 1.06 to 4.67 × 10^4 Nm^{-2}.

There presently is no standard for the adhesiveness of film coating. Because the adhesiveness of a coating reflects the bonding between the film coating and the substrate and the physical stability of the film-coated tablet, its evaluation is important in film-coating development and in product evaluation. Although the data were collected from commercial film-coated products of different formulations that probably were coated by more than a single process, they provide a range of values that describes the variation in coating adhesiveness of products that already were marketed and were regarded as acceptable from the viewpoint of processing, resistance to the environment, and handling.

In any test, the number of determinations must be decided to provide a statistically valid sample. To calculate the sample size, n, a tolerance interval containing a certain proportion, p, of the population must be developed. When both the population mean and the standard deviation are known, $\mu \pm k\sigma$ may be used as a tolerance level, where μ is the population mean, σ is the population standard deviation, and k is a constant.

When both the population mean and the standard deviation are unknown, the tolerance limits, which will include on the average a proportion, p, of the normal universe, are:

$$\bar{x} \pm t_{1-\alpha,n-1}\sqrt{\frac{n+1}{n}}S \qquad \text{(Eq. 1)}$$

where $\bar{x}$ is the mean of a sample of n observations, S is the sample standard deviation, and $t_{1-\alpha,n-1}$ is a Student t value for $n-1$ degrees of freedom that is exceeded in absolute value by the probability, α.

By equating the tolerance intervals, the minimum number of observations, n, needed to provide a significant result is obtained with:

$$K_{s,p} = t_{1-\alpha,n-1}\sqrt{\frac{n+1}{n}} \leq \frac{k\sigma}{S_{max}} \qquad \text{(Eq. 2)}$$

To determine the number of film-coated tablets needed, the adhesive force values of both sides of the tablet were averaged and the standard deviations were calculated (Table I). The estimated population mean of 313.6 ± 107.2 g was taken as the mean of the nine product means (Product J was excluded). A tolerance level of 313.6 ± 214.4 g was selected at which k equals 2.

The standard deviation, S_{max}, of Product D that had the highest value among the film-coated tablets was used. Thus:

$$K_{s,p} = t_{1-\alpha,n-1}\sqrt{\frac{n+1}{n}} \leq \frac{2 \times 107.2}{49.6} = 4.323 \qquad \text{(Eq. 3)}$$

The value of $K_{s,p}$, which relates sample size, n, and tolerance intervals, is obtained from the statistical table (8). For a 95% confidence limit, the minimum n that gives a $K_{s,p}$ value of ≤4.323 is 4. Thus, at least four film-coated tablets are required; the adhesive force is measured on their eight film coatings to give a statistically significant result with 95% confidence.

Influence of Humidity—The influence of humidity on the film-coating adhesiveness is shown in Table II. With Products E and F, there

Table II—Adhesiveness of Film-Coated Tablets at Various Relative Humidities

Product	Adhesiveness × 10^{-4}, Nm^{-2}: 0%	20%	45%	70%	90%
A	1.36	2.08	1.90	1.30	1.96
C	1.54	2.38	2.28	—[a]	—[a]
E	0.77	0.84	0.75	1.22	—[a]
F	1.38	1.52	1.71	1.66	2.30

[a] Spongy and deformed.

Table III—Adhesiveness of Hydroxypropylcellulose Coatings Applied from Various Solvent Systems

Solvent System	Adhesive Force[a]: g	Adhesive Force[a]: N	Area, cm^2	Adhesiveness × 10^{-4}, Nm^{-2}
Methylene chloride–methanol (9:1)	295.0	2.89	0.97	2.98
Ethanol, 95%	237.0	2.32	0.97	2.39
Acetone–water (9:1)	199.5	1.96	0.97	2.02
Chloroform	142.5	1.40	0.97	1.44
Water	70.5	0.69	0.97	0.71

[a] Average obtained from 10 film-coated tablets.

[7] Klucel, Hercules, Wilmington, Del.

was a linear relationship with a slight increase in adhesiveness as the relative humidity was increased.

With Products A and C, the maximum value of adhesiveness occurred at ~30% RH. With Product A, a minimum value of adhesiveness was reached at 70% RH, and then the adhesiveness increased with a further increase in humidity. With Product C at >50% RH, the tablet and the coating became spongy and deformed so that measurements could not be made.

Since the coating material, solvent, coating process, and substrate were unknown, speculation on these differences serves no useful purpose; however, the results confirm the applicability of this method to the detection of changes occurring in a film-coated product.

Influence of Solvent—The solvent from which a film coating is applied may affect the adhesion of the film to the substrate (2). When hydroxypropylcellulose was applied from the five solvent systems shown in Table III, there was a twofold difference ($1.44–2.98 \times 10^4$ Nm^{-2}) in adhesiveness among the organic solvents. When hydroxypropylcellulose was applied from aqueous solution, the adhesiveness (0.71×10^4 Nm^{-2}) was one-fourth to one-half as great as that from the organic solvents.

Applications—The method may be used to evaluate the stability of a film-coated tablet to moisture and its physical stability during shipment. The method also may be used in product development to express quantitatively the bonding between the film coating and the tablet surface and to compare the effect of various solvents on the bonding.

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Role of α- and β-Adrenergic Activation in Ventricular Fibrillation Death of Corticoid-Pretreated Rats

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Received March 5, 1979, from the *Department of Pharmacology, New York Medical College, Valhalla, NY 10595.* Accepted for publication November 8, 1979.

Abstract □ Death in ventricular fibrillation was induced consistently in desoxycorticosterone acetate-pretreated rats by the β-adrenergic agonist isoproterenol but not by norepinephrine or epinephrine, both of which possess α- as well as β-adrenergic activity. Aminophylline, which enhances β-adrenergic activity, and phenoxybenzamine, an α-receptor blocking agent, were used to study the roles of α- and β-adrenergic stimulation in the production of ventricular fibrillation. With the addition of aminophylline, both norepinephrine and epinephrine produced death in ventricular fibrillation, and the existing cardiotoxicity of isoproterenol was potentiated. Similarly, in the presence of phenoxybenzamine, doses of norepinephrine and epinephrine that had been well tolerated became lethal. Interventions that favor β-adrenergic preponderance, either by enhancing β-effects or by blocking protective α-adrenergic activation, apparently increase the arrhythmogenic propensity of norepinephrine and epinephrine in steroid-pretreated rats. The similarity of some forms of stress to the experimental protocol of chronic steroid treatment followed by acute catecholamine exposure is discussed.

Keyphrases □ Ventricular fibrillation—role of α- and β-adrenergic activity, desoxycorticosterone acetate-pretreated rats □ Arrhythmias—catecholamine induced, effect of steroid pretreatment □ Aminophylline—effect on catecholamine-induced arrhythmias, steroid-pretreated rats □ Phenoxybenzamine—effect on catecholamine-induced arrhythmias, steroid-pretreated rats

Earlier studies in this laboratory showed that, following pretreatment of the albino rat with the steroid desoxycorticosterone acetate and saline as the drinking fluid, the administration of isoproterenol elicited severe cardiac arrhythmias at dose levels that otherwise are well tolerated (1, 2). The enhanced cardiotoxicity was reflected in a shift of the isoproterenol LD_{50} from 680 mg/kg (3) in untreated rats to 14.5 μg/kg in desoxycorticosterone acetate–saline-pretreated rats (4), a nearly 47,000-fold potentiation. The deaths produced by this drug–drug interaction usually occurred within 60 min and consistently were due to ventricular fibrillation, while the mortality observed in untreated rats developed over 24 hr and usually was attributable to acute heart failure, lung edema, and shock. Recent studies showed that prednisone, administered either subcutaneously or orally, also can sensitize the myocardium to the arrhythmogenic effect of isoproterenol (4). It has been suggested that this type of drug interaction may expose patients such as asthmatics, taking steroids and isoproterenol simultaneously, to potentially life-threatening cardiac arrhythmias (5).

The mechanism underlying this phenomenon is not well understood. Alterations in the myocardial electrolyte content may be a factor in the increased myocardial vulnerability to isoproterenol. Electrolyte changes such as those seen with this treatment (6) have been well documented as increasing the propensity of the heart to arrhythmias and ventricular fibrillation (7).

The ability of steroids to affect protein synthesis also might be important in the sensitization process. In preliminary studies, agents that inhibit protein synthesis blocked the steroid-induced myocardial sensitization to isoproterenol (8).

The present investigation was undertaken to determine: (*a*) whether norepinephrine and epinephrine, which are both α- and β-adrenergic agonists, exhibit enhanced arrhythmogenic activity following steroid pretreatment comparable to that observed with isoproterenol; and (*b*) whether aminophylline, an agent administered frequently

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