Table VII—Statistical Comparison for Data Shown in Table VI[a]

Comparison	Area (0–27 hr)	Peak Radioactivity
Cellulose *versus* colestipol hydrochloride	N.S.	N.S.
Cellulose *versus* cholestyramine	N.S.	$p < 0.05$
Colestipol hydrochloride *versus* cholestyramine	$p < 0.05$	$p < 0.05$
Water *versus* cellulose	$p < 0.05$	$p < 0.05$

[a] The p values indicate level of significance; N.S. indicates not significant.

tivity (1489 *versus* 1877 dpm), and serum radioactivity at 1, 2, and 4 hr were significantly reduced by cellulose treatment. These results may reflect the bulk effect of cellulose, which would increase stomach emptying time and delay entrance of the drug into the intestine, where presumably the major portion of digitoxin is absorbed.

Colestipol hydrochloride is an anion-exchange polymer that would be expected to bind with ionized drugs by electrostatic forces, although other forces such as hydrogen bonding, dipole–dipole interactions, van der Waals forces, nonelectrostatic interactions, and intermolecular attractions of like molecules may be important factors in the binding process. The concurrent administration of nicotinic acid and colestipol hydrochloride reduced peak radioactivity at the high dose of the polymer; total drug availability, as measured under the time–concentration curve, was reduced but did not vary significantly from the control. Competition for binding sites on the polymer with bile acid anions and inorganic physiological anions (*e.g.*, phosphate, chloride, and bicarbonate) present in the GI tract could possibly explain these results.

The early binding of warfarin and the subsequent release from the drug–polymer interaction by these competing forces could weaken the electrostatic attraction of colestipol hydrochloride and the drug. Similarly, cholestyramine (357.5 mg/kg) in rats significantly depressed the plasma warfarin levels at all time intervals during a 4-hr test (10). Further tests on plasma prothrombin times used to calculate the relative clot index, at time intervals for 4 days, indicated that, although cholestyramine may delay early absorption of warfarin, the pharmacological effect was not significantly altered by a single dose of the drug and the polymer.

However, significant differences were noted between cholestyramine and colestipol hydrochloride in interfering with hydrochlorothiazide or digitoxin absorption from the GI tract of the rat. Whether results in rats are predictive of results in humans remains to be determined.

REFERENCES

(1) T. M. Parkinson, K. Gundersen, and N. A. Nelson, *Atherosclerosis*, **11**, 531(1970).

(2) T. M. Parkinson, J. C. Schneider, Jr., and W. A. Phillips, *ibid.*, **17**, 167(1973).

(3) J. R. Ryan and A. Jain, *J. Clin. Pharmacol.*, **12**, 268(1972).

(4) E. Marmo, A. P. Caputi, S. Cataldi, and A. Amelio, *G. Arterioscler.*, **8**, 229(1970).

(5) C. J. Glueck, S. Ford, Jr., D. Scheel, and P. Steiner, *J. Am. Med. Assoc.*, **222**, 676(1972).

(6) E. R. Nye, D. Jackson, and J. D. Hunter, *N. Z. Med. J.*, **76**, 12(1972).

(7) D. S. Goodman, R. P. Noble, and R. B. Dale, *J. Clin. Invest.*, **52**, 2646(1973).

(8) W. A. Phillips, J. R. Schultz, and W. W. Stafford, *J. Pharm. Sci.*, **63**, 1097(1974).

(9) W. H. Johns and T. R. Bates, *ibid.*, **59**, 329(1970).

(10) D. G. Gallo, K. R. Bailey, and A. L. Scheffner, *Proc. Soc. Exp. Biol. Med.*, **120**, 60(1965).

(11) W. A. Phillips, W. W. Stafford, and J. Stuut, Jr., *ibid.*, **143**, 733(1973).

(12) G. W. Snedecor and W. G. Cochran, "Statistical Methods," 6th ed., Iowa State University Press, Ames, Iowa, 1967, p. 258.

(13) W. H. Johns and T. R. Bates, *J. Pharm Sci.*, **59**, 788(1970).

(14) A. A. Sinkula, *ibid.*, **63**, 842(1974).

(15) J. M. Thorp, *Lancet*, **1**, 1323(1962).

(16) H. J. Hahn, W. Eiden, M. Schettle, M. Hahn, E. Walter, and E. Weber, *Eur. J. Clin. Pharmacol.*, **4**, 142(1972).

(17) C. Harvengt and J. P. Desager, *ibid.*, **6**, 19(1973).

(18) D. F. Magee, "Gastro-intestinal Physiology," Charles C Thomas, Springfield, Ill., 1962, p. 144.

(19) G. T. Okita, *Fed. Proc.*, **26**, 1125(1967).

(20) N. J. Greenberger and F. B. Thomas, *J. Lab. Clin. Med.*, **81**, 241(1973).

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[x] To whom inquiries should be directed.

Effects of Film Coatings on Tablet Hardness

PHILIP W. STERN

Abstract □ The effects of five conventional film-coating materials on tablet hardness were studied. Placebos showed apparently linear increases in hardness as coatings were applied. Completely coated samples exhibited hardness increases from 50 to 140%, with a corresponding 3% increase in tablet weight. Equations were derived relating hardness changes to the "breaking strength" of the film on the tablet. Findings indicate that the coatings exert their influence primarily along the diameter of the tablet in a direction perpendicular to an applied compressional force. Furthermore, the coating process itself did not alter core hardness since tablets from which the film could be stripped showed original values.

Keyphrases □ Film coatings—five different, effects on tablet hardness □ Hardness, tablet—effects of five different film coatings □ Tablet hardness—effects of five different film coatings □ Dosage forms—tablets, effects of five different film coatings on tablet hardness

The term "tablet hardness" is widely used today in a nonspecific or generic manner as an all-inclusive description of several important tablet parameters. Included among these parameters are bending or attrition resistance and impact or crushing strength (1–4). Of the four, measurement of crushing strength is probably the

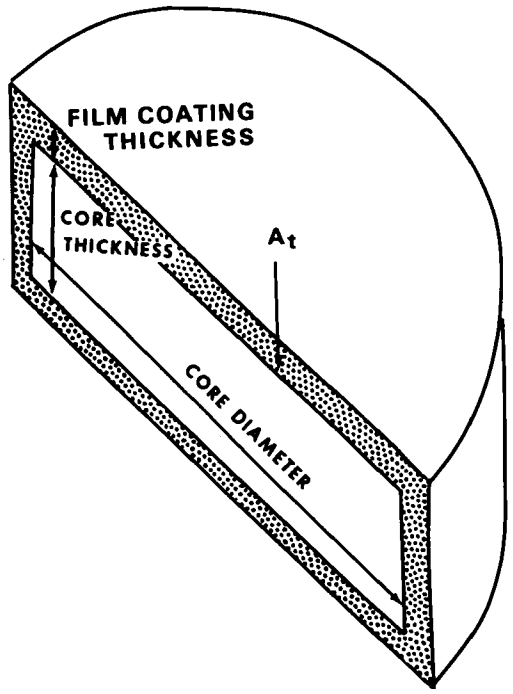

Figure 1—*Idealized cross-sectional view of film-coated tablet detailing the area of the film, A_t, subjected to tensile stress under transverse compression testing.*

most widely used to assess tablet integrity. Crushing strength may be defined as the minimal compressional force that, when diametrically applied to a tablet, causes it to fracture (4). Under exacting experimental conditions, the values associated with crushing strength may be interpreted as an indication of the tablet's tensile strength. Detailed studies have reported the use of transverse compression testing as a means of assessing tensile strength (5–7), but commercial products often possess shapes or heterogeneities that make quantification difficult.

Tablet hardness is known to be influenced by manufacturing methods, environmental conditions, and internal constituents. However, at a time when film-coated tablets have proliferated, comparatively little has been reported regarding the effects of thin film coatings on tablet hardness. Therefore, this study was undertaken to gain a mechanistic insight into the relationship between various film-coating materials and changes in tablet hardness that occur as a result of their application.

THEORY

Consider an uncoated round tablet core having an original hardness, H_o, with H_o determined by tensile failure along the tablet diameter. The hardness at any later time, t, then equals the original value plus the increase in hardness imparted by the film coat after a coating time of t. Therefore, the change in hardness at time t, ΔH_t, is the difference between two directly measurable quantities:

$$\Delta H_t = H_t - H_o \qquad \text{(Eq. 1)}$$

If one initially assumes that the tablet core is unaffected by the coating process, which will be verified, then any change in hardness is attributable to the film coat. Furthermore, from basic physical considerations, it is not unreasonable to assume that ΔH_t can be linearly related to the tensile strength, σ, of the film. In this case, the term A_t, the cross-sectional area of the film along the tablet diameter at time t over which a compressive testing force will manifest itself as tensile stress, can be introduced as the proportionality factor in:

$$\Delta H_t = \sigma A_t \qquad \text{(Eq. 2)}$$

Recently, Hiestand and Peot (7) detailed the difficulties in experimentally measuring true tensile strength values of tablets by diametral compression. Due to unequal stress distribution along a tablet's diameter and the possibility of brittle fracture or crack propagation, tablet failure may occur at values of applied stress below the true tensile strength. In addition to these considerations, three possible time sequences should be considered in the fracturing of a film-coated tablet: (*a*) concomitant fracture of the film and tablet at equal strain levels; (*b*) fracture of the tablet first, which immediately distributes the load to the film and breaks it; and (*c*) rupture of the film first, followed by tablet failure.

Under the experimental conditions reported in this study, discrimination among these three sequences was not possible, although the second seems most reasonable. In that case, the load at the instant of fracture produces enough tensile stress to fracture the core and

Table I—Solvent Systems for Coating Materials

Formula	Material	Percent (w/w)
1[a]	Hydroxypropyl methylcellulose[b]	5.0
	Methanol	30.0
	Methylene chloride	65.0
2	Ethylcellulose[c]	4.75
	Acetylated monoglyceride[d]	0.25
	Acetone	25.0
	Methylene chloride	70.0
3	Cellulose acetate phthalate[e]	4.75
	Triacetin[e]	0.25
	Methanol	20.0
	Acetone	75.0

[a] Formula 1 is used for hydroxypropyl cellulose (Klucel LF, Hercules Inc., Wilmington, Del.) and zein (Zein CG, Amcon Industries Inc., Buena Park, Calif.) also. [b] Methocel E-15 Premium, Dow Chemical Co., Midland, Mich. [c] Ethocel-10 cps, Dow Chemical Co., Midland, Mich. [d] Myvacet 9-40, DPI, Rochester, N.Y. [e] Eastman Kodak, Rochester, N.Y.

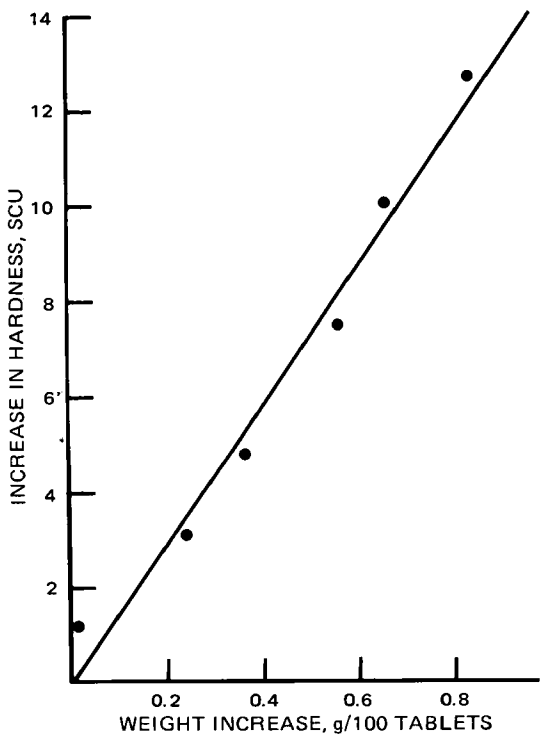

Figure 2—*Effect of hydroxypropyl methylcellulose film deposition on hardness values based on the measured increases in tablet weights.*

Table II—Hardness of Coated and Stripped Tablets

Material	Time after Coating	Average Hardness (±SD), SCU		
		Uncoated	Coated	Stripped
Hydroxypropyl methylcellulose	0.5 hr	9.1 (1.0)	22.4 (0.6)	7.7 (1.1)
	24 hr	8.1 (0.7)	22.5 (0.5)	7.0 (0.7)
	1 month	7.7 (0.9)	21.8 (1.6)	7.3 (1.1)
Ethylcellulose	0.5 hr	9.4 (1.0)	16.0 (2.0)	9.5 (0.9)
	24 hr	7.8 (0.6)	16.0 (1.5)	8.3 (0.9)
	1 month	7.5 (0.6)	14.6 (1.2)	7.6 (1.2)
Cellulose acetate phthalate	0.5 hr	9.4 (0.9)	15.4 (1.2)	9.1 (0.9)
	24 hr	8.4 (0.9)	17.5 (1.6)	8.1 (0.8)

partially stress the film. As the core breaks, the entire load must be absorbed by the film which then ruptures.

Because of the foregoing considerations, attempts to correlate measured hardness values quantitatively with the true tensile strength values of the film while on the tablet would be most difficult. Therefore, an effective "breaking strength" constant, k, was selected to serve as a measure of the stress to which the film was subjected. Substituting k for σ in Eq. 2 gives:

$$\Delta H_t = kA_t \qquad \text{(Eq. 3)}$$

An idealized graphic representation of A_t is given in Fig. 1. Combining Eqs. 1 and 3 gives a simple linear equation relating tablet hardness at any time to the breaking strength of the applied film:

$$H_t = kA_t + H_o \qquad \text{(Eq. 4)}$$

The term A_t can be calculated using Eq. 5:

$$A_t = \frac{RPt}{SD} \qquad \text{(Eq. 5)}$$

where R = gravimetric rate of film solids application per tablet, P = perimeter of the tablet along the breaking diameter, t = coating time, D = density of free dry film, and S = surface area per tablet. The term A_t can be further verified in some cases by directly measuring the thickness of the film coat when removed from a tablet. Substituting the right-hand side of Eq. 5 for A_t in Eq. 4 gives:

$$H_t = \frac{kRPt}{SD} + H_o \qquad \text{(Eq. 6)}$$

Equation 6 predicts that a plot of H_t *versus* coating time will be linear, with a slope proportional to k and intercept H_o. On the basis of this discussion, studies were designed and conducted to verify the applicability of these postulates to pharmaceutical coating systems.

EXPERIMENTAL

Materials—Five film-forming materials were selected for evaluation. Each was individually formulated in a compatible solvent system to produce a high quality film (Table I). A plasticizer was added to the formulation when the film former was too brittle for use alone. In all cases, the solids content of the solution was 5% (w/w).

Placebo tablets were made from a dicalcium phosphate (74%)–microcrystalline cellulose (20%)–starch (5%)–magnesium stearate (1%) direct compression mix and compressed on 0.874-cm diameter by 1.11-cm radius of curvature punches. Uncoated as well as coated cores prepared from this formulation consistently fractured cleanly along the diameter, indicating tensile failure during hardness testing.

Table III—Comparison of Tensile and Breaking Strength of Coating Materials

Coating Material	Tensile Strength of Free Film, kg/cm² (±SD)	Calculated Breaking Strength of Film on Tablet, kg/cm²
Hydroxypropyl methylcellulose	650 (65)	740
Zein	525 (80)	480
Cellulose acetate phthalate	505 (40)	410
Ethylcellulose	210 (55)	370
Hydroxypropyl cellulose	165 (15)	350

Fracture in this manner was necessary for applicability of the developed theory.

Free Films—Solutions described in Table I were spread on glass plates with an adjustable film-casting knife[1] to obtain free film samples for tensile strength measurements. The plates were allowed to air dry for 1 hr, after which film samples were cut with a scalpel and template designed such that the portion of the film at which the break was to occur was 0.5 cm wide. Typical samples were 0.02–0.08 mm thick, corresponding to the experimental film thickness on the coated placebo tablets. Tensile strength measurements[2] were made and values were calculated by dividing the force necessary to rupture the film by the original measured cross-sectional area of the film.

Film Coating—Coating experiments were carried out in a 61-cm baffled coating pan[3] rotating at 24 rpm and containing 15 kg of placebos. An automated airless spray system was used to control coating solution application from a pressure tank at approximately 85 psi through a 0.28-mm stainless steel nozzle orifice. The hydraulic pressure was adjusted slightly to equalize the delivery rates of the various coating solutions.

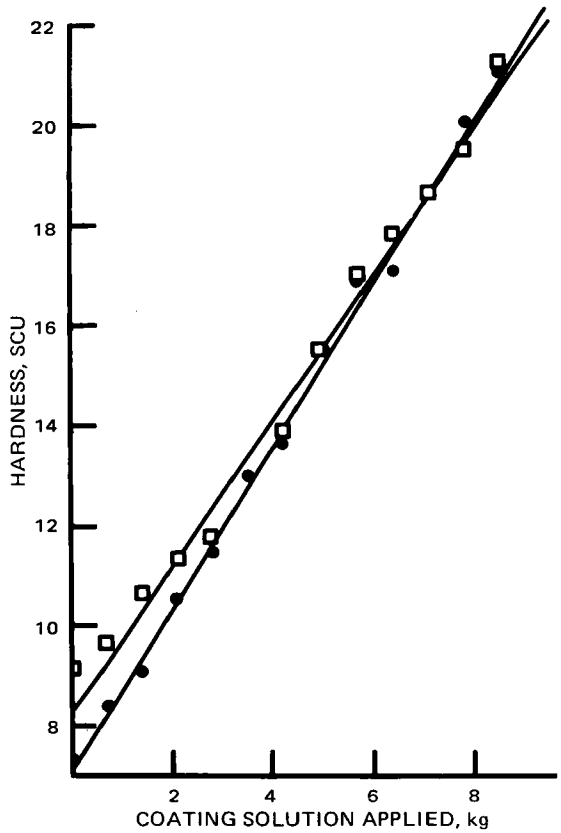

Figure 3—*Effect of time on hardness values of hydroxypropyl methylcellulose-coated tablets. Determinations were made 0.5 (□) and 24 (●) hr after coating.*

[1] Model AG-3820, Gardner Laboratory, Inc., Bethesda, Md.
[2] Instrom model TM, Instrom Corp., Canton, Mass.
[3] C. Skerman & Sons Ltd., London, England.

Table IV—Effects of Film-Coat Integrity and Orientation on Tablet Hardness

Material	Average Hardness (±*SD*), SCU				
	Uncoated Tablet	Coated Tablet	Film Cut Perpendicular to Applied Force	Film Cut Parallel to Applied Force	Film Cut Around Outside Edge
Hydroxypropyl methylcellulose	7.2 (0.4)	19.1 (2.1)	19.5 (1.7)	10.2 (1.0)	16.6 (0.6)
Cellulose acetate phthalate	7.2 (0.4)	16.8 (1.9)	14.9 (1.0)	8.3 (0.6)	15.5 (1.6)
Zein	7.2 (0.4)	14.8 (0.7)	14.8 (1.0)	8.0 (0.8)	14.3 (0.8)

Spraying operations were specifically performed in this low pressure region to minimize loss of material from spray drying and at the same time to promote uniform spreading of the solution on the tablet surface. Ten kilograms of each coating solution was applied over 130 min following a 10-sec spray–5-sec dry cycle. At appropriately selected times, samples were withdrawn and the hardness values of 10 tablets were measured[4].

RESULTS AND DISCUSSION

The increase in measured hardness values of the placebos due to hydroxypropyl methylcellulose film deposition is shown in Fig. 2. The maximum increase in tablet weight encountered in this study was approximately 3% of the original 0.292-g core weight, while the corresponding increase in hardness was 13 Strong-Cobb units (SCU) or 140% (1 SCU = 1.4 kg). From this result, it is apparent that a small amount of film-coating material on the tablet surface produced increases in hardness far exceeding estimates based on weight increases alone. To appreciate this finding, one should know that although the cross-sectional area of the tablet core along the diameter was approximately 0.2 cm^2 while the cross-sectional area of the film, A_t, at the same position on a fully coated tablet was approximately 0.013 cm^2, the film clearly dominated the hardness profile.

The effect of time on hardness measurements is shown in Fig. 3. The initial hardness determinations were made 0.5 hr after coating; another sample with the same amount of coating was evaluated after 24 hr of storage at coating room conditions of 24° and 40% relative humidity. It was generally observed that the hardness was slightly lower for the stored samples with low percentages of coating; those with greater coverage showed no changes with time. Overall, these time-dependent changes were considered to be of minimal importance, indicating that the films assume their final physical characteristics soon after coating ceases. Solvent penetration or entrapment appears to be insignificant.

In developing the theory, an initial assumption was made that any increase in measured hardness values was attributable to the film coat. This assumption directly implied that the tablet core was unaffected by the coating solvents or process. The data in Table II show the close agreement in hardness values between uncoated cores and coated cores from which the hydroxypropyl methylcellulose, ethylcellulose, or cellulose acetate phthalate coating had been carefully stripped. Hydroxypropyl cellulose and zein adhered tenaciously to the tablet surface and could not be removed without ruining the tablet. This observation that cores from which the film coat has been stripped exhibit hardness values equivalent to uncoated cores lends credence to the belief that the film alone is responsible for hardness changes.

The experimental data for hydroxypropyl methylcellulose, ethylcellulose, and hydroxypropyl cellulose coatings plotted in accordance with Eq. 6, *i.e.*, hardness *versus* time, are shown in Fig. 4. Here one can see the apparently linear increases in tablet hardness with coating time for each material. The standard deviations are shown only for hydroxypropyl methylcellulose but are representative of all five materials. The data for cellulose acetate phthalate and zein were separated from the other three sets for clarity (Fig. 5). Hydroxypropyl methylcellulose produced the most pronounced increase in hardness for a given amount of applied coating.

From the slopes of the least-squares regression lines, the breaking strength, k, of each film on the tablets was calculated using Eq. 6. These results are summarized in Table III and compared to the tensile strength values of the free films. Although significant quantitative differences exist between the breaking strength and tensile strength of a given film in some cases, which are not unexpected, the data do show rank-order correlation.

In all cases observed, when a coated or uncoated tablet fractured,

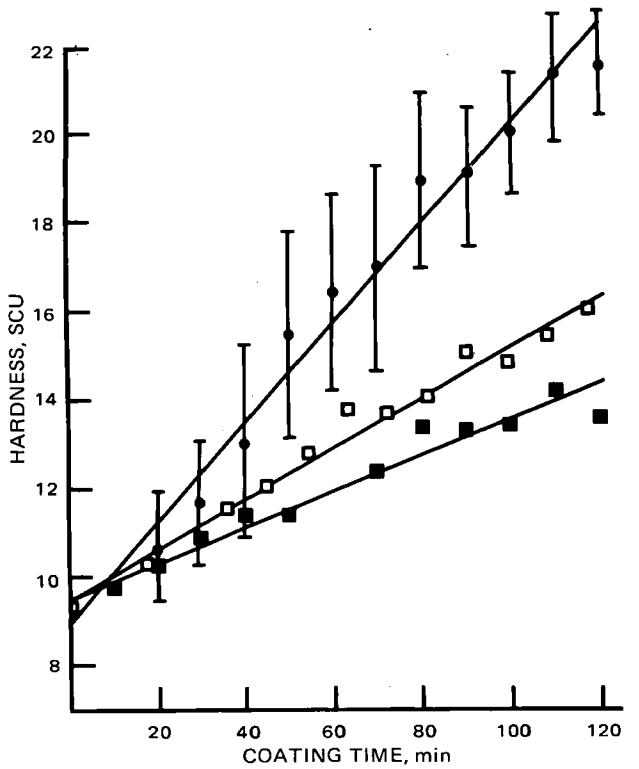

Figure 4—*Comparison of the increases in hardness for tablets coated with three cellulose-based coating materials. Key: ●, hydroxypropyl methylcellulose; □, ethylcellulose; and ■, hydroxypropyl cellulose.*

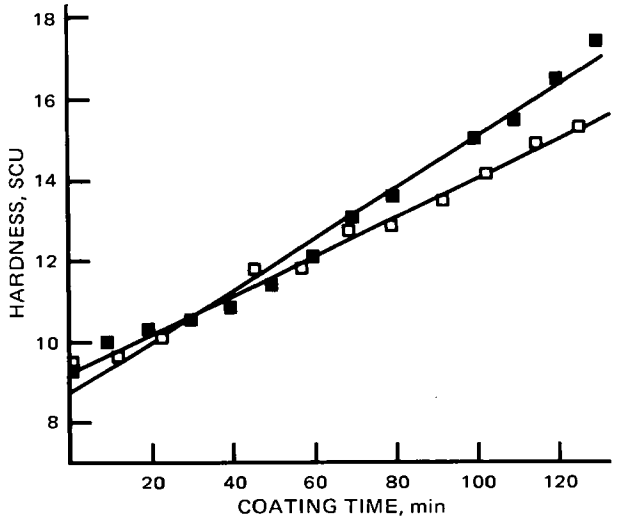

Figure 5—*Observed increases in tablet hardness for samples coated with zein (■) and cellulose acetate phthalate (□).*

[4] Heberlein tester, Cherry-Burrell Corp., Park Ridge, Ill.

it did so diametrically along a sharp line parallel to the direction of the applied force. It appears then that the film exerted its primary influence along this line under the test conditions employed. To verify this observation, cuts were carefully made with a scalpel through the coating along the diameter while other samples had cuts made around the circumference. The tablets with the cuts along the diameter were placed in the hardness tester such that the cut was either parallel or perpendicular to the applied force. Hardness measurements were made on these tablets (Table IV).

In cases where the cut was perpendicular to the applied force or the cut was around the outside edge, only minimal changes in hardness from intact coated tablets were observed. However, when the cut was aligned parallel to the applied force where normal tensile failure occurs, the film was unable to absorb any tensile stress and hardness values fell close to those for uncoated cores. These data support the use of the term A_t as the proportionality factor introduced in Eq. 2.

REFERENCES

(1) C. J. Endicott, W. Lowenthal, and H. M. Gross, *J. Pharm. Sci.*, **50**, 343(1961).

(2) H. J. Fairchield and F. Michel, *ibid.*, **50**, 966(1961).

(3) J. A. Seitz and G. M. Flessland, *ibid.*, **54**, 1353(1965).

(4) D. B. Brook and K. Marshall, *ibid.*, **57**, 481(1968).

(5) J. T. Fell and J. M. Newton, *J. Pharm. Pharmacol.*, **20**, 657(1968).

(6) J. T. Fell and J. M. Newton, *J. Pharm. Sci.*, **59**; 688(1970).

(7) E. N. Hiestand and C. B. Peot, *ibid.*, **63**, 605(1974).

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Quantitative Precorneal Disposition of Topically Applied Pilocarpine Nitrate in Rabbit Eyes

THOMAS F. PATTON * and JOSEPH R. ROBINSON ˣ

Abstract □ The present study was designed to quantitate the influence of several precorneal factors on the disposition of topically applied ophthalmic drugs. With tritiated pilocarpine nitrate, methodology was developed for *in vivo* assessment of the relative contribution of tear turnover, instilled solution drainage, and nonproductive absorption to the loss of drug from the precorneal area. Studies were conducted in both awake and anesthetized rabbits whose drainage ducts were either unobstructed or plugged, and the loss of drug was monitored directly from the precorneal area or as appearance in the aqueous humor. By selective variation in experimental conditions, the influence of tear turnover, instilled solution drainage, and nonproductive absorption on ocular drug bioavailability was separately studied and quantitated. Instilled solution drainage was by far the largest contributing factor in the loss of drug from the precorneal area of the eye and, in the range of instilled volumes normally employed, tear turnover played a relatively minor role in drug loss. Compared to the cornea, precorneal tissue other than the cornea has a considerably greater surface area and thus is a potentially significant route for drug loss. However, under normal circumstances, loss by this route was minimal as compared to loss *via* instilled solution drainage.

Keyphrases □ Pilocarpine nitrate—topically applied, precorneal disposition, effect of tear turnover, instilled solution drainage, and nonproductive absorption □ Precorneal disposition—pilocarpine nitrate, topically applied, effect of tear turnover, instilled solution drainage, and nonproductive absorption □ Bioavailability—pilocarpine nitrate, topically applied, effect of tear turnover, instilled solution drainage, and nonproductive absorption □ Topically applied drugs—pilocarpine nitrate, precorneal disposition □ Ophthalmic drugs—pilocarpine nitrate, topically applied, precorneal disposition

Topical application of drugs to the eye is the most frequently employed route of administration for the treatment of various eye disorders. Unfortunately, the disposition of drugs administered by this route is not well understood, although it is generally agreed that the bioavailability of topically applied drugs is extremely poor. The present study was designed to provide a quantitative accounting of the precorneal distribution of pilocarpine nitrate and to generate some mechanistic insight into its relatively poor bioavailability.

Many factors can affect the bioavailability of topically applied ophthalmic drugs. The presence of tears in the cul-de-sac dilutes any instilled drug, and the continual addition and removal of tears can cause a significant loss of applied drug. In addition, the efficient drainage apparatus, used for removal of tears, also serves as a conduit through which instilled drug solutions can be lost from the precorneal area. Moreover, substances normally present in tear fluid can bind and/or degrade instilled drugs. Finally, topically applied drugs may be absorbed into a variety of ocular tissues, most notably the cornea and conjunctiva. To maximize therapy with topically applied ocular drugs, it is necessary to know the amounts and rates at which drugs are lost to these various precorneal routes and the relative contribution of each to the bioavailability question.

Numerous studies over the years were directed toward an understanding of tear properties, production, and drainage (1–20). However, only recently has attention been focused on the role of tear turnover and instilled solution drainage on ocular drug bioavailability (21). Studies describing some interactions of drugs with the components of tears also were reported (22, 23).

Topically applied drugs in the eye that are not lost to the drainage apparatus nor absorbed by the cornea are potentially available to be absorbed by the conjunctiva and, ultimately, the sclera or to be absorbed onto the lids. These routes are referred to as nonproductive, since it is unlikely that much or any drug from these areas will penetrate the interior portions of the eye due to rapid removal by local circulation (24–29).

The present study attempted to evaluate individually these routes of drug loss and to quantitate drug move-