REFERENCES

(1) "Remington's Pharmaceutical Sciences," 15th ed., A. Osol and J. B. Hoover, Eds., Mack Publishing Co., Easton, Pa., 1975, p. 1269.
(2) J. T. Miyahara and R. Karler, *Biochem. J.*, **97**, 194 (1965).
(3) J. T. Sheehan, *J. Am. Chem. Soc.*, **70**, 1665 (1948).
(4) E. Wenis and T. S. Gardner, *J. Am. Pharm. Assoc., Sci. Ed.*, **38**, 9 (1949).
(5) U.S. pat. 2,604,488 to Rhom-Poulenc (Merck Index, 8th ed., Merck and Co., Rahway, N.J., 1968).
(6) S. Maruyama and H. Imamura, *J. Am. Chem. Soc.*, **74**, 2589 (1952).
(7) G. V. Jadhav and R. N. Thakkar, *J. Univ. Bombay, Sec. A*, **18**, 29 (1949); through *Chem. Abstr.*, **44**, 5845i (1950).
(8) Beilsteins Band X, System No. 1051–1054 (1927).
(9) N. G. Gaylord and P. N. Kamath, *Org. Synth. Coll. Vol.*, **4**, 178 (1967).
(10) A. N. Meldrum and N. W. Hirve, *J. Indian Chem. Soc.*, **5**, 95 (1928); through *Chem. Abstr.*, **22**, 4514 (1928).
(11) J. H. Beynon, R. A. Saunders, and A. E. Williams, *Ind. Chim. Belge*, **1964**, 311.
(12) M. M. Bursey and F. W. McLafferty, *J. Am. Chem. Soc.*, **88**, 5023 (1966).
(13) J. H. Beynon, G. R. Lester, and A. E. Williams, *ibid.*, **63**, 1861 (1959).
(14) S. Meyerson, I. Puskas, and E. K. Fields, *ibid.*, **88**, 4974 (1966).
(15) J. H. Beynon, "Mass Spectrometry and Its Application to Organic Chemistry," Elsevier, Amsterdam, The Netherlands, 1960, p. 268.
(16) J. H. Beynon, R. A. Saunders, A. Tapham, and A. E. Williams, *J. Chem. Soc.*, **1965**, 6403.
(17) W. Gardy, *J. Chem. Phys.*, **7**, 163 (1939); through *Chem. Abstr.*, **33**, 3262^5 (1939).
(18) R. A. Nyquist, *Spectrochim. Acta*, **19**, 1655 (1963).
(19) V. S. Korbkov, *Opt. Spektrosk.*, **17**, 938 (1964); through *Chem. Abstr.*, **62**, 11302c (1965).
(20) J. D. Swalen, "Progress in NMR Spectroscopy," vol. 1, Pergamon, New York, N.Y., 1966, p. 240.
(21) F. Scheinmann," An Introduction to Spectroscopic Methods for the Identification of Organic Compounds," vol. 1, Pergamon, New York, N.Y., 1970, p. 69.
(22) D. J. Pasto and C. R. Johnson," Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N.J., 1969, p. 183.
(23) J. R. Dyer, "Application of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N.J., 1965, p. 58.
(24) A. Burger, "Selected Pharmacological Testing Methods," Dekker, New York, N.Y., 1963, p. 100.

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Conductivity and Hardness Changes in Aged Compacts

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Abstract □ Batches of sodium, potassium, and ammonium chloride tablets containing no excipients and spray-dried lactose tablets containing 0.5% magnesium stearate were stored at 20 and 76% relative humidity. Electrical resistance and hardness measurements were made within 1 hr after compression and at intervals during a 45-day period. Hardness values of sodium, potassium, and ammonium chloride tablets stored at 20% relative humidity increased from 70 to 200% at 45 days, while conductances decreased 10-fold. Tablets stored at 76% relative humidity showed no increases or slight decreases in hardness with slight increases in conductance. Lactose tablets decreased slightly in hardness with corresponding increases in conductance.

Keyphrases □ Conductivity, electrical—effect of aging and humidity, various compressed tablets □ Hardness—effect of aging and humidity, various compressed tablets □ Tablets, compressed—effect of aging and humidity on electrical conductivity and hardness

The effect of aging on the physical characteristics of tablets has been discussed by several investigators. Increased hardness was reported in hydrochlorothiazide tablets formulated with acacia (1). Dibasic calcium phosphate dihydrate tablets displayed no significant changes in hardness over a 4-month period but showed significant increases in disintegration and dissolution times when stored at 25° and 50% relative humidity (RH) (2).

The crushing strength of sodium chloride compacts prepared from dried samples doubled 1 hr after compaction (3). No significant changes in crushing strength were observed when compacts were stored for longer periods at low humidities. This phenomenon was attributed to time-dependent relaxations, resulting in stress release within the compacts which increased interparticulate contact and bonding. Compacts with higher moisture content possessed low tensile strength compared to those with lower moisture content, which was attributed to weakening of interparticulate bonding by trace moisture (3).

Significant increases in hardness were observed in sodium chloride tablets stored for several days (4). These changes correlated with changes in electrical conductances calculated from measured dissipation factors.

The electrical conductance of a compact is determined in part by the number of interparticulate contact points and the effective internal surface area resulting from microscopic cracks and imperfections (5). Hardness changes in compacts should be associated with conductance changes that reflect changes in the contact area and internal surface. Increases in compact strength should be correlated with decreases in electrical conductance, measured under conditions in which there is no substantial increase in compact moisture content.

This study was designed to verify the expected relationship between conductance and hardness changes in compacts and to establish the role of moisture in affecting these changes in compacts of directly compressible salts.

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Table I—Conductance and Hardness (±*SD*) of Aged Sodium Chloride Compacts

	20% RH			76% RH		
Storage Period, days	Apparent[a] Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	W/T[b] Ratio, g/cm	Hardness, kg	Apparent Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	W/T Ratio, g/cm	Hardness, kg
Initial	1.238 (0.098)	2.566 (0.008)	2.54 (0.91)	1.260 (0.0.98)	2.586 (0.024)	2.65 (0.01)
2	0.818 (0.067)	2.544 (0.007)	3.44 (0.04)	1.159 (0.088)	2.589 (0.036)	3.20 (0.08)
7	0.141 (0.041)	2.541 (0.011)	5.01 (0.11)	0.862 (0.067)	2.597 (0.049)	3.36 (0.06)
15	0.073 (0.008)	2.544 (0.009)	6.22 (0.09)	1.144 (0.046)	2.588 (0.006)	3.25 (0.01)
30	0.055 (0.003)	2.571 (0.062)	6.36 (0.05)	1.144 (0.056)	2.589 (0.008)	2.91 (0.04)
45	0.049 (0.006)	2.600 (0.011)	6.42 (0.04)	1.190 (0.049)	2.595 (0.032)	2.66 (0.09)

[a] Average of five observations. [b] Weight to thickness.

Table II—Conductance and Hardness (±*SD*) of Aged Potassium Chloride Compacts

	20% RH			76% RH		
Storage Period, days	Apparent[a] Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	W/T[b] Ratio, g/cm	Hardness, kg	Apparent Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	W/T Ratio, g/cm	Hardness, kg
Initial	0.219 (0.034)	2.338 (0.006)	3.52 (0.02)	0.207 (0.028)	2.332 (0.008)	3.50 (0.06)
2	0.081 (0.021)	2.342 (0.005)	4.32 (0.04)	0.186 (0.018)	2.338 (0.008)	3.54 (0.02)
7	0.042 (0.008)	2.351 (0.008)	4.95 (0.06)	0.172 (0.034)	2.344 (0.006)	3.63 (0.05)
15	0.028 (0.008)	2.334 (0.005)	6.12 (0.03)	0.194 (0.038)	2.333 (0.005)	3.52 (0.02)
30	0.017 (0.004)	2.337 (0.008)	7.61 (0.04)	0.225 (0.031)	2.346 (0.010)	3.37 (0.01)
45	—	2.333 (0.006)	8.59 (0.03)	0.230 (0.072)	2.254 (0.028)	3.13 (0.02)

[a] Average of five observations. [b] Weight to thickness.

Table III—Conductance and Hardness (±*SD*) of Aged Ammonium Chloride Compacts

	20% RH			76% RH		
Storage Period, days	Apparent[a] Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	W/T[b] Ratio, g/cm	Hardness, kg	Apparent Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	W/T Ratio, g/cm	Hardness, kg
Initial	3.090 (0.120)	1.896 (0.012)	3.40 (0.05)	3.280 (0.083)	1.895 (0.009)	3.37 (0.03)
2	0.513 (0.063)	1.899 (0.018)	3.59 (0.05)	3.710 (0.112)	1.889 (0.006)	3.40 (0.04)
7	0.220 (0.041)	1.898 (0.021)	4.20 (0.07)	2.560 (0.086)	1.897 (0.012)	3.48 (0.03)
15	0.124 (0.033)	1.876 (0.008)	4.86 (0.03)	3.641 (0.041)	1.878 (0.008)	3.33 (0.01)
30	0.081 (0.018)	1.876 (0.006)	5.44 (0.03)	3.855 (0.132)	1.876 (0.006)	3.45 (0.03)
45	0.064 (0.008)	1.902 (0.011)	5.53 (0.04)	3.758 (0.098)	1.875 (0.010)	3.28 (0.02)

[a] Average of five observations. [b] Weight to thickness.

EXPERIMENTAL

Materials—Since different lots of the same material show variations in electrical properties (6), single lots of USP grade sodium chloride, potassium chloride, ammonium chloride[1], and spray-dried lactose[2] were studied. Saturated solutions of sodium acetate (analytical reagent) and potassium acetate (analytical reagent) were used to maintain ~20 and 76% RH in 5-liter desiccators. The chloride salts were screened to isolate the 40–50-mesh fractions, which were dried at 65° for 24 hr before compaction.

Preparation and Treatment of Compacts—Batches of compacts were prepared from the 40–50-mesh fraction of unlubricated sodium, potassium, and ammonium chlorides and spray-dried lactose blended with 0.5% magnesium stearate. The latter was included as an example of a formulation that showed no significant hardness changes on aging. Tablets were compressed manually, using a 1.27-cm diameter punch and die assembly, on a single-punch tablet press[3].

Compacts of suitable weight, thickness, and hardness were produced and stored in the 20 and 76% humidity chambers. Resistance and hardness values were determined within 1 hr of compression and after 2, 7, 15, 30, and 45 days of storage. The 20 and 76% RH conditions were selected to observe the effect of drying and atmospheric moisture on compact conductance and hardness.

In some experiments, sodium chloride compacts were stored at 76% RH for 10 days and then transferred to 20% RH. Resistance and hardness values were measured at the time of transfer and after up to 45 days of storage at 20% RH.

A small batch of sodium chloride compacts was prepared using the 1.27-cm punch and die assembly on a hydraulic press[4] at 1800-, 2700-, and 3600-kg gauge pressures. Pressure was applied for at least 15 sec. Compacts were stored at 20% RH until subject to resistance and hardness measurements.

Conductance Measurements—The complete system for measurement of the electrical resistance of compacts was described previously (7). Compacts were placed on a grounded steel plate attached to the lower stage of the hydraulic press. A 2.5-cm diameter shielded tablet punch, which was fixed to the upper stage of the press through an insulating acrylic[5] block, served as the active electrode. A shielded cable connected the punch to an electrometer[6]. The lower stage of the press was raised until the tablet contacted the punch face.

A minimal pressure (<50 kg) was applied to minimize contact resistance. Stable resistance values were attained within 1 min and recorded. The thickness and weight of each compact were measured before testing for hardness. Specific conductances were calculated from the measured resistance and dimensions. This procedure was repeated on five different compacts to obtain each experimental point.

Hardness Measurements—A 1.27-cm diameter standard concave punch was fastened to the platform of a motorized linear drive[7] so that it was exactly centered beneath an indentation probe. The latter consisted

[1] Fisher Scientific Co., Springfield, N.J.
[2] Foremost-McKesson, Appleton, Wis.
[3] Manesty model E2, Key Industries, Farmingdale, N.J.
[4] Model C, Fred S. Carver, Menomonee Falls, Wis.
[5] Lucite.
[6] Model 610C, Keithley Instruments, Cleveland, Ohio.
[7] Model LTCM, John Chatillon and Sons, New York, N.Y.

Table IV—Conductance and Hardness (±*SD*) of Aged 40–50-Mesh Sodium Chloride Compacts Stored under 76% RH for 7 Days and then Transferred to 20% RH

Storage Period, days	Apparent[a] Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	W/T[b] Ratio, g/cm	Hardness, kg
Initial[c]	0.800 (0.041)	2.589 (0.007)	3.24 (0.02)
2	0.477 (0.028)	2.570 (0.009)	3.59 (0.01)
7	0.165 (0.013)	2.558 (0.010)	4.46 (0.02)
15	0.076 (0.008)	2.556 (0.009)	6.14 (0.02)
30	0.057 (0.008)	2.560 (0.007)	6.36 (0.01)
45	0.052 (0.004)	2.553 (0.006)	6.45 (0.01)

[a] Average of five observations. [b] Weight to thickness. [c] Represents 7 days of storage at 76% RH.

of an 0.4-cm diameter stainless steel ball bearing fixed to a threaded shaft, which was fastened to a 22.7-kg (50-lb) load cell[8]. The output of the load cell was amplified[9] and recorded[10]. The motorized drive was operated at a platform speed of 0.5 cm/min.

Compacts were placed on edge on the punch face, and the identation probe was driven diametrically into the compact, which split into two equal halves. Figure 1 shows a plot of measured force on the tablet as a function of time. Point A represents the onset of stress; point B represents the maximum stress the compact experienced prior to splitting, shown by line BC, which represents the sudden release in stress. In Fig. 1, AC represents the degree of indentation required to split the tablet. Hardness values were expressed in terms of the maximum force in kilograms required to split the compact.

RESULTS AND DISCUSSION

Tables I–III summarize observed conductance and hardness values of sodium, potassium, and ammonium chloride compacts stored at 20 and 76% RH for 45 days. Figure 2 shows relative changes in hardness compared to initial values as a function of time. Sodium and potassium chloride compacts stored at 20% RH exhibited marked increases in hardness along with significant decreases in specific conductance. Constant hardness and conductance values were observed after 15 days with

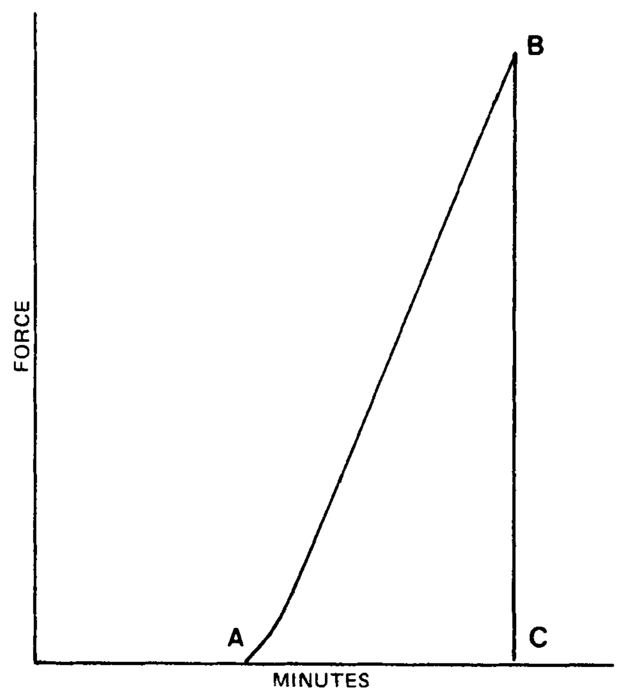

Figure 1—*Typical force-time plot observed in indentation testing of tablet hardness (see text).*

[8] Models UC3 and UL4-50, Statham Instruments, Los Angeles, Calif.
[9] Model UR3, Statham Instruments, Los Angeles, Calif.
[10] Model 680 recorder, Hewlett-Packard, Palo Alto, Calif.

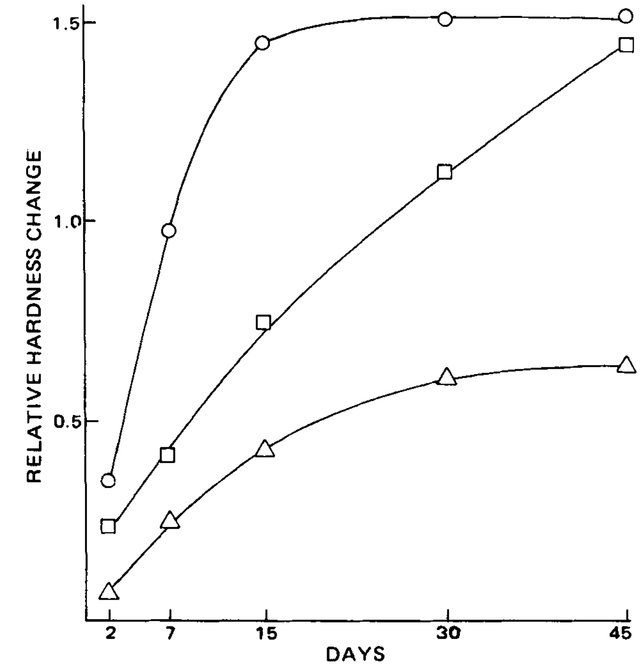

Figure 2—*Relative hardness changes observed in sodium (○), potassium (□), and ammonium chloride (△) compacts stored at 20% RH.*

sodium chloride and after 45 days with ammonium chloride. However, potassium chloride compacts continued to increase in hardness after 45 days. Measurements were made on compacts of equal density, as indicated by the constancy of the weight to thickness ratio.

No significant changes in hardness or conductance were observed in compacts stored at 76% RH, except for sodium chloride where hardness increased and conductance decreased slightly in the first 7 days of storage. Table IV summarizes observations made on sodium chloride compacts stored at 76% RH for 7 days before transfer to 20% RH. The same degree of conductance and hardness changes was observed as for compacts stored at 20% RH initially.

Table V summarizes conductance and hardness values for sodium chloride compacts prepared on the hydraulic press and stored at 20% RH. While the initial values varied as expected with the pressure used to form the compacts, essentially the same conductance and hardness values were observed after 30 days of storage. These data suggest that maximum bonding was attained in all three batches of sodium chloride compacts at the same time.

The observed significant increases in hardness of sodium, potassium, and ammonium chloride compacts when stored under low humidity is evidence of strong interparticulate bond formation during storage. Rees and Shotton (3) reported a doubling of the strength of sodium chloride compacts prepared from sodium chloride dried at 110° within 1 hr after compression with negligible changes after 140 hr. They also reported that exposure of salt compacts to 76% RH prevented the hardness increase. It was not possible to prepare satisfactory compacts from completely dried salts in the pressure ranges available on the single-punch press. The traces of moisture present in the materials used in this study contributed to the delayed hardening in contrast to Rees and Shotton's data, which may also reflect increased crystal defects owing to the higher temperatures required to dry the salt completely.

Not all of the potential bond strength developed immediately at the time of compression. Some of the bonded areas formed during compression might have broken during tablet elastic recovery when pressure was released. Sufficient bonding remained to permit the compacts to maintain their shape while new, stronger interparticulate bonding developed.

The data suggest that the principal mechanism of hardening occurs because of a loss of moisture traces at low humidities. This conclusion is supported by the observations summarized in Table IV since compacts stored at 76% RH increased in hardness when transferred to a significantly lower humidity. The amount of moisture involved did not significantly contribute to compact weight.

Rees and Shotton (3) also observed that sodium chloride compacts with a high moisture content had lower tensile strengths than those with a low moisture content. At high humidities, loss of moisture, which results in

Table V—Conductance and Hardness (±*SD*) of Aged Sodium Chloride Compacts Produced at Different Compaction Pressures and Stored at 20% RH

Storage Period, days	1800 kg: Apparent[a] Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	1800 kg: W/T[b] Ratio, g/cm	1800 kg: Hardness, kg	2700 kg: Apparent Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	2700 kg: W/T Ratio, g/cm	2700 kg: Hardness, kg	3600 kg: Apparent Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	3600 kg: W/T Ratio, g/cm	3600 kg: Hardness, kg
Initial	0.998	2.470	3.17	0.856	2.488	3.32	0.836	2.481	3.46
	(0.069)	(0.005)	(0.11)	(0.053)	(0.008)	(0.008)	(0.021)	(0.009)	(0.03)
2	0.560	2.469	4.28	0.343	2.468	4.39	0.307	2.465	4.46
	(0.030)	(0.007)	(0.11)	(0.069)	(0.006)	(0.10)	(0.028)	(0.013)	(0.02)
7	0.095	2.466	5.35	0.076	2.477	5.60	0.073	2.471	5.64
	(0.021)	(0.009)	(0.09)	(0.023)	(0.002)	(0.09)	(0.080)	(0.011)	(0.06)
15	0.063	2.476	6.52	0.060	2.473	6.32	0.056	2.478	6.66
	(0.008)	(0.005)	(0.09)	(0.031)	(0.007)	(0.09)	(0.003)	(0.008)	(0.04)
30	0.054	2.472	6.70	0.052	2.486	6.68	0.052	2.472	6.73
	(0.021)	(0.004)	(0.10)	(0.004)	(0.008)	(0.06)	(0.008)	(0.006)	(0.02)
45	0.053	2.473	6.72	0.052	2.474	6.76	0.051	2.473	6.78
	(0.011)	(0.005)	(0.10)	(0.003)	(0.011)	(0.04)	(0.003)	(0.011)	(0.04)

[a] Average of five observations. [b] Weight to thickness.

Table VI—Conductance and Hardness (±*SD*) of Aged Spray-Dried Lactose Compacts Containing 0.5% Magnesium Stearate and Stored under 20% RH

Storage Period, days	Apparent[a] Specific Conductance, $ohms^{-1} cm^{-1} \times 10^9$	W/T[b] Ratio, g/cm	Hardness, kg
Initial	0.630 (0.018)	1.668 (0.005)	2.99 (0.12)
2	0.610 (0.022)	1.697 (0.009)	2.95 (0.13)
7	0.641 (0.028)	1.674 (0.006)	2.88 (0.11)
15	0.682 (0.031)	1.673 (0.008)	2.53 (0.18)
30	0.736 (0.042)	1.664 (0.011)	2.46 (0.11)
45	0.781 (0.038)	1.674 (0.016)	2.41 (0.13)

[a] Average of five observations. [b] Weight to thickness.

the deposition of salt around existing contact regions, is inhibited. The differences observed between the different chloride salts is related to the different tendencies of the salts to pick up moisture at 76% RH, which is the critical deliquescence point for sodium chloride. Potassium and ammonium chlorides are more deliquescent at this humidity.

Compacts prepared from spray-dried lactose containing lubricant showed a slight decrease in hardness with an increase in conductance at 20% RH (Table VI). Previous investigators (8) suggested that consolidation in lactose occurs mainly by brittle fracture, in contrast to plastic deformation in sodium chloride. Compacts stored at reduced humidity lose traces of moisture; at a reduced moisture content, magnesium stearate decreases hardness.

The data in this study support the expected relationship between conductance and hardness changes. In all cases, increased hardness was accompanied by more than 10-fold decreases in conductance. Conductance values were stable if hardness was stable. These effects were most pronounced in ionic materials whose electrical resistance was directly measurable. Compacted spray-dried lactose represented the upper limit of resistance measurement with the equipment employed.

REFERENCES

(1) A. S. Alan and E. L. Parrott, *J. Pharm. Sci.*, **60**, 263 (1971).

(2) J. M. Lausier, C.-W. Chiang, H. A. Zompa, and C. T. Rhodes, *ibid.*, **66**, 1636 (1977).

(3) J. E. Rees and E. Shotton, *J. Pharm. Pharmacol., Suppl.*, **22**, 17S (1970).

(4) E. J. Hanus, Ph.D. thesis, Rutgers—The State University, New Brunswick, N.J., 1967.

(5) W. Bollmann, "Crystal Defects and Crystalline Interfaces," 1st ed., Springer-Verlag, New York, N.Y., 1970.

(6) K. Marshall, *J. Pharm. Pharmacol.*, **15**, 413 (1963).

(7) R. P. Bhatia and N. G. Lordi, *J. Pharm. Sci.*, **68**, 222 (1979).

(8) E. T. Cole, J. E. Rees, and J. A. Hersey, *Pharm. Acta Helv.*, **50** (12), 28 (1975).

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