

Dissolution and Compatibility Considerations for the Use of Mannitol in Solid Dosage Forms

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Abstract □ Data to substantiate the inertness of mannitol and its acceptability for use in tablets and capsules are presented. Accelerated stability studies demonstrate the compatibility of mannitol with several general classes of possible drug actives. Reflectance measurements through tristimulus filters made with equilibrated samples of mannitol, lactose, dextrose, and sucrose in combination with oxytetracycline hydrochloride indicate the absence of chemisorptive properties with these four excipients. The effect of these excipients on the dissolution rate of benzoic acid in water has been investigated by reported tablet and granule methods. Deviations from the cube root law are shown for mannitol and lactose.

Keyphrases □ Mannitol—solid dosage forms □ Compatibility—mannitol, drugs □ Dissolution rates—mannitol dosage forms, granules □ UV spectrophotometry—analysis □ IR spectrophotometry—analysis □ Reflectance measurements—analysis

A number of factors are of primary concern in resolving the value of an excipient for solid dosage forms. The most important factor undoubtedly is compatibility with the drug active. Oxidation, reduction, hydrolysis, acidic, basic, amine and atmospheric reactions, lubricant interaction, and chemisorption are of interest.

Mannitol is stable in the dry state and not affected by atmospheric oxygen in the absence of catalysts. Several literature references are available on its non-hygroscopicity (1), and its acceptability in vitamin tablets because of its low moisture content (2). While one U.S. patent (3) substantiates the inertness of mannitol toward sensitive therapeutic entities, little reported information is available which would provide useful stability data for the use of mannitol in tablets and capsules.

The possibility of chemical adsorption between an excipient and active ingredients must be considered in formulation of solid dosage forms. The measurement of chemisorption by diffuse-reflectance has been reported by Lach (4). The dissolution of a drug in the presence of an excipient must also be considered of prime importance in formulation.

Studies conducted in the authors' laboratories were designed to estimate the value of mannitol as an excipient from the standpoint of inertness in commonly reported interactions and chemisorption and its effect on the dissolution rate of drug formulations.

EXPERIMENTAL

Reagents—Tartaric acid, ammonium chloride, sodium bicarbonate, arsenic trioxide, dextrose, α -lactose, β -lactose, spray-dried lactose, sucrose, benzoic acid, magnesium trisilicate, magnesium stearate, calcium stearate (Fisher Scientific Co.); mannitol (Atlas Chemical Industries); phenyl salicylate (Eastman Kodak); ascorbic acid (Roche Chemical Co.); aminophylline (K. & K. Laboratories); chloroform; oxytetracycline HCl (Pfizer & Co.).

Compatibility Considerations—To evaluate various compatibility factors, seven materials (arsenic trioxide, ascorbic acid, ammonium

chloride, tartaric acid, aminophylline, sodium bicarbonate, and phenyl salicylate) were chosen to act as representatives of various classes of actives to be used for stability testing in combination with mannitol, sucrose, dextrose, and lactose in gelatin capsules. The seven incompatibilities to be evaluated were respectively: reduction (5), oxidation; release of ammonia (6); reaction with an acid; amine browning (7); reaction with a base; production of phenolic odor (8).

Mixtures of equal parts of the actives with each of the four excipients were prepared and 100 No. 00 gelatin capsules of each, weighing 600 mg., were manufactured. Initial assays were run on 10 capsules. Thirty capsules were placed in a single layer in open aluminum cups at each of three stability stations, 40, 5 and 25° at 50% relative humidity. The capsules were observed at weekly intervals for physical changes and assays of the actives and excipients were performed at the end of 1 and 3 months.

Tartaric acid mixtures were titrated using standard alkali and sodium bicarbonate mixtures were assayed by titration with standard acid. Iodometric titration (as described in USP 17th revision, page 47) was used to assay ascorbic acid. To assay for ammonium chloride, samples were made alkaline with sodium hydroxide, the released ammonia was distilled into boric acid, and a titration with standard acid followed. Aminophylline contents were determined by UV measurement of λ_{\max} at 268 m μ in ethanol: water solutions and phenyl salicylate at 307 m μ with a Beckman DKII spectrophotometer. IR measurement of $A_{475 \text{ cm.}^{-1}}$ (corrected for the $A_{475 \text{ cm.}^{-1}}$ due to excipient) for arsenic trioxide was accomplished using a Perkin-Elmer model 21 IR spectrophotometer.

Any changes in the excipients were determined by comparing the IR spectra of the storage samples with those of the initial mixtures and with the spectra of unmixed drug and excipient.

Reflectance Measurements—Using the data of Lach (4) as background, the Gardner Multipurpose Reflectometer No. 870 equipped with a M-5 condensing lens and sample ring template for reading small surface areas was employed in measuring 45°, 0° reflectance through tristimulus filters. The instrument employs a null method, *i.e.*, light from a single source is directed along two paths to two photoelectric cells and the amounts of light along these two paths are varied by mechanical means until the cells produce the same currents as registered on a galvanometer. During instrument operation, a fixed comparison specimen is always placed in one beam, then unknown specimens are compared with a standard in the other.

A Gardner plate No. 60EB and MgCO₃ USP were used as standards for testing. Nonaqueous equilibration of samples of the excipients and oxytetracycline hydrochloride was performed using the method of Lach with the following changes: (a) the samples were prepared in 50-ml. flasks sealed with Saran wrap and cellophane tape; (b) the samples were held at 30 ± 0.5° in a Blue M (Magna-Whirl) constant-temperature bath (model MW-1120A) for 24 hr.; (c) drying was completed in a Cenco drying oven at total vacuum at 95°. Physical mixtures of the drug and excipients were used as controls. Special 10.2 × 10.2 cm. (4 × 4-in.) sample plates with a 2.54-cm. (1-in.) square depression 1.1 mm. deep were prepared to allow observation of the powders as a smooth surface.

Readings of reflectance made at 1, 2, and 7 days after preparation were corrected to the standard plate values and then calculated using MgCO₃ as 100% reflectance.

Lubricant Interaction—A series of 1.58-cm. (0.625-in.) flat-face tablets was prepared by direct compression which contained only mannitol, or lactose and equal parts mixtures of mannitol with both spray-dried and β -lactose. One-half of each lot was lubricated with magnesium stearate and the other half with calcium stearate. Two percent magnesium stearate was used to lubricate the mannitol and 0.5% was used for lactose. One percent and 0.25%, respectively, were required when calcium stearate was utilized. The tablets were

Table I—Weight Percent of Drug Actives in Gelatin Capsules Stored at 40°C. for 12 Weeks

Drug	Mannitol		Lactose		Sucrose		Dextrose	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
Tartaric acid	50.2	49.9	49.9	50.3	50.3	50.2	49.4	51.1
Aminophylline	44.3	45.7	48.0	46.7	47.1	46.7	46.3	51.3
Phenyl salicylate	51.4	52.1	48.0	46.7	47.1	46.7	47.9	46.3
Ascorbic acid	49.6	48.6	49.9	49.7	48.8	49.9	52.2	47.2
Ammonium chloride	49.4	53.1	48.5	52.7	49.1	52.1	50.3	52.9
Sodium bicarbonate	50.7	50.4	49.9	50.1	50.7	50.4	49.9	50.0
Arsenic trioxide	42.3	43.0	42.7	23.6	36.5	6.2	48.1	32.3

stored at 5, 25, and 40° in closed bottles and observed periodically over a 12-month period.

Tablet Dissolution—For measurement of dissolution of benzoic acid from tablets in the presence of the excipients the method of Parrott *et al.* (9) was used. Weight and dimensional changes were used to determine the dissolution rate. Flat cylindrical tablets of the test material weighing 1.024 ± 0.036 g. were agitated in a 0.1 M test solution of the excipients held at constant temperature. The solvent phase was frequently renewed to prevent an appreciable build-up of the solute concentration. Measurements of the weight, diameter, and thickness of the tablets were taken initially and at various time intervals. The extent of dissolution was further checked by titration of the solvent phase.

Granule Dissolution—The tape method of Goldberg *et al.* (10) was utilized to measure particulate dissolution rates. Forty milligrams of -50, +60 mesh benzoic acid granules were exposed to water (control) and 0.2 M solutions of the four excipients. Ten-milliliter samples were withdrawn at specified times and assayed using a Beckman DB recording spectrophotometer.

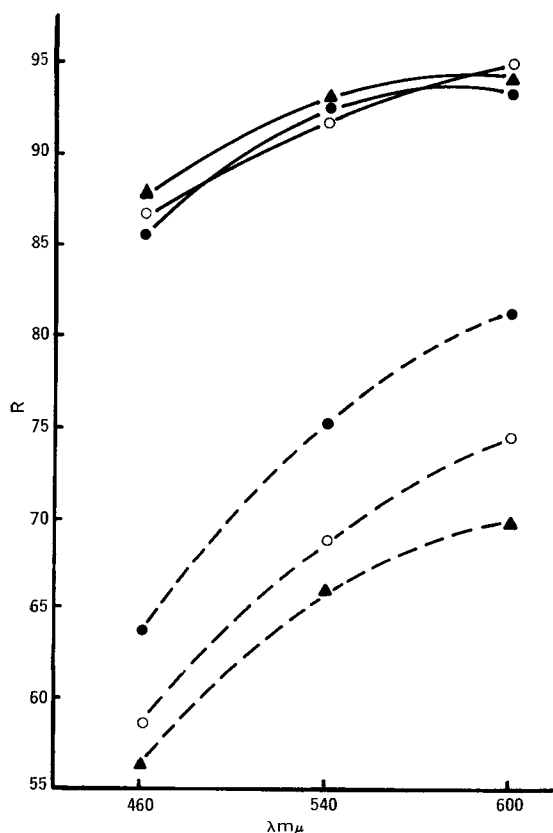


Figure 1.—45°, 0° reflectance of oxytetracycline HCl (60 mg.) and magnesium trisilicate (2.0 g.). Key: Nonaqueous equilibrated sample, ---; control (physically mixed components), ---; ●, 1 day; ○, 2 days; ▲, 7 days.

RESULTS AND DISCUSSION

Drug Storage Samples—Except for some loss of excipient crystallinity in 4-week storage samples, no significant changes were seen in the excipients when used for tartaric acid, ascorbic acid, phenyl salicylate, NH_4Cl , NaHCO_3 , and As_2O_3 . The excipients behaved similarly with aminophylline except in the case of dextrose where an appreciable change in crystallinity was noted.

Assay values for the drug actives initially and after 12 weeks storage at 40° are shown in Table I. Changes in drug content noted with aminophylline, phenyl salicylate, tartaric acid, sodium bicarbonate, and ammonium chloride all represented normal experimental error. As_2O_3 , measured by IR analysis, showed marked decomposition in every excipient except mannitol, in some cases before the initial samples could be analyzed. Capsules containing ascorbic acid as the drug with lactose, mannitol, and sucrose showed changes in drug content over the 3-month storage period, within expected experimental variation. A large variation (+9.7% relative) in the capsules containing dextrose and ascorbic acid suggests a definite reaction between these two compounds during storage.

Definite physical changes were noted in the stored capsules. At 5° the capsules containing dextrose and aminophylline developed a yellow cast after 1-week exposure. At 25°, capsules from the same lot were dark in color while capsules containing ascorbic acid and lactose became pink after 4 weeks. The mixture of ascorbic acid and sucrose developed a pink color after 5 weeks. At 40°, the aminophylline-dextrose powder was very dark and the ascorbic acid-

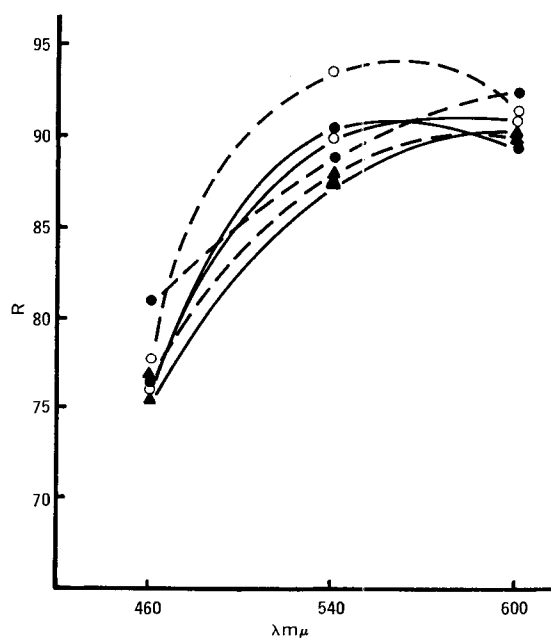


Figure 2.—45°, 0° reflectance of oxytetracycline HCl (60 mg.) and mannitol (2.0 g.). Key: Nonaqueous equilibrated sample, ---; control (physically mixed components), ---; ●, 1 day; ○, 2 days; ▲, 7 days.

Table II—Reflectance Measurements of Nonaqueous Equilibrated Samples of Excipients and Oxytetracycline Hydrochloride

$\lambda, m\mu$		Mannitol	Control	Lactose	Control	Sucrose	Control	Dextrose	Control	Mg Tri-silicate	Control
460	1	81.0	76.8	78.4	78.9	71.0	66.3	61.4	60.4	63.6	85.4
	2	77.9	76.3	76.7	77.6	69.2	66.1	62.3	59.5	58.4	86.8
	7	76.7	75.9	74.7	78.7	68.6	67.3	62.8	59.5	56.2	87.9
	SD	1.21 (1.54%)	0.32 (0.41%)	1.31 (1.71%)	0.30 (0.37%)	0.57 (0.83%)	0.46 (0.68%)	0.50 (0.81%)	0.37 (0.61%)	2.69 (4.5%)	0.89 (1.02%)
540	1	88.7	90.1	91.3	91.9	85.7	84.2	84.1	82.1	75.3	92.4
	2	93.5	90.1	91.4	91.6	82.3	81.5	82.1	82.5	68.4	91.9
	7	87.7	87.5	88.8	90.4	83.4	82.8	81.7	80.6	66.0	93.5
	SD	2.19 (2.40%)	1.06 (1.19%)	1.04 (1.15%)	0.56 (0.61%)	1.23 (1.46%)	0.96 (1.15%)	0.91 (1.1%)	0.69 (0.84%)	3.41 (4.8%)	0.58 (0.62%)
600	1	92.3	91.1	91.3	93.0	87.4	85.7	85.1	86.6	81.5	93.3
	2	91.5	91.1	92.1	92.5	86.2	86.1	87.0	85.9	74.7	94.6
	7	90.2	90.4	90.9	92.5	85.0	85.8	85.4	84.2	70.0	94.4
	SD	0.75 (0.82%)	0.29 (0.31%)	0.43 (0.47%)	0.21 (0.22%)	0.72 (0.84%)	0.15 (0.17%)	0.72 (0.84%)	0.87 (1.01%)	4.09 (5.4%)	0.50 (0.52%)

lactose was pink after 1 week. At the end of 2 weeks the ascorbic acid-sucrose capsules were pink. The ascorbic acid-dextrose mixture developed a pink cast by the end of 5 weeks. No physical changes were noted in capsules containing mannitol with any of the compounds tested.

Chemisorptive Properties—Lach (4) has demonstrated the application of reflectance to determination of adsorption between oxytetracycline hydrochloride and magnesium trisilicate. Physical evidence of the interaction was also readily noted in visually perceptible color changes. As the color change progresses, indicative of interaction, decreased reflectance is observed.

Both aqueous and nonaqueous equilibrated samples of oxytetracycline hydrochloride and magnesium trisilicate were observed for decreased reflectance. Samples involved directly with the study were nonaqueous in nature due to the solubility of the excipients in-

cluded. Measurements of reflectance for nonaqueous equilibrated samples of magnesium trisilicate and oxytetracycline hydrochloride stored at 25°, 50% R.H. at 1, 2, and 7 days demonstrate not only the immediate chemisorption noted by Lach but the progressive reaction which occurs between the two materials (Fig. 1).

None of the four excipients studied showed interaction with oxytetracycline hydrochloride. When compared to Fig. 1 the clustering of data in Fig. 2 demonstrates the absence of the chemisorption process between the drug and mannitol. Data collected for dextrose, sucrose, and lactose are comparable to that shown for mannitol. Table II contains the reflectance measurements.

Lubricant Interaction—Darkening of dosage forms containing lactose and alkaline compounds has been reported (11) and is the underlying chemical reaction responsible for darkening of lactose in the presence of calcium stearate. This interaction was verified by the authors' testing. Tablets containing 100% lactose or an equal parts blend of mannitol and either β -lactose or spray-dried lactose showed discoloration as early as two months, stored at 25 and 40°. No color changes were noted in tablets containing lactose lubricated with magnesium stearate.

Tablets of mannitol, lubricated with either stearate, retained their original appearance.

Tablet Dissolution—Parrott *et al.* (9) demonstrated that when neutral nonionic organic compounds were employed as additives the dissolution rate of benzoic acid tablets was linearly dependent upon the solubility of benzoic acid in the particular solvent system. This effect was studied with mannitol, lactose, dextrose and sucrose in water.

Tablets prepared from equal parts blends of the excipients and benzoic acid were found to disintegrate readily rendering them useless in the procedure. Tablets of benzoic acid in solutions of the excipients followed expected dissolution patterns as predicted by Parrott's data (9).

The data collected was evaluated by use of the Hixson and Crowell derived relationship of the Noyes-Whitney law:

$$-\frac{dW}{dt} = 3KS = 3Kaw^{2/3}$$

where $3K$ represents the dissolution rate per unit of surface (g./hr./cm.²), S is the surface at time t , W is the weight at time t ; and a is the constant

$$\frac{\alpha SV}{p^{2/3}} = \frac{6.0}{p^{2/3}}$$

Table III—Determination of Dissolution Rate by Weight Method

Excipient	$p^{2/3}$	Ka	$a = 6.0/p^{2/3}$	K	$3K$
Control	1.166	0.0764	5.15	0.0148	0.0444
Sucrose	1.160	0.0808	5.17	0.0157	0.0471
Lactose	1.173	0.0813	5.12	0.0159	0.0477
Dextrose	1.162	0.0873	5.17	0.0168	0.0504
Mannitol	1.178	0.0890	5.09	0.0174	0.0522

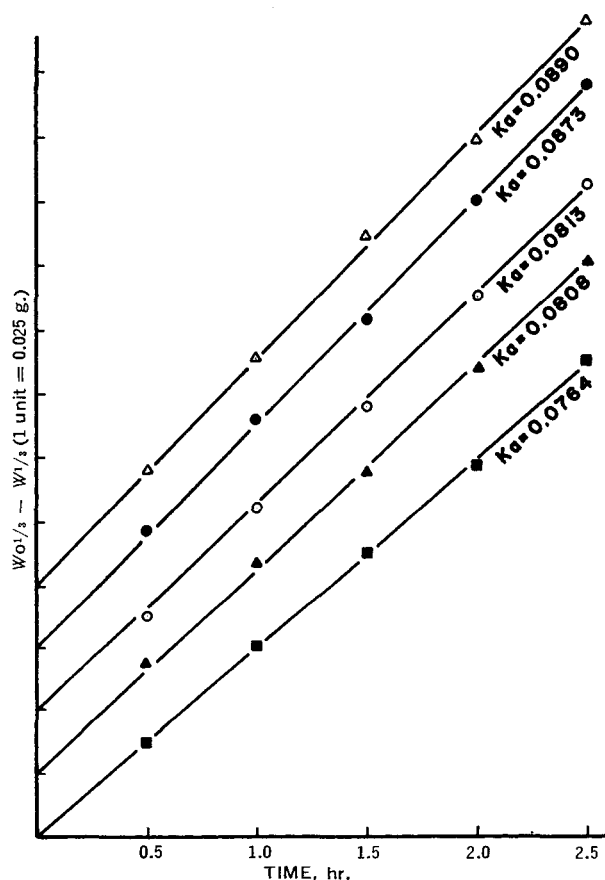


Figure 3—Evaluation of K_a from the slope of $W_0^{1/3} - W^{1/3}$ versus time; benzoic acid tablets in 0.1 M solutions of organic tablet excipients. Key: ■, control (water); ▲, sucrose; ○, lactose; ●, dextrose; △, mannitol.

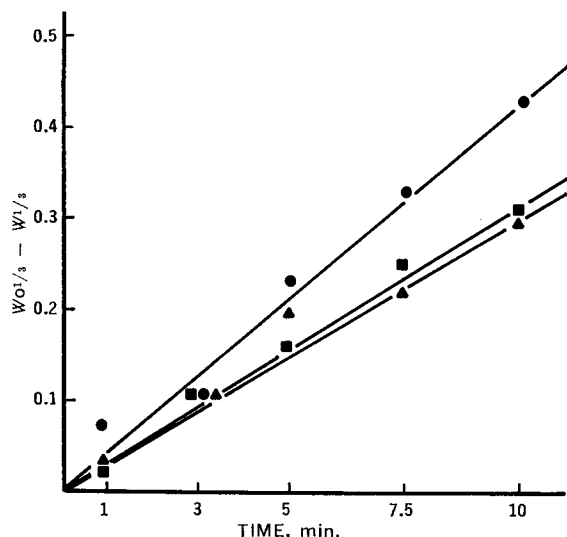


Figure 4—Dissolution data fitted to the extended Hixson-Crowell equation; benzoic acid granules in 0.2 Molar solutions of organic tablet excipients. Key: ■, control (water); ●, dextrose; ▲, sucrose.

$p^{2/3}$ being the cube root of the square of the density of a cylindrical disk. The integrated form, $Kat = W_0^{1/3} - W^{1/3}$ was used to determine the velocity constant for each situation. The values for Ka were obtained as the slope of the line when $W_0^{1/3} - W^{1/3}$ was graphed versus time (Fig. 3). The calculated dissolutions (3K) indicate increased rates with all four excipients (Table III).

Granule Dissolution—The measurement of particulate dissolution rate by the tape method of Goldberg *et al.* (10) assumes the system which would be present in the gastrointestinal tract, *i.e.*, a slowly dissolved active in the presence of a solution of the tablet diluent.

The observed concentrations of benzoic acid at specified time intervals were calculated and a cumulative correction was applied to account for previously removed samples. The dissolution process was then evaluated in a quantitative manner using the Hixson-Crowell equation in the form

$$W_0^{1/3} - W^{1/3} = Kt$$

where K is the product of the intrinsic dissolution rate constant, solubility, density, and shape factors for the drug being tested.

Results obtained with sucrose and dextrose solutions correlate with the tablet dissolution data. The dissolution in 0.2 M sucrose is much like the control while the rate in 0.2 M dextrose is somewhat greater (Fig. 4). The curve for the mannitol solution shows an increase in dissolution rate but one which is not linear. The dissolution in the lactose solution is also nonlinear (Fig. 5). The cube root law does not appear to apply to mannitol and lactose under these conditions.

CONCLUSIONS

Accelerated stability studies with seven representative compounds demonstrate the inertness of mannitol in various mechanisms associated with drug-excipient compatibility. In addition several specific incompatibilities of various inorganic and organic excipients have been determined nonexistent with mannitol. Reflectance measurements of nonaqueous equilibrated mixtures of mannitol, sucrose, lactose or dextrose with oxytetracycline hydrochloride indicate that commonly used organic excipients are not prime candidates for chemisorptive processes. Investigation of the

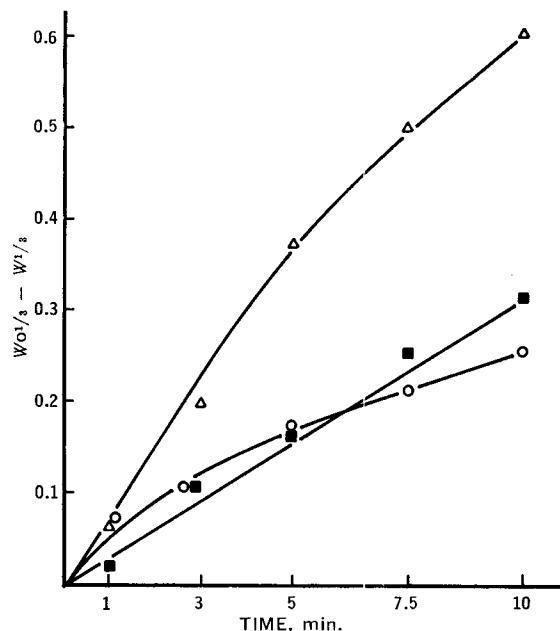


Figure 5—Dissolution data fitted to the extended Hixson-Crowell equation; benzoic acid granules in 0.2 Molar solutions of organic tablet excipients. Key: ■, control (water); ○, lactose; △, mannitol.

dissolution process amplifies the necessity for consideration of the effects of adjuvants on the release of drug actives from tablets and capsules.

REFERENCES

- (1) Pharmaceutical Bulletin LM-20, "Hygroscopicity Comparison Study of Mannitol and Sorbitol as Chewable Tablet Excipients," Atlas Chemical Industries, Inc., Wilmington, Del., August, 1963.
- (2) K. Wai, H. G. DeKay, and G. S. Banker, *J. Pharm. Sci.*, **51**, 1076(1962).
- (3) H. C. Krahnke and W. E. Becker, U. S. pat. 3,033,754, May 8, 1962.
- (4) J. L. Lach and M. Bornstein, *J. Pharm. Sci.*, **54**, 1730(1965).
- (5) R. H. Miller, in "Husa's Pharmaceutical Dispensing," 8th ed., Mack Publishing Co., Easton, Pa., 1966, p. 121.
- (6) *Ibid.*, p. 121.
- (7) J. K. Dale, *ibid.*, p. 647.
- (8) *Ibid.*, p. 634.
- (9) E. L. Parrott, D. E. Wurster, and T. Higuchi, *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 269(1955).
- (10) A. H. Goldberg, M. Gibaldi, J. L. Kanig, and J. Shanker, *J. Pharm. Sci.*, **54**, 1722(1965).
- (11) J. K. Dale, in "Husa's Pharmaceutical Dispensing," 8th ed., Mack Publishing Co., Easton, Pa., 1966, p. 669.

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