Effect of Water Vapor Pressure on Moisture Sorption and the Stability of Aspirin and Ascorbic Acid in Tablet Matrices

By SUMTUNG LEE, H. GEORGE DEKAY, and GILBERT S. BANKER

A study of the effects of temperature and humidity conditions on the stability of aspirin and ascorbic acid in various solid matrices was conducted. Among the diluents studied, cellulose and calcium sulfate were found to confer maximum stability on formulations of aspirin and ascorbic acid. The tablet matrices were found to sorb water according to Van der Waal's adsorption mechanisms. The stability of the drugs was found to vary according to an interrelationship between tablet hardness and the moisture sorption of the compressed matrix. Two parameters, (*a*) the stability ratio or the ratio of the residual drug concentration of the tableted drugs in closed containers to the residual drug concentration of exposed tablet samples and (*b*) the moisture uptake of the dosage units in closed containers, were established to evaluate the packaging methods. Cellophane or aluminum foil strip packaging single dosage containers were found to be superior to well-closed glass or plastic containers as moisture barriers under the intermediate-to-high water vapor pressure conditions studied.

IT IS WELL KNOWN that most hydrolytic processes occur by moisture catalyzed reactions. Yet published investigations of drug deterioration, as affected by the moisture sorption by solid dosage forms, are quite limited. In particular, the relationships between the amount of water vapor sorbed by compressed tablets according to formulation, tablet hardness, or other properties and the degree of drug decomposition are largely unreported. In addition, mechanisms of moisture sorption by solid compressed dosage forms have not been widely studied and exploited to prepare uncoated tableted products of maximum stability, at least according to published reports. The moisture sorption of certain pharmaceutical powders under different storage conditions has been studied using adsorption isotherms (1). Attempts have been made to relate the water vapor barrier characteristics of certain packaging materials to the adsorption isotherms of the packaging materials (2). From a study of water vapor permeability of cellophane, it was concluded that when a constant vapor pressure was maintained on the low-pressure side of the membrane, the mass flow rate was independent of the vapor pressure used (3). Kovacs (4) reported that the rate of absorption of water vapor by cellulose films followed Fick's law of diffusion and that the absorption from the liquid state was greater than that from the vapor state. In a study of moisture penetration through closures, Blaug *et al.* (5) revealed that the cap liner was just as important as the cap itself for effective moisture proof sealing. They also reported the effect of reduced moisture contents in tablet formulations and indicated that tablets prepared with anhydrous calcium sulfate as the filler in place of lactose exhibited the best color stability (6). Selected water-sensitive drugs such as ascorbic acid are known to undergo extensive deterioration in the presence of even trace amounts of moisture (7). Leeson and Mattocks (8) have investigated the effects of humidity and temperature on aspirin stability in the solid state, and postulate that a monomolecular layer of water is adsorbed on the aspirin particles, which then produces drug decomposition as though the drug is in solution. The object of this project was to study the mechanism and extent of water sorption by compressed solid dosage forms according to the various humidity and temperature (water vapor pressure) conditions and to observe the effect of tablet formulation and properties on water sorption, as well as the effect of all of these variables on the stability of two commonly used moisture sensitive drugs.

Received April 30, 1965, from the School of Pharmacy, Purdue University, Lafayette, Ind.
Accepted for publication May 26, 1965.

THEORETICAL BACKGROUND

The relationship between the extent of adsorption and the pressure of a gas at constant temperature, according to Langmuir's adsorption theory (9), can be expressed as

$$a = \frac{k_1 p}{k_2 p + 1} \qquad \text{(Eq. 1)}$$

Rearranging and putting $a = x/m$,

$$p/\frac{x}{m} = \frac{1}{k_1} + \frac{k_2 p}{k_1} \qquad \text{(Eq. 2)}$$

where p is the vapor pressure, $k_1 k_2$ the proportionality constants, and x/m the increase in moisture per gram of adsorbent. Since the vapor pressure used in this system is low (25–95 mm. Hg), Eq. 2

TABLE I.—STORAGE CONDITIONS

Temp., °C.	Relative Humidity, % 0	45	80	100
30°	Exsiccated calcium sulfate	...	Sat. NaCl soln.	...
37°	Exsiccated calcium sulfate	Sat. soln. $MgCl_2 \cdot 6H_2O$	Sat. NaCl soln.	Dist. water
50°	Exsiccated calcium sulfate	Sat. soln. $MgCl_2 \cdot 6H_2O$	Sat. NaCl soln.	Dist. water

can be reduced to the following by neglecting k_2p in comparison with unity in the denominator of Eq. 1 and Eq. 2 becomes

$$x/m = k_1p \qquad \text{(Eq. 3)}$$

Thus, from Eq. 3, the extent of adsorption is directly proportional to the vapor pressure of the gas. A graph of x/m *versus* p gives a straight line.

EXPERIMENTAL

Assay of Ascorbic Acid.—The U.S.P. XVI method was used to determine the ascorbic acid concentration in the various samples (10).

Assay of Aspirin.—The acetylsalicylic acid concentration of the aspirin tablet samples was determined according to the method of McBay and Tinker (11). The aspirin tablets were reduced to a fine powder, and a portion of the powder was accurately weighed and dissolved in analytical grade chloroform.[1] The spectral readings were taken at 277 and 307 mμ with a Beckman DU spectrophotometer.

Preparation of Tablet Samples

General Procedure.—Aspirin and ascorbic acid were separately compressed with diluents of amylose, cellulose,[2] calcium sulfate, spray-dried lactose, and mannitol–starch (10:1). The diluents were either pregranulated for mixture with the drugs or were double dry compressed with the drugs. In addition to being dry granulated, the 10:1 mannitol–starch mixture was also wet granulated using 10% PVP[3] in isopropanol.

The wet granulated product, after drying and sizing was then mixed with drug and running powder and was compressed. Starch (10%) and talc (5%) were used as disintegrants and lubricants. All formulations were prepared to contain 325 mg. of drug in each 500-mg. tablet, with the exception of lactose and mannitol–starch granulated with PVP. The amount of drug to granulation per tablet for these two formulations was 100:400 and 325:325 mg. The calcium sulfate diluent granulation was prepared according to the method of Perlman (12). The powder was granulated with 10% starch paste and was passed through a (No. 5 drilled) screen with a Fitzpatrick comminutor, running at medium speed with impact forward. The granulation was then sized through a No. 30 mesh.

[1] J. T. Baker Chemical Co., Phillipsburg, N. J., lot No. 22162.

[2] Purified microcrystalline cellulose. Marketed as Avicel by the American Viscose Corp., Marcus Hook, Pa.

[3] Plasdone K-30, Antara Chemical Co., Division of General Aniline and Film, New York, N. Y.

Humidity and Storage Conditions

The various humidity conditions were established using selected salt solutions in an enclosed chamber at a constant temperature (13). The storage conditions recorded in Table I were obtained.

Stabilization of water vapor pressure within the sealed humidity chambers was obtained within 7 days. Variations in hygrometric readings were ±2%, and variations in oven temperatures were ±1°. To convert the per cent relative humidity to vapor pressure, the relative humidity is multiplied by the vapor pressure of pure water at that same temperature. The water vapor pressures used in this study are shown in Table II.

Moisture Determination

The moisture sorption by various tablet matrices of ascorbic acid and aspirin was determined by subjecting the samples to different conditions of temperature and humidity (Table II). The tablets, immediately after manufacture, were placed in a vacuum oven for 6 hr. at 40° at a pressure of 10–15 mm. Hg to remove moisture sorbed during granulation or compression. Initially weighed, the tablet samples were then exposed to the given storage conditions for periods of 1 and 2 months. Moisture uptake by the tablet samples was determined gravimetrically.

RESULTS AND DISCUSSION

Moisture Adsorption Studies

From the results of the moisture uptake data (Table III) graphs of vapor pressure *versus* per cent moisture adsorbed by the various tablet formulas were prepared, producing the types of adsorption isotherms shown in Figs. 1 to 4. Most adsorptions were found to agree with a Van der Waal's type of adsorption (Table V).

TABLE II.—PER CENT RELATIVE HUMIDITY–VAPOR PRESSURE RELATIONSHIP

Temp., °C.	Vapor Pressure of Pure Water,[a] mm. Hg	R.H., %	Equivalent Water Vapor Pressure, mm. Hg
30	31.82	80	25.6
37	47.07	45	21.2
		80	37.7
		100	47.1
50	92.51	45	41.6
		80	74.0
		100	92.5

[a] Washburn, E. W., "International Critical Tables," vol. I, McGraw-Hill Book Co., Inc., New York, N. Y., 1926, p. 67.

TABLE III.—PER CENT MOISTURE UPTAKE IN ASPIRIN AND ASCORBIC ACID TABLET FORMULATIONS DIRECTLY EXPOSED TO VARIOUS WATER VAPOR PRESSURE CONDITIONS (50°) FOR 60 DAYS

Drug	Diluent	Water Vapor Pressure, mm. Hg: 0	41.6	74.0	92.5
Ascorbic acid	Calcium sulfate	−3.205	0.393	1.23	[a]
	Cellulose	−2.274	1.028	4.219	[a]
	Amylose	−1.96	1.51	3.404	[a]
	Lactose	−1.21	1.013	2.05	1.93
	Mannitol–starch	−1.485	0.765	1.937	[a]
	Mannitol–starch PVP	−0.773	0.434	1.57	9.688
Aspirin	Calcium sulfate	−0.773	...	1.14	[a]
	Cellulose	−1.46	1.28	2.88	6.28
	Amylose	−0.481	−0.807	2.693	4.98
	Lactose	−1.96	−0.317	1.088	8.581
	Mannitol–starch	−0.712	−0.374	0.863	11.26

[a] No data are given for the samples stored at 92.5 mm. Hg (100% relative humidity at 50°) in which moisture condensation was observed in the open containers causing the tablet samples to be wetted by direct water contact.

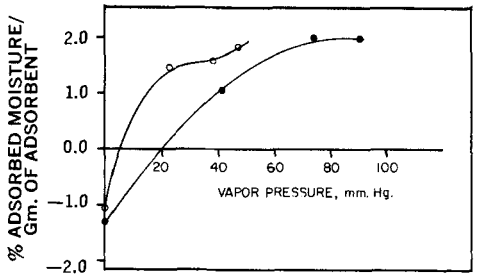

Fig. 1.—Adsorption isotherm curves for ascorbic acid in lactose. Key: O, type V (37°); ●, type I (50°).

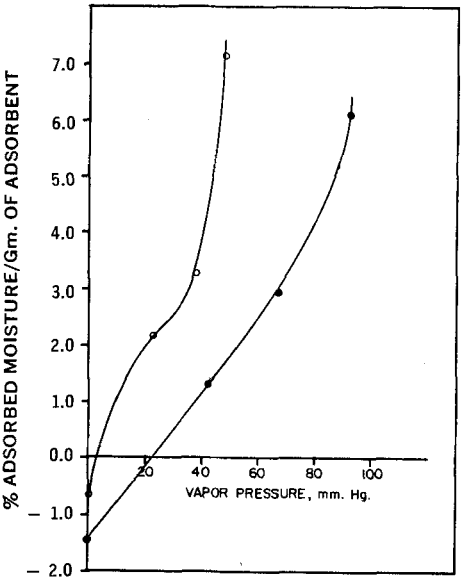

Fig. 2.—Adsorption isotherm curves for aspirin in cellulose. Key: O, type IV (37°); ●, type III (50°).

The efficiency of a screw-cap glass container[4] and a snap-top plastic container[5] as moisture

[4] This is a cylindrical amber glass capsule bottle (2–3 dram) with plastic cap, which has a cardboard liner, one surface of which is coated with plastic. Supplied by Armstrong Co., Inc., Lancaster, Pa.

[5] This is a cylindrical plastic bottle (approximately 120 ml.) with snap-top closure. Supplied by Lermer Co., Garwood, N. J.

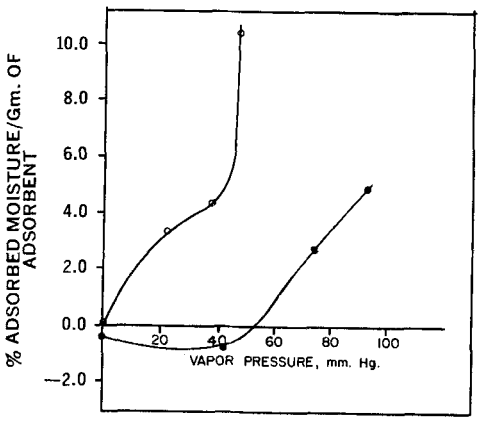

Fig. 3.—Adsorption isotherm curves for aspirin in amylose. Key: O, type IV (37°); ●, type I (50°).

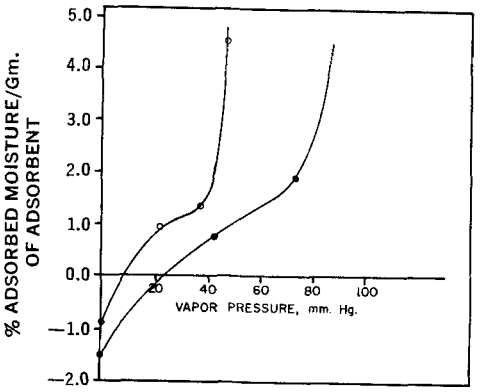

Fig. 4.—Adsorption isotherm curves for ascorbic acid in mannitol–starch. Type II. Key: O, 37°; ●, 50°.

TABLE IV.—MOISTURE UPTAKE OF ASCORBIC ACID–CALCIUM SULFATE TABLETS IN CLOSED AND OPEN CONTAINERS EXPOSED TO DIFFERENT CONDITIONS FOR 30 DAYS

Packing Method	Storage Conditions: 0% R.H. 30° 0 mm. Hg	45% R.H. 21.2 mm. Hg	80% R.H. 74 mm. Hg	100% R.H. 92.5 mm. Hg
Exposed container	0.49	0.896	0.805	15-20[a]
Closed screw-cap glass container	−1.174	0.135	1.120	6.76
Closed plastic container	−0.350	0.329	0.614	12.12

[a] This figure is an approximation due to moisture condensation within the bottle at saturation humidity conditions.

TABLE V.—TYPES OF VAN DER WAAL'S ADSORPTION DEMONSTRATED BY THE VARIOUS DRUG–DILUENT TABLET SYSTEMS

Type I	Type III	Types IV or II[a]	Type V
Ascorbic acid	Amylose (37 and 50)	Mannitol–starch with PVP (50°)	Mannitol–starch with PVP (37°)	...
...	Lactose (50°)	...	Mannitol–starch (37° and 50°)
...	Cellulose	...	Lactose (37°)
Aspirin	...	Cellulose (50°)	Amylose (37°)	Amylose (50°)
...	...	...	Cellulose (37°)	...
...	...	...	Lactose (37° and 50°)	...

[a] The points obtained for the isotherm curves were insufficient to distinguish the two types of adsorption.

TABLE VI.—MOISTURE SORPTION, TABLET HARDNESS, AND THE DRUG STABILITY RELATIONSHIP

Diluents	Moisture Sorption,[a] %	Av. Tablet Hardness,[b] lb.	Residual Concn. of Ascorbic Acid at 50°C. after 60 Days' Storage 0% R.H.	45% R.H.	80% R.H.	100% R.H.
Calcium sulfate	0.061	6.00	93.58	95.97	95.38	35.90
Cellulose	3.30	20.75	100.37	99.22	96.88	57.57
Amylose	5.62	11.39	93.74	90.63	85.14	50.36
Lactose	49.10	3.10	89.84	89.22	81.02	5.11
Mannitol–starch	0.023	5.32	89.72	91.15	84.09	36.35
Mannitol–starch (PVP)	0.082	7.05	88.42	85.12	69.80	13.46
			Residual Concn. of Aspirin at 50°C. after 60 Days' Storage			
Calcium sulfate	0.061	14.07	95.56	89.39	90.29	90.79
Cellulose	3.30	14.00	93.29	82.62	88.59	85.54
Amylose	5.62	6.96	79.44	73.90	63.46	55.27
Lactose	49.10	22.77	69.11	83.75	85.99	82.67
Mannitol–starch	0.023	11.37	90.66	90.81	84.12	79.32

[a] Moisture sorption of powdered tablet diluents after 40 hr. of exposure to 80% relative humidity at 37°C. Moisture sorption by compressed tablets is shown in Table III. [b] Average tablet hardness was computed from 20 readings using the Pfizer hardness tester. The tablets were from samples stored in closed bottles at room temperature for 6 months.

TABLE VII.—EVALUATION OF SCREW-CAP GLASS CONTAINERS *Versus* SNAP-TOP PLASTIC CONTAINERS FOR PROTECTION OF MOISTURE SENSITIVE DRUGS UNDER VARIOUS STORAGE CONDITIONS OF TEMPERATURE AND HUMIDITY ACCORDING TO RESIDUAL DRUG CONCENTRATION AND STABILITY RATIO

	Residual Concn. of Ascorbic Acid After Storage							
	30°C.		37°C.		50°C.			
	30 Days 0%	60 Days 0%	30 Days 45%	60 Days 45%	30 Days 80%	60 Days 80%	30 Days 100%	60 Days 100%
Closed Screw-Cap Containers initial concn. 333.65 mg.	86.84%	46.98%	85.07%	46.06%	88.43%	83.28%	46.26%	37.72%
stability ratio[a]	0.940	0.538	0.880	0.495	0.891	1.310	0.485	1.051
Closed Plastic Containers initial concn. 333.65 mg.	86.16%	46.12%	86.51%	45.94%	88.74%	75.67%	42.30%	14.95%
stability ratio	0.932	0.528	0.865	0.494	0.894	1.190	0.443	0.416
Control, Container Exposed initial concn. 333.65 mg.	92.40%	87.40%	98.34%	93.02%	99.30%	63.57%	95.38%	35.90%

[a] Ratio of per cent residual concentration of ascorbic acid in the closed container to that in the open container. A ratio of more than one would mean that the residual drug concentration in the closed container was greater than in the open container, and the closed container has afforded protection to the drug. The higher the ratio, the greater the protection afforded by the closed container.

barriers was studied by placing tablets in the containers, closing them tightly, and storing the samples for 1 and 2 months. The moisture increase or decrease for a tablet formulation stored in the two types of containers is given in Table IV, which shows clearly that neither the screw cap nor snap-on was completely effective as a moisture barrier, even though they were initially tightly closed. Failure of the closures as moisture barriers must have been due to moisture penetration through or around the closure. Under actual shelf storage conditions, in which some temperature cycling occurs, even more moisture absorption might occur in supposedly closed containers due to expansion and contraction of the container and closure.

Table V indicates the type of adsorption found for each formulation. The figures in parentheses indicate the temperature of the storage compartment at which the type adsorption indicated was found. Type I involves a monomolecular layer of adsorption. Types II and III involve a multilayer adsorption (9). When condensation of vapor

TABLE VIII.—EVALUATION OF CELLOPHANE AND ALUMINUM FOIL STRIP PACKAGING MATERIALS FOR PROTECTION OF MOISTURE SENSITIVE DRUGS UNDER VARIOUS STORAGE CONDITIONS OF TEMPERATURE AND HUMIDITY

Packaging Methods	Stability Ratio[a]															
	30°C.						37°C.				50°C.					
	30 Days	60 Days	30 Days				60 Days				30 Days				60 Days	
	80%	80%	0%RH	45%RH	80%RH	100%RH	0%RH	45%RH	80%RH	100%RH	0%RH	45%RH	80%RH	100%RH	0%RH	45%RH	80%RH	100%RH
Cellophane																		
Ascorbic acid tablets with $CaSO_4$ as diluent	0.85	0.96	0.88	0.93	0.93	1.07	0.97	1.03	0.99	1.46	0.97	0.92	0.88	[b]	1.02	[b]	0.98	2.66
Ascorbic acid tablets with mannitol–starch as diluent	0.99	1.14	0.99	1.01	0.97	1.12	1.09	1.09	1.04	1.08	1.08	1.03	1.06	1.28	1.09	1.06	1.13	2.57
Aluminum Foil																		
Ascorbic acid tablet with $CaSO_4$ as diluent	0.86	0.92	0.88	0.88	0.91	1.08	0.97	1.01	0.93	1.42	0.97	0.92	0.88	[b]	1.04	[b]	0.96	2.63
Ascorbic acid tablets with mannitol–starch as diluent	0.91	1.13	1.00	1.01	0.96	1.11	1.07	1.05	1.08	1.05	1.00	1.05	1.06	1.27	1.10	1.04	1.11	2.05

[a] Ratio of residual concentration of ascorbic acid in packed foils to that of exposed samples. [b] At 50°C., the seals of the cellophane and aluminum foil failed in these cases and the data were omitted

occurs in the small pores and capillaries of the adsorbent, types IV or V adsorption is produced. Adsorption isotherms for ascorbic acid in cellulose and amylose and lactose at 50° were found to follow Langmuir's adsorption theory. All remaining absorbents showed Van der Waal's adsorption isotherms of one type or another.

Moisture Sorption, Tablet Hardness, and the Drug Stability Relationship

The results as tabulated in Table VI demonstrate that there is a definite relationship between moisture sorption, tablet hardness, and drug stability. The ascorbic acid–lactose formulation showed the highest moisture sorption and the greatest deterioration at a tablet hardness of 3.10 lb. which was the softest tablet compressed. Other examples of the relationship between tablet hardness and moisture sorption of the diluents and drug stability are apparent. Calcium sulfate which had a lower moisture sorption than cellulose, was slightly inferior as a diluent for ascorbic acid when the cellulose tablets were more than three times as hard as the calcium sulfate tablets. However, the aspirin tablets with cellulose and calcium sulfate were equal in hardness, and the calcium sulfate diluent produced more stable tablets than cellulose in every case. In all cases but one, the diluents with the lowest moisture sorption, when compressed into hard tablets with the two drugs, produced tablets of greater stability. The exception was ascorbic acid in mannitol–starch with PVP where deterioration was considerable, even though the tablet hardness was 7.05 lb. This phenomenon may be due to the hygroscopicity of PVP, producing a tablet having an increased affinity for moisture (Table III) with consequent greater drug decomposition.

Thus, it may be generalized that the stability of a drug in a particular formulation is influenced to a great extent by the interaction of two factors, the moisture adsorptive capacity of the diluent in the tablet matrix (Table III) at the particular hardness of the tablet matrix.

Evaluation of Packaging Methods

Screw-Cap Bottles Versus Plastic Containers.—The purpose in evaluating a glass and a plastic container was to observe whether differences in container type affected resistance to moisture penetration and to consider the feasibility of establishing standards for containers used for drug storage. The U.S.P. monographs fail to establish any requirements for the use of containers for finished pharmaceutical packaging, the only stipulation being, "preserved in tight containers, protected from light, etc."

Two parameters were established to evaluate the efficiency of the two types of containers: (*a*) moisture uptake in closed containers (Table IV) and (*b*) the stability ratio. The stability ratio is defined as the ratio of the per cent of residual drug concentration of the samples stored in a closed container to that stored in open containers under identical storage conditions. When the ratio is unity, no protection is offered by the container as compared to exposed containers. When the ratio is less than 1, the closed container is providing a less satisfactory environment for drug storage than an open container; and when the ratio is greater

than unity, the container is providing positive drug stability.

A case in which a closed container provides less product protection than an open container might be in the event that moisture condensation is promoted in the closed container. Higher water vapor pressures may also be established in closed containers at elevated temperatures, depending on the initial moisture content of the dosage form. According to Table VII, at low temperature and humidity conditions, no real differences were shown between closed plastic and screw-cap glass containers and open containers with exposed drug. There was less than 2% difference in the stability ratios between the closed glass and plastic containers at water vapor pressures of 21.2 mm. Hg or less (45% R.H. and 37°) (Table VII). However, under higher water vapor pressures the protection offered by closed screw-cap and plastic containers became evident. At the maximum water vapor pressure of 92.5 mm. Hg (100% R.H. and 50°), the glass container had a ratio of over twice that of the plastic container (1.051 *versus* 0.416), showing clearly that the screw-cap glass container offered better protection than the snap-top plastic container under extreme conditions.

Aluminum Foil Versus Cellophane Strips.—Table VIII shows the protection afforded ascorbic acid tablets in two different diluents by unit packaging the samples in cellophane[6] and aluminum foil[7] and subjecting the samples to the same general temperature and humidity conditions used for the samples stored in glass and plastic containers (Table VII). In the calcium sulfate formulation, no real differences in the degree of protection between cellophane and aluminum foil were apparent at any of the storage conditions. Likewise, there were no real differences in the stability of ascorbic acid formulations except at the maximum stress storage condition of relative humidity and 50° for 60 days' storage period, in which case the stability ratio of cellophane was 25% better than aluminum foil. Thus, the two strip packaging materials offered good protection to the ascorbic acid tablets in a moisture stable diluent (calcium sulfate) as well as in a less moisture stable diluent (mannitol–starch), except under the most extreme storage conditions.

In comparing cellophane and aluminum foil strip packaging materials to screw-cap glass bottles and plastic vials as containers for moisture sensitive drugs under storage conditions of high humidity, the single unit dosage strip packing approach was found to afford superior product protection to the glass or plastic containers.

[6] 300 gauge cellophane coated with 10 mil. polyethene, Wrap-Ade Machine Co., Inc., Clifton, N. J.

[7] 0.1 mil. aluminum foil coated with 10 mil. polyethylene, H. P. Smith Paper Co., Chicago, Ill. The samples were strip packaged by the courtesy of Rowell Laboratories Inc., Baudette, Minn.

SUMMARY AND CONCLUSIONS

1. The applicability of expressing moisture adsorption of compressed tablets according to Van der Waal's adsorption isotherms is demonstrated. The type of the adsorption isotherm and hence the probable mechanism of moisture adsorption was found to vary with the various diluents studied, as well as with the temperature of the humidity chamber (and hence the water vapor pressure) for some of the drug diluent systems.

2. The moisture adsorptive capacity of each compressed tablet formulation affected the stability of the two drugs to a great extent, and was directly related to an interrelationship of moisture sorption and tablet hardness. (The harder the tablet, the less moisture it sorbed and the more stable the drug.) Thus, diluents which have low levels of moisture sorption and which are most readily compressed into hard, nonporous tablets apparently produce the best tablet matrices for moisture sensitive drugs.

3. Of the six diluents systems studied, calcium sulfate and cellulose produced the most stable tablets of aspirin and ascorbic acid.

4. Under stress storage conditions, screw-cap glass bottles proved to be a better moisture proof container than a snap-top plastic vial. Under low humidity and temperature conditions, no substantial difference in the protective properties of the two containers was demonstrated.

5. Cellophane and aluminum foil strip packaging materials were about equally effective as single unit protective containers for the two drugs in tablet form, and they were much more effective than the glass or plastic containers.

6. The stability ratio or the ratio of residual drug concentration in closed containers of packages to the residual concentration of exposed samples is suggested as a means of setting standards for the use of containers for pharmaceutical packaging.

REFERENCES

(1) Strickland, W. A., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 657(1958).

(2) Heiss, R., *Chem. Ing. Tech.*, **28**, 763(1956); through *Chem. Abstr.*, **51**, 3873*c*(1957).

(3) Archer, W. L., and Mason, S. G., *Can. J. Chem.*, **37**, 1655(1959); through *Chem. Abstr.*, **54**, 7141*e*(1960).

(4) Kovacs, A., *J. Chim. Phys.*, **45**, 258(1948); through *Chem. Abstr.*, **44**, 10457(1950).

(5) Blaug, S. M., Hickman, E., and Lach, J. L., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 54(1958).

(6) Blaug, S. M., Chakravarty, D., and Lach, J. L., *Drug Std.*, **26**, 199(1958).

(7) Vega, de la, F. A., *Galenica Acta Madrid*, **3**, 297 (1950); Blaugh, S. M., Chakravarty, D., and Lach, J. L., *Drug Std.*, **26**, 199(1958).

(8) Leeson, L. J., and Mattocks, A. M., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 329(1958).

(9) Glasstone, S., "Textbook of Physical Chemistry," 2nd ed., D. Van Nostrand Co., Inc., Princeton, N. J., 1946, p. 1202.

(10) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 67.

(11) Tinker, R. B., and McBay, A. J., *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 315(1954).

(12) Perlman, K. P., *Drug Cosmetic Ind.*, **94**, 660(1964).

(13) Washburn, E. W., "International Critical Tables," vol. I, McGraw-Hill Book Co., Inc., New York, N. Y. 1926, p. 67.