Pharmaceutical Applications of the Concept of Equilibrium Moisture Contents

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Equilibrium moisture content (EMC) data have been obtained for two representative tablet granulations. These data are useful in analysis of drying operations and particularly in predicting final moisture contents obtainable in "dried" products. The effects of drying variables, such as relative humidity and inlet air temperature, on product moisture levels are established. Similarly, the influence of storage conditions on moisture gain is predictable. Data obtained from drying studies with a lactose placebo granulation are used to illustrate the relationship between equilibrium moisture content values and minimum required drying times. The importance and economic advantages obtainable by review of this type data before establishment of moisture specifications for dried materials is illustrated. In addition, equilibrium moisture content values for several tablet fillers, disintegrants, and other pharmaceuticals are presented. Based on these preliminary studies, the EMC concept may have useful applications in the design of moisture stable products.

INTRODUCTION

ADJUSTMENT AND CONTROL of moisture levels is of general importance in the development and manufacture of superior pharmaceutical products. The difficulties encountered in establishing proper levels of moisture can be broadly divided into two categories. The first category includes problems connected with processing and handling operations, such as drying and bulk powder filling, etc. Those problems which relate more directly to formulation design, such as the stabilization of moisture sensitive materials, are included in the second category. Unfortunately, proper attention has not been devoted to either of these problem areas in the pharmaceutical literature.

Scattered reports are available which deal with the effects of moisture on specific pharmaceuticals. Leeson and Mattocks (1) have examined the stability of aspirin stored under elevated humidity conditions. These workers present kinetic interpretations of the data and show that decomposition is dependent on the aqueous vapor pressure and storage temperature. The stability of ascorbic acid at high relative humidities has been studied by de la Vega (2), while Blaug, *et al.* (3), discussed methods of preparing ascorbic acid tablets with reduced moisture sensitivity. The adverse influence of moisture on the flowability of pharmaceutical powders also has been demonstrated (4). The report of Craik and Miller on this subject is noteworthy (5). Attention has been paid also to the moisture vapor transmission characteristics of packaging components used for pharmaceuticals (6). A generalized approach to the problems of moisture control—capable of leading to the improvement of formulation techniques, processing operations, and storage procedures—has not been developed yet.

The present study was undertaken to explore the potential usefulness of the equilibrium moisture content concept as applied to materials of pharmaceutical interest. This concept serves as a basic tool in the design of drying, air conditioning, and humidification operations (7) and would seem to represent a correct starting point for the study of moisture relationships in pharmaceutical products.

EQUILIBRIUM MOISTURE CONTENT

If a solid is exposed to a continual supply of air at constant temperature and relative humidity, the solid will either lose moisture by evaporation or gain moisture until an equilibrium condition is obtained. The moisture present in the solid at this point is defined as the equilibrium moisture content (EMC) under the given exposure conditions. Rigorous thermodynamic treatments of the equilibrium state have appeared in the literature (8, 9). For all cases of practical importance, equilibrium will be established when the vapor pressure exerted by the moisture in the solid equals the partial pressure of the water vapor in the air. A new equilibrium moisture content results with a change in the partial pressure of water in the air. It is customary to

Received March 26, 1962, from the Department of Pharmaceutical Technology, Warner-Lambert Research Institute, Warner-Lambert Pharmaceutical Co., Morris Plains, N.J.
Accepted for publication April 18, 1963.
Presented to Scientific Section, A.PH.A., Las Vegas meeting, March 1962.

express these partial pressures in terms of relative humidities (R.H.) and to express the moisture contents of the solid on a dry basis. The collection of such EMC–relative humidity data can be used to prepare an entire moisture equilibrium curve for the solid. The EMC relationship for a hypothetical hygroscopic solid is shown in Fig. 1.

Point X_S in Fig. 1 represents the EMC of the solid after exposure to air at 100% R.H. Since the partial pressure of moisture in air at this humidity is equal to the vapor pressure of liquid water, all moisture contents above X_S consist in part of liquid water capable of exerting its full vapor pressure. The moisture level between X_S and some higher level X_H is the "unbound moisture" of the solid.

At all moisture contents less than X_S, the moisture present is not capable of exerting its full vapor pressure. This water is "bound" within or on the solid and may be held by chemical or physical adsorption, in capillaries, as the solvent in soluble portions of the solid, or by other mechanisms (7).

Point X_E represents the EMC of the solid after exposure to air at 50% R.H. X_E is the limiting level of "dryness" which can be achieved by treating the solid (initially at some higher moisture content, such as X_H) with air at 50% R.H. The difference between X_H and X_E is defined as the "free water" content of the solid (7).

Equilibrium moisture content curves have been reported for numerous materials including dehydrated foods (10), cereal grains (11, 12), soils (13), and cotton, wood, and leather (14). These EMC curves vary greatly with the type of solid examined. For example, nonporous insoluble solids such as zinc oxide generally show relatively low EMC values over a wide range of relative humidities (14). Fibrous, cellular, and porous solids exhibit broader variations in their EMC levels with changes in relative humidity. Hysteresis effects have been reported (15), and equations describing the adsorption isotherm have been applied (8, 10). Methods for conducting the EMC determinations by static and dynamic (forced convection) techniques have been adequately reviewed in the literature (8).

EXPERIMENTAL

Materials.—Equilibrium moisture content curves were established for the following categories of materials. U.S.P. or N.F. grades were used where specific sources of supply are not listed.

Tablet Fillers: Mannitol, lactose, terra alba (extra pure grade, C. Chrystal and Co.), kaolin, sucrose, and dibasic calcium phosphate.

Tablet Disintegrators: Starch, guar gum (grade A-20-D, Steinhall and Co.), Solka Floc (Brown Co.), and bentonite (C. Chrystal and Co.).

Binding Agents: Ethylcellulose, 10 cps.; methylcellulose, 15 and 400 cps.

Tablet Lubricants: Talc, stearic acid, and magnesium stearate.

Tablet Granulations and Tablets:

Placebo granulation (12–20 mesh) consisting of 85% lactose, 5% methylcellulose (400 cps.) and 10% starch (wet granulated with water).

Antacid granulation (12–20 mesh) based on magnesium trisilicate and wet granulated with syrup.

Ferrous sulfate tablets consisting of 8% ferrous sulfate, 5% anhydrous calcium chloride, 86% of gelatin–terra alba filler, and 1% magnesium stearate compressed to a hardness of 6, 8, and 10 Strong-Cobb units.

Fifty-milligram ascorbic acid tablets containing 86% of gelatin–terra alba filler and 1% magnesium stearate.

Procedure.—Static EMC determinations were made by placing samples of each material into desiccators containing one of the following saturated solutions: ammonium dihydrogen phosphate (93% R.H.), ammonium sulfate (81.1% R.H.), ammonium chloride plus potassium nitrate (71.2% R.H.), magnesium nitrate hexahydrate (52% R.H.), potassium carbonate dihydrate (43% R.H.), and calcium chloride hexahydrate (31.0% R.H.). These specific agents were chosen because the relative humidity established above the saturated solution is relatively constant over the (narrow) range of temperature (25 ± 1°) encountered in this study.

Approximately 15 Gm., or 50–100 tablets, of each test material was used as the sample. Weight gains were recorded after various intervals of storage. When constant weight was achieved, L.O.D. was determined using the Cenco moisture balance (90 volts for 7 minutes). These L.O.D. values were converted to moisture contents (dry basis) and plotted *versus* relative humidity to yield the equilibrium moisture content curves.

Assays for ferrous sulfate and ascorbic acid were done according to the U.S.P. methods.

RESULTS AND DISCUSSION

Pharmaceutical Engineering Considerations.—Figure 2 illustrates the EMC curves for the antacid and placebo tablet granulations. It is recognized that the antacid granulation is far more sensitive to changes in relative humidity than the placebo formulation. The variations in EMC curves obtainable with different materials is clearly illustrated by these data.

EMC relationships (as illustrated in Fig. 2) have immediate usefulness in the selection of proper drying conditions for tablet granulations. For example, the EMC for the placebo granulation at 40% R.H. is approximately 1%. Once this equilibrium moisture content has been reached, no further reduction in moisture content can be achieved by further drying with air at 40% relative humidity. Thus, the moisture contents of tablet granulations during the course of actual drying cycles can be compared to the EMC value to determine when the granulation has reached "dryness." This information can then be used to establish the minimum drying time required under the particular process conditions employed.[1]

The effects of changes in the relative humidity of the drying air on the moisture content of the granulation also are obtainable from Fig. 2. With the antacid granulation, a significant decrease in moisture content is observed with decreasing R.H. With the placebo, however, a decrease from 70 to 30% R.H. has little or no effect on final moisture

[1] For dryer calculations, it is preferable to determine EMC values from moisture desorption studies. The use of adsorption data may introduce slight errors if hysteresis effects are present.

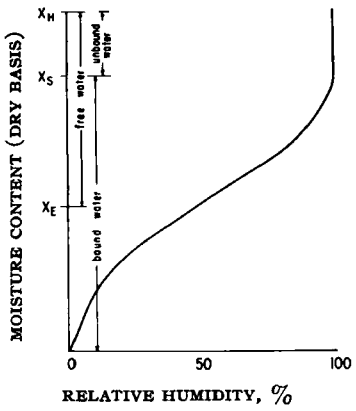

Fig. 1.—EMC curve for a hypothetical hygroscopic solid.

content. If the level of moisture finally present in the placebo granulation after drying with air at 70% R.H. adversely influenced compression characteristics, little improvement would be obtained by drying with air at 30% R.H. This illustrative example can be extended to other properties of the granulation (which are moisture content dependent) such as flow behavior, friability, caking tendencies, etc.

In the case of tray dryers and other units which have heating elements external to the drying chamber, estimates of the EMC at various elevated temperatures can be obtained. This is accomplished by first determining, from psychrometric charts (7), the decrease in relative humidity produced by heating the air to the desired temperature. The equilibrium moisture content of the solid at the elevated temperature is then read from the EMC curve using the new R.H. value as the parameter.[2] These calculations are concerned only with factors of equilibrium moisture contents and do not relate to any changes in the rates of drying which result with changes in R.H. or air temperature. Detailed analyses of these latter factors have appeared in the literature (7).

The EMC curves also have utility in establishing the influence of storage conditions on the moisture content of the product. It is clear that products dried to one moisture level under a given set of drying (or storage) conditions will assume new moisture content values if stored under conditions of different R.H. In the case of the antacid granulation illustrated in Fig. 2, about 9% moisture will be present after storage at 70% R.H. regardless of the moisture content obtained in previous drying operations.[3] No attempt should be made in the drying operations, therefore, to reduce the moisture content of the granulation lower than 9% if the product is subsequently stored at 70% R.H. for protracted intervals.

The compression and flow characteristics of many tablet granulations are influenced by relatively small variations in moisture content. Since quantities of moisture may be adsorbed during "in process" storage, the moisture specifications governing acceptability of such granulations should be based at a level at which successful tableting occurs and not on the moisture content obtained immediately after drying. Limits on the moisture content of the granulations leaving the dryer can be applied, of course, for control of dryer performance.

The moisture level specified for the dry granulation has an important influence on the "throughput" and efficiency of a given dryer. For products

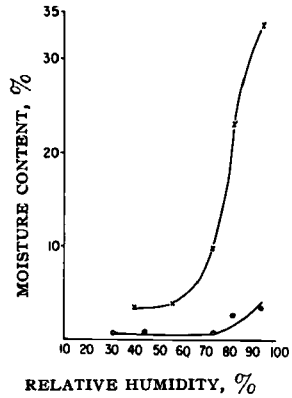

Fig. 2.—EMC curves for placebo and antacid tablet granulation. Key: ×—× antacid, O—O placebo.

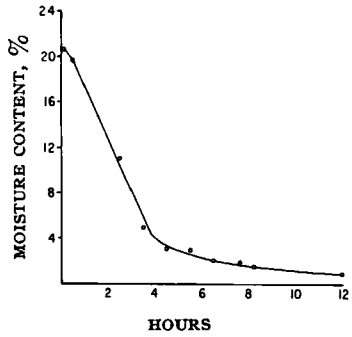

Fig. 3.—Moisture content data for tray drying placebo granulation (inlet air at 104°).

dried to their EMC, drying rates may decrease significantly as the EMC is approached. Thus, disproportionately large amounts of time are required to remove the last amounts of free water. This is illustrated in Fig. 3 with data obtained in tray-drying studies with the placebo. In this case, approximately 6 hours of the total drying time of 10–12 hours was utilized in reducing the moisture content from 3 to 1%— a reduction of only 2%. If it were determined that the granulation was actually acceptable at the 3% moisture content, the drying cycle could be reduced by 6 hours. This would double the output of the tray dryer. Overall thermal efficiency would be increased by an even higher factor. Further, during the last 6 hours of drying, the product temperature will be near that of the inlet air so that elimination of this interval may minimize product decomposition during the drying cycle.

Formulation Considerations.—Figure 4 presents

[2] Temperature has a slight humidity-independent effect on EMC (8). This can be neglected in first approximations with most systems.

[3] This assumes that the storage at 70% R.H. is of sufficient duration for equilibrium to be established. For shorter storage times the moisture content of the product may adjust only partially. Hysteresis effects also are assumed to be negligible.

the EMC curves for representative tablet disintegrators. The high EMC sensitivity of these materials to changes in relative humidity is apparent. These EMC characteristics are not surprising since tablet disintegrators, as a class, comprise agents which are chosen (in a sense) for their water adsorptive abilities. No attempt to select the "best" disintegrators on the basis of EMC criteria was made since other factors also influence their performance.

EMC curves for three modified cellulose tablet binders are shown in Fig. 5. The water insoluble

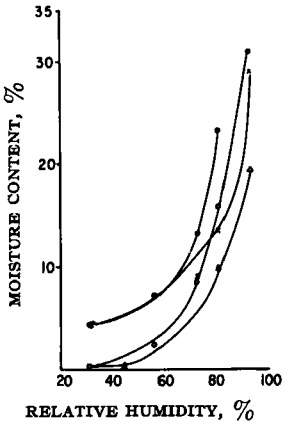

Fig. 4.—EMC curves for tablet disintegrators. Key: Δ—Δ starch, ×—× Solka Floc, O—O guar gum (A-20-D), ●—● bentonite.

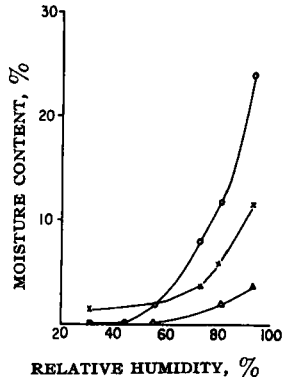

Fig. 5.—EMC curves for tablet binders. Key: O —O methylcellulose (400 cps), × —× methylcellulose (15 cps), Δ —Δ ethylcellulose, (15 cps).

ethylcellulose shows low moisture levels which are sensitive nevertheless to changes in relative humidity. Both grades of methylcellulose have high EMC values, and clear differentiation between the two grades is observed.

Lubricants examined in this study included talc, magnesium stearate, and stearic acid. EMC values for the first two materials were less than 0.5% at all test humidities. Slightly higher results of about 1% were observed for stearic acid. It is probable, however, that this moisture value includes a significant error arising from the loss of other volatile substances (in addition to moisture) which are removed from the acid during the Cenco moisture determination. It was noted further in this study that determinations of moisture levels of less than 1% by the Cenco technique were not generally reliable.

Tablet lubricants are water insoluble materials without pronounced water adsorptive abilities. It is expected that lubricants such as mineral oil, sterotex, and calcium stearate, etc., would show EMC curves similar to those observed above.

Tablet fillers including kaolin, mannitol, terra alba, and dicalcium phosphate had equilibrium moisture contents of less than 1% at all humidities tested. Sucrose was included in this study and, although it evidenced high moisture gain, it did not reach moisture equilibrium at the test humidities during a long storage period (60 days). No reason for this anomalous behavior was apparent. For lactose, the EMC (at the highest humidities) was approximately 2%. This value is higher than that seen with the other fillers and reflects the relative hygroscopicity of this agent.

Extensions of the above considerations to simple formulations can be made. In systems which consist of physical mixtures of two or more agents, each material can seek and reach its own EMC under given storage conditions. The EMC of the mixture will represent a weighted average of the EMC values for the individual components, and predicted EMC values can be obtained for each humidity of interest. Knowledge of the EMC curves for the individual components can be applied in this way to make first estimates regarding the moisture gain of the mixture. This approach also allows a preliminary basis for selection of formula components in line with the desired moisture characteristics of the product.

If no chemical reactions occur during the granulation or tableting of physical mixtures, it can be expected that the EMC curve for these materials will also be related to the EMC values for their individual components. (Changes in particle size of the powders during granulation or compression will effect the absolute values.) The antacid granulation containing high concentrations of relatively hygroscopic materials (sucrose and magnesium trisilicate) therefore would be expected to show higher EMC levels than obtained with the lactose based placebo. Figure 2 indicates that this is true. Similar observations demonstrating the comparative moisture sensitivity of the antacid were made when tablets of both formulations were studied.

EMC values for the placebo granulation were

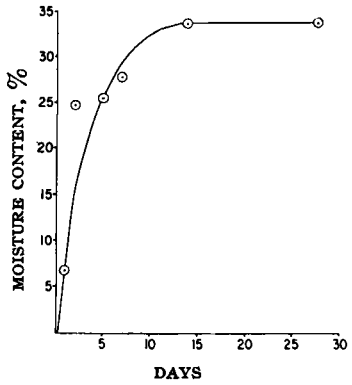

Fig. 6.—Rate of moisture adsorption for antacid granulation at 93% relative humidity.

TABLE I.—STABILITY CHARACTERISTICS OF ASCORBIC ACID TABLETS AT VARIOUS HUMIDITIES

Time, Days		Relative Humidity 93%	81%	73%	56%
3	Assay, %	69	92	100	100
	Moisture gain, %	0.7	0.6	0.0	0.0
5	Assay, %	62	90	97	100
	Moisture gain, %	11	1.4	0.5	0.0
30	Assay, %	29	68	81	84
	Moisture gain, %	46	7.1	1.5	0.1

predicted (from a weighted average of the component EMC values) at 4.6, 3.3, and 2.5% at 93, 83, and 71% R.H., respectively. These predictions are in reasonable agreement with the experimentally determined values of 3.5, 2.8, and 1%. While further studies are required to confirm the quantitative aspects of this approach, these experiments do demonstrate the value of the EMC concept for qualitative predictions of moisture content–humidity interrelationships. It is interesting to note that the use of humectants in cosmetic formulations (16) and flow conditioners in fertilizer products (17) are based on similar considerations.

Stability Considerations.—The static equilibration technique used in the present experiments is similar to that generally employed in following the stability of pharmaceuticals under exaggerated humidity conditions. In such systems, little or no flow of air across the sample is obtained, and mass (moisture) transfer occurs by molecular diffusion alone. Rates of moisture adsorption, therefore, can be expected to be low and prolonged storage times will be required before samples attain their equilibrium moisture content. In the present study it was found that storage intervals of at least 15 days were necessary for samples to achieve equilibrium. This is illustrated in Fig. 6 with representative data for the antacid granulation.

For moisture sensitive materials, significant decomposition can occur in the early storage intervals during which nonequilibrium (moisture) conditions prevail. The rate of decomposition observed during this period should be related, however, to the moisture actually present in (or on) the sample. While the moisture content will be influenced in turn by the storage humidity utilized, simple relationships between relative humidity and decomposition rates may not exist.

These points are illustrated by the data of Table I which gives the assay results and corresponding moisture gain of ascorbic acid tablets stored for various time intervals at four different humidities. At any given humidity, increasing amounts of moisture were adsorbed as the storage time was extended. (EMC levels were not established within a 30-day interval). The amount of moisture adsorbed during any given time period decreased with decreasing humidity. Further, assay values of ascorbic acid were related to the amounts of water adsorbed. Kinetic analysis of the data is difficult, however, since moisture equilibrium was not obtained. Rates of moisture transmission in elevated humidity studies of this type may be, in fact, the overall rate-limiting consideration in the decomposition process.

Rates of moisture gain under exaggerated humidity conditions will be influenced by the physical characteristics of the sample such as its surface area and porosity, etc. For tablets, moisture adsorption rates will be related in part to hardness. Increasing tablet hardness should decrease moisture transfer rates within the solid and thereby decrease the overall rate of moisture gain. This should result, in turn, in improved stability with increasing tablet hardness. To test these predictions, tablets were made from a ferrous sulfate granulation and compressed to hardness of 6, 8, and 10 Strong-Cobb units. After a 3-day storage period at 93% R.H. moisture gain was 8.5, 7.2, and 6.8%, respectively. The decomposition of ferrous sulfate in these tablets was 31.7, 28.3, and 24.1%, respectively, and was in line with the moisture gain values.

Further experiments are required to extend these initial observations. For such kinetic studies, vapor diffusion effects which may limit the overall rates of decomposition will have to be considered. Dynamic techniques for achieving rapid moisture equilibration in the solid will be more useful than the static methods routinely employed in such studies.

CONCLUSIONS

The concept of equilibrium moisture content (EMC) defines the relationship between moisture adsorption and relative humidity. This concept is useful in establishing proper drying and storage conditions for pharmaceutical materials.

Equilibrium moisture contents have been obtained for a number of representative pharmaceutical materials. This data is useful in predicting the effects of storage humidity on the moisture adsorbed by simple physical mixtures. The stability of products containing moisture sensitive active ingredients may be related to their moisture content which in turn is predictable from the EMC curves of individual components.

REFERENCES

(1) Leeson, L. J., and Mattocks, A. M., THIS JOURNAL, **47**, 329(1958).
(2) de la Vega, F. A., *Galencia Acta (Madrid)*, **3**, 61(1940).
(3) Blaug, S. M., Chakravarty, D., and Lach, J. L., *Drug Std.*, **26**, 199(1958)
(4) Irani, R. R., Callis, C. F., and Leis, T., *Ind. Eng. Chem.*, **51**, 1285(1959).
(5) Craik, D. J., and Miller, B. F., *J. Pharm. Pharmacol.*, **10** (Supp.), 136T(1958).
(6) Blaug, S. M., Hickman, E., and Lach, J. L., THIS JOURNAL, **47**, 54(1958).
(7) Perry, J. H., "Chemical Engineers Handbook," 3rd ed., McGraw-Hill Book Co., New York, N.Y., 1954, pp. 757–811.
(8) Markowitz, M. M., and Boryta, D. A., *J. Chem. Eng. Data*, **6**, 16(1961).
(9) Henderson, S. M., *Agr. Eng.*, **33**, 29(1952).
(10) Taylor, A. A., *Food Technol.*, **15**, 536(1961).
(11) Hogan, J. T., and Karon, M. L., *J. Agr. Food Chem.* **3**, 855(1955).
(12) Becker, H. A., and Sallans, H. R., *Cereal Chem.*, **33**, 79 (1956).
(13) Thomas, M. D., *Soil Sci.*, **25**, 409(1928).
(14) "International Critical Tables," vol. 1, 1st ed., McGraw-Hill Book Co., New York, N.Y., 1927, pp. 321–325.
(15) Seborg, H., *Ind. Eng. Chem.*, **29**, 169(1937).
(16) Harry, A. G., "Cosmetics, Their Principles and Practices," Chemical Publishing Co., New York, N. Y., 1956, pp. 735–748.
(17) Irani, R. R., Vandersall, H. L., and Morgenthaler, W. W., *Ind. Eng. Chem.*, **53**, 141(1961).