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Review Article

AN APPROACH TO THE EVALUATION OF HYGROSCOPICITY FOR PHARMACEUTICAL SOLIDS

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INTRODUCTION

Understanding the nature of moisture adsorption by pharmaceutical substances has long been recognized as an important, and usually formidable, task of the solid dosage formulation chemist. For a drug that degrades in the presence of water, characterization of both the equilibrium moisture content (EMC) of the formulated material, as well as the rate at which this level is achieved, is imperative. These properties are often referred to as the 'hygroscopic' properties of the substance, a term not clearly defined, but implying both kinetic and thermodynamic criteria of behavior. Often 'trial and error' approaches are taken by the formulator to develop a successful formulation for a drug subject to moisture effects detrimental to its stability. Were the actual mechanisms controlling hygroscopic phenomena better understood, the frequently encountered problems of chemical (drug) and physical (formulation) instability induced by moisture could be systematically avoided.

Of the wealth of water adsorption literature available, far more attention has been devoted to the thermodynamic rather than the kinetic aspects of the sorption process. Numerous studies of water uptake by insoluble inorganic materials, such as silicaceous substrates (Young, 1958; Boehm and Sappok, 1972; Dollimore et al., 1973; Van Olphen, 1976; Dubinin, 1977), have appeared. Klier and Zettlemoyer (1977) examined the molecular dynamics of this type of water–surface interaction using various spectroscopic techniques. Both spectroscopic and gravimetric methods have been used to probe the hydration mechanism of natural and synthetic polypeptides (Bull, 1944; Eley and Leslie, 1966; Fuller and Brey, 1968; Breuer and Kennerley, 1971; Rochester and Westerman, 1976a, b, 1977; Gascoyne and Pethig, 1977). Other macromolecules such as mucopolysaccharides (Bettelheim and Ehrlich, 1963; Ehrlich and Bettelheim, 1963) and synthetic polymers (Yano, 1955; Dickel and Fiederer, 1972) have been similarly investigated. Recently Tanaka et al. (1979) reported and interpreted thermodynamically the adsorption isotherms of crystalline surfactant solids.

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Many materials of commercial interest are affected by the detrimental effects of uncontrolled moisture adsorption, such as fertilizers, foods, fibers, textiles and woods. With the aim of learning to control these effects, a myriad of definitions for 'hygroscopicity' and approaches to its measurement have been proposed over the years (Wilson and Fuwa, 1922; Edgar and Swan, 1922; Browne, 1922; Adams and Merz, 1929; Mikulinskii and Rubinshtein, 1937; Yee and Davis, 1944; Griffin, 1945; Wink, 1946; Griffin et al., 1952; Markowitz and Boryta, 1961; Modrzejewski and Pokora-Bartyzel, 1966; Onischak and Gidaspow, 1969; Kuvshinnikov et al., 1971; Fedoseev et al., 1973; Admirat and Grenier, 1975; Panidi et al., 1976; Addou and Vast, 1976; Chikazawa and Kanazawa, 1978). In their study of fertilizer salts and related compounds, Edgar and Swan (1922) presented one of the first studies which addressed specifically the factors determining hygroscopic behavior. They predicted a priori that the rate of moisture adsorption could be expected to depend on: (1) the difference between the partial pressure of water vapor in the atmosphere and that above the saturated aqueous solution of the hygroscopic substance, (2) temperature, (3) surface area of the solid exposed to the water vapor, (4) 'velocity of movement' of the moist air and (5) a 'reaction constant' characteristic of the solid. This first step in understanding the phenomenon of hygroscopicity, however, involved measuring only equilibrium vapor pressures of the saturated solutions; unfortunately, the intended collection of kinetic data was not reported.

In a study of similar intent, Adams and Merz (1929) attempted to predict the storage and handling properties of pure and mixed fertilizer salts by measuring their hygroscopicity, which they defined as the maximum relative humidity (RH) in which a material can exist without becomming moist – clearly a thermodynamic condition. They observed that the hygroscopicity of the mixtures was generally greater than that of the more hygroscopic constituent, unless the components reacted to form a compound or double salt of lower hygroscopicity, i.e. one of greater equilibrium vapor pressure over its saturated solution. In a comparable study Browne (1922) failed to show any fixed relationship between the EMCs of various carbohydrates and the RHs in which they were equilibrated.

Mikulinskii and Rubinshtein (1937) directed their attention to the rate of adsorption which they proposed, based on their study of moisture uptake by magnesium sulfate, depended on a two-step process: (1) surface adsorption, occurring at a rate simply proportional to the difference between partial pressures of water vapor in the atmosphere compared to that of the saturated salt solution; and (2) water diffusion into the crystal, at a rate dependent on the product of the diffusion coefficient and water concentration gradient.

Later Griffin (1945) alluded to the significance of moisture uptake rate in a report on glue hygroscopicities, which he defined for his immediate purpose as the EMC of a material under varying RHs. He considered only equilibrium studied feasible at the time, however. Examination of typical glues softened with sorbitol and glycerol in various proportions proved again that the hygroscopicities of individual components are not additive once formulated, especially at low RHs. Griffin then collaborated with several cosmetic chemists in studying the function of humectants in cosmetic formulations (Griffin et al., 1952), this time addressing more directly the rate processes involved. The authors attempted to lay a foundation of terms and definitions to describe the hygroscopicity of humectants and thereby better define the manner in which these agents exert their desired effects on a formulation. The three basic terms they introduced are (1) 'equilibrium hygroscopicity' – the state or condition which exists when an aqueous solution neither gains nor loses noisture at a given RH; (2) 'dynamic hygroscopicity' – the rate at which a substance or its aqueous solution gains or loses water while approaching equilibrium (expressed only as a relative quantity); and (3) 'volatility' – the tendency of a product to evaporate. They further suggested that the factors governing the latter two kinetic properties include sample thickness (relating to available surface area) and 'inherent rate' of the product, as well as RH and temperature.

At about the same time, Yee and Davis (1944) developed an 'accelerated method' for determining the EMCs of various inorganic salts and fertilizers. They reduced the time required to reach equilibrium by modifying the sample preparation and by agitating the atmosphere within the constant-RH test chamber. The authors also collected sorption rate data in an effort to measure systematically, if perhaps only grossly, the effects of bed depth, number of samples per chamber, sample container size and temperature on uptake rates.

Emphasizing the experimental elusiveness of the kinetic aspects of hygroscopicity, Markowitz and Boryta (1961) more recently proposed the theoretical suitability and experimental advantage of the thermodynamic approach. They chose as a criterion for hygroscopicity the negative value of the free energy change accompanying the transfer of water to the condensed (absorbed) phase from the atmosphere, as driven by the imbalance of chemical potential of water between the two systems. They term the $-\Delta G$ value the 'hygroscopicity potential' (HP) as given by

$$\mathrm{HP} = -\Delta G = \mu_{\mathrm{H_2O,pure}} - \mu_{\mathrm{H_2O,sys}} = RT \ln\left[\frac{P_{\mathrm{H_2O,pure}}}{P_{\mathrm{H_2O,sys}}}\right] \tag{1}$$

Acknowledging the kinetic character of the hygroscopic process, the authors claimed only that such thermodynamic measurements 'probably allow some insight' into the rate processes involved, 'especially for systems in which a saturated solution results' on water uptake. They referred to the chemical reaction nature of hygroscopicity, that is, the fact that it is characterized by a thermodynamic driving force and a kinetic rate. They further declared that the 'customary kinetic experiment' is unable to resolve the individual factors upon which this rate depends, and is therefore of little theoretical significance. Their experimental results included calculation of the HP values for various saturated inorganic salt solutions at different temperatures.

Another thermodynamic correlation was discussed by Admirat and Grenier (1975) in which the critical relative humidities (CRH, usually used to indicate that RH in equilibrium with a saturated solution of the salt) of hygroscopic salts at low temperature were shown to correspond to eutectic data. The authors then expressed the CRHs for the salt–water systems as P-T-mole fraction diagrams.

A kinetic study of the hygroscopicity of water-soluble salts and minerals was undertaken by Kuvshinnikov et al. (1971), who recognized the inadequacy of the pure thermodynamic approach. They defined a 'hygroscopicity coefficient' as the logarithm of the initial slope of the kinetic curve of moisture uptake. They described their observed sorption curves successfully by the relation

$$W = W_\infty(1 - e^{-kt}) \quad (2)$$

where W = moisture content, W_∞ = equilibrium moisture content, k = constant of uptake and t = time. Using the same hygroscopicity coefficient, Panidi et al. (1976) evaluated the moisture uptake of various double sodium potassium phosphate salts under a constant RH of 81%. From their results they attempted to infer structural characteristics of the mixed salts.

Another approach to the study of moisture adsorption kinetics is that typified by the work of Onischak and Gidaspow (1969). The purpose of their study was to determine the mechanism of water vapor sorption by anhydrous lithium chloride, sufficiently rapid that it was assumed to be gas diffusion-controlled. Using what is often referred to as a 'dynamic' rather than a 'static' method, these authors monitored the moisture content of inlet and outlet air streams flowing through a parallel plate reactor which contained a compressed bed of the salt. Appropriate diffusion conditions and boundary values were assigned. Comparing theoretical and observed data, they concluded that the rate-controlling step may be the formation of the solution which must then diffuse into the dry salt matrix, and that equilibrium conditions cannot be assumed to prevail at the surface of the salt.

Addou and Vast (1976) used a rather novel approach to investigate the hygroscopicity of various pure and mixed potassium salts. After passing humid air through a column of the salt, they measured weight uptake as a function of column length. They proposed that the weight uptake profile with length and its development with time correlated with salt hygroscopicity. From the profiles collected, they concluded that moisture is first chemisorbed, followed by dissolution of the salt on the surface of each crystal leading to saturation, and that, in the case of mixed salts, actual ion displacement can occur.

A recent series of articles by Chikazawa, Kanazawa and others emphasized the interfacial chemistry governing the hygroscopic adsorption process. Testing the dependence of surface area, surface conductivity and X-ray diffraction measurements on the extent of moisture adsorption onto soluble alkali metal halides, the authors speculated on the mechanism of sub-monolayer adsorption (Chikazawa et al., 1972, 1976, 1977a, 1978; Kaiho et al., 1972, 1973; Kanazawa et al., 1973). Of particular interest in this series is their review on the hygroscopicity of these salts (Chikazawa and Kanazawa, 1978) in which they discussed surface interaction mechanisms in detail. Here they proposed that the formation of 'hydrated ions' precedes solubilization on the crystal surface and eventual deliquescence. Other studies in the same laboratory related adsorption isotherm data to observed changes in bulk behavior, e.g. caking of powdered halides (Kaiho et al., 1974; Kanazawa et al., 1975; Chikazawa et al., 1977b). Hall and Rose (1978) recently reported striking differences between the isotherms of different ammonium halides. There is evidence that even small modifications in crystal lattice structure, or extent of crystallinity, can account for changes in hygroscopic properties (Barraclough and Hall, 1974; Hüttenrauch, 1977).

Among the earliest pharmaceutical studies addressing the determination of hygroscopicity is that of Büchi (1938), who measured the rate of water uptake by a number of dried plant extracts. Without attempting to quantitate the relation, he correlated hygroscopicity with these rates. The work of Griffin et al. (1952) with humectants, discussed above, represents the next substantial attempt to define, manipulate and control the effects of hygroscopicity on pharmaceuticals. Other studies on the function and effective use of humectants in cosmetic formulations have appeared since the work of Griffin et al. (Livengood, 1948; Henney et al., 1958; Bryce and Sugden, 1959) and were later summarized in practical texts like DeNavarre's volume on the manufacture of cosmetics (DeNavarre, 1975).

Studies focussing specifically on the nature of hygroscopicity, such as those just cited, legitimately distinguish themselves from general moisture adsorption work by virtue of their nearly exclusive attention to highly water-soluble materials. Yet the majority of the pharmaceutical literature in this area concerns itself with adsorption onto less soluble powders and the resulting changes in bulk properties. The practical implications of bulk behavior are no less significant for this distinction, however; therefore a brief discussion of moisture sorption by powders follows.

Strickland (1962) gathered the first substantial set of moisture isotherms for pharmaceutical powders, both drug and excipient. Using the method of desiccator storage, he studied adsorption and desorption profiles. The pronounced hysteresis that appeared in most of the curves was attributed to failure to attain equilibrium. Also reported was an extensive list of materials, mostly active agents, which neither gained nor lost moisture on exposure to extreme RHs. Initial screening tests suggested that procaine base had a CRH below which no moisure was adsorbed, but above which adsorption was rapid and extensive. Using the more sensitive quartz spring adsorption apparatus, further study of its adsorption in the sole presence of water vapor revealed clear formation of a dihydrate with no hysteresis on desorption. Rate studies at very high RH indicated zero-order reaction between the base and water on hydration.

The following year Scott et al. (1963) measured the EMCs and moisture uptake rates of various pure excipients, granulations and tablets. They euggested that by knowing the EMCs of a formulation's components, one should be able to predict by weight-averaging the EMC of the final formulation. This information could in turn be used to predict suitable drying regimes. They further theorized that the adsorption isotherm of a 'hygroscopic solid' should resemble a Type II isotherm (Brunauer classification; Brunauer, 1943) in which multilayer adsorption occurs.

In a series of articles concerning the sensitivity of pharmaceuticals to the conditions of manufacturing and storage, von Czetsch-Lindenwald (1964) presented extensive data on the moisture uptake by various adjuvants and active compounds. He later studied specific climate effects on numerous formulations (von Czetsch-Lindenwald, 1968b) and discussed methods for controlling the problems that can arise from them (1968a). Similarly, Nürnberg (1969) measured the hygroscopicity of 28 drugs and excipients in order to determine suitable product packaging.

Shotton with Harb and Rees tested the effects of humidity and temperature on the EMC (1965), cohesion (1966a) and compaction properties (1966b) of several classes of carbohydrate powders. In an attempt to resolve the controversy of whether moisture remains 'free' (physically adsorbed) or 'bound' (chemisorbed), the authors applied the Clapeyron equation to their data to yield heats of adsorption. These calculated quantities for the starches and alginic acid were low, reflecting weak bonding characteristic of physical adsorption. They also noted a linear relationship between the logarithm of the EMCs of these materials and the RH, with little dependence on temperature. By contrast, the moisture contents of the sugars capable of chemical hydration were more temperature-dependent, typical of chemisorption.

The Clausius–Clapeyron relation is frequently applied over limited temperature ranges to yield heats of adsorption. This approach is limited in applicability, however, by the assumption implicit in its use that the adsorption process be truly reversible with respect to temperature and pressure. Furthermore, in the study of soluble compounds, heats of adsorption determined either from this or from immersional calorimetry techniques are rendered less accurate because of the usually large heats of solution accompanying the measurement process. Sensitive, direct calorimetric measurement of the heat evolution accompanying admission of vapor to a sample of necessarily large total surface area may provide a more accurate means of determining this important experimental quantity.

Others have examined the effects of additives on the moisture absorbing nature of starches (von Czetsch-Lindenwald et al., 1965; El-Khawas et al., 1966; Lowenthal, 1972) and sugars (Kearsley and Birch, 1975). In their determination of sugar hygroscopicities, Yamamoto and Takahashi (1952) reported the interesting result that the CRH of a blend of citric acid, glucose and sucrose equalled the product of the CRHs of the pure compounds, revealing, as seen earlier, an elevated blend hygroscopicity. In companion articles, the same authors presented CRH and EMC data for a list of deliquescent, hygroscopic and effluorescent drugs and excipients and discussed the effects of excipient dilution on formulation CRH (Yamamoto and Takahashi, 1953, 1954). The general effects of moisture on bulk formulation properties, such as flow and cohesion, have been thoroughly reviewed (Craik and Miller, 1958; Hiestand, 1966; Johnson, 1967; Eaves and Jones, 1970; Pilpel, 1971).

Recently Coelho and Harnby (1978a, b) treated the moisture adsorption by insoluble non-porous powders in a theoretical manner. They based their arguments on the Brunauer–Emmett–Teller (BET) model of layered adsorption, as governed by the Kelvin and Laplace equations once liquid bridges form between two particles. Such bridges, they contended, will remain stable above a certain critical relative humidity, below which moisture is present only as adsorbed vapor. The form of the water so retained, whether liquid or vapor, is thus determined by this critical vapor pressure. Furthermore, they proposed that the binding forces in each situation and the bulk properties they induce in the powder are continuous functions of the actual humidity. A similar model for desorption was proposed by El-Sabaawi and Pei (1977) for insoluble porous powders. They suggested that at high RHs, capillary evaporation governs desorption, and that at lower RHs one could predict EMCs in terms of multilayer coverage.

One of the primary purposes of Yamamoto and Takahashi's work was to establish control over the degradative effects of moisture on various pharmaceuticals through the use of effective packaging (Yamamoto and Takahashi, 1956). To quantify the success of their efforts, they proposed the following relation to describe the rate of moisture gain (or loss) of a given sample:

$$W = Kt(P_a - P') \qquad (3)$$

where W = sample weight gain per unit area of effective surface area, K = proportionality constant, t = time, P_a = water vapor pressure of the external atmosphere and P' = water vapor pressure over the saturated solution of the substance. (Symbols have been modified for consistency with the present notation.) They implied that the packaging of the product influenced only K which they termed the 'moisture transmission factor of the container'.

More recently, Carstensen (1977) utilized the same relation as given in Eqn. 3, but in differential form where he used an initial uptake rate, $(dW/dt)_{initial}$ in which W represents the total weight of the sample, rather than weight gain per unit area. Converting this expression to weight percent gain per unit time (initial), W_i', and to percent relative humidities (where $RH = 100(P/P_0)$, P_0 = vapor pressure of pure water at the given temperature), one obtains the working relation

$$W_i' = kA_sP_0(RH_i - RH_0) \tag{4}$$

where RH_i = relative humidity of atmosphere during the course of the experiment, RH_0 = relative humidity prevailing over a saturated solution of the substance (to which the 'critical relative humidity' usually refers), and where K has been separated into a new proportionality constant, k, multiplied by the specific surface area of the sample, A_s. Carstensen further proposed that such initial rates will be constant, i.e. weight gains (or losses) are initially linear in time, varying in slope (W_i') depending on RH_i. It then follows from the above arguments that when $RH_i = RH_0$, the rate of moisture uptake will be zero. If a plot of W_i' versus RH_i is prepared, a straight line should result whose x-intercept ($W_i' = 0$) should represent RH_0.

In demonstrating the validity of these relations for moderately hygroscopic materials, Carstensen used the familiar technique of storing samples in desiccators wherein saturated aqueous solutions of various inorganic salts (of known RH_0 values at room temperature) had been allowed to equilibrate, providing the experimental RH_i. Periodic and successive withdrawal and weighing of the samples resulted in the collection of the desired rate data.

Many of the adsorption studies cited heretofore have relief on the static method of desiccator storage, a simple and sufficiently accurate method under the appropriate circumstances of materials, conditions and experimental intention. There are many unassessable and uncontrollable variables inherent in this method, however, which render it unsuitable for accurate kinetic determinations of the rapid moisture uptake by highly hygroscopic materials. For those studies requiring more sensitive, accurate in vacuo measurement, the McBain–Bakr spiral quartz spring has long provided a popular gravimetric method (McBain and Bakr, 1926). Less frequently used are volumetric techniques, satisfactory only for measuring equilibrium adsorption isotherms. In the last decade, however, the commercial production of the electronic microbalance has revolutionized the range of gravimetric capabilities with respect to sensitivity, precision, simplicity of data collection, continuous recording, and the ease of monitoring the sample simultaneously by other surface analysis techniques. A review by Cadenhead and Wagner (1976) presented a thorough discussion of gravimetric instrumentation and its primary applications. Czanderna and Vasofsky's recent review (1979) offered exhaustive coverage of the adsorption literature whose data was generated using microbalance techniques (including electronic beam, helical spring and quartz oscillator types), and in addition discussed recent technological developments in the area.

In this paper an apparatus is described which is designed to measure with microgravimetric accuracy and sensitivity the initial rapid moisture uptake by hygroscopic solids under a controlled atmosphere. Adsorption data collected on the apparatus for a series of choline halides are presented in support of the general kinetic relations proposed by Carstensen (1977). From these data certain general conclusions are drawn regarding the sorption behavior of the salts. Limited speculation over the parameters which may be used to define their hygroscopicity quantitatively and the physiochemical properties governing them is then offered.

MATERIALS AND METHODS

Materials

Choline chloride, bromide and iodide were all used as received [1]. Whenever possible, manipulation of the more hygroscopic chloride and bromide salts was performed within a plastic inflatable glove bag [2] in which sub-ambient RH of 25–30% was maintained.

Various physical property measurements were made to characterize the halides. Densities were approximated to ±0.04 g/ml by suspending each salt in a series of non-solubilizing organic solvents of varying density. Geometric surface areas were estimated by microscopic examination [3] of a dilute suspension of the salt in light mineral oil. The least hygroscopic halide, choline iodide, was also examined using the Fisher sub-sieve sizer [4]. Approximate aqueous solubilities at 25°C were determined by weight loss upon evaporation of supernatant solution aliquots withdrawn from saturated solutions of the salts.

Apparatus design

Fig. 1 shows a schematic drawing of the high vacuum manifold and microbalance apparatus. All glass parts of the apparatus are Pyrex [5] fused by oxygen-gas torch. A single gas ballast rotary high vacuum pump [6] (F no. 1) served as the primary forepump for the main vacuum manifold (M). A similar pump [7] (F no. 2) was used only to regulate the bulb pressure on the McLeod gauge [8] (MC). A two-stage mercury diffusion pump [9] (DP) driven by the main forepump was capable of maintaining a 10^{-4} Torr vacuum over the entire apparatus. Water vapor or dry air pressure could be monitored by the mercury manometer (G) or oil manometer (O) using a cathetometer [10] capable of readings to the

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[1] Sigma Chemical Co., St. Louis, Mo. 63178, U.S.A.

[2] Model X-27-27, Instruments for Research and Industry, Cheltenham, Pa. 19012, U.S.A.

[3] Instrument Division, Nikon, Garden City, N.Y. 11530, U.S.A.

[4] Fisher Scientific Co., Instrument Division, Pittsburgh, Pa. 15219, U.S.A.

[5] Corning Brand borosilicate glass, Corning Glass Works, Corning, N.Y. 14830, U.S.A.

[6] Cenco Hyvac 7, Central Scientific Co., Chicago, Ill. 60623, U.S.A.

[7] Model ES35 'Speedivac', Edwards High Vacuum, Inc., Grand Island, N.Y. 14072, U.S.A.

[8] Todd Scientific Co., Cedars, Pa., U.S.A.

[9] Eck and Krebs Scientific Laboratory Glass Apparatus Co., Long Island City, N.Y. 11101, U.S.A.

[10] No. S-14785, Sargent-Welch Scientific Co., Skokie, Ill. 60076, U.S.A.

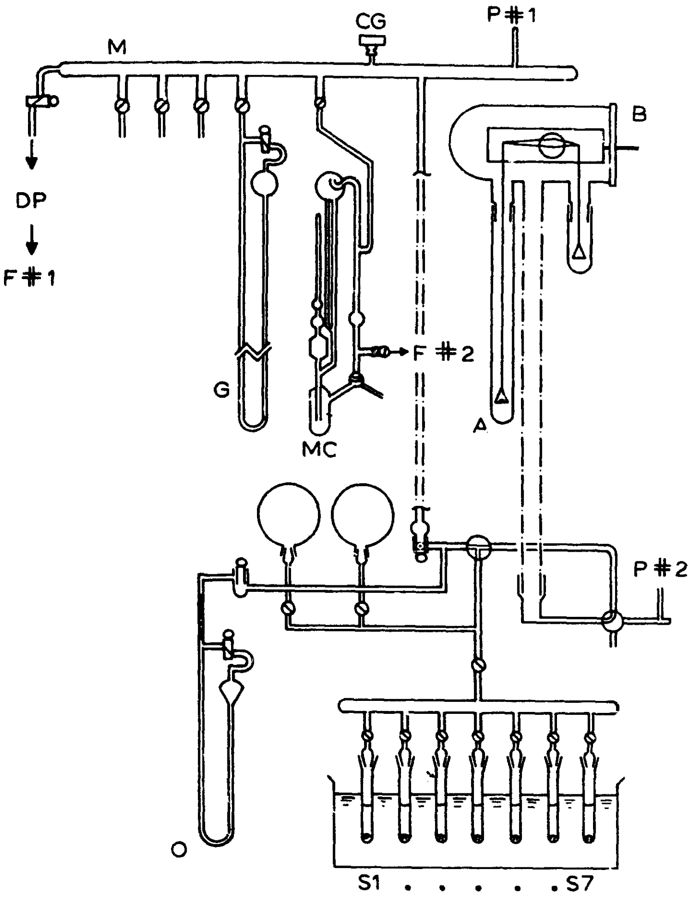

Fig. 1. Adsorption apparatus.

nearest 0.05 mm. The McLeod gauge was used solely for the measurement of dry air pressure less than 25 Torr. The system was also equipped with three electronic pressure gauges capable of very sensitive measurements at very low pressures (less than 5 Torr) but requiring careful recalibration in the presence of water vapor. These included the 'Convectron' gauge[11] (CG) and two Pirani gauges[12] (P no. 1, P no. 2) located in different regions of the apparatus. The electronic microbalance[13] (B) chosen for the apparatus is designed to operate in high vacuum or almost any controlled atmosphere. The balance has a weight capacity of 1 g with a minimum full-scale recorder range of 2×10^{-6} g. Opposite the shorter tare hangdown tube on the vacuum bottle containing the balance is the 50-cm-long sample hangdown tube (A) which could be removed during sample preparation.

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[11] Series 275 Convectron gauge, Granville-Phillips Co., Boulder, Colo. 80303, U.S.A.

[12] Cat. No. 3596, LKB Instruments, Inc., Rockville, Md. 20852, U.S.A.

[13] Model RG-HV, Cahn Instruments, Division of Ventron Corp., Cerritos, Calif. 90701, U.S.A.

Moisture adsorption was measured at 25°C in vacuo (with respect to air, i.e. air pressure less than 10^{-4} Torr) under varying relative humidities. Control of humidity was obtained by exposing the evacuated sample chamber at 'zero time' to the water vapor pressure in equilibrium over any of seven different saturated salt solutions located in chambers S1 through S7 (refer to Fig. 1). Atmosphere stability immediately following 'zero time' is critical to the collection of meaningful kinetic data; ideally the experimental RH_i should remain constant from the start to the completion of the adsorption run, despite vapor depletion caused by adsorption to the inside walls of the apparatus, to the balance mechanism or, most obviously, by rapid sample sorption. Yet diffusion of the water vapor into the sample chamber during expansion results in a finite lag time in establishing the final RH. While this lag cannot be avoided, it must at least be minimized. Furthermore, such expansion severely disrupts the equilibrium established over the exposed salt solution, contributing an additional lag time until such equilibrium is restored. A 'SOURCE : SUPPORT' principle of operation, around which the apparatus was designed, satisfactorily resolved these problems and met the desired requirements of RH stabilization.

The 'SOURCE' RH chamber (selected from S1–S7) was used to establish the initial RH prior to expansion at 'zero time'. The 'SUPPORT' RH chamber (also selected from S1–S7), containing a saturated salt solution with a vapor pressure equal to that of the anticipated final RH, was exposed to the sample immediately after expansion to stabilize the RH_i so established. Potential SOURCE : SUPPORT combinations required the equality of two ratios: (1) the ratio of the equilibrium RHs (initial : final), which is equivalent to SOURCE RH_0 : SUPPORT RH_0, and (2) the ratio of the volumes (final : initial) on expansion, or the 'expansion ratio'. Accurate volume calibrations were obtained for all isolatable regions of the apparatus. The initial volume included at least the manifold region immediately above the salt chambers (see Fig. 1). The many combinations in which ballast could be added to either the initial or final volume afforded over thirty expansion ratios, ranging in value from 1.46 to 18.0. Using an appropriate selection of salts for chambers S1–S7, ranging in RH_0 values of 22–93%, 13 SOURCE : SUPPORT pairs (of a potential 21) were available to the system.

Temperature gradients throughout the apparatus were minimized since they could affect the performance of the various pressure gauges and render their indicated RH values invalid for the effective RH in the sample chamber. A water bath maintained at 25°C was used to stabilize the temperature of the S1–S7 RH chambers; the temperature of the sample tube and sample was similarly stabilized using a water jacket. Heat-producing components were insulated from other parts of the apparatus.

Method of adsorption

Following balance calibration, the sample was loaded onto the sample pan, the hang-down tube replaced, and the entire apparatus evacuated. A crucible furnace [14] was raised into position around the sample region to desiccate the sample at approximately 130°C until its weight stabilized. This resulted in a weight loss of less than 5% for all samples. The furnace was then removed, the water jacket set in place, and the sample

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[14] Type 56311, Lindberg, Division of Sola Basic Industries, Chicago, Ill. 60612, U.S.A.

allowed to return to 25°C. The sample and balance region was isolated from the rest of the system while the SOURCE RH chamber was allowed to equilibrate into the appropriate initial volume. The SOURCE chamber was then closed. At 'zero time' the evacuated sample chamber was opened to the rest of the system; immediately thereafter the SUPPORT chamber and oil manometer were opened. Sample weight was recorded continuously during adsorption. Relative humidity was recorded manually at 10–15 s intervals by monitoring both the 'Convectron' gauge and oil manometer response. The latter gauge was 'preset' to the anticipated final RH prior to expansion in order to minimize its response lag.

RESULTS AND DISCUSSION

The results of various physical property measurements are given in Table 1. Fig. 2 demonstrates the relative success of the SOURCE : SUPPORT approach to stabilizing the RH_i during the critical period of initial adsorption.

The choline halides were examined under varying RHs according to the procedure described. Results of selected runs are shown in Figs. 3, 4 and 5, along with their corresponding RH profiles as monitored throughout each run. From these adsorption curves, initial rates of uptake were calculated, as taken from the earliest portion of the curve where the RH was stable. The approximate onset of observable deliquescence is noted on the curves with a star and is seen to correspond well with the onset of non-linearity, considered to represent the conclusion of 'initial uptake'. These initial rates expressed in weight percent gain per time (W_i') were then plotted as a function of RH_i for each of the salts in Fig. 6. For comparison with Fig. 3, results of water vapor adsorption by choline chloride at room temperature and atmospheric pressure using the desiccator storage method are given in Fig. 7. 'Initial uptakes rates' estimated from these curves have values approximately 0.1% the values obtained at comparable RHs in vacuo, confirming the relative insensitivity of the desiccator method.

Choline chloride is a vitamin in the vitamin B-series and is listed as 'deliquescent'

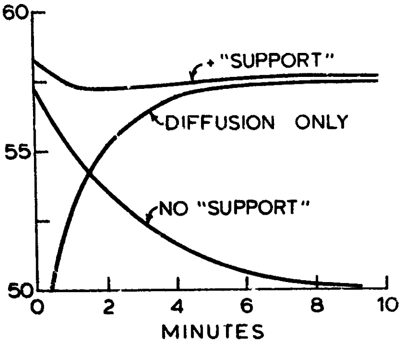
TABLE 1

PHYSICAL PROPERTIES OF THE CHOLINE HALIDES [a]

	Cl	Br	I
Molecular weight	139.6	184.1	231.1
density (g/ml)	1.20	1.52	1.78
Surface area:			
Microscope, A_{geom} (cm^2/g)	132.0	230.0	349.0
Sub-sieve sizer, A_{true} (cm^2/g)	–	–	670.0
Solubility (g/ml)	6.36	5.83	3.63
Molar solubility [b]	46.0	32.0	16.0

[a] Chloride and bromide samples oven-dried prior to testing.

[b] Approximate values since densities of sample solutions were undetermined.



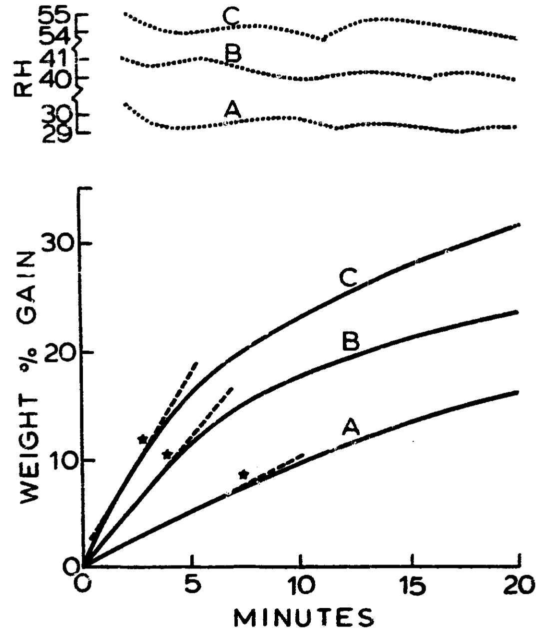
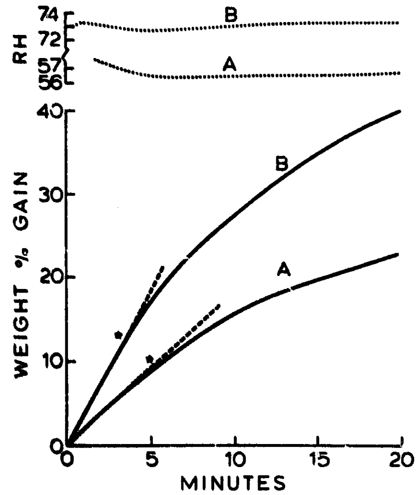


Fig. 2. Stabilization of RH$_i$ (final RH = 57.5%) by SOURCE : SUPPORT operation (no sample present).

Fig. 3. Selected curves illustrating adsorption of water vapor by choline chloride at 25°C; corresponding RH$_i$ profiles above. (Only representative curves shown by graphical clarity.) A: 29.5% RH$_i$; B: 40.5% RH$_i$; C: 54.5% RH$_i$; * marks onset of deliquescence.



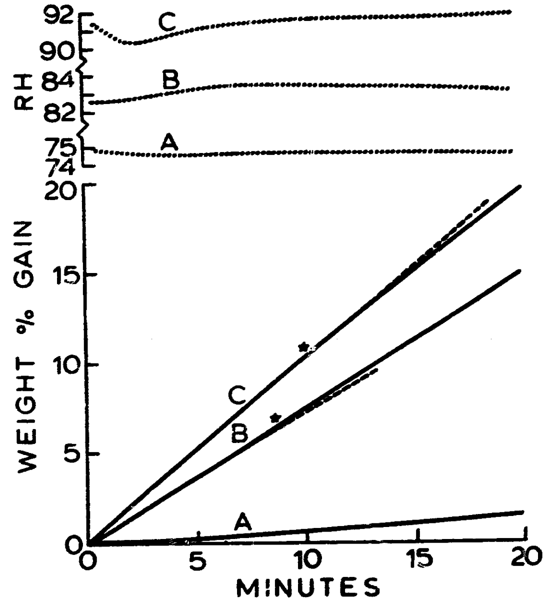
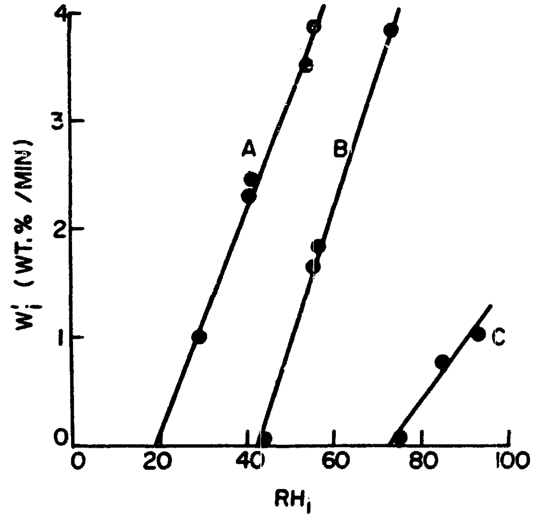


Fig. 4. Selected curves illustrating adsorption of water vapor by choline bromide at 25°C; corresponding RH$_i$ profiles above. (Only representative curves shown for graphical clarity.) A: 56.5% RH$_i$; B: 73% RH$_i$; * marks onset of deliquescence.

Fig. 5. Selected curves illustrating adsorption of water vapor by choline iodide at 25°C; corresponding RH$_i$ profiles above. A: 75% RH$_i$; B: 83% RH$_i$; C: 91% RH$_i$; * marks onset of deliquescence.



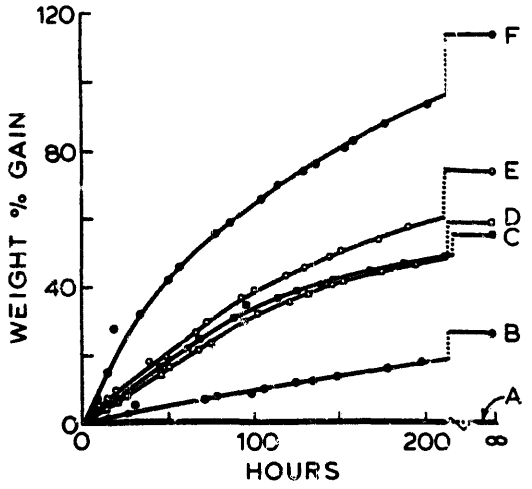


Fig. 6. Rate of moisture adsorption by choline halides at 25°C plotted as a function of relative humidity (RH_i). A: chloride; B: bromide; C: iodide.

Fig. 7. Adsorption of water vapor by choline chloride at room temperature using the desiccator storage method. A: 12% RH_i; B: 31% RH_i; C: 52% RH_i; D: 64% RH_i; E: 79.5% RH_i; F: 100% RH_i.

(Hoover, 1975), implying extreme hygroscopicity to the extent of solubilization in sorbed moisture. The choline halide series in particular was studied because of the range of hygroscopicities it provided, because they are molecularly simple, and because they contain a quaternary ammonium moiety which appears common to many other drugs reputedly hygroscopic, such as chloral betaine, acetylcholine chloride, methacholine bromide, tetraethylammonium bromide and gallamine triethiodide.

The adsorption behavior exhibited by the curves in Figs. 3–5 is characteristic of many soluble substances and can be rationalized in the following way: the critical relative humidity (CRH and RH_0) which exists over a saturated solution of the material determines the minimum RH at which adsorption will proceed to any significant extent. Below this RH, at most 2–3 layers of vapor will adsorb onto the clean, dry surface (Walter, 1971; Kaiho et al., 1972; Barraclough and Hall, 1974; Chikazawa and Kanazawa, 1978). Under this condition there exists no driving force sufficient to cause further adsorption. Above its RH_0, however, the material will adsorb water until the adsorbed film is sufficiently dilute for its vapor pressure to be in equilibrium with the atmosphere. For a highly soluble compound this readily leads to complete dissolution or deliquescence, at a rate governed by the difference in RHs (i.e. $RH_i - RH_0$) and by sample size. Once deliquescence has occurred, further moisture uptake depends on the solution properties of the dissolved substance, no longer on the 'hygroscopicity' of its solid surface. It is apparent from the adsorption curves that uptake is approximately linear up to the observed onset of bulk deliquescence. This is consistent with the notion that the factor $A_s(RH_i - RH_0)$ in Eqn. 4 remains essentially constant until deliquescence occurs. Beyond this point, however, A_s begins to decrease as droplets form and ultimately coalesce. Additionally, as the film of saturated solution on the crystal surface grows thicker, it is diluted too rapidly by extended adsorption to maintain saturation. The RH_0 term is then replaced by a function of time, RH(t), reflecting the increasing relative vapor pressure over the increasingly diluted film. The driving force for further adsorption becomes $RH_i - RH(t)$, which decreases with time until the EMC is reached. Thus the course of extended adsorption as equilibrium is approached could be described well by an exponential function like that of Eqn. 2.

It is the initial linearity of the uptake curves, however, that is of primary interest here. Fig. 6 summarizes the initial uptake rates of the halides as a function of RH. According to Eqn. 4 the slopes of these curves are equal to the product of the 'intrinsic material constant', k, the (constant) vapor pressure of pure water at 25°C (P_0) and the specific surface area, A_s (where $A_s = A/W_{initial}$). Accordingly, the linearity of these curves depends on a constant A_s for a given material. Since the chloride adsorbed moisture under ambient laboratory conditions, the A_s for this material could have changed during sample preparation. Recrystallization could occur on in situ desiccation, leading to crystal agglomeration and a decrease in A_s. This could easily account for any scatter observed in the data of Fig. 6, especially that of the more hygroscopic compounds.

From the slopes indicated in Fig. 6 and the estimated geometric surface areas given in Table 1, the intrinsic material constants could be estimated for each salt, where slope (min^{-1}) = kA_sP_0. The values so obtained are given in Table 2 along with the values of RH_0 as determined by the x-intercepts. On consideration of both parameters, the hygroscopicity of the halide series decreases in the order Cl > Br > I. Significantly, the ratios of these k values are of the same magnitude as the corresponding ratios of the estimated molar solubilities, i.e. the k : molar solubility ratio is approximately equal for all three salts. This seems intuitively predictable since both k and solubility reflect the intrinsic affinity of the substance for water. An analysis of solubility data or inorganic salts supports the thermodynamic prediction that RH_0 values should correlate with solubility within a common cation series. While solubility appears to influence both hygroscopic parameters, correlation of k and RH_0 values with other properties such as EMC, density and crystal lattice features should lend further insight into the chemical and physical factors governing hygroscopicity.

TABLE 2

HYGROSCOPIC PARAMETERS OF THE CHOLINE HALIDES (25°C)

	Cl	Br	I
k (g/cm^2-Torr-min)	3.22×10^{-5}	2.21×10^{-5}	6.45×10^{-6}
RH_0 (%)	18.5	42	74

CONCLUSIONS

In contrast to most other 'static' methods, the adsorption apparatus described here is capable of immediate, sensitive and accurate response to initial moisture adsorption, necessary to the proper study of adsorption kinetics for highly hygroscopic compounds. Lack of precision in data generated by the present method is primarily attributable to other experimental factors, such as sample preparation, which will require better control in future studies.

It is suggested that the hygroscopic behavior of the solid surface is best reflected in data collected prior to deliquescence, i.e. the very initial portion of the adsorption curve for a highly hygroscopic salt. This initial moisture uptake appeared to be linear in time at a given RH. In turn, these rates of uptake increased linearly with atmosphere RH, indicating the predicted proportionality between rate and the difference between the water vapor pressure present and that which prevails over a saturated solution of the solid. From these latter plots, given that A_s was known, the intrinsic material constant, k, and the RH_0 values could be determined for each salt. It is proposed that these two parameters define the hygroscopicity of a soluble substance, where increasing hygroscopicity can be associated with increasing k and decreasing RH_0 values.

SUMMARY

Hygroscopicity has long managed to escape clear quantitative definition. An historical review of the numerous approaches taken to characterize hygroscopic behavior and quantify its effects is presented.

A general kinetic relation to describe the hygroscopic process is proposed. An apparatus capable of sensitive and accurate measurement of rapid moisture adsorption under conditions of constant relative vapor pressure is described. The kinetics of water adsorption onto hygroscopic choline halide salts were examined using this apparatus, the preliminary results of which support the proposed kinetic model.

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