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Research Article

Preformulation Studies Involving Moisture Uptake in Solid Dosage Forms

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The rates of moisture sorption and the resultant effect on stability of a moisture-sensitive drug blended or formulated with different components are addressed. Total moisture increase was determined by weight gain, and change in mobile water level by water activity measurements. Equilibrium relative humidity is a useful tool in predicting the stability of a moisture-sensitive drug in solid dosage forms. Since immobile water is perceived not to react chemically, the amount of mobile water rather than total water is the critical parameter in degradation reactions involving hydrolysis. Materials that have a high capacity for binding water equilibrate more slowly to higher levels of mobile water and consequently show greater chemical compatibility with a moisture-sensitive drug than materials with lower binding capacities for water.

KEY WORDS: free water; mobile water; immobile water; unbound water; bound water; water activity; equilibrium relative humidity; moisture sensitive; solid dosage forms.

INTRODUCTION

Moisture often plays a key role in the physical and chemical stability of a solid dosage form. Although care in the manufacture and the selection of protective packaging can reduce the product's exposure to moisture, it is preferable to select components for a solid dosage form which minimize the moisture sensitivity of the product.

Water found in the matrix of a tablet or capsule is generally classified as either mobile or immobile (1–3). Mobile water (sometimes called unbound or free water) is loosely adsorbed on the surface of the solid. Immobile water is either (i) hydrated in the crystalline structure, (ii) linked by hydrogen bonding, or (iii) sorbed or entrapped within the amorphous structure (2). Although the degree of binding may vary significantly, immobile water is generally perceived as not readily available for chemical interaction with other species (1–3). On the other hand, mobile water has many of the properties of pure water including availability for chemical reactions (1–3). Thus, the amount of mobile water rather than the amount of total water is critical to the stability of a drug substance that is moisture sensitive.

The measurement of free or mobile water is expressed by water activity (A_w) or equilibrium relative humidity (ERH). The water activity of a substance is defined as the ratio of the vapor pressure of water due to the substance (P_{sub}) to the vapor pressure of pure water (P_{H_2O}) at the same temperature:

$$A_w = \frac{P_{sub}}{P_{H_2O}}$$

Equilibrium relative humidity is water activity expressed as a percentage:

$$ERH = \frac{P_{sub}}{P_{H_2O}} \times 100 = A_w \times 100$$

Both A_w and ERH are commonly used to describe the free water of a material (4). Numerically ERH equals the relative humidity generated by the product in a closed system.

The ERH of any substance will eventually reach the relative humidity (RH) of the atmosphere in which it is stored, since thermodynamically, the water activity of a solid will equal the water activity of the environment at equilibrium (4). For example, a material stored at 20% RH in time will reach an ERH of 20%. If the material is then moved to an atmosphere of 65% RH, the free water will increase to 65% ERH; if moved to a 10% RH atmosphere, the free water will decrease to 10% when equilibration is achieved. The rate at which the ERH of the material reaches that of the atmosphere varies with the individual substances, however (4). Also, the total water content of different substances which have reached equilibrium in the same humidity conditions may be vastly different even though the substances all have the same water activity. Since immobile water is not perceived to be available for chemical reactions, the free water content and the rate at which the water activity of the solid dosage form reaches the humidity of the storage atmosphere are important parameters in predicting stability of a formulation involving a moisture-sensitive drug.

Because of the critical role of moisture in the stability of

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pharmaceutical solid dosage forms, product specifications commonly define moisture limits. However, the limits typically specify total moisture content as determined by loss on drying or Karl Fischer titration rather than being definitive for mobile or immobile water. Sorption–desorption isotherms relate total moisture to the relative humidity in which the substance is stressed (5,6). These isotherms define equilibrium moisture content (EMC) which has been used as a hygroscopicity classification (7–9).

The food industry has long recognized the usefulness of free water measurements. Correlation of water activity in foods with microbial growth (4,10,11), storage problems (12–14), and oxidation of fats (13) and in plants with germination (14) have been described. As a result of the importance of free water to the food industry, a variety of instrumentation is available for the determination of water activity (10). The measurement of water activity is traditionally less common to the pharmaceutical industry, although in most cases the equipment used in the food industry is also suitable for pharmaceutical products.

In a preliminary compatibility screening test, powder blends of Drug A with 21 potential excipients and 4 antacids were stored at 50°C for 4 weeks (15). Drug A was stable both alone and with nearly all of the various blends when subjected to thermal stress only. However, the addition of 5% (w/w) water to the thermal stress resulted in degradation of Drug A in addition to changes in appearance. This was not surprising since Drug A is known to be moisture sensitive. However, in several cases, remarkable stability was obtained with more hygroscopic excipients as opposed to materials with a low affinity for water. This result prompted more experimentation.

The relationship of water activity and total moisture to the stability of drug substance is described in the following preformulation study.

MATERIALS AND METHODS

Materials

The following pharmaceutical excipients and actives were studied: Drug A, a proprietary active ingredient; dicalcium phosphate dihydrate (Emcompress, Edward Mendell Co. Inc., Caramel, NY); magaldrate, (Tomita, Tokushima, Japan); microcrystalline cellulose (MCC-2; Avicel PH-102, FMC Corp. Philadelphia, PA); microcrystalline cellulose, (MCC-3; Avicel PH-103, FMC Corp., Philadelphia, PA); pregelatinized starch (Starch 1500, Colorcon, Inc., West Point, PA); and pregelatinized starch, low moisture (Starch 1500LM, Colorcon, Inc., West Point, PA).

HPLC-grade methanol was used in the HPLC mobile phase preparation. All other chemicals and solvents used in the analyses were reagent grade.

Instrumentation

The HPLC system consisted of a Model 600 gradient pump, a Model 481 variable-wavelength detector, and a WISP 712 autoinjector (all from Waters Chromatography Division, Millipore Corp., Milford, MA). Data were acquired with a Model 1000 computer (Hewlett-Packard, Palo Alto, CA) using Computer Inquiry Services software (Beckman Instruments, San Ramon, CA). The separation used a reverse-phase column (Partisil-10 ODS, 10-μm particle size, 25 cm × 4.6-mm ID; Whatman Inc., Clifton, NJ). The mobile phase was 85:15 methanol:0.1 *M* ammonium acetate buffer at a flow rate of 2 ml/min monitored at 322 nm. Samples were extracted with methanol and assayed for intact Drug A. The method is stability indicating for the Drug A (15). All data reported represents an average of duplicate preparations.

The water activity measurement system was a cooled-mirror dew point instrument (Model CX-1, Decagon Devices, Pullman, WA). The digital reading reflects the mobile water (as expressed by water activity) for powdered or granular material. In the case of whole tablets, the reading reflects the surface mobile water level. When the mobile water is homogeneous throughout the tablet, the depth of the measurement is not critical in assessing the mobile water content of the entire tablet. Therefore, tablets which are fully equilibrated to the relative humidity in which they were stored can be read intact. However, when tablets are exposed to a sudden change in humidity and are in the process of equilibrating to a higher or lower value, the tablets should be crushed in order to obtain an accurate free moisture level for the entire tablet. A wire disk cut from 60-mesh screen to the internal diameter of the sample cup is placed over the powdered material to prevent the dust from contaminating the internal mirror. The time required to measure the water activity of crushed tablets or powdered material is about 2 min. Whole tablets require slightly longer times. The lower reading limit of the water activity system is 3% ERH. Data below the limit are reported as nil for convenience and plotted as 0. CURVEFIT from STATPAD, version A-1.1 (John A. Clements, Professional Applications Development, Weywouth, MA), computer software was used to determine equations for the curves generated from the experimental data for the change in ERH versus time.

Three controlled-temperature and -humidity chambers were used: a 30°C/60% RH and a 40°C/ambient humidity walk-in chamber (Bally Case and Cooler, Inc., Bally, PA) and a 40°C/80% RH reach-in incubator (Model 39841, Forma Scientific, Marietta, OH). Desiccators with silica gel and saturated solutions of magnesium chloride and cobalt chloride stored in the 40°C/ambient chamber provided environments of 40°C and 3, 25, and 48% relative humidity.

Experimental Conditions

Experiment I: Weight Gain and Mobile Water Change of Raw Materials and Drug A. The weight gain and change in water activity versus time for the raw materials and Drug A placed in open glass containers at a bed depth of 2–3 mm and subjected to storage at 30°C/60% RH in a walk-in chamber were determined on materials that were either untreated or pretreated by drying at 105°C for 3 hr (loss on drying conditions for microcrystalline cellulose as per Official Monograph of National Formulary XVII). All weight measurements were taken within the walk-in chamber on an analytical balance that had fully equilibrated to the conditions. In a similar manner, the mobile water was determined using a water activity system that had fully equilibrated to the conditions in the walk-in chamber.

Experiment II: Compressed Tablets Containing Drug A.

Table I. Ratio of Substance to Drug A

Formulation	Drug A	Magaldrate	MCC-2	Starch	Magnesium stearate
A	1	—	11	—	0.1
B	1	—	5.5	5.5	0.1
C	1	8.4	0.5	—	0.1
D	1	8.4	—	—	0.1
E	1	8.4	—	0.5	0.1

Five direct-blend tablet formulations containing Drug A were prepared at the ratios listed in Table I and compressed on a rotary tablet press (Manesty Beta Press, Thomas Engineering, Hoffman Estates, IL) to a target hardness of 16 kp, consistent with normal tableting procedures. The average tablet weight of each formulation was determined after the tablets were dried in a convection oven in a single layer at 90°C for 1 hr, which is analogous to the temperature that the product is exposed to during the film coating process. The tablets were stored in a single layer in open containers at 40°C/3% RH, 40°C/25% RH, 40°C/48% RH, and 40°C/80% RH. Total weight gain, ERH, and HPLC analysis for intact Drug A were determined initially and after 1, 2, and 4 weeks of storage on the 40°C/80% RH samples and initially and after 4 weeks only on the 40°C sample at 3% RH, 25% RH, and 48% RH. The containers were capped just prior to removal from the various humidity chambers and allowed to equilibrate for 0.5 hr at room temperature prior to determining ERH and weight gain. Comparison of ERH readings taken on samples equilibrated to 40°C/80% RH and read at 40°C versus ERH readings from samples stored at 25°C for 0.5 hr after removal from the 40°C chamber showed to significant difference in the ERH provided that the sample was tightly sealed upon removal. The rate of change in ERH for the five formulations was also studied. Tablets dried at 90°C for 1 hr were exposed to 40°C/80% RH. The change in ERH and weight gain was monitored throughout the equilibration in the humidity chamber. The tablets were crushed just prior to the ERH reading since the mobile water is not homogeneous in tablets that are in the process of equilibrating to different humidity levels.

Table II. Loss on Drying

Substance	% LOD after 3 hr at 105°C	Raw material specifications
Drug A	Nil	nmt 0.1% loss on ignition
Magaldrate	5.41	nmt 10% LOD; 3 hr at 105°C 10–20% LOD; 4 hr at 200°C
MCC-2	3.88	nmt 5.0% LOD; 3 hr at 105°C
MCC-3	2.92	nmt 3.0% LOD; 3 hr at 105°C
Calcium phosphate dihydrate	3.84	nlt 24.5% and nmt 26.5% loss on ignition; theoretical water due to hydrate = 20.9% (w/w)
Pregelatinized starch, low moisture	3.65	nmt 7.0% LOD; 4 hr at 120°C

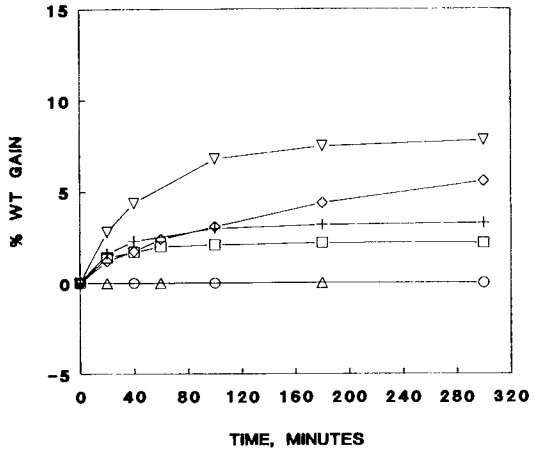

Fig. 1. Percentage of weight gain versus time of undried raw materials exposed to 30°C/60% RH: Drug A (○); dicalcium phosphate dihydrate (△); MCC-2 (□); MCC-3 (+); magaldrate (◇); pregelatinized starch, low moisture (▽).

RESULTS

Experiment I studied the moisture uptake (both total weight gain and change in mobile water) when various materials are exposed to high-humidity conditions. Drug A, four diluents (microcrystalline cellulose at two different initial moisture levels, dicalcium phosphate dihydrate, and low-moisture pregelatinized starch) and an antacid (magaldrate) were selected for this study based on the preliminary compatibility screening test (15). The average weight loss of replicate determinations for the raw materials dried at 105°C for 3 hr is shown in Table II. This drying condition is less severe than compendial methods of LOD of some of the substances but was selected as a moderate condition to which all materials tested could be subjected without danger of decomposition. All of the materials show a significant loss on drying at 105°C except for Drug A.

The percentages weight gain versus storage time at 30°C/60% RH for the dried and undried raw materials are shown in Figs. 1 and 2, respectively. Neither Drug A nor

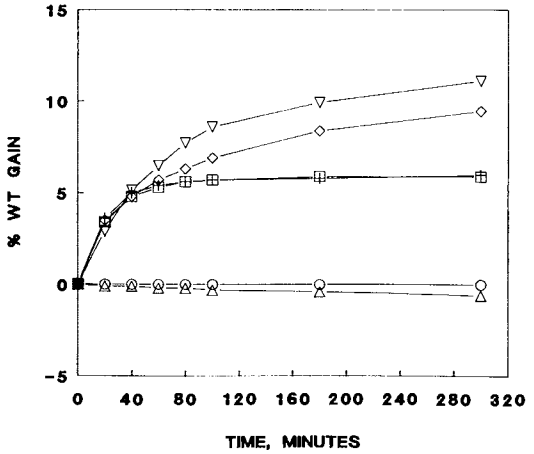

Fig. 2. Percentage weight gain versus time of dried raw materials exposed to 30°C/60% RH: Drug A (○); dicalcium phosphate dihydrate (△); MCC-2 (□); MCC-3 (+); magaldrate (◇); pregelatinized starch, low moisture (▽).

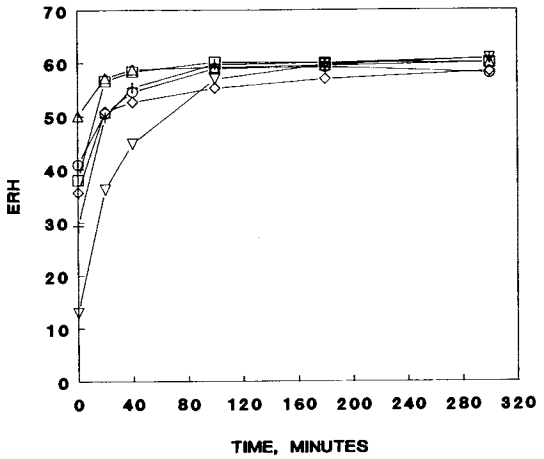

Fig. 3. Changes in percentage ERH versus time for undried raw materials exposed to 30°C/60% RH: Drug A (○); dicalcium phosphate dihydrate (△); MCC-2 (□); MCC-3 (+); magaldrate (◇); pregelatinized starch, low moisture (▽).

dicalcium phosphate dihydrate gain weight when exposed to 60% relative humidity. In fact, the dried dicalcium phosphate dihydrate exhibits a weight loss at this condition, a characteristic previously reported (1). Other materials all demonstrate significant weight gain.

Figures 3 and 4 demonstrate the change in ERH versus time at 30°C/60% RH for the dried and undried raw materials, respectively. The water activity of both Drug A and dicalcium phosphate dihydrate equilibrates rapidly to that of the 60% RH of the storage condition as compared to the other four materials. The two types of microcrystalline cellulose studied, MCC-2 and MCC-3 (low moisture), have essentially the same ERH and weight gain profiles when the materials are dried. The total amount of water present in the material after reaching equilibrium in the elevated humidity was the same for both.

The amorphous structure of starch provides a high capacity for moisture sorption. Although starch equilibrates slowly, the total weight gain for both the dried and the undried starch is the largest of the six materials studied (Figs. 1 and 2). The ERH of the starch also approached the storage conditions of 60% RH more slowly than the other materials listed (Figs. 3 and 4). The initial 13.0% ERH of the undried starch material is also significantly lower than any of the other undried materials.

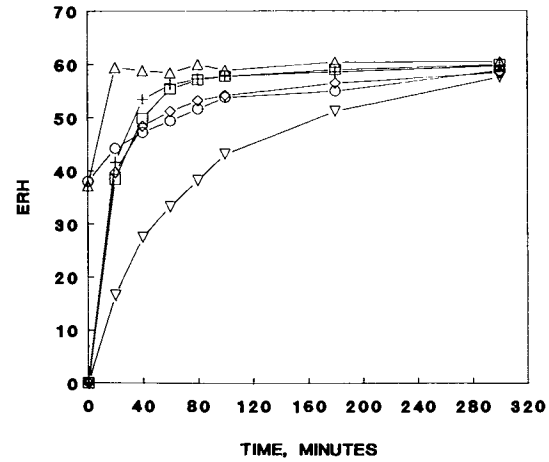

Fig. 4. Change in percentage ERH versus time for dried raw materials exposed to 30°C/60% RH: Drug A (○); dicalcium phosphate dihydrate (△); MCC-2 (□); MCC-3 (+); magaldrate (◇); pregelatinized starch, low moisture (▽).

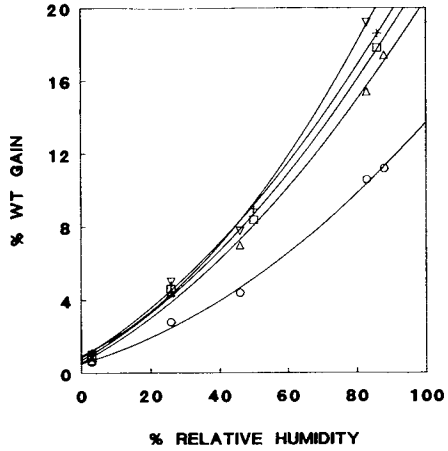

Fig. 5. Percentage weight gain after 4 weeks at 40°C and various percentage RH: Formulation A (○); Formulation B (△); Formulation C (□); Formulation D (+); Formulation E (▽).

Experiment II dealt with the effect of total moisture, free water, and the rate of change of free water versus stability of Drug A for the five tablet formulations. Significant percentage weight gain occurs for the different formulations when subjected to 4 weeks storage at 40°C and four different relative humidities (Fig. 5). However, in spite of the high moisture burden, no loss of Drug A was detected in any of the formulations after 4 weeks of storage except at the 80% relative humidity station (see Table III). Furthermore, at 80% RH the formulations with a greater level of total water content showed significantly better stability for Drug A. Figure 6 relates the direct correlation of percentage weight gain to percentage intact Drug A in the different formulations. All data points represent the average of duplicate analyses. The correlation coefficient for the linear regression is 0.9775.

Further investigation of the water uptake in these formulas was made by observing change in ERH versus time for each formula when subjected to the 40°C/80% RH chamber. Although the ERH for the different formulations all eventually equilibrate to the relative humidity of the chamber in which they are stored, the rate at which the ERH of the individual formulas reaches equilibrium with the chamber is different. Formulas C, D, and E take 6–8 days to equilibrate, while Formula A equilibrates in about 5 hr. Fig-

Table III. Percentage of Initial Drug A Remaining After 4 Weeks Storage at 40°C and Various Relative Humidities

Formulation	3% RH	25% RH	48% RH	80% RH
A	100.0	100.0	100.4	64.2
B	100.9	98.7	98.3	82.5
C	101.8	99.8	99.0	83.9
D	99.8	99.1	98.0	83.0
E	102.0	100.4	101.6	92.2

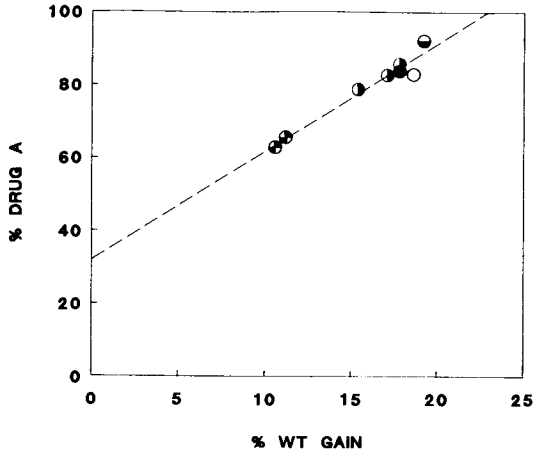

Fig. 6. Percentage Drug A remaining after 4 weeks of storage at 40°C/80% RH versus percentage weight gain from initial dried weight: Formulation A (◒); Formulation B (◑); Formulation C (●); Formulation D (○); Formulation E (◒).

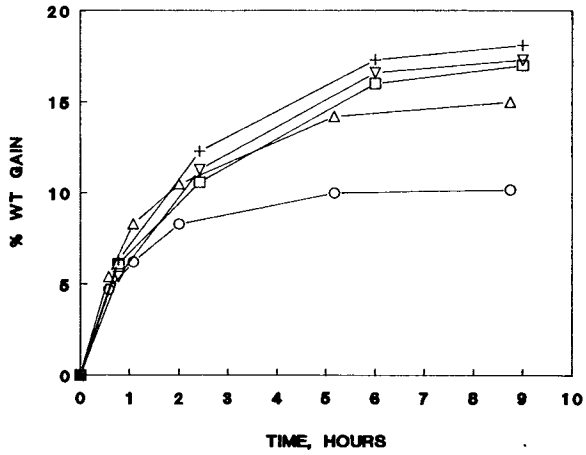

Fig. 8. Weight gain in compressed tablets versus time exposed to 40°C/80% RH: Formulation A (○); Formulation B (△); Formulation C (□); Formulation D (+); Formulation E (▽).

ures 7 and 8 show the change of ERH and weight gain respectively for the five formulations exposed to 40°C/80% RH.

DISCUSSION

Over the 30–80% range, the ERH relates linearly to weight gain for each formulation during the equilibration process (Fig. 9). The variation in the slopes of the regression of lines demonstrates that the relationship of total moisture to mobile water may be different depending upon the components present.

The equation for the curve representing the change of ERH versus time for each formulation is obtained by fitting the experimental data for the first 24 hr of equilibration to a series of equations using STATPAD software. The following general equation was the best fit for each of the five formulations (range of correlation coefficient for curve fit of five formulations = 0.970 to 0.998):

$$\text{ERH} = a + b/t + c/t^2$$

where t is time in minutes.

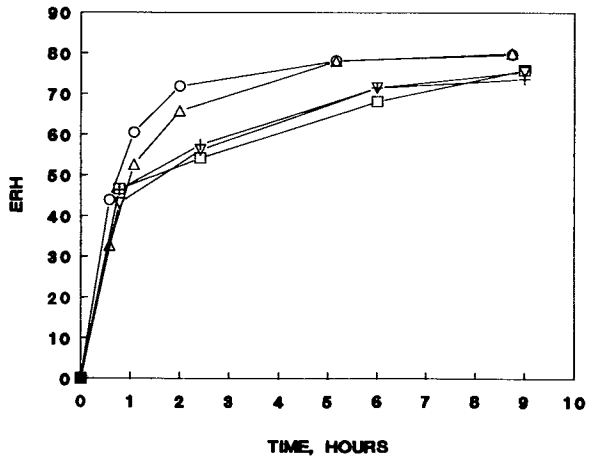

Fig. 7. Change in ERH in compressed tablets versus time exposed to 40°C/80% RH: Formulation A (○); Formulation B (△); Formulation C (□); Formulation D (+); Formulation E (▽).

The first derivative of this equation represents the rate of change of ERH:

$$d\text{ERH}/dt = -b/t^2 - 2c/t^3$$

Table IV lists the rate of change of ERH for various times within the first 9 hr. As the ERH approaches equilibrium with the environment, the rate of change decreases.

As predicted from the rate of change of ERH in the respective raw materials, the mobile water in formulations which contain components with a strong affinity for binding water and hence a larger moisture burden shows slower equilibration of the ERH to the higher humidity levels than that in formulations containing less hygroscopic materials. Thus, increased drug stability is obtained since the water activity does not reach a threshold level as rapidly. The relationship of the rate of change of ERH (dERH/dt) at 9 hr to intact Drug A after 4 weeks of incubation for the five for-

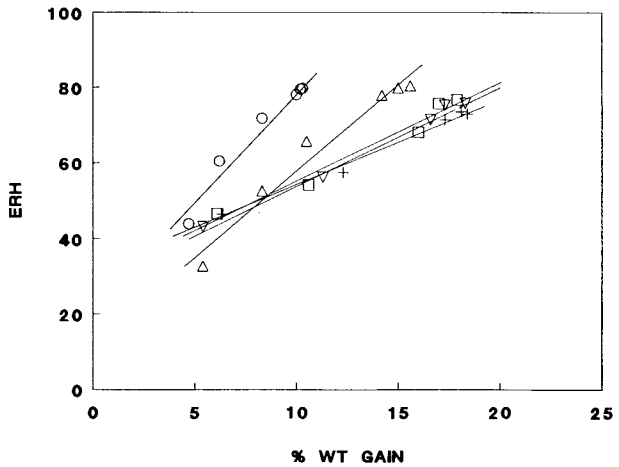

Fig. 9. Weight gain versus ERH in compressed tablets exposed to 40°C/80% RH for 24 hr. The respective slope of the line with corresponding correlation coefficient follows each symbol. Formulation A (○), 5.956, 0.9803; Formulation B (△), 4.572, 0.9822; Formulation C (□), 2.636, 0.9843; Formulation D (+), 2.316, 0.9951; Formulation E (▽), 2.652, 0.9959.

Table IV. Rate of Change of ERH (*d*ERH/*dt*) for Dried Formulas Exposed to 40°C/80% RH

Formulation	Time (min)				
	120	180	240	360	540
A	0.0891	0.0405	0.0228	0.0101	0.0045
B	0.1370	0.0636	0.0365	0.0166	0.0075
C	0.1668	0.1016	0.0649	0.0323	0.0154
D	0.1318	0.0738	0.0458	0.0272	0.0104
E	0.1613	0.0915	0.0571	0.0278	0.0131

mulations is depicted in Fig. 10. The regression line (correlation coefficient = 0.785) predicts that if water activity is equal to 80% ERH at time zero in the study (no time required for equilibration to the test environment), about 38% of the drug would decompose within 4 weeks at 40°C/80% RH. This point is supported by the data collected in the excipient compatibility study, where water is added directly to the test vial (15). Likewise the seemingly unexpected increase in stability of the moisture-sensitive drug in formulations which show the greatest moisture uptake as shown by weight gain (Fig. 6) is explained since the ERH in these formulations equilibrates more slowly when exposed to humidity.

CONCLUSIONS

This study demonstrates the importance of water activity as opposed to total water in preformulation compatibility studies involving a moisture-sensitive drug substance. Commercially available equipment provides rapid measurement of water activity of powders, granulations, or tablets. Even though an ingredient may have a large moisture component (i.e., starch and magaldrate), if the water activity associated with the material equilibrates slowly to the high levels, the moisture component may not necessarily preclude its use with drugs known to be moisture sensitive. In fact, hygroscopic excipients may enhance drug stability by preferentially binding moisture and decreasing the rate at which the ERH reaches equilibrium with the environment, thus making the dosage form less susceptible to fluctuations in atmospheric humidity during manufacture, shipment, storage, or patient use.

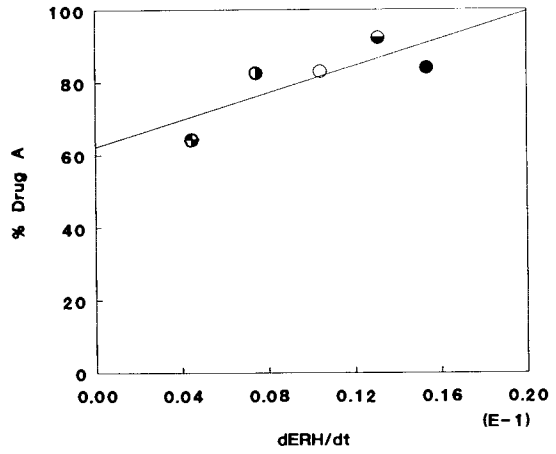

Fig. 10. *d*ERH/*dt* at 9 hr versus Drug A at 4 weeks, 40°C/80% RH: Formulation A (◒); Formulation B (◑); Formulation C (●); Formulation D (○); Formulation E (◒).

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